Cancer of the upper aerodigestive tract:

assessment and management of upper aerodigestive tract mucosal cancers

Appendix H: Evidence Review

Developed for NICE by the National Collaborating Centre for Cancer

1. Information and support

Information needs

Clinical question: What are the specific information and support needs reported by patients with cancer of the upper aerodigestive tract and their carers?

Background

The diagnosis and treatment of cancer of the upper aerodigestive tract (CUADT) is complex, often requiring multi-modality treatment resulting in significant side-effects and life-altering outcomes, both short and long term. Currently no gold standard exists for the information that should be provided to patients with CUADT to guide discussions regarding treatment. Patients and carers report receiving varying amounts of information at diagnosis and throughout treatment. Such variations can potentially lead to delays in decision-making, lack of understanding of treatment options and patient anxiety.

Whilst information needs to be individualised it is important that guidance exists on the level and timing of information and who should provide it. This will improve understanding by the patient at each stage of their pathway.

Evidence statements

Information, communication, and support needs

One systematic review summarised evidence about the quality of life and support needs of patients with oral cancer, excluding qualitative studies (Moore 2014a). This review concluded that patient support needs are varied, with specific needs relating to oral health and functional impairment, swallowing issues, pain, speech, nutrition and weight loss, depression, anxiety, appearance/body image, sexuality/relationships, and financial support.

The systematic review by Lang (2013) reported on the psychological experience of living with head and neck cancer (HNC), and included only qualitative studies. A key finding was that supportive relationships with HNC peers and healthcare professionals are important to patients. Support after treatment is sometimes limited, which can contribute to feelings of isolation and anxiety.

A third review collated evidence about the psychological health of HNC carers (Longacre 2012). This review reported that caregivers describe considerable perceived burden and care-related strain and can experience poor psychological health (distress and anxiety). Some evidence suggests that increased support may attenuate caregiver burden.

A further 12 individual studies reported on the information and support needs of patients with HNC (Moore 2014b, Fang 2012, Newell 2004, Oskam 2013, Llewellyn 2006, Furness 2005, Edwards 1998, Llewellyn 2005, Glavassevich 1995, Rogers 2015, Nund 2014, Brockbank 2015).. Common themes from these studies indicate that patients require support for acute needs resulting from treatment such as pain, nutrition, changes in speaking and swallowing, and coping with the disfigurement of

facial surgery. Patients often report satisfaction with the information they received prior to treatment, although some are not fully informed about the side effects of treatment and feel underprepared for the extent of the impact on their lives. Many studies highlight the lack of long-term support after treatment, relating to patients ability to work, financial advice, information about support groups, and a fear of cancer recurrence.

Information and support needs of people with HPV-related cancer

One qualitative interview study (Baxi 2013) and one cross-sectional questionnaire study (Milbury 2013) reported that some patients with HPV-related oropharyngeal cancer feel uninformed about the risk of transmission of their disease and were uncertain about HPV as a cause of their cancer. Further information was often sought from sources such as the internet.

Supportive care needs of oral cancer patients

Three studies conducted in Taiwan (Chen 2009, Chen 2010, Chen 2013) assessed the supportive care needs of patients with oral cancer using the Cancer Needs Questionnaire (CNQ). The top care needs for newly-diagnosed patients related to 'coping with anxiety about having treatment or surgery'. In surgically-treated patients the main care need was 'to be fully informed about the benefits and side-effects of treatment or surgery before having it'. The highest level of supportive care needs for patients who received radiotherapy was at two months after treatment. Head and neck cancer specific needs remained constant up to 6 months after treatment.

Patients concerns over follow-up

One study (Kanatas 2013) reported the results of a cross-sectional questionnaire designed to elicit patients concerns over follow-up using the Patient Concerns Inventory (PCI). Fear of recurrence was common to all clinical groups (n = 447). Speech issues were more common with laryngeal cancers, and saliva issues with oropharyngeal tumours. Apart from early-stage laryngeal cancers, patients consistently reported issues concerning dental health and chewing.

Support from fellow HNC patients

A qualitative interview study (Egestad 2013) of 11 HNC patients after radiotherapy described the importance to participants of meeting other cancer patients who had undergone similar treatments. Contact with fellow patients can lead to less loneliness, and reduce uncertainty and negative feelings. However, a few participants reported feeling sadness and fear in meeting with fellow patients. One longitudinal questionnaire study (Ma 1996) reported that the social support needs of patients with nasopharyngeal cancer increased between the diagnostic and treatment phase and remained stable from treatment to post-treatment. Patients consistently chose health professionals as the first source of overall support, followed by family and friends.

The impact of a gastronomy tube

The results of focus groups with six patients who had a gastronomy tube placed for nutritional support and three of their carers were reported by Mayre-Chilton (2011). Patients had developed strategies to cope with the feeding tube and acknowledged the positive reasons for needing a tube. The patients and carers expressed a positive impact on approaching the hospital MDT, especially where they had access to the doctor, dietician, nurse and other professionals in one clinic. Some patients expressed a lack of active care after their treatment and discharge into the community.

Palliative care

Ledeboer (2008) reported a cross-sectional questionnaire study, where relatives or close friends (n = 45) of patients with incurable HNC were asked about their experience of palliative care services. The majority of respondents reported that the patient had more need for psychosocial and physical support than was provided. The overall care and support of the department was rated as good by most patients. However, information about the terminal stage and bereavement support was often lacking.

Study characteristics and quality

Evidence about the information and support needs of patients with cancer of the upper aerodigestive tract (CUADT) was identified from three systematic reviews and 22 individual studies, which were either qualitative interview/focus group-based (n=10) or questionnaire studies (n=12). A summary of the included studies is provided in Table 1.1.

The three systematic reviews were well conducted, although they all included only qualitative or questionnaire studies. The review by Longacre (2012) did not specifically focus on information and support needs.

The individual studies included in the evidence review used small samples recruited from single cancer centres/hospitals, which limits their generalisability to wider patient populations. Some studies selected patients using convenience sampling; people who participate in these studies may have information and support needs that are not representative of other CUADT patients. A majority (n=17) are cross-sectional studies, meaning that data were collected at only one point in time. Thirteen studies were conducted in countries other than the UK, so their relevance to current UK practice may be limited. Recall bias may have been present in some studies where participants were asked to retrospectively recall the information and support that was provided before or during their treatment.

1 **Table 1.1. Characteristics of included studies**

Reference, Country, Study type	Quality	Population	Method	Key findings
Moore 2014a Systematic review of the QoL and support needs of patients with oral cancer	Well conducted and relevant review. Date of search not reported.	Included studies of HNC populations if inclusive of patients with oral cancer.	Systematic review of 31 studies. The impact of support needs on QoL and its prevalence was reported. Excluded qualitative studies.	Oral cancer support needs are subjective and varied. Support needs relate to: oral health and functional impairment, swallowing issues, pain, speech, nutrition and weight loss, depression, anxiety, appearance /body image, sexuality/relationships, and financial support.
Lang 2013 Systematic review of qualitative studies to summarise the psychological experience of living with HNC	Well conducted and rigorous review. Aims and methods clearly defined.	Included studies of HNC populations (using NCI's definition)	Meta-ethnography used to synthesise the findings of 29 qualitative studies.	Patient's support from their social network, HNC peers and HCPs were particularly important in order to cope with living with and beyond HNC. Support following treatment completion was sometimes limited and left patients feeling isolated. Patients are sometimes reluctant to report side-effects and other problematic consequences of treatment.
Longacre 2012 Systematic review of studies reporting on the psychological health of HNC carers	Relevant review although not specifically focused on information & support needs.	Studies of caregivers of patients diagnosed with HNC	11 relevant papers were included and psychological factors from each study were reported	Caregivers experience poor psychological health (emotional distress and anxiety) compared to population norms and HNC patients. The 6-month interval following diagnosis is a significant time of stress. Caregivers report considerable perceived burden and care-related strain.
Moore 2014b Australia Qualitative interview study of support needs in patients with HNC	Well reported study. Patients recruited from a support group which limits generalisability to wider HNC population	8 patients who had treatment for HNC	Semi-structured interview data analysed using content analysis. Study guided by stress, appraisal and coping model	Support needs that affect QoL relate to acute needs (e.g. pain, nutrition) while undergoing treatment and support in coping in the long-term (fatigue, returning to work). Coping was influenced by the loss of access to a supportive hospital environment after treatment.
Baxi 2013 USA Qualitative interview study	Method of data analysis not reported. Limited generalisability of study sample.	10 men with HPV-related oropharyngeal cancer. No evidence of disease at time of	Semi-structured interviews. Transcripts analysed for general themes.	Participants were satisfied with doctors' care but some reported a lack of information about HPV and uncertainty about transmission and latency. Some patients worried about their partner's risk. The internet was a common source of information about

Reference, Country, Study type	Quality	Population	Method	Key findings
of the experience of patients with HPV-related oropharyngeal cancer		study.		HPV, but it was not easily navigable.
Milbury 2013 USA Cross-sectional questionnaire about the information and support needs of patients with HPV-related oropharyngeal cancer	Small sample size. Cross-sectional study. Only included patients who had a partner.	62 patients with HPV-positive oropharyngeal cancer. Mostly males and married.	Questionnaire assessed HPV-related knowledge, information needs and psychological concerns.	66% correctly identified their HPV status but only 35% recognised HPV as a cause of their cancer. A majority felt uninformed regarding transmission risks and precautions. 39% wanted their oncologist to discuss more about HPV-related issues and 58% sought this information from other sources.
Fang 2012 USA Cross-sectional questionnaire about information needs of HNC patients	Small sample size. Convenience sampling used. Cross-sectional study. Respondents limited to choosing the information needs presented in the survey.	65 patients with HNC presenting for treatment at a cancer centre. Mostly Caucasian males.	Questionnaire assessed information needs by choosing from 10 topics relating to medical, physical, practical, social, and emotional needs.	Patients desired additional information regarding treatment options, managing changes in speaking and swallowing, and staying healthy after treatment. Patients with early-stage disease reported more informational needs than advanced-stage disease. Younger patients were more interested in receiving information about sexuality after treatment than older subgroups.
Newell 2004 UK Qualitative interview study to explore information needs of HNC patients before surgery	Small sample size. Patients asked to retrospectively evaluate the information received – possible recall bias.	19 patients and 13 of their immediate relatives who had surgery for HNC. Mostly laryngectomy or neck dissection.	Semi-structured interviews to explore the content and satisfaction with information received prior to surgery	Patients reported diverse information needs. Many felt unprepared about the long-term lifestyle changes from treatment. Support and information during the postoperative period was judged to be inadequate. Patients often reported difficulty absorbing information and often looked for information from other sources such as internet or support groups.
Oskam 2013 The Netherlands	Small sample size and only long-term survivors included	26 long-term survivors (range 8-11 years) with oral or	Questionnaire completed at baseline (pre-treatment) and long-term follow-up.	At time of treatment, the need for supportive care was highest for: dental hygienist (77%), physical therapist (73%), speech therapist (42%), and dietician

Reference, Country, Study type	Quality	Population	Method	Key findings
Longitudinal questionnaire study to evaluate need for and use of supportive care	which limits generalisability. Only one participant lost to follow-up	oropharyngeal cancer treated with free-flap reconstruction and post-operative radiotherapy	Questionnaire developed to evaluate need for and use of supportive care.	(38%). At long-term follow-up, the need for supportive care was: dental hygienist (46%) and physical therapist (23%). Only small differences between perceived need and actual use of supportive care.
Llewellyn 2006 UK Longitudinal questionnaire study to assess HNC patients satisfaction with information	Around 40% of participants did not complete follow-up – who may have had lower levels of satisfaction. Information may have been received by participants after completing the first questionnaire.	82 newly diagnosed HNC patients. 47% advanced stage. 21% laryngeal, 15% floor of mouth, 15% oropharynx.	Questionnaire completed between diagnosis and treatment (n=82), 1 month after treatment (n=68), and again 6-8 months later (n=50). Measures included the Satisfaction with Cancer Information Profile (SCIP)	Patients were generally satisfied with information. Key areas of improvement were identified: the provision of information about support groups, where to go for financial advice, and long-term effects of treatment on ability to work, physical functioning and QoL. Some patients were not fully informed before treatment about the specific side effects of treatment and the severity of surgery.
Chen 2010 Taiwan Cross-sectional questionnaire study to explore supportive care needs of newly diagnosed oral cancer patients	Study may be of limited relevance to UK population. Participants were limited to reporting care needs provided in the questionnaire.	165 newly diagnosed oral cancer patients awaiting surgery. Grouped according to anxiety scores on HADS	Patients completed questionnaires via face-to-face interview. Supportive care needs were assessed using the Cancer Needs Questionnaire Short Form (CNQ-SF) and The Head and Neck Cancer Specific Needs Questionnaire (developed by the authors).	The top unmet care need for both those with and without anxiety was 'coping with anxiety about having treatment or surgery'. Other high ranking care needs included 'dealing with fears about the cancer returning' and 'to be fully informed about all the benefits and adverse effects of treatment and surgery before you have it'
Chen 2009 Taiwan Cross-sectional questionnaire study to explore unmet information	Study may be of limited relevance to UK population.	222 oral cavity cancer patients: 109 were newly diagnosed and 113 who had received surgical treatment	Participants completed the Cancer Needs Questionnaire Short Form – information subscale	Newly diagnosed patients had significantly higher overall care information needs. The top care information needs for diagnosed patients were ''to be fully informed about cancer remission" and ''to be fully informed about all of the benefits and side effects of treatment or surgery before you agree to have it". The top care information needs for treated

Reference, Country, Study type	Quality	Population	Method	Key findings
needs in newly diagnosed and surgically treated oral cancer patients				patients were ‘‘to be fully informed about all of the benefits and side effects of treatment or surgery before you agree to have it” and “To be fully informed about the odds of treatment success”.
Chen 2013 Taiwan Longitudinal questionnaire study to explore the supportive care needs in newly diagnosed oral cavity cancer patients receiving radiotherapy	Small sample size. Study may be of limited relevance to UK population.	82 oral cavity cancer patients who had received tumour dissection surgery before radiotherapy or chemoradiotherapy.	Participants completed the Cancer Needs Questionnaire Short Form – head and neck subscale before radiotherapy, then at 1, 2, 3, and 6 months after radiotherapy.	The highest level of supportive care needs at two months after treatment. The highest interpersonal communication and health information needs was prior to radiotherapy. Head and neck cancer specific needs were fairly consistent across time-points up to 6 months post-treatment.
Kanatas 2013 UK Cross-sectional questionnaire study to explore HNC patient’s concerns during consultation	58% response rate so may not be representative of wider HNC population.	447 patients treated for primary HNC between 1998-2009. 193 oral cancer, 124 oropharyngeal cancer. Included early and late stage disease.	Patients completed the patient concerns inventory (PCI) and a QoL measure.	Fear of recurrence was common to all clinical groups. Speech issues were more common with laryngeal cancers, and saliva issues with oropharyngeal tumours. Apart from early-stage laryngeal cancers, patients consistently reported issues with concerning dental health/teeth and chewing.
Egestad 2013 Norway Qualitative interview study to explore how HNC patients are affected by fellow patients during radiotherapy	Small sample size. Method of analysis well described and conducted.	11 HNC patients treated with radiotherapy. 7 male, 4 female. All received 6-7 weeks of external beam radiotherapy.	Interviews conducted about one month after radiotherapy to explore how contact with fellow patients affected participants everyday life in the treatment period. A phenomenological hermeneutic approach was used to guide the data analysis.	For all participants, it was important to meet other cancer patients who underwent a similar or the same treatment as themselves. Contact with fellow patients can lead to less loneliness, and reduction of uncertainty and negative feelings. Participants mostly talked about gaining support and help from fellow patients, however, a few reported feeling sadness and fear in meeting with fellow patients.

Reference, Country, Study type	Quality	Population	Method	Key findings
Furness 2005 UK Qualitative interview study to explore supportive care needs of facial surgery patients	Rigorous and well-conducted study. Not all patients had facial surgery for UADT cancer which limits relevance to review question	28 facial surgery patients and 9 of their significant others. 21 had surgery for cancer including 12 mouth/tongue cancer. Time since surgery 3 mo to 22y.	Focus groups and interviews conducted to allow patients to discuss their experience of adapting to facial surgery.	Many participants reported general satisfaction with information received before their surgery. Retrospective debriefing, education about physical and emotional after-effects, and information about support in the community were less consistent. Many participants experienced unexpected emotions or problems coming to terms with facial surgery. Some reported that contact with other facial surgery survivors had been very helpful to their emotional adjustment
Mayre-Chilton 2011 UK Qualitative focus group study to explore HNC patient and carer perspectives of the impact of a gastronomy tube.	Small sample size. Methods and analysis were well described.	6 HNC patients and 3 caregivers who had gastronomy tube placed for nutritional support, minimum of 3 months after tube placement.	Focus group facilitated to encourage discussion about living with a gastronomy tube from patients and their carers. Thematic analysis used to identify key themes.	Patients were more able to cope because they were the main focus of the treatment and time had been dedicated to help them make an informed decision. The patients and carers expressed a positive impact on approaching the hospital MDT, especially where they had access to the registrar, dietician, nurse and other professionals in one clinic. Some patients expressed a lack of active care after their treatment and discharge into the community, which had a negative impact.
Edwards 1998 UK Qualitative focus group study to explore the views of patients and carers about HNC services.	Study conducted over 15 years ago – may not be relevant to current service provision. No details about patients' disease or treatment	22 patients and 11 relatives from 4 hospitals and 2 support groups. Patients diagnosed more than one year previously	Focus groups were held with patients and carers. Data was analysed for key themes, issues and consistency.	Many patients felt abandoned when they were discharged and did not know where to turn. Several patients suggested that it would have helped to have one contact person who could liaise between various providers. Many had conflicting information from different professionals and some reported that they were not given enough information on the side-effects of treatment or what to expect during and after treatment.
Ledeboer 2008 Netherlands Cross-sectional	Small sample from the Netherlands. Retrospective accounts of palliative care – maybe subject	45 relatives or close friends of patients with incurable HNC. The average palliative period	Questionnaire consisted of questions about palliative care, including medical treatment, psychosocial support, information and education and	54% rated the ''overall'' care and support of the HNC team as ''good'' to ''very good. 58% reported that psychosocial support from the head and neck department in respect to problems of their relatives was insufficient. 78% of the relatives reported that the

Reference, Country, Study type	Quality	Population	Method	Key findings
questionnaire study to explore HNC carers' experiences of palliative care	to recall bias.	lasted 4 months. In most cases more than a year had passed since death of patient	terminal stage.	HNC department did not contact them after the death of their spouse. Almost none (5%) of the relatives received support from the department during the bereavement.
Llewellyn 2005 UK Qualitative interview study to explore the role of information on the development of expectations in HNC patients	Well described methods and analysis. Reliability of data checked by second reviewer. Small sample size	15 HNC patients post-diagnosis and free of disease. Time since diagnosis ranged from 1.5-18 months. All except one had surgery and majority had radiotherapy.	Semi-structured interviews to explore information received and its impact on patients expectations. Data were analysed and classified using a Framework Analysis Approach.	Many participants described the experience as being much worse than anticipated. Respondents emphasised a fine line between receiving too much and too little information. A few respondents reflected that there had been a lack of information on the long-term impact on life and information on financial benefits. Expectations were clearly related to the information given by the treating staff and the risks associated with the particular treatment recommended
Glavassevich 1995 Canada Cross-sectional questionnaire study to identify information needs of HNC surgery patients	Small sample size. No details about respondents' current health status or outcome of surgery. Retrospective study maybe subject to recall bias	32 patients who had surgery for HNC between 1990-1991. Most had neck dissection combined with oral mandibular reconstruction or laryngectomy.	Questionnaire identified the information that was most and least helpful to patients. Patients indicated which symptoms they had experienced before and after surgery.	All respondents indicated that more information was needed before surgery regarding the course of their illness and events that would occur. Complications from and reasons for the extent of surgery were also a concern. In many cases, feelings of anxiety and fear were not addressed prior to surgery. Respondents identified what to expect after surgery and the long-term prognosis as information that is most helpful and necessary to know.
Ma 1996 Hong Kong Longitudinal questionnaire study to explore social support needs in patients with nasopharyngeal cancer	Sample may not be generalisable to UK population.	111 newly diagnosed patients with nasopharyngeal cancer	Questionnaire contained social support measure that was designed specifically for the study. Measured desired and perceived social support from health professionals, family and friends. Questionnaire completed at diagnosis, 3-4 weeks after treatment started	Scores on desired social support increased between the diagnostic and treatment phase and remained stable from treatment to post-treatment. Patients consistently chose health professionals as the first source of overall support, followed by family and friends. Desired informational support was highest in the treatment phase, followed by the post-treatment phase. Similar results were reported for emotional support and desired instrumental support.

Reference, Country, Study type	Quality	Population	Method	Key findings
			and 3 months after treatment ended.	
Brockbank 2014 United Kingdom Qualitative focus groups/interview study	Small sample size. Retrospective aspects of the study maybe subject to recall bias.	24 patients with head and neck cancer treated with primary chemoradiotherapy within the previous two years.	Thematic analysis based on transcripts of focus groups and interviews.	Patient's expectations about the level of side effects they would experience differed, some felt well-prepared, but some were unprepared for the level of side effects they experienced. Most patients had received verbal and written information, finding written information helpful for being able to refer back to this at a later date. The importance of individualising the amounts and timings of information giving to each patient was highlighted.
Nund 2014 Australia Qualitative interview study	Small sample size. Retrospective aspects of the study maybe subject to recall bias.	Patients (n = 24) who had received radiotherapy (with or without systemic therapy) for a primary head and neck cancer.	Thematic analysis based on individual, semi-structured, in-depth interviews.	Participants stated that they had not anticipated the severity and duration of the side effects after treatment on eating and swallowing. Family members were identified as a significant source of support for people with dysphagia, particularly with regard to meal preparation and encouragement to keep eating. Some patients reported that they had benefited from services designed to help with swallowing difficulties, but others felt that information and advice given was too general, and not personalized or practical to their situation.
Rogers 2014 United Kingdom Questionnaire-based study	Results are reported on a per-patient basis, but the majority (63%) of patients completing the questionnaires on more than one occasion. It is not clear how any discrepancies between outcome	Head and neck cancer patients attending routine follow-up clinics. Data were available for 369 clinic attendances from 177 patients.	Qualitative analysis of results from UW-QOL v4 and PCI questionnaires.	31% (55/177) of patients reported problems with intimacy. Intimacy problems were more common in men, patients under 65 years, patients further on from diagnosis, and patients with more advanced primary tumours.

Reference, Country, Study type	Quality	Population	Method	Key findings
	reported by the same patient at different clinic visits were accounted for in the analysis.			
HNC, Head and neck cancer; HCPs, healthcare professionals; HADS, Hospital Depression and Anxiety Scale; QoL, quality of life				

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1 Evidence tables for all included studies

Reference	Moore, KA, Ford, PJ, and Farah, CS. I have quality of life but: Exploring support needs important to quality of life in head and neck cancer. European Journal of Oncology Nursing 2014b; 18(2): 192-200.
Study type	Qualitative interview study
Country	Australia
Research question(s)	What support needs influence QoL of HNC patients? How do patients appraise and cope with unmet support needs (stressors) during and post treatment?
Theoretical approach	Study guided by the Lazarus and Folkman stress, appraisal, and coping model.
Data collection	Semi-structured interview conducted by first author – an oral health therapist
Method and process of analysis	Content analysis using both inductive and deductive methods. Key components of the stress, appraisal and coping model used as coding framework to describe coping response of participants to the stress of cancer.
Population and sample collection	Convenience and snowballing sampling used to recruit 8 participants from a HNC support group. Participants eligible if they had undergone treatment for HNC and were able to provide informed consent. 7 male, 1 female. Time since treatment range 1-8y. Mean age 60y (range 51-60). Various cancers e.g. tongue, oropharyngeal. Various treatments e.g. surgery, radiotherapy
Key themes	**1. Stressors** <u>*Support needs during treatment: managing side effects of treatment*</u> The intensity of radiotherapy side effects escalated towards end of treatment. Nutritional support was most important at the end of treatment, as the taste and smell of nutritional supplements became unbearable as toxicity from cumulative fractions of radiotherapy increased. Mouth ulcers and painful sore throat, and a lack of taste provided little motivation to eat. Confusion about correct nutritional management at home during radiotherapy caused stress. Patients described difficulties with sleep deprivation, fatigue and, in some cases, coping with a feeding tube at home. Allied health and nursing staff were essential in managing supportive care needs: *"She...[a nurse] became by angel and I would bug her every time there was an ulcer, and she would say what time are you on, ok when you've finished radiation come and see me and we'll do something to alleviate the pain and treat it"* Participants struggled with the lack of communication about processes involved in moulding the stabilization mask, which was described as claustrophobic and traumatic. Being fixed in one place during radiotherapy caused anxiety and stress, especially as side effect of dysphagia and xerostomia worsened and swallowing became painful and difficult. <u>*Everyday demands while undergoing treatment*</u> Participants relied on family support networks to attend appointments, as fatigue worsened during treatment. For some without family support, the hospital became a surrogate support network during treatment. Participants reported needing help in all aspects of running a household. Out of pocket medical expenses became an unforeseen burden that added to the financial impact of being unable to work while undergoing treatment and immediately post-treatment. <u>*Coordination of the MDT*</u> Inadequate communication between MDT members caused stress and confusion about treatment. Although quality of treatment was appreciated, participants described issues with finding consistent information in the early stages of diagnosis and treatment. This confusion culminated after attending the MDT head and neck clinic for assessment and treatment planning: *"there was no overall communication, there was no one saying "this is what's going to happen"...and so I was just going from specialist to specialist...so that was a bit unsettling and also a bit confusing"* Insensitive remarks and conflicting information from doctors about treatment contributed to pre-treatment anxiety. *"I'd go and see the ear nose and throat [doctor] and he'd be very surprised at what one of the other people had said or done, you know, there just wasn't any communication between specialists"* <u>*Support needs post treatment: Managing "hangovers" of treatment*</u> In the first 6-12 months after treatment, participants struggled with a lack of organised supportive care. Participants felt isolated after discharge and did not know what to expect in terms of treatment recovery. In the absence of a dedicated contact person, participants struggled to find help in managing problems related to diet, appearance, and wound healing post-treatment. Participants struggled to find professional support and information about support therapies to mitigate the side effects of radiotherapy. *"If it's not related to the surgery or the radiation it's like getting blood from a stone to find out about other things that could help you."* Prolonged issues with muscle stiffness and atrophy, diminished function of swallowing and speech, xerostomia and appearance affected QoL. Participants described a lack of explanation prior to treatment about the life-long changes to oral health and importance of oral hygiene in preventing future complications. *"they didn't tell me that the radiation was going to kill my mouth"* A lack of formal guidance about managing oral health and changed eating abilities post treatment forced many participants to *"learn through the school of hard knocks"* *Returning to a normal life* Ongoing fatigue, difficulty eating and the ability to return to full-time employment affected participant's goals to return to full-time employment and a normal life post-treatment. A reduced income after treatment caused stress due to higher healthcare bills necessary to manage side-effects of treatment. The ongoing cost of dental care was a large concern. **2. Cognitive appraisal** Support and approachability from medical professionals lead to an increasing coping potential for managing unexpected

	complications from treatment. **3. Emotional response** Peer support provided participants with hope for recovery after treatment. Other members of support group provided hope. **4. Coping response** Participants described a number of coping responses: emotion-focused, social support, and self-control **5. Outcomes** Psychological outcomes of anxiety and depression in the first 6-12 months after treatment were described by four participants. Feelings of isolation caused by loss of connection to the previously supportive hospital network influenced depression and anxiety during this time. A lack of professional counselling within the hospital negatively affected QoL.
Additional comments/ Limitations	Convenience sampling, small sample size – results not generalizable to the wider HNC population. Did not facilitate the recruitment of additional cases to confirm that a point of data saturation was reached in the analysis. Participants recruited from a support group – may not be representative of wider HNC population.

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Reference	Moore, KA, Ford, PJ, and Farah, CS. Support needs and quality of life in oral cancer: a systematic review. International Journal of Dental Hygiene 2014a; 12(1): 36-47.
Study type	Systematic review
Country	n/a
Research question(s)	What support needs are identified by patients with oral cancer during cancer diagnosis, treatment and post-treatment and how do they affect quality of life?
Theoretical approach	n/a
Data collection	Articles were included if they described patient-reported QoL outcomes that were translatable to support needs in patients with oral cancer, were in English and were original studies. Studies reporting QoL findings from heterogeneous head and neck cancer samples were also included if they were inclusive of patients with oral cancer. Articles that described findings only in participants with cancers outside the oral cavity, were not translatable to support needs and were published in languages other than English were excluded. Studies reporting findings from heterogeneous head and neck cancer samples in which patients with oral cancer were unable to be identified were also excluded, as were qualitative and case report studies. The Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies was used to assess the methodological quality of the included studies
Method and process of analysis	Fundamental differences in study design, study population, outcome measures and methodology presented a challenge in synthesizing the key findings of the included studies. Support needs were interpreted by the authors and were formed based on the outcomes reported from symptom-specific QoL questionnaires used in the included studies. For data synthesis, 'support needs' were defined as a QoL issue that had the potential to be improved by the provision of an action or resource
Included studies	A majority of the included studies were of cross-sectional design (n = 21), followed by smaller proportion of longitudinal or prospective designs (n = 7). Two studies were of case–control design, and one study used a retrospective chart review methodology. Qualitative studies were excluded from the analysis.

Findings

Reference (country)	Study type	Study population	Data collection method	Time frame of QoL assessment	Support need/needs identified	Relative impact on QoL	Prevalence among patients	EPHPP global rating
Abendstein et al (Norway)	P n = 167	HNC	EORTC QLQ-C30; EORTC QLQ-H&N35	Diagnosis, 1 year and 5 years after treatment	Sticky saliva	High	n/a	Moderate
					Sexuality	Moderate		
Al Nawas (Germany)	C-C n = 42	OC	EORTC QLQ-C30; EORTC H&N35 and objective measures of salivary flow	After treatment. Mean time from irradiation 46 months	Xerostomia	High	Low	Weak
Bekiroglu et al. (UK)	CS n = 641	OC	UW-QoL	1–2 years after treatment	Adjuvant RT group			Strong
					Xerostomia	High	High	
					Swallowing	High	High	
					Chewing	High	High	
					Speech	High	High	
Bjordal (Norway)	L n = 213	HNC	EORTC QLQ-C30 and EORTC H&N35; GHQ-20; measures of general satisfaction with life and strength and fitness	7–11 years after RT	Xerostomia	High	Low	Weak

	Duke et al. (USA)	CS n = 86	HNC	UW-QOL; PSS-HN; FACT; dental evaluation	5 years post-treatment	Tooth loss	Moderate	Moderate	Weak
						Compromised dentition (Decayed, Missing, Filled index >14)	High	High	
						Denture use	Moderate	High	
	Epstein et al. (Canada)	CS n = 65	HNC	EORTC QLQ-C30 plus addendum sheet to assess oral symptoms and function	6–12 months after completion of treatment	Xerostomia	High	High	Weak
						Dysphagia	High	High	
						Taste	High	High	
						Tooth decay	High	Moderate	
	Epstein et al. (Canada)	P n = 20	HNC	EORTC QLQ-C30 Oral symptoms and function scale	Pre-treatment, 1 month and 6 months post-treatment	Chronic pain	High	High	Weak
						Xerostomia	High	High	
						Taste	High	High	
						Speech difficulties	High	High	
						Eating difficulties	High	High	
	Fang et al (Taiwan)	L N=77	HNC	EORTC QLQ-C30 & H&N 35	Pre-RT and 2 years post-RT	Teeth	High	Moderate	Strong
						Xerostomia	High	Moderate	
						Sticky saliva	High	Moderate	
						Social eating	High	Moderate	
	Fingeret et al (USA)	CS N=280	HNC	BIS; FACT-HN; survey designed for study	Pre-treatment and post-treatment	Body image concerns	High	High	Moderate
						Dissatisfaction with information recieved	High	Low	
	Fingeret et al. (USA)	CS n = 280	HNC	BIS; FACT-G; survey designed for study	>1 month–5 years post-diagnosis	Speech/eating concerns	High	Low	Moderate
						Body image concerns	High	High	
	Handschel et al. (Germany)	CS n = 1652	OC	Impairment scale; depression and anxiety scales	>6 months after treatment	Psychological support	High	Low	Weak
	Hassanein et al. (UK)	CS n = 68	OC	HADS; UW-QoLv1; EORTC QLQ- C30; MAC-Q;	Mean 23 months after treatment	Anxiety	High	Low	Weak
						Depression	High	Low	
	Hassanein et al. (UK)	CS n = 68	OC	UW-QoL; HADS; MAC-Q; SSQ-6	6 months to 6 years after treatment	Depression/ anxiety	High	n/a	Weak
						Coping	Moderate	n/a	
	Jenewein et al. (Switzerland)	CS n = 31	OC	WHOQOL-BREF; EORTC QLQ-C30 &H&N35; DAS	Post-treatment Mean 3.7 years since diagnosis	Marital satisfaction	Low	High	Weak
						Anxiety	Low	Low	
	List et al. (USA)	P n = 46	HNC	KPS; PSS; McMaster University Head and Neck Radiotherapy Questionnaire; FACT-H&N	3 months intervals during treatment; 6 months after treatment	Xerostomia	High	Moderate	Strong
						Difficulty tasting	High	Low	
	List et al. (USA)	CS n = 79	HNC	WOC-CA; FACT; PSS-HN; KPS; CAGE	Pre-treatment	Emotion-focused coping	High	Low	Weak
	Low et al. (UK)	CS n = 350	HNC	EORTC QLQ-H&N35 sexuality scale; UW-QoL and self-designed intimacy questions	Post-treatment	Sexuality and intimacy dysfunction	Moderate	Low	Moderate
	Millsopp et al. (UK)	R n = 278	HNC	UW-QoL	Pretreatment or 6 or 12 months after treatment	Appearance	n/a	Low	Weak
	Pandey et al. (India)	CS n = 123	HNC	DIC2; FACT-HN	During treatment	Psychological distress	high	n/a	Weak

Potash et al. (USA)	CS n = 283	HNC	HNCI; BDI; MAST	1 year post-treatment	Alcohol use	Moderate	Low	Moderate
					Alcohol abuse	Low	Low	
Rogers et al. (UK)	CS n = 123	HNC	UW-QOL v4; list of PCI issues	<6 weeks after completion of treatment	Depression	High	Moderate	Weak
					Anxiety	High	Moderate	
					Fear of recurrence	High	Low	
					Dental Health/teeth	High	Low	
					Mouth opening	High	Low	
					Swallowing	High	Moderate	
Rogers (UK)	C-C n = 68	HNC	UW-QoLv4; PCI; FOR questionnaire	Post-treatment	Fear of recurrence	High	Moderate	Strong
Rogers et al. (UK)	CS n = 243	HNC	UW-QoL v4 and self-designed PEG questionnaire	Post-treatment	Chewing dysfunction	High	High	Weak
					Dysphagia	High	Moderate	
					Long-term PEG use	High	Low	
Rogers et al. (USA)	CS n = 65	HNC	BMI; CES-D; FACT-H&N	>6 months post-treatment	Weight loss	High	Low	Weak
					Depression	High	Low	
					Nutritional support (gastronomy)	High	Low	
Rogers et al. (UK)	CS n = 447	HNC	SDI; EORTC QLQ-C30; UWQOL; self-designed questions about financial burden	Post-treatment	Financial burden	High	Low	Weak
Van Cann et al. (Netherlands)	CS n = 105	HNC	EORTC QLQ-C30 and EORTC QLQ-H&N35	2–7 years after treatment	Post-op RT			Weak
					Swallowing	High	n/a	
					Social eating	High	n/a	
					Xerostomia	High	n/a	
					Trismus	High	n/a	
					Nutritional supplements	High	n/a	
den Berg et al. (Netherlands)	P n = 47	HNC	EORTC QLQC-30 and EORTCH&N35	Pre-treatment, end of treatment and 6 months after treatment	Weight loss	High	Low	Strong
					Malnutrition	High	High following RT	
Van Wilgen et al. (Netherlands)	CS n = 154	HNC	CES-D; RAND-36	>1 year post-treatment	Shoulder and neck pain/morbidity	High	n/a	Moderate
					Depression	High	Low	
Vartanian et al. (Brazil)	CS n = 301	HNC	UW-QoL	>2 years after treatment	Decreased income	Moderate	Low	Weak
Verdock-de Leeuw et al. (Netherlands)	CS n = 85	HNC	EORTC QLQ-C30 & H&N35; HADS; Study-specific questionnaire re-employment	2 years post-treatment	Difficulty returning to work	Moderate	Low	Moderate
					Social eating	High	n/a	
					Social contact	High	n/a	
					Trismus	High	n/a	
					Sticky saliva	High	low	
Verdock-de Leeuw et al. (Netherlands)	P n = 55	HNC	EORTC QLQ-C30 & H&N35; HADS	Pretreatment and follow-up (median time since diagnosis = 4.2 months)	Emotional distress	High	Low	Moderate

BDI, Beck Depression Inventory; BIS, Body Image Scale; CAGE, Alcohol Screening Tool; C-C, Case–control; CES-D, Centre for Epidemiologic Studies Depression Scale; CRT, Chemoradiation Therapy; CS, Cross-sectional; DAS, Dyadic Adjustment Scale; DIC-2, Distress Inventory for Cancer, version 2; EORTC QLQ-C30 and EORTC QLQ-H&N35, European Organisation for Research and Treatment of Cancer Quality of Life – Core 30 and Head & Neck 35; EPHPP, Effective Public Health Practice Project; FACT, Functional Assessment of Cancer Therapy; FACT-H&N, Head and Neck; FOR, Fear of Recurrence; GHQ-20, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; HNC, Mixed Head and Neck cancer sample; KPS, Karnofsky Performance Status; L, Longitudinal; MAC-Q, Mental Adjustment to Cancer Questionnaire; MAST, Michigan Alcohol Screening Test; MSPSS, Multidimensional Scale of Perceived Social Support; n/a, Prevalence figures not available. OC, Oral Cancer; OSCC, Oral Squamous Cell Carcinoma; P, Prospective; PCI, Patient Concerns Inventory; PEG, Percutaneous Endoscopic Gastrostomy; PSS, Head and Neck Performance Status Scale; R, Retrospective; RAND-36, Dutch Version of Short Form-36; R-C, Retrospective Correlational; SDI, Social Difficulties Inventory; SSQ-6, Short Form Social Support Questionnaire; UW-QoL v4, University of Washington Quality of Life Scale version 4; WHOQoL-BREF, World Health Organisation Quality of Life abbreviated version; WOC-CA, Ways of Coping – Cancer Version.

	Low = no clinically relevant change in QoL. Moderate/high = clinically relevant change, subjective classification based on authors conclusions. Percentage of participants who reported support need. Low = <45%; Moderate = 65%–40%; High = >65%. <u>Included studies</u> Abendstein H, Nordgren M, Boysen M et al. Quality of life and head and neck cancer: a 5 year prospective study. Laryngoscope 2005; 115: 2183–2192. Al-Nawas B, Al-Nawas K, Kunkel M, Grotz KA. Quantifying radioxerostomia: salivary flow rate, examiner's score, and quality of life questionnaire. Strahlenther Onkol 2006; 82: 336–341. Bekiroglu F, Ghazali N, Laycock R, Katre C, Lowe D, Rogers SN. Adjuvant radiotherapy and health-related quality of life of patients at intermediate risk of recurrence following primary surgery for oral squamous cell carcinoma. Oral Oncol 2011; 47: 967–973. Bjordal K, Kaasa S, Mastekaasa A. 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Additional comments/ Limitations	Well conducted systematic review. Search strategy and quality assessment described. Date of search not reported. Several of the included studies described findings from small sample sizes and a lack of statistical power limited the conclusions able to be drawn from some studies. The heterogeneity of outcome measures and study populations limited the comparability of findings. The findings include results from studies with heterogeneous head and neck cancer samples, which may affect the validity of the support needs identified as it assumes that the broader head and neck cancer population and the oral cancer population share the same support needs and QoL issues. The support needs described in this review are largely derived from the findings of QoL questionnaires and as such are not a conclusive list of the support needs of patients with oral cancer, rather a suggestion of areas that may be relevant to patients.

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Reference	Lang, HD et al. The psychological experience of living with head and neck cancer: a systematic review and meta-synthesis. Psycho-Oncology 2013; 22(12): 2648-2663.
Study type	Systematic review and meta-synthesis
Country	n/a
Research question(s)	To summarise patients' experiences of HNC by examining the findings of existing qualitative studies
Theoretical approach	Noblit and Hare's 'meta-ethnography' approach to synthesise findings.
Data collection	Search conducted up to 2011. The inclusion criteria were primary qualitative studies, focusing on any aspect of the experience of HNC (using the National Cancer Institute's definition), published in English. Studies that included mixed diagnosis populations were excluded if they did not separately report the findings for HNC patients. Foreign language articles were excluded because of the difficulties in translating 'meaning' across languages. Authors appraised the quality of 46 papers using a modified Critical Appraisal Skills Programme checklist. This concise tool has a clear structure and has been used in previous meta-syntheses. 17 papers excluded on the grounds of quality.
Method and process of analysis	Noblit and Hare's 'meta-ethnography' approach to compare, re-interpret and synthesise the findings (i.e. authors' concepts and themes) of separate qualitative studies to arrive at an exhaustive description of the range, nature and variety of patients' experiences. This involves a secondary analysis of the authors' original interpretations, not a re-analysis of the raw data, to gain a deeper insight into the topic. The aim is 'interpretive rather than aggregative'. There are three broad stages to the synthesis process: (i) identifying themes and concepts from each paper; (ii) comparing meanings and interpretations across studies or 'translating the studies into one another'; and (iii) synthesising common concepts or 'translations'
Included studies	Twenty-nine papers published between 1993 and 2011 were included in the updated meta-synthesis. Most studies were based in the UK (N = 11), Sweden (N = 7) or North America (N = 5) and used only semi-structured interviews (N = 22) or an unspecified form of interviews (N = 3) to collect data. Two articles reported different analyses from the same study. Three studies were longitudinal. Most studies focused on patients with a variety of kinds of HNC (N = 17) or patients with oral cancer (N = 7). Sample sizes ranged from 1 to 60 (mean 12, mode/median 9), representing a total of 345 patients overall.
Key themes	81 concepts were identified across the 29 papers. Initial translation of these produced 11 preliminary concepts. These were further synthesised into a final six: uncertainty and waiting, disruption to daily life, the diminished self, making sense of the experience, sharing the burden and finding a path. **Six concepts from original meta-synthesis (showing original 11 themes and how these were combined)** *'Uncertainty and waiting'* This concept represents being in limbo—the uncertainty of living with the disease and of the future. *'Disruption to daily life'* (from 'Disruption to life and living' and 'The experience of symptoms') The disruption to the patient's physical functioning, emotions and social life. *'The diminished self'* (from 'Enduring or moving on' and 'The diminished self') The temporary or longer-lasting functional, social and existential losses patients experience and the impact of these. Interactions with HCPs also affect patients' views of themselves and their self-esteem. Damaging experiences include the following: HCPs not believing their initial symptoms; HCPs ignoring treatment problems and side effects including a failure to address coping with disfigurement; dominating or inconsiderate behaviour by HCPs; and feeling disregarded in treatment decisions. *"For four years I requested a cancer check of my tongue … nobody believed me (sigh and deep ventilation) until finally I was called to see a specialist … only to be told by him that it was wrong of me to have waited so long".* *'Making sense of the experience'* (from 'Information', 'Fears and expectations' and 'The significance of symptoms') This theme represents patients' continual efforts to make sense of their cancer and what is happening to them and to help their family—including their children—to make sense of their illness. Patients make sense of the illness through an inner dialogue in which they interpret their symptoms, side effects, information and care received from HCPs, and their beliefs about the causes of their cancer. As a result, they develop fears and expectations about the likely outcome, which impact on how they deal with their illness. For example, treatment side effects are often perceived as insignificant next to the threat of cancer, so are endured without seeking help from HCPs. *"… I personally think the cancer issue is far greater than the facial disfigurement …. I actually don't give a toss to what I look like because I'm alive, and I just think the issue of cancer returning and doing its worst, it's a far bigger issue than how you look"* *'Sharing the burden'* (from 'Connection with HCPs' and 'Communicating the hidden experience') The importance of a supportive relationship with HCPs whose role is crucial in instilling hope, maintaining self-worth and counteracting patients' vulnerability. Developing supportive connections with family, friends, their wider social network, HCPs and other people with HNC helps patients to cope emotionally and practically with their illness. Family and friends provide instrumental, emotional and some informational support, such as taking on the patient's responsibilities in the home or providing personal care. Spouses or partners take on the main burden of emotional and practical support. *"My husband has to take many calls as some days I am totally unable to speak and not everybody can understand my words"* *"And me [sic] daughter's very good because she works in a chemist and she'll tell me and her mum—'no don' take that'"* Other people with HNC are a significant source of emotional and informational support, with interaction sometimes taking place via the Internet. *"But there are other people out there, and other groups, that are willing to help. There are over 100,000 of us out there. Go on webwhispers.org."* Relationships with HCPs are vitally important to patients who are feeling vulnerable. Reliance on HCPs for information, guidance and reassurance was emphasised in many of the studies. *"From the very beginning you need someone who sees you through. You need someone who asks how it is. Do you manage? What do you wonder about? You feel so incredibly deserted and vulnerable".*

	Patients have a great need to feel acknowledged by HCPs—both as a person and as one who is suffering—and to have their suffering recognised. However, they are selective about what they disclose and seek help for, and often hide their distress; for example, they often downplay the difficulties of coping with treatment side effects. *"You don't like asking for things because you think it's silly … you feel it's minimal, you know, it's only feeling sick, like a slight headache, so what, or you feel tired, so what, they're only minimal things … the radiotherapy's dealing with the cancer, cancer's the big thing, having a headache, not sleeping, they're minor things so you don't want to say anything about that"* Once treatment and hence regular contact with HCPs ends, patients can feel alone. Finding a way to manage everyday life is challenging. *'Finding a path'* (originally 'finding ways to deal with an uncertain future') This concept reflects the nature of life beyond cancer. Patients perceive their future as either diminished or changed. Included studies 1. Mah MA, Johnston C. Concerns of families in which one member has head and neck cancer. Cancer Nurs 1993;16:382–387. 2. Gamble K. Communication and information: the experience of radiotherapy patients. Eur J Cancer Care 1998;7:153–161. 3. Wells M. The hidden experience of radiotherapy to the head and neck: a qualitative study of patients after completion of treatment. J Adv Nurs 1998;28:840–848. 4. Fritz DJ. Life experiences of head and neck cancer survivors: a pilot study. ORL Head Neck Nurs 2001;19:9–13. 5. Crossley ML. 'Let me explain': narrative emplotment and one patient's experience of oral cancer. Soc Sci Med 2003;56:439–448. 6. Larsson M, Hedelin B, Athlin E. Lived experiences of eating problems for patients with head and neck cancer during radiotherapy. J Clin Nurs 2003;12:562–570. 7. Moore RJ, Chamberlain RM, Khuri FR. Communicating suffering in primary stage head and neck cancer. 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Additional comments/ Limitations	Meta-synthesis was rigorous and carefully executed. Aims and methods clearly defined and explained. Systematic identification of papers, independent screening and critical appraisal by two to three reviewers.

1

Reference	Longacre, ML et al. Psychological functioning of caregivers for head and neck cancer patients. Oral Oncology 2012; 48(1): 18-25.
Study type	Systematic review
Country	n/a
Research question(s)	1. What is the psychological health of HNSCC caregivers? 2. What factors are associated with deficits in psychological health among HNSCC caregivers?
Theoretical approach	n/a
Data collection	Published articles were identified through a literature search using online databases (PUBMED, MEDLINE and PSYCINFO) for papers published in English through September 2010, which included combinations of the following key words: head and neck cancer; oral cavity cancer; laryngeal cancer; pharynx cancer; caregiving, and caregiver. Reference lists from citations were also reviewed for relevant publications. Specific article inclusion criteria included: (1) studies of caregivers of patients diagnosed with head and neck cancer; and (2) studies with qualitative or quantitative assessments of caregiver psychological health (i.e., emotional distress, depressive or anxious symptoms, or burden). Papers were excluded if: (1) samples included caregivers of patients with several forms of cancer; or (2) patients were diagnosed with cancers other than HNSCC.
Method and process of analysis	The methodological quality of the selected studies was assessed using a 7-item checklist of predefined criteria
Included studies	11 published papers met the inclusion criteria and were evaluated in detail.
Findings	

First author (year)	Sample	Study design	Measurement tools (measurement outcome)	Psychological health findings	Methodology and statistical quality
Ross et al.	89 Caregivers	Cross-sectional 6–24 months post-treatment (Avg time since diagnosis = 19 months)	CQOLC (quality of life)	• 21.6% Reported moderate emotional distress 15.9% • Reported high emotional distress • 37.5% Reported moderate to high distress on the MHI • Psychological health was negatively associated with hours spent caregiving • Gender, time since family member's cancer diagnosis, and percentage of unmet needs were not significantly correlated with caregiver psychological health • Greater hours per week were associated with less perceived disruptiveness of caregiving and greater positive adaption to caregiving	4
Chen et al	122 Patient-caregiver dyads	Cross-sectional (immediately post-tumour excision surgery, still hospitalized)	CRA (perceived caregiver burden) ISSB (Social Support) CNQ-SF (Patient Care Needs) HNCNQ (Patient Head and Neck Specific Care Needs)	• Caregivers had moderate levels of perceived caregiving burden • Burden was predicted by caregivers' social support, patients' physical and daily living needs, patients' health system and information needs, and patients' psychological needs	6
Hodges and Humphris	101 Patient-caregiver dyads	Longitudinal assessments at 3-and 6-months post patient diagnosis	HADS (Global Psychological Distress; Depression and Anxiety subscales) WOC (Fear of Recurrence)	• At 3-months, 30.7% of caregivers had anxiety symptoms suggestive of clinical anxiety (compared to 18.8% for patients) • At 6-months, 36.6% of caregivers had anxiety symptoms suggestive of clinical anxiety (20.8% for patients) • Caregivers had higher recurrence concerns than patients • Fear of recurrence was correlated with emotional distress at each time point	7
Roing et al.	7 Spouses	Cross-sectional	Open-ended interview	• Themes identified included: (1) Transitioning from spouse to supportive caregiver; (2) Negligence of self and emotional strain; (3) Restricted living (i.e., holidays); and (4) Altered sense of time (e.g., time moving fast or slow)	2

	Baghi et al.	78 Caregivers	Cross-sectional (median time since treatment = 24 months	Study specific questionnaire on QOL and personal and support needs of caregiver	• 43% of caregivers reported needing psychological care for themselves • 43% also expressed a desire to be in contact with self-help groups • Caregiver gender (female) was associated with need for psychological support • Marital status (being married) was associated with use of self-help groups • Higher education was associated with greater desire for greater psychosocial support	3
	Verdonck-de Leeuw et al.	41 Patient-spouse pairs	Cross-sectional (mean time since treatment = 29 months)	HADS (Global Psychological Distress; Depression and Anxiety subscales) SF-36 (Health Status) ACE-27 (Patient Health Status) UCL (Coping Style) EORTC QLQ-H&N35 (Patient Social and Functional Impairment) CRA (Perceived Caregiver Burden)	• Clinical levels of emotional distress were identified in 20% of spouses • Spouse distress was associated with disrupted schedule, vitality, passive coping style, and patient use of feeding tube • Emotional distress was not associated with tumor site, time interval since treatment or treatment type • Emotional distress was significantly related to CRA Disrupted Schedule subscale	6
	Ostroff et al.	80 Patient-caregiver dyads	Cross-sectional (completed treatment within prior 6–24 months)	MHI (Global Mental Health; Psychological Distress and Psychological Well-being subscales) PAIS-SR (Psychological Adjustment to Illness) FAD (Family Functioning) FACT-HN (Cancer-specific QOL)	• Caregivers reported poorer psychological health than population norms	6
	Vickery et al.	44 Partners (and 51 patients)	Cross-sectional assessment conducted post-treatment (mean time since treatment = 11 months)	HADS (Global Mental Health; Psychological Distress and Psychological Well-being subscales) PAIS-SR (Psychological Adjustment to Illness DAS (Quality of Spousal Relationship)	• Median anxiety scores for partners were suggestive of borderline clinical anxiety• 40% of partners had symptoms suggestive of clinical or borderline levels of anxiety• Median anxiety scores for partners were suggestive of borderline clinical anxiety	6
	Watt-Watson and Graydon[5]	18 Patients and their caregivers	Longitudinal (immediately before patient discharge and 4-weeks post-discharge)	Open-ended interview	• Patients and caregivers expressed fears of recurrence	3
	Blood et al.	75 Spouse caregivers	Cross-sectional (time since surgery ranged from 2 to 48 months)	CSI (Caregiver burden and strain) BI (Perceived Burden) GARS (Current Stress Levels) HS-MOS (Health Status)	• Caregivers at 2–6 months post-diagnosis had higher mean caregiver stress than caregivers farther from diagnosis	5

	Mah and Johnston	4 Families	Longitudinal (before treatment, during treatment, and during rehabilitation) over a period of 5-months	Semi-structured interview and chart reviews	• Five major types of concerns were revealed: cancer and its meaning; social relations; experience with hospitalization; treatment; and, future care placement • At pretreatment, families focused on treatment implications • During treatment, families focused on social relations • During rehabilitation, older family caregivers focused on future care placement	2

Abbreviations used include: ACE-27: Adult Co-morbidity Evaluation 27; BI: Burden Interview; CNQ-SF: Cancer Needs Questionnaire Short Form; CQOLC: Caregiver Quality of Life Index; CRA: Caregiver Reaction Assessment; CSI: Caregiver Strain Index; DAS: Dyadic Adjustment Scale; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module; FACT-HN: Functional Assessment of Cancer Therapy-Head and Neck; FAD: Family Assessment Device; FIN: Family Inventory of Needs; GARS: Global Assessment of Recent Stress; HADS: Hospital Anxiety and Depression scale; HNCNQ: Head and Neck Specific Cancer Needs Questionnaire; HS-MOS: Health Survey of the Medical Outcomes Study-short form; ISSB: Inventory of Socially Supportive Behaviors; MHI: Mental Health Inventory; PAIS-SR: Psychological Adjustment to Illness Scale-SR; UCL: Utrecht Coping List; WOC: Worry of Cancer.

Included studies
Ross S, Mosher CE, Ronis-Tobin V, Hermele S, Ostroff JS. Psychosocial adjustment of family caregivers of head and neck cancer survivors. Support Care Cancer. 2010;18(2):171–8.
Chen SC, Tsai MC, Liu CL, Yu WP, Liao CT, Chang JT. Support needs of patients with oral cancer and burden to their family caregivers. Cancer Nurs. 2009;32(6):473–81.
Hodges LJ, Humphris GM. Fear of recurrence and psychological distress in head and neck cancer patients and their carers. Psychooncology. 2009;18(8):841–8.
Roing M, Hirsch JM, Holmstrom I. Living in a state of suspension – a phenomenological approach to the spouse's experience of oral cancer. Scand J Caring Sci. 2008;22(1):40–7.
Baghi M, Wagenblast J, Hambek M, et al. Demands on caring relatives of head and neck cancer patients. Laryngoscope. 2007;117(4):712–6.

Verdonck-de Leeuw IM, Eerenstein SE, Van der Linden MH, Kuik DJ, de Bree R, Leemans CR. Distress in spouses and patients after treatment for head and neck cancer. Laryngoscope. 2007;117(2):238–41.
Ostroff J, Ross S, Steinglass P, Ronis-Tobin V, Singh B. Interest in and barriers to participation in multiple family groups among head and neck cancer survivors and their primary family caregivers. Fam Process. 2004;43(2):195–208.
Vickery LE, Latchford G, Hewison J, Bellew M, Feber T. The impact of head and neck cancer and facial disfigurement on the quality of life of patients and their partners. Head Neck. 2003;25(4):289–96.
Watt-Watson J, Graydon J. Impact of surgery on head and neck cancer patients and their caregivers. Nurs Clin North Am. 1995;30(4):659–71.
Blood GW, Simpson KC, Dineen M, Kauffman SM, Raimondi SC. Spouses of individuals with laryngeal cancer: caregiver strain and burden. J Commun Disord. 1994;27(1):19–35.
Mah MA, Johnston C. Concerns of families in which one member has head and neck cancer. Cancer Nurs. 1993;16(5):382–7.

Additional comments/ Limitations	The included papers assessed caregivers of patients with varied disease characteristics (e.g., cancer site, stage, treatment regimen and length of time since diagnosis). Treatment regimen was often not described or it varied considerably among the patients in each study – caregiving tasks and experiences may vary extensively by treatment modality. Lack of longitudinal studies. Review not specifically focused on the information and support needs of carers.

1

Reference	Baxi, SS et al. Sharing a diagnosis of HPV-related head and neck cancer: the emotions, the confusion, and what patients want to know. Head & Neck 2013; 35(11): 1534-1541.
Study type	Qualitative interview study
Country	USA
Research question(s)	Aim: to increase understanding of patients' experiences with a diagnosis of HPV-related oropharyngeal cancer by exploring the communication, comprehension and psychological impact of the diagnosis.
Theoretical approach	None reported
Data collection	Semi-structured interviews conducted within a single-institution NCI-designated comprehensive cancer center. interview transcript was developed by a multidisciplinary team of oncologists and behavioural psychologists based on a thorough review of the published literature on HPV in general and HPV in the context of cancer, specifically focusing on communication, knowledge and psychosexual consequences of the diagnosis. The semi-structured interview included open-ended questions in four domains: 1) communication about HPV, 2) knowledge about HPV, 3) psychological reaction to a diagnosis of HPV, and 4) sexual impact of a being diagnosed with HPV. Participants were able to independently interpret the questions and answer freely in their own words. A trained research study assistant completed the interviews. These interviews were conducted in a private interviewing space and were audio taped. The recordings were thereafter transcribed verbatim.
Method and process of analysis	Transcripts were analyzed for general themes. A multidisciplinary team of reviewers consisting of a medical oncologist, a surgical oncologist and a behavioural scientist independently read and analyzed each of the transcripts. The distinct domains of the interview guide provided the structure and framework for these analyses. Each reviewer's analytic process involved drawing general conclusions from specific statements in each domain from the interviews and identifying key quotes to support these conclusions. When there was a discrepancy in interpretation, the three reviewers met in person to discuss the differences and reached a consensus analysis. The reviewers then identified recurring thematic concepts and patterns across the interview domains and ultimately reached consensus at an in-person meeting regarding overarching key themes across all ten interviews.
Population and sample collection	All patients were screened during routine outpatient follow-up visits to assess eligibility for the larger study (age >18, fluent in English, pathologic confirmation of an oropharyngeal squamous cell carcinoma, HPV-status of tumour known or specimen available for HPV-testing, between 1 and 5 years from treatment completion, treatment completed at MSKCC, and no evidence of disease). Although initially open to both male and female participants, given the preponderance of male patients with this

	diagnosis seen in clinics, only male patients were ultimately asked to participate in this qualitative study. The first ten men who were eligible and agreeable to participate in this aim of the study were interviewed. The median age at diagnosis was 57 years (range 42–63). All patients had been diagnosed with and treated for stage III or IV HPV-positive oropharyngeal squamous cell carcinoma. None had evidence of disease at the time of the study interview, with a median follow-up of 22.5 months (16–43 months) from treatment completion. Primary treatment included concurrent chemotherapy and radiation in nine patients and surgery with adjuvant radiation in one patient. At the time of the interview, all 10 men were being followed by both a head and neck surgeon and a radiation oncologist, and 9 of the 10 were also followed by a medical oncologist. Six participants were treated on a therapeutic study protocol. All of the participants were Caucasian. Six participants were married; two were unmarried in monogamous relationships, and two reported being single. All ten participants were employed at the time of the survey. Seven participants had never smoked, and three were former smokers. Two patients reported no alcohol use; five reported drinking less than one alcoholic beverage daily, and three consumed more than one drink daily.
Key themes	**1. Disclosing the diagnosis** All participants reported that the diagnosis of an HPV-related tumor was disclosed before the onset of their initial treatments. However, HPV was often overshadowed by broader conversations about the cancer itself. HPV was discussed within the context of an improved oncologic prognosis, which generated an encouraging response in participants. *"Well, it was discussed… how it was obtained and that it would be more favorable for me if I had [HPV] as opposed to not having it, and that was… that was sufficient. I had it, and I had to deal with… what was the cause of it."* Beyond prognosis, the content of the discussion regarding HPV varied greatly based on both patient interest and physician delivery. **2. Relationship with clinicians** All participants reported that physicians were their primary source of information about HPV. Although they indicated a high overall level of satisfaction with their doctors' handling of the conversation about HPV, some participants felt that they had questions that remained unasked and unanswered. *"I don't think that [doctors] gave enough information. I think they gave the information that they want to be able to give. They want to give you as much good news as possible, but no one ever discussed anything like… maybe you want to find out or contact or what the… sexual ramifications … How could it affect you?"* Reasons reported for not asking further questions included patients' perceptions about: 1) physician time constraints, 2) limited physician knowledge about HPV, and 3) patient or physician discomfort discussing HPV. **3. Sources of additional information** Not all participants sought additional information; one avoided any and all HPV-related information, while another had little to no interest in learning about HPV beyond its immediate relationship with his cancer. For the eight participants who did seek out HPV-specific information, the internet was by far their most common source. In fact, all patients interested in learning about HPV reported using the internet to some degree to help fill the gaps in their understanding. Participants indicated that while a great deal of information was available on the internet, it was not patient-centric. Further, many patients had difficulty navigating and comprehending the information they found on the internet, and several also expressed concerns about its reliability. *"If you go on the search engine and put 'head and neck cancer and HPV,' you'll get a… a drop down of various articles. Getting into something which is substantive and understandable from a layman's standpoint can take a little more digging."* Many participants reported attempting to synthesize what they learned from the internet and confirming its veracity with their physicians. **4. Misconceptions, knowledge gaps, and concerns** All participants understood that: 1) HPV is a sexually transmitted pathogen, 2) HPV is widely prevalent in the United States, and 3) HPV has a positive prognostic implication in HNSCC. Beyond this, participants' knowledge about HPV varied significantly. This variation was attributed to patients' interest in learning about HPV, time spent researching the topic, and comprehension of and trust in online information resources. *"My doctors all explained how you contracted it and… the nature of it. It was… simple enough. It wasn't something we dwelled on… that extensively… I had no desire to dwell on it that much. I had other things coming my way, such as the radiation… and the rest of my treatment."* Few participants understood the mechanism of HPV transmission. For this reason, many unanswered questions concerned viral transmissibility and latency, relating to both the source of original infection and the potential consequences for participants' current or future partner(s). *"Can you get it… You know, just from kissing someone? You know, from saliva, from mouth-to-mouth. Possibly, you know, but then, you know, I don't know."* **5. Psychological impact from HPV** Three participants indicated that they felt a sense of stigma or embarrassment associated with their diagnosis of a sexually transmitted disease. *"...my wife's got an oncologist. As soon as she [wife's oncologist] heard that I had [HPV], thought that I was having some like crazy wild, you know, gay party lifestyle that my wife didn't know about."* Further, the belief that antecedent behaviours may have indirectly led to the development of cancer resulted, for some, in anger, sadness, or helplessness. *"Obviously… the prospect of this being sexually transmitted can be somewhat embarrassing to think about that. That, you know, something I did when I was single 25, 30 years ago came back to haunt me. You know, was all-in-all embarrassing to say the least."* When assessing their emotional responses, participants struggled to separate the sentiments associated with HPV from those related to their cancer diagnosis. About half of the participants indicated that the cancer itself occasionally or always

	overshadowed the impact of HPV. Relief and optimism were common emotional responses to the improved prognosis implied by HPV-related HNSCC. *"Actually, I felt relieved because in that… I felt that it enhanced my chances of recovery, so I wasn't… I wasn't that upset with it I guess."* **6. Impact on intimacy** The discomfort regarding HPV transmission and latency persisted long after the completion of treatment in the study cohort. Of eight participants who discussed the impact of their diagnosis on sexual relationships (one was not sexually active, another did not want to discuss this topic), five had decreases in intimacy that were at least partly related to their HPV diagnosis, mostly due to transmission-related fears. Some participants attributed decreases in intimacy to treatment-related effects rather than (or in addition to) HPV. *"During treatment, of course when I had all the sores, and I developed thrush, that was a different story. I gotta… I gotta basically say I was an outcast, you know. There would be no kissing."* **7. Need for better dissemination of information** Although patients have different information requirements, all but one of the participants requested more information about HPV. Many remarked that a cohesive, comprehensive and trusted resource would be valuable, and some patients specifically requested an informational pamphlet or handout. *"A simple handout that you guys could do in a few minutes may make a world of difference in easing someone's mind or making them very nervous, but at least it's getting the information out."* As a result, the study team, in conjunction with the MSKCC Committee on Patient Educational Materials, developed a paper-based pamphlet containing information about HPV and its role in head and neck cancer.
Additional comments/ Limitations	Small number of participants from a single institution. Participants were all Caucasian males mostly from a higher socioeconomic background – limits generalizability of findings to other patient populations. Study does not specifically address the needs of patients who have not yet had an HPV diagnosis disclosed or of HPV-negative HNSCC patients who may have questions about HPV. Method of analysis not reported, although transcripts were analysed independently by different authors.

1

Reference	Milbury, K et al. An exploratory study of the informational and psychosocial needs of patients with human papillomavirus (HPV)-associated oropharyngeal cancer. Oral Oncology 2013; 49(11): 1067-1071.
Study type	Questionnaire study
Country	USA
Research question(s)	Aim: to assess the informational and psychosocial needs of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) patients and identify any social or relationship challenges associated with having an oropharyngeal cancer that is attributed to HPV
Theoretical approach	None reported
Data collection	Written surveys were completed by participants within 2 weeks of starting treatment for HNC. Patients were asked whether they had HPV infection and whether it caused their cancer. Open-ended questions about their cancer cause. 7-point Likert scale question about if they felt the need to keep their HPV a secret from others and if so why. Asked if disclosed HPV to current sexual partner (yes or no) and whether they thought that their HPV infection had increased their partner's risk of developing cancer (7-point Likert scale) and whether they talked with their partner about the likelihood of HPV transmission (yes or no). Patients also asked about how informed they felt about HPV, the extent of information provided by physician. Patients asked to describe informational needs with open-ended questions. Demographic information, Alcohol use, distress, and self-blame also assessed.
Method and process of analysis	Means, standard deviations, correlations and frequencies calculated. Responses to open-ended questions were tabulated and categorised and reported in summary fashion.
Population and sample collection	Patients initiating radiotherapy for a newly diagnosed HNC at a cancer centre in southwestern USA were eligible if the patient had ECOG PS score ≤2, was able to provide informed consent, could speak, read and understand English, aged 18 or over, had a domestic partner who they lived with for at least 1 year. Of the 124 participants in the parent study, 79 (64%) had OPSCC. HPV-related information extracted from pathology reports. Results presented for the 62 patients who were identified as HPV-positive by in situ hybridisation or p16 by immunohistochemical analysis as a surrogate marker. Mean age 55.9±6.4 years. Mean 6.9±9.9 weeks since diagnosis. 86.5% male. 96% married/cohabiting. 59.7% base of tongue cancer, 33.9% tonsil cancer. 59% former smoker, 0% current smoker, 39% current use of other tobacco products. 65% alcohol consumers, 10% problem drinkers.
Findings	Only 66% self-declared as having a HPV-positivetumour. 16% were unsure, 18% said they did not have a HPV-positivetumour. Patients reported moderate levels of distress (mean 3.52, SD=2.54, possible range 1-10) and relatively low levels of self-blame (mean=2.27, SD=1.23, possible range 1-4). The majority of patients felt uninformed about whether precautions should be taken to safeguard their partner from HPV. 34% said that they were not at all informed, 43% felt somewhat informed. 39% reported that their oncologist did not discuss issues relating to HPV and HNC with them, 45% said that this information was only somewhat discussed. 58% reported seeking this information from sources other than their oncologist. 37% said they would be interested in receiving any information; 18% wanted more information about how HPV causes cancer, 15% wanted information about vaccinations for HPV (particularly for children), 10% wanted information about how to prevent transmission to their partner, 10% wanted to know if there were any treatments for HPV.

Additional comments/ Limitations	Small sample size, mostly males – limits generalisability to other patient populations. Only cohabiting patients included – may not generalise to single patients e.g. concerns starting new relationships.

1

Reference	Newell, R et al. The information needs of head and neck cancer patients prior to surgery. Annals of the Royal College of Surgeons of England 2004; 86(6): 407-410.
Study type	Qualitative interview study
Country	UK
Research question(s)	To describe the common themes in the experiences and expressed information needs of patients undergoing head and neck surgery
Theoretical approach	n/a
Data collection	The guide questions and probes were relatively focal and asked respondents to describe their perceptions of what had happened during the interview when they were told their diagnosis and need for surgery, including how information was given to them, how well they felt they understood the information given, how involved they felt in treatment decisions and what other information they would have liked to have received. Patients who met the study criteria were recruited from out-patient departments in the participating hospitals. Consent was sought at this time and the research officer arranged to meet and interview the participant in the patient's home.
Method and process of analysis	Data analysis occurred alongside data collection, using the method of constant comparison to assess the point at which data became saturated to the extent that no new themes were emerging. The principal form of analysis was content analysis to identify categories and themes emerging from responses to the open question elements of the interview schedule. An independent review of transcripts was undertaken to ensure sampling adequacy and showed saturation had occurred after 29 patients and 13 relatives/friends had been interviewed.
Population and sample collection	Purposive sampling. Participants included patients who had undergone surgery for head or neck cancer (n = 29) and their immediate relatives who were present at the initial consultation with the surgeon (n = 13). Patients were recruited from out-patient departments in two hospitals in the north of England. Of the 29, 14 had previously undergone a laryngectomy, 9 had undergone radical neck dissections and 2 had had oral cavity or oropharyngeal tumours treated surgically. 9 female and 20 male. Mean age of male participants was 65 years, mean age of female participants was 63 years.
Key themes	*Content of information* The type and amount of information individual patients wanted regarding surgery differed enormously and the information patients received did not reflect the diversity of their needs. In the majority of cases, patients appear to have been offered a package of information that seemed to relate exclusively to the type of surgery they were facing.

Topics participants wanted information about prior to surgery	n
Potential communication difficulties	10
Potential difficulties eating and swallowing	13
Psychological adjustment and coping	8
Time-scales to judge own progress against	7
Length of time hospitalised	10
Appearance after surgery	7
Support groups	3

Opinions about and response to volume of information and manner presented	n
Too much information	6
Too little information	14
Unable to understand information	11
Wanted individualised information	18
Wanted truth and honesty	9
Response to information	
Felt shock numbness	18
Caused anxiety	6
Reduced anxiety	8
Facilitated coping	10

Patients often reported difficulty absorbing information. This appeared to be related to the fact that almost all information about treatment was given during the same consultation as diagnosis. The way the information was given was significant for most patients. The use of medical jargon and technical terms often adversely affected the participant's ability to understand the information adequately. Often participants found it necessary to gain information from other sources such as the internet or support groups to help them to understand what they had been told in the consultation. When participants were asked how they felt about receiving information about treatment at the same time as diagnosis, most perceived there to be no alternative due to the urgency of much of the surgery

Barriers to satisfactory delivery of information	n
Problematic use of medical jargon	12
Given at same time as diagnosis	18
Noisy environment	10
Not reinforced by written information	9
Others in room	6
Hearing problems	5
Lack of time	5

Factors reported as enhancing satisfaction with information giving	n
Opportunity to ask questions	10
Attended appointment with a relative	11
Reinforced with written information	8
Felt able to control the interaction	12
Adequate time available for discussions	8

Most participants perceived there to be no choices to be made by themselves regarding treatment options but considered this to be the responsibility of the doctor. The few participants who wanted to be involved in decision-making experienced difficulty accessing the information that would have enabled them to do so. When participants were asked if they thought they had a choice about whether or not they had any treatment at all, most explained that they were aware if they did not have the treatment they would have died.

There were some common themes in participants' psychological responses to their diagnosis and consequent treatment. Almost all attributed difficulties absorbing information to feeling in shock or dazed when told their diagnosis. Most participants had only a vague recollection of this time and it was not possible to determine accurately how long this period of shock or numbness lasted. Participants varied in their desire to be given detailed information about their appearance; some reported that if they knew what they were going to look like, they would be even more frightened. Many elderly male participants said that their appearance was of little consequence and focused on the fact that the surgery would hopefully cure them of the disease. Several participants explained how they became depressed or 'low' several months after the surgery because their relief at surviving the illness in the short term began to be over-shadowed by the fact that fundamental changes to their lifestyle had occurred. There was little professional support available to participants at this time.

Psychosocial impact	N
Shock/numbness	18
Onset of depression	6
Disruption to social life	6
Altered friendships/relationships	12
Disruption to career	15
Lifestyle change, no holidays, *etc.*	17
Difficulty adjusting to altered appearance	12
Isolation	8
Physiological impact	
Difficulty eating	16
Difficulty communicating	15
Weight loss	21
Pain	10
Loss/alteration of taste	8

Limitations	Small sample size. Responses from patients and carers not reported separately. Time since surgery not reported. Potential for recall bias.

1

Reference	Fang, CY. Informational needs of head and neck cancer patients. Health and Technology 2012; 2(1): 57-62.
Study type	Cross-sectional questionnaire study
Country	USA
Research question(s)	Aims: 1) characterize patients' informational needs; and 2) describe preferred formats and time points for receiving such information. Also whether patient characteristics or psychological distress are associated with informational needs and preferences
Theoretical approach	n/a
Data collection	Questionnaire measures: The Impact of Events Scale was used to measure cancer-related distress (15 items rated on a 4-point Likert-type scale) To characterize informational needs, participants were provided with a list of ten topics and instructed to indicate whether having additional information on each topic would be helpful to them. Topics were broadly designed to relate to medical needs (e.g., information about head and neck cancer and its treatment options), physical needs (e.g., changes in swallowing), practical needs (e.g., strategies to improve speech after treatment), emotional needs (e.g., managing emotional distress and anxiety), and social needs (e.g., managing social situations). In addition, participants were provided with an open-ended item to add any other

topics about which they would like to receive more information.
Participants were asked to indicate at which time points during their cancer treatment they would like to receive such information. Ranging from cancer diagnosis (pre-treatment), during cancer treatment, shortly after completing treatment (1–3 months post-treatment) or longer (more than 3 months post-treatment). To assess preferred mode of information delivery, participants were provided with a variety of options including one-on-one (face-to-face) meetings with a health educator or healthcare professional; group meetings with other head and neck cancer patients led by a health educator or healthcare professional; receiving pamphlets or booklets that patients could view at home; receiving DVDs that patients can view on their home TV or computer; or receiving an Internet-based program that patients can log onto from the computer. Participants were allowed to select more than one mode of delivery. Participants also reported whether they had a computer in the home and whether they had access to the Internet.

Method and process of analysis

Descriptive statistics were used to characterize participants' informational preferences and choices. Chi-square analyses or one-way analyses of variance (ANOVAs) were used to evaluate potential associations between demographic variables, psychological distress, and preferences regarding informational needs, delivery time point, and delivery format.

Population and sample collection

Participants were 65 head and neck squamous cell carcinoma (HNSCC) patients presenting for treatment at a comprehensive cancer centre. Participants were predominately male (73.8%) and non-Hispanic white (92.3%). The mean age of participants was 56.3 years. Fewer than half (43.1%) had early stage disease.

Findings

Topic	% of Patients	Early-stage	Advanced	χ^2
1. How to stay healthy after treatment	75.4%	78.6%	72.2%	0.34
2. Information about treatment and side effects	53.8%	50.0%	55.6%	0.20
3. Information about changes in swallowing and speaking	52.3%	53.6%	50.0%	0.08
4. Strategies to improve eating and speaking issues	46.2%	50.0%	41.7%	0.44
5. Tips for coping with emotional stress and anxiety	32.3%	46.4%	19.4%	5.34*
6. How to highlight positive things in one's cancer experience	30.8%	42.9%	19.4%	4.14*
7. How to improve communications with family members	20.0%	35.7%	8.3%	7.30**
8. How to cope with changes in appearance	18.5%	21.4%	16.7%	0.23
9. How to manage social situations and social interactions	15.4%	17.9%	13.9%	0.19
10. Close relationships, intimacy, and sexuality	13.8%	21.4%	8.3%	2.24

*p < 0.05
**p < 0.01

Four participants completed the open-ended item and requested information specifically on: future pregnancies after cancer and radiation treatment; nutrition; post-surgical care; and the availability of support programs in other geographic regions and locations.
Female patients were more likely to want information on coping with stress and anxiety (62.5%) compared to male patients (20.8%), $\chi2(1)=9.70$, $p=0.002$. Similarly, female patients (56.3%) were also more interested in highlighting the positive aspects of one's cancer experience relative to male patients (20.8%), $\chi2(1)=7.21$, $p<0.01$. With respect to age, the youngest subgroup of patients (29–49 years) expressed interest in receiving information about intimacy and sexuality after cancer (31.3%) compared to patients who were 50–64 years of age (11.8%) or older (0%), $\chi2(2)=6.35$, $p<0.05$.

Delivery preferences: time point and format
Participants reported varying preferences for when and how they desired to receive additional information, but almost 25% wanted to receive information at more than one time point in their cancer experience. Approximately 39% wanted to receive informational programs at diagnosis, 31% desired such programs during treatment, and 34% preferred this information during the 1- to 3-month period following treatment. Few participants (14%) wanted to receive such information more than 3 months post-treatment.
Younger patients (29–49 years) were more likely to desire receiving additional programs at diagnosis (62.5%) compared to their older counterparts (32.4% of patients aged 50–64, and 21.4% of patients aged 65+), $\chi2(2)=6.19$, $p<0.05$. A greater proportion of patients with early-stage disease (46.4%) was interested in receiving programs during the 1- to 3-month period following treatment compared to patients with advanced disease (22.2%), $\chi2(1)=4.19$, $p<0.05$. No other factors were associated with patients' preferred time point for receiving such programs.

With respect to delivery format, 9 participants (13.8%) selected none of the provided options

Information delivery format preferences*	
Internet-based program @ home	43.1%
DVD that can be viewed @ home	40.0%
Pamphlets/booklets @ home	36.9%
Group meeting led by health prof	21.5%
One-on-one meeting with health prof	15.4%

A greater proportion of women were receptive to one-on-one meetings (31.3%) compared to men (10.4%), $\chi2(1)=3.95$, $p<0.05$, and women were significantly more interested in receiving an Internet-based program (68.8%) compared to men (35.4%), $\chi2(1)=5.42$, $p<0.02$. Higher educational attainment was also associated with greater preference for an Internet-based program,

	with 66.7% of participants with post-graduate education preferring an Internet-based program compared to 44.1% of college-educated participants, 53.1% of those with some college or trade school education, and 24.0% of high school educated participants, $\chi2(3)=7.73$, $p=0.052$. Age was not significantly associated with any program preferences, including Internet-based programs, $\chi2(2)=4.00$, $p>0.13$.
Additional comments/ Limitations	Small sample size and convenience sampling method used. Population was ethnically homogenous – may not be representative of HNC patients in general. Cross-sectional assessment at one point in time. Respondents limited to choosing the information needs presented in the survey.

1

Reference	Oskam, IM et al. Prospective evaluation of health-related quality of life in long-term oral and oropharyngeal cancer survivors and the perceived need for supportive care. Oral Oncology 2013; 49(5): 443-448.
Study type	Prospective questionnaire study
Country	The Netherlands
Research question(s)	To evaluate long-term changes in health related quality of life (HRQOL) in oral/oropharyngeal cancer survivors and their need for and use of supportive care.
Theoretical approach	n/a
Data collection	The HRQOL of 26 patients (response rate 96%) was assessed with the EORTC QLQ-C30 and QLQ-H&N35 questionnaires at four points in time: pre-treatment (baseline), and at 6 months, 12 months (short term) and 8-11 years (long-term) follow up. A 61-item study specific questionnaire was developed to evaluate the need for and use of supportive care (allied health services, peer contact, psychosocial care, and complementary care) and was completed at the period of treatment and at long-term follow up. All questionnaires were self-administered at home and collected via postal mail.
Method and process of analysis	Frequency of need for and use of supportive care was calculated.
Population and sample collection	Between 1999 and 2001, patients with advanced squamous cell carcinoma of the oral cavity or oropharynx treated with free-flap reconstruction and postoperative radiotherapy were included in a prospective study of whom 27 patients were long-term survivors (mean 9.2 years, range 8-11 years). Patients excluded if over 75 years, cognitive impairment, lacking basic fluency in Dutch. One of the 27 survivors was lost to follow-up and not included in final analysis. Mean age 51 years (range 24-71). 31% heavy alcohol users, 23% smokers. 38% oral cavity tumours, 62% oropharynx. 38% stage II, 31% stage III, 46% stage IV. 92% post-operative radiotherapy.
Findings	HRQoL: A number of HRQOL domains worsened significantly ($p < 0.01$) in the long-term: emotional functioning, social functioning, swallowing, speech, taste/smell, dry mouth, sticky saliva and coughing assessed by the mixed effects statistical model. Supportive care: At time of treatment, the need for supportive care was the highest for a dental hygienist (77%), a physical therapist (73%), a speech therapist (42%), a dietician (38%), and a special diet (62%). At long-term follow up, the need for supportive care was limited to a dental hygienist (46%) and a physical therapist (23%). Only small differences were observed between the perceived need for and actual use of supportive care.

	During treatment		**Long-term follow-up**	
	Need for *n* (%)	**Use of *n* (%)**	**Need for *n* (%)**	**Use of *n* (%)**
Allied health services				
Speech therapist	11 (42)	10 (38)	1 (4)	1 (4)
Physical therapist	19 (73)	19 (73)	6 (23)	7 (27)
Nurse care	5 (19)	5 (19)	1 (4)	1 (4)
Dental hygienist	20 (77)	19 (73)	12 (46)	14 (54)
Dietician	10 (38)	13 (50)	2 (8)	2 (8)
Smoking cessation counselling	0 (0)	0 (0)	0 (0)	0 (0)
Alcohol cessation counselling	1 (4)	2 (8)	2 (8)	2 (8)
Rehabilitation programme	2 (8)	0 (0)	1 (4)	0 (0)
Psychosocial care				
Social worker	1 (4)	1 (4)	0 (0)	1 (4)
Psychologist	5 (19)	4 (16)	1 (4)	0 (0)
Pastoral worker	1 (4)	0 (0)	0 (0)	0 (0)
Peer contact				
Patients association	2 (8)	1 (4)	1 (4)	0 (0)
Individual peer contact	5 (19)	1 (4)	1 (4)	1 (4)
Complementary care				
Massage	7 (27)	4 (16)	5 (19)	2 (8)
Yoga	2 (8)	0 (0)	2 (8)	0 (0)
Herbs, vitamins, or special diet	13 (50)	9 (35)	4 (16)	4 (16)

Limitations	Small sample size (n=26). Only long-term survivors included.

2

<table>
<tr><td>Reference</td><td>Llewellyn, CD, McGurk, M, and Weinman, J. How satisfied are head and neck cancer (HNC) patients with the information they receive pre-treatment? Results from the satisfaction with cancer information profile (SCIP). Oral Oncology 2006; 42(7): 726-734.</td></tr>
<tr><td>Study type</td><td>Prospective longitudinal study</td></tr>
<tr><td>Country</td><td>UK</td></tr>
<tr><td>Research question(s)</td><td>To assess HNC patients levels of satisfaction with information on illness and treatment, and to assess whether patients ratings significantly change after treatment</td></tr>
<tr><td>Theoretical approach</td><td>n/a</td></tr>
<tr><td>Data collection</td><td>July 2003 to July 2004, consecutive, newly diagnosed patients with confirmed SCC of the head and neck were recruited from 4 hospitals in south east England. Baseline data obtained between diagnosis and prior to treatment through self-completed questionnaires and medical records. Patients completed measures 1 month later after end of treatment and again 6-8 months later.
Measures include the satisfaction with cancer information profile (SCIP); the General Health Survey Questionnaire short-form 12 (SF-12 v2); the Hospital Anxiety and Depression Scale (HADS)</td></tr>
<tr><td>Method and process of analysis</td><td>Change in satisfaction over time was assessed. Binary data tested using McNemar tests for repeated measures. Wilcoxon Signed Ranks test for two-related samples were conducted on ordinal data. Correlations between measures were calculated using cross-lag Spearman correlation coefficients and linear regression.
Content analysis of open-ended questions.</td></tr>
<tr><td>Population and sample collection</td><td>82 newly diagnosed HNC patients (76% response rate). 66% male. Mean age 60 (range 23-89). 47% early stage, 47% advanced stage. 23% tongue, 15% floor of mouth, 15% oropharynx, 21% laryngeal/glottis, 9% tonsil, 5% lip. 27% surgery only, 26% RT only, 31% surgery+RT, 11% RT+chemo, 5% surgery+RT+chemo.
At one month follow-up (T2), 68 patients responded (83%) and at 6-8 months follow-up (T3), 50 patients responded (61%). 6% died during study, 17% had recurrences, 2% entered palliative care, 1 had severe complications after surgery.</td></tr>
<tr><td>Key themes</td><td>Levels of satisfaction before and after treatment
Satisfaction scores were negatively skewed pre (median=11; mean=9.9; SD=9.9) and post-treatment (median=11; mean=10.1; SD=4) with ranges of 14. Satisfaction scores with the type and timing of information were more normally distributed with a pre-treatment range of 13 (mean =28.8; SD=3.5) and post-treatment range of 21 (mean =27.4; SD=5.1)
Lack of information pre and post-treatment
<table>
<tr><th>SCIP item</th><th>Not supplied with any information pre-treatment n (%)</th><th>Not supplied with any information post-treatment n (%)</th></tr>
<tr><td>Where to ask/where to go for financial support</td><td>64 (78)</td><td>41 (60)</td></tr>
<tr><td>Patient support groups for you and your partner</td><td>43 (52)</td><td>23 (34)</td></tr>
<tr><td>What you should do if you experience side effects</td><td>41(50)</td><td>19 (28)</td></tr>
<tr><td>Whether your treatment interferes with other medications</td><td>37 (45)</td><td>21 (31)</td></tr>
<tr><td>How your treatment may impact on your quality of life</td><td>35 (43)</td><td>34 (50)</td></tr>
<tr><td>Whether you may need further treatment in the future</td><td>30 (37)</td><td>29 (43)</td></tr>
<tr><td>The effects of treatment on your ability to work</td><td>29 (35)</td><td>21 (31)</td></tr>
<tr><td>What the risks of you experiencing complications are</td><td>29 (35)</td><td>17 (25)</td></tr>
<tr><td>The long-term impact of treatment on functioning</td><td>26 (32)</td><td>19 (28)</td></tr>
<tr><td>How long you expect recovery to take</td><td>22 (27)</td><td>18 (26)</td></tr>
<tr><td>What the risks of experiencing side-effects are</td><td>19 (23)</td><td>4 (6)</td></tr>
<tr><td>Whether the treatment has any unwanted side effects</td><td>18 (22)</td><td>5 (7)</td></tr>
<tr><td>How you may expect to feel immediately after treatment</td><td>15 (18)</td><td>5 (7)</td></tr>
<tr><td>The effect of treatment on your appearance</td><td>15 (18)</td><td>15 (22)</td></tr>
</table>
Is there any further information you wish you had received?
Content analysis of open-ended question. 52% of pre-treatment sample required no further information compared with 31% of post-treatment sample. Areas of interest ranged from; more detail on the physical effects of treatment, to more information on the long-term effects of treatment and the likely length of recovery. Patients were not fully informed before treatment of some of the specific side effects of treatment (both related to surgery and radiotherapy) and the severity of surgery.
Satisfaction with type and timing of information was significantly lower post-treatment than pre-treatment ($p<0.05$). There was significant reduction in levels of satisfaction in key areas after treatment e.g. the usefulness of the information to the patient, the detail of the information, the understanding of the information. Satisfaction with the 'amount and content' of information was lower post treatment in 36% (n=22) although 42% (n=25) reported higher satisfaction after treatment compared to pre-treatment levels.</td></tr>
<tr><td>Limitations</td><td>Fairly small sample size. Information may have been received after the first questionnaire was completed. Because of drop-outs, post-treatment group may have been skewed towards higher levels of satisfaction. Patients who did not complete follow-up may have had lower levels of satisfaction. No differences between sample at baseline and follow-up in terms of socio-demographic and clinical factors.</td></tr>
</table>

1

Reference	Chen, SC et al. Prevalence and correlates of supportive care needs in oral cancer patients with and without anxiety during the diagnostic period. Cancer Nursing 2010; 33(4): 280-289.
Study type	Cross-sectional questionnaire study
Country	Taiwan
Research question(s)	Aims: (1) examine and compare levels of disease impact, symptom distress, and supportive care needs between newly diagnosed oral cancer patients with and without anxiety during the diagnostic period; (2) examine and compare the prevalence of unmet care needs between the 2 groups; and (3) examine and compare the correlates of supportive care needs in the 2 groups.
Theoretical approach	n/a
Data collection	The 2 groups of patients who met the inclusion criteria were interviewed face-to-face using structured questionnaires in the consulting rooms by a trained research assistant. The interviews lasted approximately 10 to 15 minutes. • Patients' supportive care needs were assessed using the Cancer Needs Questionnaire Short Form (CNQ-SF). • The Head and Neck Cancer Specific Needs Questionnaire (HNCNQ) was developed based on oral cancer patients' disease-related supportive care needs derived from literature review and expert evaluation and suggestion. Responses are scored the same as the CNQ-SF. Higher scores indicate higher unmet oral cancer-related needs. • The psychological impact from cancer diagnosis was assessed by the Impact-of-Event Scale • The 27-item Symptom Distress Scale Modified for Head and Neck Cancer (SDS-mhn) was modified from the Symptom Distress Scale • Patients' anxiety was assessed using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS)
Method and process of analysis	Descriptive statistics (frequency distribution, percentage, means, SDs) were used to analyze patient demographics, clinical characteristics, patients' perceived disease impact, symptom distress, supportive care needs, and prevalence of unmet care needs. Independent-samples t tests were used to compare age, disease impact, symptom distress, and supportive care needs in the 2 groups. The Chi-squared test was used to examine differences between patients with and without anxiety. Pearson product moment correlation was used to identify the correlates of the supportive care needs (dependent variable) for the 2 separate groups
Population and sample collection	Consecutive sampling was performed to recruit subjects from inpatient otolaryngology head and neck surgery wards medical centre in northern Taiwan. The inclusion criteria for patients with anxiety were: (1) new diagnosis of oral cancer and patient awareness of the cancer diagnosis; (2) admission to the hospital after tumour biopsy and status of awaiting surgery; (3) knowledge conveyed by the attending physicians and head and neck nurse practitioners of the planned surgical procedures; (4) assessment for anxiety using the anxiety subscale of the HADS, with a score of 11 or higher; and (5) agreement to participate in the study after being informed of its purposes and ability to communicate orally or in writing. Inclusion criteria for patients without anxiety were the same as those for patients with anxiety, except for a score of 10 or lower on the HADS anxiety subscale. Of the 71 patients with anxiety who met the criteria, 6 refused to participate because they were already overburdened by their medical and emotional conditions; of the 108 eligible patients without anxiety, 100 agreed to be interviewed. A total of 165 patients (92.2% response rate) were included in the final data analysis. Most participants ranged in age from 40 to 64 years (n = 129). Within each group, more than half of the patients were male, employed, and married, with the most common educational level being junior or senior high school, and the most common reported religion being Buddhism or Taoism. Most of the participants were in cancer stage I (n = 76) or stage II (n = 56). The most common sites of cancer were the buccal mucosa (n = 69) and the tongue (n = 52). The mean (SD) time since diagnosis was 3.97 (1.91) days for patients with anxiety and 4.43 (1.84) days for patients without anxiety. Most participants had good performance status (KPS index range, 80-100)
Findings	The patients' perceived overall supportive care needs were determined from the summed scores for the CNQ-SF and HNCNQ. The mean (SD) CNQ-SF scores were 39.89 (7.79) and 37.84 (7.03) for patients with and without anxiety, respectively. The mean (SD) HNCNQ scores were 30.79 (12.17) and 25.94 (10.70) for patients with and without anxiety, respectively. No statistically significant differences in the mean scores of individual domains and overall supportive care needs were found between the 2 groups (P > .05) except for the "physical and daily living needs" domain. The dimensions of top 3 supportive care needs ranked according to descending mean scores in the 2 groups were (1) health system and information needs, (2) psychological needs, (3) patient care and support needs, and (4) head and neck cancer-specific needs

Prevalence of top-rank unmet care needs in oral cancer patients

		With anxiety (n=65)		Without anxiety (n=100)		X^2
Unmet care needs	**Domain of care needs**	**Rank**	**%**	**Rank**	**%**	
Coping with anxiety about having treatment or surgery	Psychological	1	93.9	1	92	4.44
Coping with disturbed sleep	Physical/daily living	2	79.2	6	63.7	9.21
Dealing with fears about the cancer spreading or returning	Psychological	3	75.4	4	81.8	6.90
To be fully informed about the possible effects of cancer on the length of life	Health system/information	4	67.7	3	82	10.57
To be fully informed about all of the benefits and adverse effects of treatment and surgery before you have it	Health system/information	5	58.4	2	87	19.88
To be fully informed about cancer remission	Health system/information	6	55.4	7	43	5
To be fully informed about the odds of treatment success	Health system/information	7	49.2	5	72	11.42

	To be allowed to have family or friends with you in hospital	Patient care/support needs	8	46.2	8	37	5.43
	To be given a full explanation for every test and treatment procedure you go through	Health system/information	9	43.1	9	33	16.06
	Coping with fears about the pain and suffering you might experience	Physical/daily living	10	20	10	27	5.72
Additional comments /Limitations	Study used a cross-sectional design in which oral cancer patients were studied only during the diagnostic period. Thus, the study did not identify changes in the patients' level of anxiety or supportive care needs, comorbidities, or medical treatments at the disease and recovery stages. The study participants were recruited only from the inpatient wards of a medical centre in northern Taiwan, all awaiting surgery, which limits the generalizability of the results. Self-reported questionnaire – patients limited to reporting care needs provided in the CNQ-SF – other support needs may have been present.						

1

Reference	Kanatas, A et al. Issues patients would like to discuss at their review consultation: variation by early and late stage oral, oropharyngeal and laryngeal subsites. European Archives of Oto-Rhino-Laryngology 2013; 270(3): 1067-1074.
Study type	Cross-sectional questionnaire study
Country	UK
Research question(s)	Aims: to report the use of the patient concerns inventory (PCI) across various HNC sub-sites and stages of disease, and to describe the main concerns that these patients want to discuss in their clinic appointment.
Theoretical approach	n/a
Data collection	A questionnaire package was sent in February 2011, containing covering letter, consent forms, instructions and the questionnaires – the University of Washington Quality of Life questionnaire (UW-QoL) and the PCI
Method and process of analysis	Results were analysed within clinical subgroups defined by tumour site (oral, oropharyngeal, laryngeal, other (unknown primary) and overall clinical stage (early-stage disease = 0–2, late-stage disease = 3–4) based on the clinical tumour, node, metastases (TNM) classification.
Population and sample collection	447 patients (58% response rate) treated for primary head and neck squamous cell carcinoma between 1998 and 2009. Exclusion criteria: cutaneous and salivary gland malignancy, treated with palliative intent, current recurrence or ongoing disease, over 85 years old, cognitive impairment, living overseas or previously declining to participate in further studies. Oral cancer (n=193), oropharyngeal (n=124), laryngeal (n=112), other sites (n=18). **Primary treatment (%)**

	Oral		**Oropharyngeal**		**Laryngeal**	
	Early stage (n=136)	**Late stage (n=57)**	**Early stage (n=34)**	**Late stage (n=90)**	**Early stage (n=77)**	**Late stage (n=35)**
Surgery alone	82	44	50	19	51	29
Surgery + RT	16	54	41	46	14	49
Primary RT	1	2	9	36	35	23
Median time from primary treatment (months)	50	47	44	41	33	48

2

Key themes

Overall, in response to the question about the PCI the ten most prevalent concerns that patients wanted to discuss in clinic were fear of the cancer coming back (39 %, 174), dental health/teeth (28 %, 123), chewing/eating (23 %, 102), swallowing (22 %, 100), fatigue/tiredness (22 %, 100), salivation (21 %, 95), pain in head and neck (19 %, 84), shoulder (18 %, 79), mucous production (17 %, 75) and speech/voice/being understood (16 %, 73).

Fear of recurrence concerns were reported consistently by one-third or more patients (range 32–67 %) and were the dominant concerns of patients with early stage tumours. For late-stage patients fear of recurrence was just one of many concerns of similar prevalence. Speech issues were more often raised by patients with laryngeal tumours than by other patients whilst issues relating to saliva were particularly common for patients with oropharyngeal tumours (32 % early, 48 % late). Apart from early-stage laryngeal tumours, patients consistently reported issues concerning dental health/teeth and chewing. The median (IQR) number of concerns raised overall was 4 (2–7) and there was significant variation ($p<0.001$) between clinical groups ranging between 2 (1–6) for early-stage oral to 6 (2–10) for late-stage oropharyngeal and 7 (5–9) late-stage laryngeal.

Ten most common concerns raised by patients on the PCI

FOC=fear of cancer coming back, Pain H&N=pain in head and neck, Speech= speech/voice/being understood, Dental= dental health/teeth, Mucous= mucous production

Oral				Oropharyngeal				Laryngeal			
Early stage (n=136)		Late stage (n=57)		Early stage (n=34)		Late stage (n=90)		Early stage (n=77)		Late stage (n=35)	
Item	%	Item	%	Item	%	Item	%	Item	%	Item	%
FOC	38	FOC	32	FOC	44	Salivation	48	FOC	42	Swallowing	43
Dental	30	Dental	32	Swallowing	32	Chewing	40	Speech	27	Speech	40
Chewing	19	Chewing	28	Salivation	32	Swallowing	38	Fatigue	19	Fatigue	40
Fatigue	17	Taste	23	Fatigue	26	FOC	37	Coughing	18	Coughing	40
Pain H&N	15	Swallowing	23	Dental	21	Dental	34	Breathing	14	Mucous	37
Sleeping	15	Fatigue	19	Chewing	21	Pain H&N	30	Mucous	14	FOC	37
Shoulder	14	Appetite	19	Shoulder	18	Taste	29	Cancer treatment	13	Dental	34
Weight	13	Speech	18	Pain H&N	18	Shoulder	29	Weight	13	Appetite	29
Swallowing	13	Salivation	16	Pain elsewhere	15	Fatigue	28	Swallowing	12	Pain H&N	29
Speech	13	Pain H&N	16	Mucous	15	Mucous	26	Shoulder	12	Weight	26
Salivation	13	Mucous	16	Anxiety	15					Shoulder	26
		Anxiety	16	Depression	15					Chewing	26

The members of staff that patients would like to see at clinic or be referred on to

Wanting to see the surgeon was dominant (range 26–44 %) across all clinical groups apart from late-stage laryngeal patients (who wanted to see clinical nurse specialist, 40%). Surgeon, dentist or dental hygienist, clinical nurse specialist, speech and language therapist, dietician and radiotherapist/oncologist consistently occupied the top five selections made by these clinical groups. The median (IQR) number of staff members selected overall was 1 (0–2) with little difference between clinical groups.

Additional comments/ Limitations

Response rate of 58% - may not be representative of all patients. Cross-sectional questionnaire – no insight into changes over time. Patients were at different points of time within and beyond 5-yr follow-up regime.

1

Reference	Egestad, H. The significance of fellow patients for head and neck cancer patients in the radiation treatment period. European Journal of Oncology Nursing 2013; 17(5): 618-624.
Study type	Qualitative interview study
Country	Norway
Research question(s)	Aim: to explore how daily life of head and neck cancer patients are affected by fellow patients in the radiation treatment period.
Theoretical approach	Phenomenological hermeneutic approach
Data collection	The interviews took place in the patients' homes about one month post radiation therapy during 2010 and the spring of 2011. The interview consisted of open questions about their thoughts and feelings when they received radiotherapy. Every interview began with 'Please tell me about your experiences of the treatment'. The follow-up questions related to the participants narratives and focused on how the contact with fellow patients affected everyday life in the treatment period. The purpose was to obtain knowledge of how patients experienced contact with fellow patients. Each interview lasted for approximately one and one-half hours, recorded with a tape recorder and transcribed.
Method and process of analysis	The interview transcripts were analyzed within a phenomenological hermeneutic framework that was inspired by Gadamer (1999) and presented as a stepwise research method by Fleming et al. (2003) and Van Manen (1997). The analysis consisted of three phases: naïve reading; structural analyses; and comprehensive understanding.
Population and sample collection	11 participants who had been diagnosed with head and neck cancer were interviewed. Patients were recruited through a radiology department in Norway. Patients were eligible if they had been diagnosed with HNC and were going to receive radiotherapy. 7 male, 4 female. Two participants lived at home during the first weeks of treatment, the other participants stayed in a hospital hotel. In the last three weeks of treatment, all participants stayed in the hospital because they were too sick to stay at home. Nine participants were married; one was single, and one a widow. The median age was 57 (range 35- 76). Eight participants were employed full-time and three participants were retired. Two participants worked part time in the first 3-4weeks of treatment. All participants received a curative dose of external beam radiation therapy to their affected area over a period of 6-7 weeks. As the weeks of treatment passed, the participants were increasingly fatigued by the side effects. In the last two or three weeks, the side effects were intolerable; the participants had severe problems with eating, some had to be tube-fed, they were in a great deal of pain, had mucus, and had difficulty in speaking. In addition, the participants felt

<table>
<tr><td></td><td>very sick.</td></tr>
<tr><td>Key themes</td><td>
Social contact
For all participants, it was important to meet other cancer patients who underwent a similar or the same treatment as themselves. They were looking for other patients with cancer diagnosis. It was important to find someone who was ‘in the same boat’

<table>
<tr><th>Participants want</th><th>Examples</th></tr>
<tr><td>Social contact</td><td>“I was so lonely before I found other patients with same disease. We were in the same boat” (8).
“I found two fellow patients; we went for walks and talked together. It was very nice having someone to spend the time with; otherwise I think the treatment would have been lot worse” (4).</td></tr>
<tr><td>Other contact with patients</td><td>“It was important to have contact with others who had cancer, we had so much in common”(9).
“It was tough to be the only cancer patient in the ward. I felt like a foreign element, I had no one to talk to and to discuss illness and treatment. All fellow patients had rheumatism or skin diseases” (8).</td></tr>
<tr><td>Activities</td><td>“I got some fellow patients to go with me to the gym where we interacted socially...had bit of fun. I think we all appreciated it” (1).
“We were a group; we enjoyed ourselves” (2).</td></tr>
<tr><td>Humour</td><td>“We talked together and relieved the pressure, we had a bit of gallows humor about our situation” (4).
“We had fun together” (2).</td></tr>
</table>

Gaining support
The results showed that participants shared information about the radiation therapy and related side effects. They compared information from health professionals and gave each other additional information. The information participants received from fellow patients was of great importance. It was important to have insight into other people’s personal experience with radiation therapy, including how they dealt with the side effects. By gaining insight into fellow patients’ thoughts and feelings, participants own experiences were seen as normal reactions, and their sense of being different was reduced

Participant’s statement about how fellow patients supported them and gave them training.

<table>
<tr><th>Participants experienced</th><th>Examples</th></tr>
<tr><td>Receive information</td><td>“It was important to get information from fellow patients, they had experienced the treatment themselves. We were three patients together, when one of us received information we told the other” (4).
“It was very helpful to talk to other with the same cancer disease” (8).</td></tr>
<tr><td>Emotional support</td><td>“Having someone in same situation who knows what you are talking about is very good. It was very good to have fellow patients to talk to, then I knew that we all experienced it in the same way, and I felt like a normal person” (4).
“Very good to be in same situation, they understood what I was talking about”(5).</td></tr>
<tr><td>Be trained</td><td>“Those who were in front of me told me how the treatment was and how I could cope with the side effects” (3).
“We supported each other in the way to deal with treatment and side effects” (1).</td></tr>
</table>

Encouragement from fellow patients
Most participants said they supported fellow patients. The results demonstrated that the participants experienced that it was important and good for them to provide encouragement to fellow patients. The participants felt that the contact resulted in their being more at ease during the intensive treatment period.
<table>
<tr><th>Support and encouragement gained from fellow patients</th><th>Examples</th></tr>
<tr><td>Support</td><td>“It was very good to be able to help by telling my story. The patient was so far away from home and was so sad” (7).
“I told the patients who came after me how the treatment was. They were happy to get the information. They had not believed that the treatment was so hard” (2).</td></tr>
<tr><td>Provide understanding</td><td>“We supported each other in how we should think about the treatment. It was best not to begin the countdown of the treatments immediately, but rather set up partial goals, take a week at a time” (1).</td></tr>
</table>

Emotional distress
Participants mostly talked about support and help from fellow patients; however, a few narratives were about feeling sadness and fear in meeting with fellow patients. Some participants described that they were physically ill and mentally diminished in the treatment period. Participants felt that it was mentally tough to be with other persons who were seriously ill. A few participants said that when they met fellow patients who were very sick from the treatment this affected them negatively.
</td></tr>
</table>

	The participants became scared. **Participants experienced** / **Examples** Sadness: *"I was mentally tired of just being with others who were seriously ill" (1).* *"What made the biggest impression on me was meeting other patients and seeing how they looked and how they suffered, I found it very straining"(2).* Fear: *"The worst was seeing other patients in whom the disease had further developed and knew I actually had same disease, it was terrible" (9).*
Additional comments/ Limitations	Rigorous and detailed method of analysis. However, analysis only performed by one researcher. Tumour site not reported. Small sample size from one radiation department.

1

Reference	Furness, PJ. Exploring supportive care needs and experiences of facial surgery patients. British Journal of Nursing 2005; 14(12): 641-645.
Study type	Qualitative interview study
Country	UK
Research question(s)	Aim: to explore facial surgery patients' and relatives' perceptions of professional support and ways in which care could be improved
Theoretical approach	Grounded theory
Data collection	Focus groups and interviews were conducted, with participants allowed to select their mode of participation. Interviews were conducted by the researcher. Focus groups were facilitated by the researcher and an assistant. Participants were asked to discuss their experiences of adapting to facial surgery, and to reflect on the care they or their friend or family member bad received.
Method and process of analysis	For the purposes of this study, a focused coding technique was used guided by grounded theory methods to identify data related to the study aims. Data were coded and themes relating to professional care and support developed. Participants were sent a descriptive summary of their own interview, and their comments sought regarding its accuracy.
Population and sample collection	A purposive sample of 38 participants was recruited: 28 facial surgery patients and 9 significant others (eight marital partners and one close family member), interviewed as part of a larger project exploring the predictors and process of individual adaptation to facially disfiguring surgery (one participant was later excluded from the data as she was found not to meet the criteria. Eligible persons were introduced to the study by clinicians in hospital clinics and through posters in GP surgeries. Advertisements were also placed in a national disfigurement charity newsletter. Consenting persons were asked whether they were prepared for a close relative or friend to be contacted to take part, and to nominate the person they considered closest. Mean age of 38 participants was 59 years, with 22 men and 15 women. 32 were married, and the remainder either single (n=3) or widowed (n=2). Time since surgery varied from 3 months to 22 years (mean 5.4 years). 21/29 patients had surgery for cancer. 3 ocular cancer requiring enucleation, 4 jaw cancer, 12 mouth/tongue cancer, 2 skin cancer.
Key themes	**Information strengths: preoperative information about surgery** Many participants reported general satisfaction with information from registered medical practitioners before their surgery about surgical procedures, risks and the possibility of varying outcomes. For most, preoperative information reduced participants' uncertainties and helped them to cope, while a few felt that it highlighted, rather than resolved uncertainties, exacerbated anxieties, and created additional distress: *'Knowing that this [worst case scenario] might happen, that was in a lot of ways worse than coping with the surgery afterwards... the pressure and stress' (Caroline).* **Information deficits: postoperative information** While participants reported being well-informed about the surgery itself, retrospective debriefing, education about physical and emotional after-effects, and information about support in the community were less consistent. In several cases where surgery had been more extensive than planned, participants reported receiving little postoperative information about what the surgeon had done, but had instead gradually discovered this for themselves. Others had experienced distressing physical symptoms after surgery or problems with prostheses, for which they were unprepared. Deficits were apparent in staff preparation of patients for the psychological aftermath of surgery. Many participants had experienced unexpected emotions or problems coming to terms with facial surgery, e.g. there were numerous accounts of the shock of first seeing their face postoperatively: *'The doctor came one day, and said: "You can get out of bed today, Mrs B." Oh good, I'll go to the bathroom and have a wash, lots of hot water, lovely. And that's when I saw my face. Nobody had told me anything. I don't want that to happen to anyone else'* (Edith) Some participants bad been in contact with support networks since discharge, and reported that contact with and support from other facial surgery survivors had been very helpful to their emotional adjustment. Although a few participants bad been told about support groups or been referred by healthcare workers, especially cancer nurse specialists, this experience was exceptional. Most heard nothing from staff about availability of support in the community, contact sometimes occurring by chance.

	Strengths in informational support • **Surgical procedures** • **Risks of surgery** **Deficits in informational support** • **Retrospective debriefing** • **Physical after-effects** • **Emotional and psychological after effects** • **Information about support in the community** **Information for friends and family** Partners also expressed a desire for information about what was happening to their loved one. Conversely, a lack of involvement left some relatives feeling excluded and less able to support their partner, and resulted in unnecessary anxiety and distress. **Material and practical help** This category comprised support with the physical changes created by surgery, such as prostheses, mobility aids and referral to social services for practical help. There were differences in the type of support participants wanted, and in its origin and effectiveness. **Emotional and Psychological care: Availability and need** This subcategory comprised participants' need for emotional support and its perceived availability from staff. Several participants were satisfied with the support received because they felt it met their needs, or because they did not perceive a need for support: *'There was no counselling as such, you know. As I say I don't really think I needed it — it was just a matter of getting my strength back'* (Ray). Others expressed needs, but reported being offered little help: *'Trying to be normal for the children, for the family, it was so hard. And at that time, that was one of the times when I feel that somebody to talk to, some support, would have been, would have made all the difference'* (Caroline). **Components of support** **Staff approachability and positive attitudes:** The quality of the relationship between patients and the team caring for them in hospital, which depended on staff being approachable, kind and concerned, was an important element of positive emotional support. On the other hand, impersonal consultations, lack of concern and negative or dismissive staff attitudes dented confidence and eroded participants' sense of support. **Awareness, education and training:** Many participants felt staff underestimated the psychological consequences of facial surgery. Awareness and understanding were seen as important components of the ability to give effective patient support. **Long term follow-up:** Timing of emotional support came up in several interviews. Some participants felt emotional support should be given immediately after surgery. Others suggested people might not need support at this time, because of relief at having survived, but felt that need for support might alter over time with changes in the ability to cope. For most who had found themselves in need of support some time after surgery, these changes had run counter to their expectations, and had thus found them unprepared: *'it's that period of time down the line, when you think to yourself, you should be back to normal, and you're not. That's when it hits you, and that's when I think people need support...'* (Caroline) Some participants with facial cancers mentioned Macmillan nurses. In general, these participants were happy with this support. Several reported proactive specialist nurses, who helped established support groups. However, those whose surgery was trauma-related enjoyed no ongoing support. The lack of support and sense of isolation was, for some, implicated in continuing distress, anxiety and depression: *'There hasn't been anybody to talk to... I feel right depressed, sometimes'* (Eileen). **Time to talk:** Lack of time was a perceived barrier to emotional support-giving by staff. Some felt that surgeons were not appropriate people to offer, or be asked for, emotional support because of the pressure on their time. Eileen stated, *'there's always a roomful' and 'I don't like to take his time up by asking...'* Others suggested that emotional care might have been better, had staff taken the time to discuss how they were coping, but acknowledged this was not always realistic: *'You know, they could ask you, "how do you feel now you look like that", or, you know, "how've you been doing?". They don't seem to do that enough. Mind you, they probably haven't got time, doing the blooming operations have they?' (Paul).* However, when staff took the time out of their busy schedule to talk, this was appreciated and was associated with a sense of being supported and less isolated. Although hospital medical and nursing staff were perceived as having little time to offer emotional support, GPs and district nurses were praised for taking time to visit and talk after discharge: *'We get support from the district nurse. We've got wonderful district nurses. And when it first happened, the sister came, and she used to sit here with me on the floor and talk to me about gardening' (Carol).*
Additional comments/ Limitations	Rigorous analysis - Reliability of data coding checked by participants and a second analyst. Not all participants had facial surgery for UADT cancer – limits applicability to review question.

1

<table>
<tr><td>Reference</td><td>Mayre-Chilton, KM, Talwar, BP, and Goff, LM. Different experiences and perspectives between head and neck cancer patients and their care-givers on their daily impact of a gastrostomy tube. Journal of Human Nutrition and Dietetics 2011; 24(5): 449-459.</td></tr>
<tr><td>Study type</td><td>Qualitative focus group study</td></tr>
<tr><td>Country</td><td>UK</td></tr>
<tr><td>Research question(s)</td><td>Aim: to explore HNC patients and caregivers views and experiences of living with a gastrostomy tube.</td></tr>
<tr><td>Theoretical approach</td><td>None reported</td></tr>
<tr><td>Data collection</td><td>Qualitative focus group interviews were planned to provide a systematic, ordered system of topics with related prompt questions. All topics were started with an open question and example to encourage the group discussion and allow the views and experiences of daily living with the gastrostomy tube from the patients' and care-givers' perspective to emerge separately. All sessions were run by the investigating researcher and assisted by the nonclinical co-author. Sessions were recorded and transcribed at a later date.</td></tr>
<tr><td>Method and process of analysis</td><td>Analytical self-reference guides or templates were produced for each topic using thematic analysis to identify themes, patterns and key words per topic. To reduce the subjective nature of the qualitative analysis template guides, a predetermined number of key words were used to help assign and sort the data appropriately.</td></tr>
<tr><td>Population and sample collection</td><td>6 patients and 3 care-givers participated (out of 21 adult patients who were randomly selected from a dietetic led gastrostomy database at University College London Hospitals Head and Neck centre and invited to participate). Criteria for inclusion were patients diagnosed with head and neck cancer, who had a gastrostomy tube placed for nutritional support undergoing cancer treatment with a minimum of 3 months after tube placement, who were well enough to attend the session and provide their informed consent. All other patients were excluded. All patients were informed of the purpose of the study and invited to attend a patient focus group. Patients were requested to offer their primary care-giver an opportunity to attend a separate carer focus group session.
The patient group consisted of four males with an average (range) age of 55 (51–60) years and two females with an average (range) age of 64 (27–92) years. 2 oropharynx, 2 larynx, 1 sarcoma mandible, 1 unknown primary. All patients had a gastrostomy tube placed endoscopically by the 'pull method' to support their nutrition when undergoing cancer treatment. Out of these five were prophylactic gastrostomy tubes before treatment, based on trust wide head and neck enteral feeding guidelines and one patient had a gastrostomy tube placed during radiotherapy before the guidelines were implemented. At the time of the session, four of the patients still had their tubes in situ and two had theirs removed.</td></tr>
<tr><td>Key themes</td><td>Knowledge and understanding of why the tube was necessary
Through the topics of decision-making and getting home with a gastrostomy tube, patients and care-givers expressed an opposite impact. The lack of knowledge and understanding had an evident negative impact on the care-givers, especially once they got home, which reflected their anxiety towards having the gastrostomy tube removed. There was an element of conflicting advice and the omission of information, which resulted in a negative impact on the patients.
Overall, patients were more able to cope because they were the main focus of the treatment and time had been dedicated to help them make an informed decision.
'lots of information before I had the operation … they did show me the tube, explained how it worked … I had lots of reading material' (Patient)
Gastrostomy tube dependency
The patients acknowledged positive reasons for needing the tube feed; some were early in the treatment and others at a later stage, and this appears to be the result of major physiological changes that prevented them from normal eating habits. Both groups expressed many possible reasons that prevented them from weaning off the gastrostomy tube onto normal foods (e.g. being unable to swallow). Timely dietetic management helped them wean off tube reliance with more confidence. Overall, the data highlight the many influential factors, such as taste, smell, lack of saliva, pain, length of time taken to eat and psychological concerns, that the tube feeding helps them to cope with.
Support network
The patients and care-givers expressed a positive impact on approaching the hospital multidisciplinary team, especially those patients receiving radiotherapy who attended the weekly treatment multidisciplinary clinic, where they had access to the registrar, dietician, nurse and other professionals in one clinic. Dental extractions in preparation for radiotherapy and dental rehabilitation after treatment were expressed as a negative impact by all participants. Some patients expressed a lack of active care after their treatment and discharge into the community, which had a negative impact on them. Issues about waiting for funding for a low profile gastrostomy tube by the Primary Care Trust were expressed as a negative impact. The financial burden of bills, expenses and increased purchases, as well as not being more psychologically prepared, had a negative impact on the care-givers lives.
<table>
<tr><td>Topic</td><td>Branching themes</td><td>Patient (n=6)</td><td>Care-giver (n=3)</td></tr>
<tr><td>Support from health professional</td><td>Specialist team</td><td>F: 'being able to contact my hospital … I personally prefer the fact that I can contact the actual dietician team… she was the first contact I had when I came ….She was ... quite good with the PEG'</td><td>C: 'to have that in place, that is psychologically one of the pillars of keeping you peaceful, and confident and not worried …that date in your diary. … Amazed by the amount of backup, and how well planned … how thoughtfully it had been arranged …you are in once a week and...see everybody'</td></tr>
<tr><td>Challenges and issues raised by participants</td><td>Dental</td><td>H: 'I don't think there is adequate support ….. you can't get them on the NHS. …. there needs to be more oral care in the hospital.''
F: ''I had my teeth removed. I have false teeth and I had to learn how to eat'</td><td>B: 'the dental extractions, … quite distressing'
C: 'there is nothing wrong with them, so why do they have to come out?... they take them out on NHS and don't do anything afterwards'
G: 'She then had to start feeding
but she has no dentures anyway'</td></tr>
</table></td></tr>
</table>

		Active care	A: 'the after care because once the treatment is over it's like that's it you are on your own now'	
		Psychology		G: 'very important for the carer is to understand the psychology… sometimes carers feel totally isolated'
	Financial implications	Bills and purchases	H: I am waiting for my PCT to grant the funding for one… (low profile PEG)'	G: 'these are expenses…. I have built a bathroom'
Additional comments /Limitations	Transcripts were checked by co-author. Co-authors also selected 10% of the transcript and followed the guides to check for inter-rater reliability. Small sample size limits generalisability.			

1

Reference	Edwards, D. Head and neck cancer services: views of patients, their families and professionals. British Journal of Oral & Maxillofacial Surgery 1998; 36(2): 99-102.
Study type	Qualitative focus group study
Country	UK
Research question(s)	To find out what patients, their families and professionals thought of head and neck cancer services.
Theoretical approach	None reported
Data collection	Focus group interviews were held. The issues for discussion were developed from informal conversations with professionals and patients before the study and adapted as important issues emerged. All focus groups were recorded and transcribed in full.
Method and process of analysis	The contents of the data were analysed for themes, key issues and for consistency. A map of each focus group was built up and analysed for inter-relationships between the different aspects of the findings.
Population and sample collection	Patients and professionals from 4 hospitals and 2 patient support groups in South East England. Patients seen in the department within the past year and diagnosed more than 1 year previously were eligible. Patients were consecutively selected from lists of eligible patients compiled by the maxillofacial departments at the 4 hospitals. Additional patients were recruited from members of support groups who met at 2 of the hospitals. Patients had the option of bringing a family member with them. 22 patients and 11 relatives took part in 6 focus groups. 33 professionals took part in 4 focus groups, including maxillofacial, ENT and plastic surgeons, medical and clinical oncologists, nurses, speech therapists and other professionals involved in rehabilitation and palliative care.
Key themes	**Hospital accommodation** The patients and relatives who were happiest with their accommodation were those who were nursed in side rooms and those who were on a cancer ward or section of a ward. Many patients who had been on wards with patients having different procedures felt that the nursing staff did not know anything about their condition. Being on a non-cancer ward made mutual support more difficult. **Coordination** Many patients felt abandoned when they were discharged and did not know where to turn. Liaison between hospitals was very poor. Several patients suggested that it would have helped to have one contact person, e.g. specialist cancer nurse, who could liaise between various providers. Patients and relatives knew that their cancers were rare and supported the proposal of a specialist centre with expertise. **Information** Some patients and relatives said that they had good information on their treatment but most felt that it could be improved. Given too much information about the details of the surgical procedures but not enough on the side-effects of treatment or what to expect during and after treatment *" When I was told what they were going to do to me I was shell-shocked. I really thought it sounded like a horror film and I used to be a nurse."* Many patients had conflicting information from different professionals but did not mention it through fear of getting someone into trouble. Most people had unanswered questions about their treatment and felt that two-way communication did not occur. **Choice** Most patients wanted to be involved in their treatment, and more wanted to be involved in decisions about their treatment than actually were. In general, younger patients wanted more involvement whereas some older patients felt that it made no difference as doctors would only do as they wanted anyway. Some people were given choices in their treatment but did not have enough information on which to base a choice. Most patients wanted to make a joint decision with the advice of their clinician and have their views taken into account. There were different opinions among clinicians about how much choice patients should be given in their treatment. Many felt that patients should be involved in choices about rehabilitation and palliative care but the choice of primary treatment should be the role of the consultant. Everyone agreed that the patient should have a veto on their treatment but few clinicians presented a range of options with their relative merits either owing to time constraints or philosophical reasons. **Impact of condition** Physical, psychological and social impacts. Difficulty in eating following treatment was the most common problem, leading to

	weight loss and limited social contact. **Psychological support** Most patients said that they needed to talk about their condition. Often they talked to their partner or family, but some people needed more support than this. Most patients had not been offered counselling and some patients found it difficult to ask for as they felt that this was an admission that they could not cope. Most of the patients who had had counselling from various sources found that they had not helped as the counsellors had often not listened to them but tried to provide solutions to their problems. In contrast, people who had taken time to listen to them, e.g. a junior doctor or student nurse, had helped them to come to terms with what they were going through. The patients who were members of support groups felt that these provided a lifeline. They described the relief when they met someone who understood what they had been going through. There was access to someone at the other end of the telephone if they needed to talk. Many patients had not heard about support groups and said that they would have liked to know about them even if they decided that they did not want to attend.
Limitations	Dated study – conducted over 15 years ago. Limited relevance to current service provision.

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Reference	Ledeboer, QC et al. Experience of palliative care for patients with head and neck cancer through the eyes of next of kin. Head & Neck 2008; 30(4): 479-484.
Study type	Cross-sectional questionnaire study
Country	Netherlands
Research question(s)	Aim: to increase knowledge of how treatment and support are experienced by relatives of palliative patients with head and neck cancer during the palliative stage and after death
Theoretical approach	n/a
Data collection	A letter confirming their participation and explaining the aim of the study were sent to participants who agreed to take part from a telephone call. The questionnaire was included with the letter. Questionnaire consisted of 64 semi-structural questions, 6 open questions, and 16 general statements on palliative care. Questions were categorized as medical treatment, psychosocial support, information, and education and terminal stage.
Method and process of analysis	Descriptive, correlational statistics and cross-tabulations.
Population and sample collection	45 relatives (82% response rate) or close friends (the first contact person noted in the medical dossier) of patients with incurable head and neck cancer diagnosed or treated in one department. All patients had a histologically proven malignancy of the head and neck area. The average palliative period lasted 4 months. Participant was surviving spouse (53%) or offspring (29%). Median age 66y (range 24-82). 76% male, 24% female. Main stay in palliative period: 82% at home, 18% hospital, 1 nursing home. Almost all the relatives 'often' or 'always' accompanied the patient during their hospital visits.
Key themes	**Psychosocial support during the Palliative stage** According to more than half of the relatives (54%), the ''overall'' care and support of the head and neck oncology was ''good'' to ''very good.'' One third (32%) judged the care and support as ''reasonable,'' and the remaining felt it was ''poor.'' The relatives reported that 67%of the patients were sometimes or often depressed. In 69% of the cases, it was felt that patients needed better psychosocial support during the palliative stage.

	% of total patients	
Type of support	**Satisfaction with received support**	**Dissatisfaction with received support**
Support from family	96	4
Discussing disease in family	86	14
Psychosocial support head and neck department	51	49
Psychosocial support general practitioner	70	30

In only 23% of the cases, there was spiritual support. Patients who did not receive spiritual support judged the psychosocial support from the head and neck department less satisfactory.

There was a positive relation between having a single attending surgeon and a positive evaluation of the psychosocial support of the head and neck department (r=.353, p =.05). Additionally, there was a positive relation between continually visiting the same head and neck surgeon and how contact with the surgeon was experienced (r= .440, p =.01).

Experience of the surviving relative themselves

Contact with the head and neck surgeon was judged as follows: 16% rated ''very good,'' 34% rated ''good,'' 27% rated ''reasonable,'' and 18% rated ''poor.'' Thirty-three percent of the surviving relatives said that the head and neck surgeon did not pay sufficient attention to them. More than half (58%) claimed that psychosocial support from the head and neck department in respect to problems of the relatives themselves was insufficient.

The terminal phase of dying

Half (53%) of the patients died at home. 38% of the patients died in the hospital and 9% in a nursing home. According to the relatives, one tenth were not informed that their disease was incurable and the treatment was palliative. 49% said that symptoms related to the terminal stage were not discussed with the patient. Patients who were better informed about the stage of dying found psychosocial support more sufficient (r=.782, p= .01) and were better prepared for death (r=.570, p =.01). No relation was found between better information and acceptance of dying. Psychosocial support during the phase of dying was judged as insufficient in 63% of the cases. Two thirds of the relatives said the caregivers did not mention support in bereavement. 78% of the relatives reported that the head and neck department did not contact them after the death of their spouse. Almost none (5%) of the relatives received support from the head and neck department during the bereavement.

Limitations	In most cases more than a year had passed between death and the answering of the questionnaire – recall bias. Specific head and neck cancer problems, such as swallowing, speech, and airway problems, were not explored. Small sample from the Netherlands – may not be applicable to UK population and palliative service provision.

1

Reference	Chen, SC et al. Unmet information needs and preferences in newly diagnosed and surgically treated oral cavity cancer patients. Oral Oncology 2009; 45(11): 946-952.
Study type	Cross-sectional questionnaire study
Country	Taiwan
Research question(s)	Aims: to examine and compare the levels of care information needs, information preferences, and patients' unmet information needs between two groups of newly diagnosed oral cavity cancer patients, comprising (a) diagnosed patients and (b) surgically treated patients;
Theoretical approach	n/a
Data collection	Participants completed the following measures: Demographic and clinical information; Cancer Needs Questionnaire short form – information subscale (7 items, scoring 1 'no need/not applicable' to 5 'high need for help'); Patients' level of physical performance/function was assessed by the Karnofsky's Performance Status Index (KPS).
Method and process of analysis	Descriptive statistics (frequency distribution, percentage, means, standard deviations) were used to analyze the background characteristics, level of information needs related to care, information preferences, and unmet information needs. Independent samples t-test and Chi-squared tests used to examine differences between groups.
Population and sample collection	Consecutive sampling was conducted to recruit subjects from inpatient otolaryngology head and neck surgery wards of a medical centre in Taiwan. The inclusion criteria for diagnosed participants were: (1) newly diagnosed adult oral cavity cancer patients; (2) diagnosed and admitted as post-tumour biopsy and awaiting surgery; (3) advised by both their attending physicians and head and neck nurse practitioners of their surgical procedures; (4) agreed to participate in the study after expressing an understanding of the purposes, and able to communicate orally or in writing. Inclusion criteria for surgically treated participants were (1) newly diagnosed adult oral cavity cancer patients; (2) had received surgical treatment, and were admitted after tumour excision surgery for 14–20 days, were in the acute recovery phase; and remained inpatients in an intensive care unit that had been turned into an ordinary ward; (3) received an explanation of the final pathology report and had adjuvant radiotherapy after tumour excision surgery; (4) agreed to participate in the study after expressing an understanding of its purposes, and able to communicate orally or in writing. A total of 222 subjects comprised 109 diagnosed and 113 surgically treated adult oral cavity cancer patients. The diagnosed patients ranged in age from 23 to 78 years (average: 53.8, SD = 11.5). The surgically treated patients ranged in age from 27 to 78 years (average: 53.4, SD = 10.5). Within each group, more than half of the patients were male, employed and married, with an education level of junior and senior high school, and reported being of Buddhist or Taoist religion.
Findings	**Care information needs** The mean overall care information needs were determined by combining scores from the health information subscale of the CNQ-SF. Scores were 59.2 (SD = 11.5) and 50.8 (SD = 15.0) for diagnosed and surgically treated patients, respectively. Comparison of the two groups showed that diagnosed patients had significantly higher overall care information needs (t = 4.69, p < 0.001). The differences in mean scores for each item as well as mean overall on care information needs between the two groups were statistically significant.

Distribution of rank and mean in care information needs (n = 222).

	Diagnosed patients (n=109)			Treated patients (n=113)			
Variable	**Rank**	**Mean**	**SD**	**Rank**	**Mean**	**SD**	**t**
To be given a full explanation for every test and treatment procedure you go through	5	59.9	21.8	6	40.9	15.7	7.41*
To be fully informed about all of the benefits and side effects of treatment or surgery before you agree to have it	2	79.4	18.9	1	66.4	20.8	4.86*
To be fully informed about the odds of treatment success	4	73.6	23.3	2	48.9	28.2	7.13*
To be fully informed about your test results as soon as possible	6	38.5	28.6	1	66.4	20.8	-8.28*
To be fully informed about the possible effects of the cancer on the length of your life	3	78.9	24.6	5	41.6	16.6	13.21*
To be fully informed about cancer remission	1	60.5	27.1	3	46.7	26.4	3.86*
To be fully informed about things you can do to help yourself get well	7	23.6	22.8	4	44.9	26.1	-6.48*

*p<0.001

Information preferences and unmet information needs

Ranked in descending order, the unmet information needs for diagnosed patients were ''to be fully informed about all of the benefits and side effects of treatment or surgery before you agree to have it" (78.9%), ''to be fully informed about the possible effects of the cancer on the length of your life" (78.9%), ''to be fully informed about the odds of treatment success" (63.3%), ''to be fully informed about cancer remission" (45.9%), ''to be given a full explanation for every test and treatment procedure you go through" (37.9%), ''to be fully informed about your test results as soon as possible" (21.1%), and ''to be fully informed about things you can do to help yourself get well" (7.3%).

Unmet information needs for surgically treated patients, ranked in descending order, were ''to be fully informed about all of the benefits and side effects of treatment or surgery before you agree to have it" (51.3%), ''to be fully informed about your test

	results as soon as possible" (51.3%), ''to be fully informed about the odds of treatment success" (43.4%), ''to be fully informed about cancer remission" (37.2%), ''to be fully informed about things you can do to help yourself get well" (31.0%), ''to be fully informed about the possible effects of the cancer on the length of your life" (3.6%), and ''to be given a full explanation for every test and treatment procedure you go through" (2.7%).
Limitations	Taiwanese study – may not be applicable to the UK population. Other care needs not represented in the questionnaire may have been required by patients.

1

Reference	Chen, SC et al. Supportive care needs in newly diagnosed oral cavity cancer patients receiving radiation therapy. Psycho-Oncology 2013; 22(6): 1220-1228.
Study type	Prospective longitudinal questionnaire study
Country	Taiwan
Research question(s)	Aim: to examine changes in physical symptom severity and supportive care needs in newly diagnosed oral cavity cancer patients during 6 months after first receiving radiotherapy (RT) or concurrent chemoradiotherapy (CRT)
Theoretical approach	n/a
Data collection	Patients interviewed using structured questionnaires by a trained research assistant. Interviews lasted approximately 15mins. Patients interviewed before beginning RT (T0) and then at 1, 2, 3, and 6 months after beginning RT (T1, T2, T3, T4). Disease and treatment related factors were collected through chart review at T0. Participants were provided with incentives for participation. The following measures were completed at 5 time points: Cancer Needs Questionnaire Short Form, head and neck (CNQ-SF-hn) – scores range from 0-100, higher score indicate greater supportive care needs in six domains; Symptom Severity Scale (SSS); Hospital Anxiety and Depression Scale (HADS), Demographic and disease information.
Method and process of analysis	Descriptive statistics used to analyse frequency and mean scores. Repeated measures ANOVA used to determine differences in supportive care needs over time.
Population and sample collection	Consecutive sampling from the RT outpatient department in a medical centre in Taiwan. Inclusion criteria: 1) over 18 years old, 2) newly diagnosed oral cavity cancer, 3) received tumour dissection surgery before RT or CRT, 4) able to communicate orally or in writing, 5) agreed to participate. Exclusion: 1) patients with advanced stage, distant metastases and/or second primary cancers and received only palliative RT or CRT and 2) patients in recurrent condition. RT or CRT schedules 6-8 weeks after surgical resection. Radiation doses were 1.8 to 2 Gy daily, 5 days per week, total dose of 60 to 80Gy over 6-8 weeks by 3D conformal radiation technique. Cisplatin chemotherapy given to CRT patients. 82 patients (89% response rate) completed all 5 assessments. 80 male, 2 female. Mean (SD) age was 50.1 (10.8) years. 93% were married, 65% employed. Most patients cancer stage III (28%) or IV (68%). Cancer sites: buccal mucosa (29%), tongue (41%). 65% received radical excision with reconstruction combined with CRT. Mean radiation dose 6254cGy.
Findings	**Changes in physical symptom severity, functional level, and supportive care needs** Highest level of supportive care needs at T2 and lowest at T4. Patients reported having acceptable functional status, with lowest level reported at T2. Highest interpersonal communication and health system/information needs before RT/CRT. In general patients had the lowest overall supportive care needs and needs in most individual domains at T3 and T4. Head and neck cancer specific needs remained at moderate levels even at T4.

	T0	**T1**	**T2**	**T3**	**T4**	
Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Effect**
Overall physical symptom severity scale (SSS)	3.2 (1.3)	5 (2)	6.1 (1.8)	3 (1.1)	1.8 (0.6)	T2>T1>T0>T3>T4
Functional status (KPS)	89.4 (3.3)	88.3 (4.4)	87.8 (4.7)	89.5 (2.7)	89.8 (2.2)	T4,T3,T0>T1,T2
Supportive care needs (CNQ-SF-hn)	40.9 (12.4)	39.7 (13.3)	42.4 (12.9)	31.5 (11)	30.2 (9.5)	T2,T0,T1>T3>T4
Physical/daily living need	30.2 (11)	34.9 (13.6)	37.4 (13.4)	28.1 (9.1)	26.7 (8.3)	T2,T1>T0,T3>T4
Psychological need	43.2 (15.1)	43 (15.8)	43.9 (15.8)	32.4 (16.7)	33.7 (15.4)	T2,T0,T1>T4,T3
Interpersonal communication need	35.8 (18.7)	33.2 (16.9)	31.9 (17.7)	28.2 (14.9)	31.3 (13.9)	T0>T1,T2,T4>T3
Patient/carer support need	34.8 (18.4)	37.2 (18.8)	46.2 (23)	29.4 (14.2)	25.7 (14.2)	T2>T1,T0>T3>T4
Health system/information need	48.9 (21)	38.5 (21.6)	40 (15.8)	32.4 (14)	31.3 (14)	T0>T2,T1>T3,T4
HNC specific need	48.8 (19.5)	46.3 (19.4)	49.5 (20.6)	37.6 (13.6)	38.7 (13.4)	T2,T0,T1>T4,T3

Limitations	Small sample size (n=82). Taiwanese study – may be of limited applicability to UK population. CNQ-SF developed by authors and only tested in Taiwanese population.

2

<table>
<tr><td>Reference</td><td>Llewellyn, CD. Striking the right balance: A qualitative pilot study examining the role of information on the development of expectations in patients treated for head and neck cancer. Psychology, Health & Medicine 2005; Vol.10(2): 180-193.</td></tr>
<tr><td>Study type</td><td>Qualitative interview study</td></tr>
<tr><td>Country</td><td>UK</td></tr>
<tr><td>Research question(s)</td><td>Aims: (1) The types of expectations patients had prior to treatment and the extent to which patients considered that these expectations had been met post treatment.
(2) The role of information on the development of expectations.</td></tr>
<tr><td>Theoretical approach</td><td>Framework Analysis Approach</td></tr>
<tr><td>Data collection</td><td>Semi-structured interviews were conducted in quiet rooms in the clinics. The interviews were iterative from the beginning, meaning that the first interview schedule was transformed over the first few interviews according to the usefulness and responsiveness to certain questions. A broad opening question such as; ‘could you describe for me some of the experiences you have gone through since your diagnosis?’ was used and participants were prompted to think back over their experiences and expectations if required. Questions were presented in as neutral a way as possible to minimize potential bias. The interviewer encouraged the participant to elaborate on stories and situations to illustrate important points. All interviews were tape-recorded and lasted between approximately 15 to 55 minutes, the average being about thirty minutes in duration. Transcripts were produced shortly after each interview. Demographic and medical data were collected from hospital medical records.</td></tr>
<tr><td>Method and process of analysis</td><td>Data were analysed using a Framework Analysis Approach (Ritchie & Spencer, 1994). This is a matrix-based approach to qualitative data analysis, which, is based on transcripts produced verbatim from the taped interviews. This technique involves identifying recurring and important themes based on a combination of a priori issues, emergent themes and recurring attitudes or experiences. Major themes in the data arising in these transcripts (determined by an initial read through of all the transcripts and then in-depth analyses of the first seven transcripts) were then used as headings/themes under which the systematic charting of the content of all the transcripts was carried out. This ensured that the themes could be refined. Any new themes that subsequently arose were added to the framework.</td></tr>
<tr><td>Population and sample collection</td><td>15 patients were recruited from head and neck cancer clinics run at two London Hospital NHS Trusts and were based on a convenience sample. Recruitment criteria were any post-treatment patient up to 18 months post-diagnosis and free of disease. One male patient refused to take part and one taped interview (also a male patient) had to be discarded due to extraneous background noise (response rate of 88%).
Ten participants (67%) were female. Ages ranged from 38 to 75 (mean = 54; median = 51; SD= 10.5). All patients except 2 classified themselves as white UK ethnic origin, one patient was Asian and one patient was Iranian. The time since diagnosis ranged from 1.5 to 18 months (median =9; mean = 9.7; SD= 4.8). All tumours except one (adenocarcinoma) were squamous cell carcinomas (SCC). Three patients had carcinoma of the tongue, three of the mandible, four of the maxillary region, three floor of mouth and one each of the tonsil and palate. All patients except one had surgical treatment and the majority also had radiation therapy. All patients were free of disease at the time of interview.</td></tr>
<tr><td>Key themes</td><td>
<table>
<tr><th>Main theme</th><th>Sub-theme</th><th>Example of issues to emerge</th></tr>
<tr><td rowspan="5">1. Patient expectations:</td><td rowspan="2">Global</td><td>Unexpected enormity of treatment / recovery</td></tr>
<tr><td>Expectations being surpassed by reality</td></tr>
<tr><td rowspan="3">Specific</td><td>Side-effects of treatment</td></tr>
<tr><td>Aesthetical outcome</td></tr>
<tr><td>Recovery as a process</td></tr>
<tr><td rowspan="5">2. Information influencing expectations through:</td><td rowspan="2">Too much information</td><td>Limits to how much info can be ‘taken in’</td></tr>
<tr><td>Repercussions on ability to cope</td></tr>
<tr><td rowspan="2">Too little information</td><td>‘Missing’ information</td></tr>
<tr><td>Lack of clarity</td></tr>
<tr><td rowspan="2">Timing of information</td><td>Knowledge gap</td></tr>
<tr><td>Uncertainty</td></tr>
</table>
1. Patient expectations
Global expectations
A large proportion of respondents described the whole experience as being worse than they had imagined. A few patients expressed a sense of unexpected ‘enormity’ about the surgical treatment and the subsequent physical recovery process, particularly those who had also received radiotherapy, as emphasized by:
‘I didn’t realize how big it was all going to be . . . Even had I been told, I don’t think I would have expected what happened’. [F,42]
‘I’ll be quite honest, I didn’t realize the operation at the time would pull me down as regards health so much. I think because I lost so much weight, I felt so weak. It affected me more than I thought it was going to at the time.’ [F,70]
Similarly, patients reported feeling surprise (post-treatment) at the extent of the operation due to the relatively small part of the lesion visible to the patient. The fact the tumour was extensive but not visible had obviously not been explained to the patient.
A few respondents reported that the whole cancer experience had been better than they had been expecting. One woman described how she felt physically better now than she had thought she would:
‘Well, I did think that I may feel worse actually. Everybody says you’ll feel tired and you won’t be able to do this or won’t be able to do that but I’m doing everything so . . . ’ [F,48]

Specific expectations
Side effects. Expectations regarding specific outcomes of treatment and recovery reflected both positive and negative aspects. Respondents were able to describe their experiences of specific side effects that had exceeded their expectations, for example, ‘There was a lot less pain than I expected. I was able to eat quite quickly and I was able to talk better than I thought I would’. [F,59] Conversely, a few respondents recalled their surprise at experiencing arm and shoulder mobility problems (due to the neck dissection).

Aesthetics. Aside from functional aspects, disfigurement immediately after the operation was a particularly emotive issue due to</td></tr>
</table>

the uncertainty surrounding the extent of surgery. Many respondents chose not to look at themselves immediately afterwards due to the large amount of swelling, however, one woman's expectations were surpassed when she finally looked at herself a week later:
'I actually looked a hell of a lot better than I thought I would . . . 'cos I thought I might lose a cheek or outer skin whereas all mine is internal'. [F,47]
Respondents tentatively expressed expectations and hopes regarding future aesthetic improvement, either for further cosmetic procedures or healing with time.

The recovery process. Expectations regarding the recovery process seemed realistic in some people who recognized that recovery would take place over an extended period of time and would be challenging. For some people, pre-treatment expectations had been less realistic in hindsight, with expectations that after a couple of months they would be feeling the same or better than they had at diagnosis. For example, expectations regarding current health status, were mentioned by a couple of respondents. One woman struggled to conceal her disappointment at not recovering as quickly as she was expecting and attempted to put it in perspective by suggesting her expectations may have been unrealistically optimistic:
'I had expected it to be a little better. Maybe I was just being overly optimistic, you know (pause) but I don't expect (pause) I mean, the important thing is that the cancer is gone but I had some major setbacks on the ward'. [F,43]
Expectations regarding recovery were also revealed through expectations of returning to work. Expectations appeared to be related to prior advice from the consultant and comparison with other patients who had undergone similar procedures. These proved to be exceeded in some. For example:
'Mr X said it would be minimum 6 – 7 months up to a year, 2 years depending on individuals. I was actually back at work in November, the November after the April (7 months)'. [F,47]
Prior expectations had not been met in others:
'It had been my expectation to go back to work at the end of this month, having finished the radiotherapy at the end of October. I thought 4 – 5 weeks recovery, back to work. But no'. [M,49]
Patients' expectations were reported to change over time. Many post-treatment patients confided how shocked they were at the extent to which life in general had actually changed afterwards, despite expecting some alteration. A few respondents mentioned that their expectations changed throughout the recovery and the post-treatment period, lowering with experience of complications or problems.

2. The role of information on the development of expectations
Many respondents presented a conflicting picture of needs and requirements, between not wanting too much information on the possible complications and side effects associated with treatment but feeling in hindsight that they were 'missing' information regarding specific events. Explanations for this variation were forwarded by respondents, mainly relating to pre- treatment fear and perceived ability to cope with too much knowledge.
Too much information
Many respondents reflected that they hadn't wanted 'too much' information pre-operatively. This appeared to be related to fear and a perceived lack of ability to cope:
'I only needed to know what was needed to be known. Because if I'd had too much information you would have found me in the corner with a vodka bottle'. [F,47]
Too little information
Although the general level of satisfaction with information was reported to be high, a few respondents reflected that there had been a distinct lack of information on the long-term impact on life and information on financial benefits available. For many respondents who reported 'missing' information pre-treatment, psychological consequences (such as anxiety and depression) were revealed post-treatment. A few respondents reported unexpected long-term side effects which they related to 'missing information'. For example:
'One thing I was very shocked by was that I couldn't speak after the operation . . . It took a couple of weeks until I was sure I was going to be able to talk. The other thing I was very numb . . . No, I hadn't known about that. So it was quite missing information. I was quite shocked by that because I really had been expecting that the numbness would be temporary'. [F,47]
Expectations were clearly related to the information given by the treating staff and the risks associated with the particular treatment recommended. Many respondents reported some aspect of treatment or recovery that they were not told of (or couldn't recall being told). There was a common lack of clarity regarding the effects of radiotherapy, from hardening of the scar tissue from surgery or developing bald patches on the head, to major complications of failure of facial skin grafts. Many respondents reported a lack of understanding regarding how the effects of radiotherapy would make them feel 'setback' after recovery from surgery.
Timing of information
The lack of specific information or 'missing' information appeared to be related to the timing of information. Previous quotes have demonstrated that not all patients wanted detailed information at all stages of the illness, however, one respondent suggested that patients should have full knowledge of all possible side effects and outcomes of treatment, prior to treatment, regardless of the anxiety this may provoke. The same respondent later mentioned that not knowing the full facts when complications arose was a major source of anxiety for him:
' . . . the times when things were going wrong and nobody was telling me were the times that I became anxious, agitated and concerned . . . ' [M,49]
This was further emphasized by a couple of respondents who considered that the lack of information or clarity stemmed from a *'knowledge gap' 'between a full understanding of what's going to happen to you and what information can convey'*. [F,59] . This was perceived to be caused by two factors, namely, the lack of time between diagnosis and treatment and the fact that traumatic experiences are indescribable until they've been experienced (likened to childbirth by a couple of women). The shock of diagnosis and the lack of time to assimilate the information were highlighted thus;
'At that time, when they've just told you, you have cancer and you're just about to have major surgery, you're not really listening . . . your mind's not on it'. [M,56]
and;
'It was all carefully explained but it doesn't really register in the short time you have to think about it. You're trying to cope with a

	lot of information and you're not feeling very well'. [F,59]
Additional comments/ Limitations	Methods of data collection and analysis well described. Reliability of data analysis checked by a second reviewer. Article also included in review by systematic review by Lang (2013)

1

Reference	Glavassevich, M, McKibbon, A, and Thomas, S. Information needs of patients who undergo surgery for head and neck cancer. Canadian Oncology Nursing Journal 1995; 5(1): 9-11.
Study type	Cross-sectional questionnaire study
Country	Canada
Research question(s)	To explore the informational needs of people who undergo surgery for head and neck cancer
Theoretical approach	n/a
Data collection	A questionnaire (11 questions) was developed to collect demographic and informational needs of patients during hospitalisation and after discharge. Patients were asked to identify the information that was most and least helpful. Patients indicated which symptoms they had experienced before and after surgery. Patients were also asked if they had been informed of these symptoms prior to surgery.
Method and process of analysis	The responses to the questions were itemised by each of the investigators and categorised into predominant themes.
Population and sample collection	32 (out of 45 sent) questionnaires were completed and returned by patients who had surgery for HNC from July 1990 to February 1991. Responses were received from 21 men, 11 women. Mean age of 59.5 years. Most respondents had either neck dissection combined with oral mandibular reconstruction or laryngectomy.
Key themes	**Need for information** The reason for surgery and the nature and extent of the surgery were explained to all 32 respondents. All respondents indicated that more information was needed before surgery regarding the course of their illness and events that would occur. Complications from and reasons for the extent of surgery were also a concern. Respondents identified what to expect after surgery and the long-term prognosis as information that is most helpful and necessary to know. Prior to surgery the possibility of additional radiotherapy should be discussed. Most respondents were not prepared for some outcomes experienced following surgery such as neck stiffness, loss of sensation in the neck area, scarring and fistulas. **Source of information** All respondents received information from their physician. 10 received information from nursing staff and 1 from the physiotherapist. **Timing and sequence of information** 30 had received information before surgery and 5 had been given information after surgery. 24 had received information concerning expected post-operative course. 27 were told how they would be cared for following their surgery, which they felt prepared them for the surgical experience. The long-term effects of surgery were described to 23 respondents. 28 were told of possible complications. **Presentation of information** No content was identified as least helpful. 3 responded that the information was too simple and 5 that the information was too technical. 5 indicated that it was given too quickly and 5 that it was given too slowly. 30 respondents stated that they were given enough time to ask questions. 29 reported that they were comfortable asking questions. Written questions had been prepared for their physicians by 12 respondents. **Symptoms experienced**

	Before surgery	After surgery	Informed of symptoms before surgery
Fear	15	5	4
Anxiety	16	9	7
Pain	6	15	8
Difficulty breathing	3	7	3
Difficulty swallowing	5	15	8
Difficulty speaking	4	17	11
Change in appearance	4	18	13

In many cases, feelings of anxiety and fear were not addressed prior to surgery. Although some patients expected pain, they indicated that they experienced more discomfort than pain and less than anticipated.

Attitude towards surgery
19 responded positively towards having the surgery, viewing it as the only option. They expressed confidence in the doctors, nursing team, and satisfaction with the overall success of the surgery.

Limitations	Small sample size – respondents may not be representative of wider HNC population. No details provided about the respondents current health state or outcome of surgery. Retrospective study – recall bias.

2

Reference	Ma, JLC. Desired and perceived social support from family, friends, and health professionals: a panel study in Hong Kong of patients with nasopharyngeal carcinoma. Journal of Psychosocial Oncology 1996; 14(3): 47-68.
Study type	Longitudinal questionnaire study
Country	Hong Kong
Research question(s)	To explore social support needs and satisfaction with social support in patients with nasopharyngeal cancer
Theoretical approach	n/a
Data collection	Newly diagnosed patients were interviewed after consenting to participate in the study. Data were collected by use of a structured questionnaire. They were interviewed a second time when they returned to clinic 3-4 weeks after therapy was initiated and finally three months after therapy was terminated. A measure of social support was designed specifically for the study: measured desired social support (what three types of social support they prefer most from family, friends and health professionals on a 4-point Likert scale; perceived social support (satisfaction with support received from family, friends and health professionals);
Method and process of analysis	Scores summarised using means and frequencies, then analysed by a repeated measures ANOVA.
Population and sample collection	111 patients who completed three phases of data collection (180 started the study). Time sampling was used to include all new patients receiving acute treatment for nasopharyngeal cancer in the outpatient department of the Institute of radiology and oncology between September 1992 and January 1994. 83% (n=104) male, 17% (n=21) female. Mean age 48 years. 10% were high school graduate or above. 17% were illiterate. Median monthly income was $833.
Key themes	**Desired social support** Scores on desired social support increased between the diagnostic phase and the treatment phase and remained stable from treatment to post-treatment phase. Patients consistently chose health professionals as the first source of overall support, followed by family and friends. Desired informational support was highest in the treatment phase, followed by the post-treatment phase. Similar results were reported for emotional support and desired instrumental support. Across the 3 time points, health professionals were the first choice for desired informational, emotional and instrumental support, followed by family, the friends. Family was the patient's first choice for affiliational support. The desire for the four types of support from health professionals was strongest in the diagnostic phase and declined over time. **Perceived social support** Mean scores indicated that patients were satisfied with the support received from the 3 main sources over the course of the study.
Limitations	Sample may not be generalisable to UK population. Measure of social support was designed for the study – tested for internal reliability but not tested for validity in other samples.

1

Reference	Brockbank, S., Miller, N., Owen, S., and Patterson, J. M. Pretreatment Information on Dysphagia: Exploring the Views of Head and Neck Cancer Patients. Journal of Pain and Symptom Management 2015. 49(1): 90-98
Study type	Qualitative focus group/interview study.
Country	UK
Research question(s)	Stated aim: address the issue of how best to prepare head and neck cancer patients for chronic treatment side effects, by exploring their views on pretreatment information regarding changes to eating, drinking and swallowing after chemoradiotherapy.
Theoretical approach	Thematic analysis.
Data collection	Two initial focus groups were conducted to explore broad issues. Findings informed the development of a more focussed semistructured schedule, used for individual patient interviews.
Method and process of analysis	Field notes from observations, focus groups and interview transcripts were read in detail. One author identified sections of the data where there was similarity in meaning, and these were given preliminary codes. Where commonalities were identified, codes were organised into broader themes. The process was iterative; themes that had been developed were applied to news sections of the text if possible. Otherwise, new coded and themes were created. A subset of transcripts was reviewed by another researcher to further validate findings.
Population and sample collection	Patients (n = 24) with head and neck cancer treated with primary chemoradiotherapy within the previous two years were eligible. Participants were sampled from a range of time points after treatment. Dysphagia severity was assessed by specialist Speech and Language Therapists based on patient notes.
Key themes	**Expectations** There were different levels of expectation about treatment effects. Some patients felt well-prepared, with information given corresponding accurately to their experiences. However, some participants reported surprises centred around the severity and longevity of dysphagic symptoms. The nature and time of symptom onset was also unexpected for some patients. Frequently, participants reported that it is impossible to understand how something will feel and its effects on emotional functioning until it has been experienced. **Presentation of information** *Format*: Most patients reported that had received both verbal and written information. All agreed that verbal information should be delivered by someone with expertise in swallowing difficulties. Booklets were considered comprehensive, well-presented and easy to understand. One disadvantage of booklets was that they were perceived as too general and not individualised to each patient. *Delivery (amount, timing and detail of information)*: Participants reported that there was too much information to take in at times; some found this overwhelming and this affected their motivation to access further information. Too much pretreatment information was a common concern; conversely, a similar number of participants reported receiving too

	little information and would have preferred more. Some found being given the full range of potential outcomes desirable, to help them prepare, including for worst-case scenarios. However, one participant found receiving worst-case scenario information distressing. *Timing*: Some patients found it necessary to have all information at the outset, including that on the long-term effects of their treatment. Three participants reported that they would rather have been given information incrementally, throughout the course of treatment. Some expressed difficulty in taking in practical information after an upsetting diagnosis. **Absorption of information** Participants widely reported that they did not always take in the information presented to them, predominantly due to the shock surrounding diagnosis and prognosis. Many had difficulty remembering clinicians, sessions and information given before treatment. Other stated categorically that they had not been given verbal pretreatment information or assessment, despite a record of this in their medical notes.
Limitations	Small sample size.

1

Reference	Nund, R. L., Ward, E. C., Scarinci, N. A., Cartmill, B., Kuipers, P., and Porceddu, S. V. Survivors' experiences of dysphagia-related services following head and neck cancer: Implications for clinical practice. International Journal of Language & Communication Disorders 2014. 49(3): 354-363
Study type	Qualitative descriptive methodology with phenomenological aspects.
Country	Australia
Research question(s)	Stated aim: to explore the lived experience of adjusting to dysphagia and dysphagia-related services in the post-treatment survivorship period of head and neck cancer.
Theoretical approach	Thematic analysis using an inductive approach.
Data collection	Each participant took part in an individual, semi-structured, in-depth interview with the same investigator. Interviews consisted primarily of open-ended conversational questions adapted to each individual.
Method and process of analysis	Meanings and patterns were identified by reading interview transcripts. Open coding was used to identify statements relating to participants' expectations of eating difficulties and experiences of support services. The number of participants who commented on each category and the number of times each category was referred to was recorded. Themes were developed by considering the potential relationships between categories and how they may form an overarching message regarding the experiences of living with dysphagia. All participants were sent a written summary of the main findings from the analysis and asked to confirm the investigators' interpretations.
Population and sample collection	Participants were recruited using purposive selection and maximum variation sampling, used to select information-rich cases to capture and describe consistent themes across a broad range of participant demographics. Patients (n = 24) who had received radiotherapy (with or without systemic therapy) for a primary head and neck cancer between April 2007 and April 2012 were selected. All had self-reported swallowing difficulties during and/or following their treatment.
Key themes	**Life after treatment** Participants stated that they had not anticipated the severity and duration of the side effects after treatment on eating and swallowing. Some participants believed that the end of radiotherapy would signal the end of their struggles with dysphagia and that life would quickly then return to normal. Many participants reflected on the importance of/need for adequate education from health professionals regarding the potential side effects of dysphagia. Participants expressed feelings of doubt as to whether life, and ability to eat, would ever return to normal. Half of them stated that they were unaware of and unprepared for the amount of time needed for swallowing function to improve. **Making practical adjustments** There was extensive discussion regarding learning about food preparation and ways to assist with the passage of solid food boluses. Many patients reported using trial and error methods to select suitable foods, and would consistently eat the same food if they had success. **Making emotional adjustments** Participants reported that quite often, foods that were previously enjoyed were now problematic. Ultimately, most of the participants reached a point in their recovery where they had accepted changes to their swallowing ability. Other emotion-related strategies highlighted included remaining hopeful that their eating abilities would return to normal. **Accessing support outside hospital services** Family members were identified as a significant source of support for people with dysphagia, particularly with regard to meal preparation and encouragement to keep eating. Just under half of the participants spoke about the benefits of having the opporutiny to talk with someone else who had been through a similar course of treatment. **Perceptions of dysphagia-related services** For many, the differences between the role of speech and language therapists and dieticians in dysphagia management was unclear. Whilst some participants found the services helpful for swallowing difficulties, several were unaware of the scope of the speech and language therapist's role in its management. Some felt that information and advice was too general, and not personalized or practical to their situation. Others, however, reported that they had benefited from the service.
Limitations	Small sample size.

1

Reference	Rogers, S. N., Hazeldine, P., O'Brien, K., Lowe, D., and Roe, B. How often do head and neck cancer patients raise concerns related to intimacy and sexuality in routine follow-up clinics? European Archives of Oto-Rhino-Laryngology 2015. 272(1): 207-217
Study type	Questionnaire-based quantitative study.
Country	United Kingdom
Research question(s)	Aim: to identify how often problems with intimacy were raised by head and neck cancer patients, and what possible actions took place as a consequence of raising these concerns.
Theoretical approach	n/a
Data collection	Prospective data were collected between October 2008 and January 2011 using the Patient Concerns Inventory (PCI) and UW-QOL v.4 questionnaires.
Method and process of analysis	The UW-QOL results were analysed in terms of two subscale composite scores: physical function and social-emotional function. The intimacy single question offered a hierarchy of response options on a Likert scale: (100) 'I have no problems with intimacy as a result of my cancer', (70) 'I have problems with intimacy but it does not bother me very much', (30) 'I have problems with intimacy and this causes me some concern', and (0) 'I have major problems with intimacy and this causes me considerable concern'. Results were analysed mainly within patient subgroups defined by reference to the intimacy score (0–100) and by reference to patients wanting, through the PCI, to discuss intimacy and/or sexuality issues.
Population and sample collection	Head and neck cancer patients attending routine follow-up clinics between October 2008 and January 2011 were eligible. Data were available for 369 clinic attendances from 177 patients; 63% of patients attended more than once in the study. The majority (126, 71%) had oral tumours; 41 (23%) had pharyngeal tumours and 10 (6%) has other tumours. 103 (58%) had surgery alone as their primary treatment; 56 (32%) had surgery with adjuvant radiotherapy; and 18 (10%) had radiotherapy/chemotherapy without surgery.
Key results	On the UW-QOL-based intimacy scale 31% (55/177) of patients reported problems, with 5% having major problems causing considerable concern, 8% having problems causing some concern, and 18% having problems that did not bother them much. 'Intimacy' was selected as a concern on the PCI by 9/177 (5%) and 'sexuality' by 4/177 (2%), with two patients selecting both. Almost all patients who wanted to discuss intimacy/sexuality issues had self-reported problems, but many patients with problems did not want to discuss them in a clinical setting. Intimacy problems were more common in men, patients under 65 years, patients further on from diagnosis, and patients with more advanced primary tumours.
Limitations	Results are reported on a per-patient basis, but the majority (63%) of patients completing the questionnaires on more than one occasion. It is not clear how any discrepancies between outcome reported by the same patient at different clinic visits were accounted for in the analysis.

2

1 Evidence search details and references

2 ***Review question in PICO format***

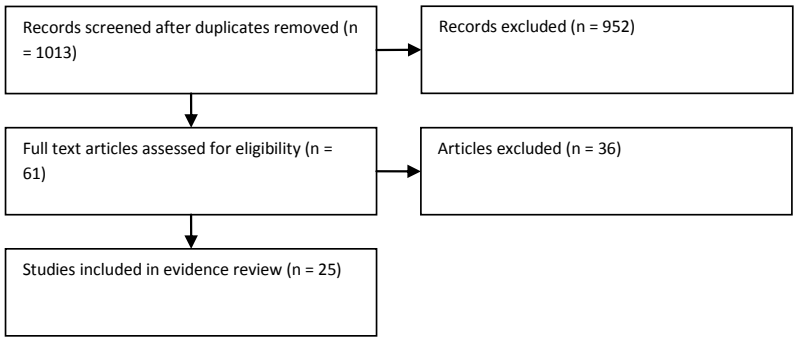
Population	Themes
Adults with cancer of the upper aerodigestive tract & their carers: • At diagnosis • Pre-treatment • During treatment • End of treatment/discharge/follow up • During end of life • During palliative care	Information, communication and support needs associated with upper aerodigestive tract cancer diagnosis and treatment e.g. psychological difficulties; disfigurement; pain; nutrition/tube feeding; treatment complications and toxicity; rehabilitation; work and social impact; speech and swallowing problems; therapeutic decision making. The role of individuals, such as volunteers, in supporting people with upper aerodigestive tract cancers.

3

4 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Qualitative (any relevant quantitative data will also be included).
Language	English only
Study design	Any relevant qualitative or quantitative (or mixed methods) study.
Status	Published studies only
Other criteria for inclusion / exclusion of studies	None specified
Search strategies	None specified
Review strategies	We will extract qualitative and quantitative data (depending on what studies are found from the search) and present the results using the relevant evidence tables (NICE Guidelines Manual appendix J) according to study type. Consideration will be given to the timing, delivery (by who), and format of the information. The quality checklist for qualitative data (NICE guidelines manual appendix H) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Data will be presented according to the stage of disease and the management options available to patients, where possible and appropriate.

Figure 1.1. Study flow diagram



Included studies

Baxi, SS et al. Sharing a diagnosis of HPV-related head and neck cancer: the emotions, the confusion, and what patients want to know. Head & Neck 2013; 35(11): 1534-1541.

Brockbank S, Miller N, Owen S, Patterson JM. Pretreatment Information on Dysphagia: Exploring the Views of Head and Neck Cancer Patients. Journal of Pain and Symptom Management 2015; 49(1):90-98.

Chen, SC et al. Prevalence and correlates of supportive care needs in oral cancer patients with and without anxiety during the diagnostic period. Cancer Nursing 2010; 33(4): 280-289.

Chen, SC et al. Supportive care needs in newly diagnosed oral cavity cancer patients receiving radiation therapy. Psycho-Oncology 2013; 22(6): 1220-1228.

Chen, SC et al. Unmet information needs and preferences in newly diagnosed and surgically treated oral cavity cancer patients. Oral Oncology 2009; 45(11): 946-952.

Edwards, D. Head and neck cancer services: views of patients, their families and professionals. British Journal of Oral & Maxillofacial Surgery 1998; 36(2): 99-102.

Egestad, H. The significance of fellow patients for head and neck cancer patients in the radiation treatment period. European Journal of Oncology Nursing 2013; 17(5): 618-624.

Fang, CY. Informational needs of head and neck cancer patients. Health and Technology 2012; 2(1): 57-62.

Furness, PJ. Exploring supportive care needs and experiences of facial surgery patients. British Journal of Nursing 2005; 14(12): 641-645.

Glavassevich, M, McKibbon, A, and Thomas, S. Information needs of patients who undergo surgery for head and neck cancer. Canadian Oncology Nursing Journal 1995; 5(1): 9-11.

Kanatas, A et al. Issues patients would like to discuss at their review consultation: variation by early and late stage oral, oropharyngeal and laryngeal subsites. European Archives of Oto-Rhino-Laryngology 2013; 270(3): 1067-1074.

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Reason for exclusion: narrative review

Smoking cessation

Clinical question: Does smoking cessation affect outcomes for people with (undergoing treatment or post treatment) cancer of the upper aerodigestive tract?

Background

The benefits of smoking cessation are both short and long term. Smokers are at a higher risk of surgical complications which may delay post-operative rehabilitation and the commencement of adjuvant treatments such as radiotherapy. Smoking may increase the toxicity of radiotherapy and reduce its efficacy. Long term benefits of smoking cessation include a reduction in the risk of secondary cancers leading to increased survival rates.

The optimal timing of smoking cessation interventions may be difficult to judge in view of the distress and anxiety caused by a new diagnosis of CUADT and associated treatment discussions.

Evidence statements

Survival

Very low quality evidence from a systematic review (van Imhoff 2015) of observational studies (three trials, 1110 patients) suggests that stopping smoking after diagnosis improves overall survival in smokers with cancer of the larynx, pharynx, or oral cavity. The absolute risk difference for overall survival was 21% to 35% greater in patients who stopped smoking ('former smokers') compared to those who continued to smoke after treatment or diagnosis ('active smokers'). Two further observational studies (very low quality evidence) not included in the systematic review were also identified: one study (Moore 1973, 203 patients) also reported improved overall survival in patients who stopped smoking; the second study (Sandoval 2009, 85 patients) found no significant difference in overall survival between former and active smokers.

Two further observational studies (very low quality evidence) measured overall mortality, but measured smoking status differently. One study (Chen 2011, 202 patients) suggests that in people with cancer of the upper aerodigestive tract (CUADT), overall mortality is reduced in ex smokers who quit either before or at the time of diagnosis compared with people who smoke during their cancer treatment (RR 0.62, 95% CI 0.49, 0.78). A second study (Browman 2002, 148 patients) suggests uncertainty regarding the relative overall mortality of people with CUADT who are light (≤1 cigarette per day) or heavy (>1 cigarette per day) smokers during their radiotherapy treatment (RR 0.81, 95% CI 0.53, 1.24).

Second primary tumours

Very low quality evidence from five observational studies (Castigliano 1968, Gorsky 1994, Moore 1971, Silverman 1972, Silverman 1983) suggests that in people with CUADT, the incidence of second primary tumours (follow up range 1–18 years) is reduced in former smokers compared with active smokers (RR 0.37, 95% CI 0.25, 0.53).

Two further observational studies (very low quality evidence) also measured incidence of second primary tumours; both included smokers who quit either several years before or after their cancer diagnosis. Because of these differences in the time of quitting relative to cancer diagnosis, the results could not be pooled with those above. One study (Chen 2011, 202 patients) suggests

uncertainty over the incidence of second primary tumours in continued smokers with CUADT compared with ex smokers who quit at any time before diagnosis (RR 0.88, 95% CI 0.45, 1.70). A second study (Garces 2007, 94 patients) suggests uncertainty over the incidence of second primary tumours in continued smokers with CUADT compared with ex smokers who quit at any time up to five years after their cancer diagnosis (RR 0.21, 95% CI 0.01, 3.26).

Tumour recurrence

Very low quality evidence from a systematic review (van Imhoff 2015) of observational studies (five trials, 1440 patients) suggests that stopping smoking after diagnosis reduces the rate of tumour recurrence in smokers with cancer of the larynx, pharynx, or oral cavity. In three of the studies, the absolute risk difference for tumour recurrence was significantly lower (by 23% to 30%) in former smokers compared to active smokers; two studies did not find a significant difference between former smokers and active smokers. One further observational study (Sandoval 2009, 85 patients, very low quality evidence) not included in the systematic review was also identified, and did not report a significant difference in tumour recurrence between former and active smokers.

Treatment-related morbidities

Four observational studies provided very low quality evidence on the incidence of treatment-related morbidities in smokers with CUADT who quit smoking or continue to smoke during treatment. All the studies included patients who received radiotherapy as their primary treatment. The results could not be combined due to the differences in the outcomes measured by each study, but individual study results in general suggest uncertainty over the incidence of treatment-related morbidities in smokers with CUADT who quit smoking or continue to smoke during treatment. For most outcomes, people who stopped smoking during radiotherapy experienced less treatment-related morbidities, with shorter duration, but the differences between groups were not statistically significant.

Quality of life

No evidence was identified on whether smoking cessation affects quality of life in people with CUADT who are smokers at the time of their diagnosis.

Study characteristics and quality

One systematic review (including six trials) and a further twelve individual studies met the inclusion criteria for the review. Study characteristics are summarised in table 1; for detailed information on design and results, refer to section 4.

All studies were non-randomised trials; this is to be expected as a study design that randomised people to either stop or continue smoking would not be possible. Patients therefore ‘self-allocated’ to smoking cessation or continued smoking. For all but one study (Chen 2011), it is not clear whether former and active smokers were comparable at study baseline for factors which may have affected outcomes independently of smoking status, such as disease severity, pre-existing comorbidities, alcohol use/abuse and quality of life.

In most studies, the majority or all patients were smokers at baseline and outcomes were measured according to whether patients chose to stop smoking after diagnosis (‘former smokers’) or continue smoking (‘active smokers’). The time of smoking cessation varied from study to study as detailed in

table 1. Some studies categorised smokers differently (as light or heavy smokers during treatment) or included smokers who had stopped smoking several years before or after their cancer diagnosis.

Table 1.2. Characteristics of included studies

STUDY	CANCER SITE(S)	TREATMENT RECEIVED	SMOKING MEASUREMENTS	OUTCOMES	LENGTH OF FOLLOW UP
Van Imhoff 2015 (systematic review)	Oral, pharyngeal or laryngeal	RT (four studies); surgery with/without RT (one study); surgery with/without RT, or chemo alone (one study)	Smoking cessation after diagnosis/treatment vs. continued smoking	Overall survival Tumour recurrence	4.4 to 5 years for overall survival 3 to 5 years for tumour recurrence
Browman 2002	Oral cavity; hypopharynx; oropharynx; larynx	Radical RT	Smoking status during RT: cessation vs. continued smoking or light (≤ 1 cigarette/day) vs. heavy smoking (≥ 1 cigarette/day)	Response to treatment (former vs. active smokers) Overall (2 yr) survival (light vs. heavy smokers)	Minimum of 3 years
Castigliano 1968	Oral cavity; tonsil; larynx; pharynx	Surgery; RT; surgery+RT	Smoking status after appearance of first cancer: cessation vs. continued smoking. Measured retrospectively after ≥ 3 years follow up	Incidence of a second primary cancer in a tobacco critical region	Minimum of 3 years
Chen 2011	Oral; larynx; tonsil; hypopharynx	Primary RT; surgery with postop RT	Smoking status during RT: former smokers (quit either before or at the time of cancer diagnosis) vs. active smokers	Overall mortality Disease recurrence Locoregional recurrence Acute toxicity (grade 3 or above) Late toxicity (grade 3 or above) Incidence of second primary	Median 49 months (range 6-115)
Garces 2007	Oral; oropharynx; hypopharynx; larynx; major salivary glands	Surgery; RT; surgery+RT	Smoking status in head and neck cancer cases after nicotine dependence centre consultation (not concurrent with cancer treatment/diagnosis in all patients): smoking cessation vs. continued smoking 6 months after consultation.	Incidence of tobacco-related second primary tumour	Median 3.7 years

STUDY	CANCER SITE(S)	TREATMENT RECEIVED	SMOKING MEASUREMENTS	OUTCOMES	LENGTH OF FOLLOW UP
Gorsky 1994	Oral; oropharynx; nasopharynx; larynx; lip	Surgery ± chemo or RT	Smoking status after diagnosis (measured at least one year after treatment): former smokers vs. continued smokers	Incidence of second primary oral/oropharyngeal cancer	Median 4 years
Moore 1971	Oral; larynx; pharynx; tonsil	Surgery; X-ray; surgery+X-ray	Smoking status after first cancer: former vs. continued smokers	Incidence of second primary tumour Overall survival (mean 7.3 years follow up) Death from secondary primary tumour Overall survival (up to 5 years)	Mean 7.3 years (range 3-18 years)
Rugg 1990	Head and neck (requiring irradiation of the oral/oropharyngeal mucosa)	RT	Smoking status during and after RT: quit permanently before RT vs. quit temporarily during RT vs. continued smoking	Duration of mucositis following radiotherapy	Not reported
Sandoval 2009	Oral; oropharyngeal	Surgery; RT	Smoking status after cancer diagnosis: former vs. continued smokers	Incidence of recurrence	Minimum 2 years
Silverman 1983	Head and neck (nasopharynx; oropharynx; larynx; oral)	Not reported	Smoking status after first cancer: former vs. continued smokers	Incidence of second primary oral/oropharyngeal cancer	Not reported
Silverman 1972	Oral; oropharyngeal	Surgery; RT; surgery+RT	Smoking status after treatment: former vs. continued smokers	Incidence of second primary oral cancers	Up to one year: 17% of patients One to three years: 37% Over three years: 46%
Van der Voet 1998	Larynx (T1 glottic)	RT	Smoking status during and after RT: quit before RT vs. quit after RT vs. continued smoking	Incidence of larynx complications	Median 89 months
Zevallos 2009	Larynx; pharynx	RT	Smoking status during RT: former vs. active smokers	Incidence of radiotherapy complications	Median 533 days (former smokers); 396 days (continued smokers)

1

GRADE evidence tables and meta-analysis

Table 1.3. GRADE evidence profile: former versus active smokers after cancer diagnosis

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Former smokers	Active smokers	Relative (95% CI)	Absolute	
Overall mortality											
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/251 (33.1%)	96/190 (50.5%)	RR 0.65 (0.51, 0.83)	177 fewer per 1000 (from 86 fewer to 248 fewer)	⊕OOO VERY LOW
Tumour recurrence											
3	observational studies	serious[1,2]	no serious inconsistency	serious[2]	no serious imprecision	none	79/236 (33.5%)	30/80 (37.5%)	RR 0.88 (0.62, 1.25)	45 fewer per 1000 (from 142 fewer to 94 more)	⊕OOO VERY LOW
Incidence of second primary tumour											
5	observational studies	serious[1,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/327 (11.3%)	111/373 (29.8%)	RR 0.37 (0.25, 0.53)	187 fewer per 1000 (from 140 fewer to 223 fewer)	⊕OOO VERY LOW
Incidence of complete tumour response to radiotherapy											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	21/35 (60%)	70/110 (63.6%)	RR 0.94 (0.69, 1.28)	38 fewer per 1000 (from 197 fewer to 178 more)	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Former smokers	Active smokers	Relative (95% CI)	Absolute	
Death from second primary tumour											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/81 (2.5%)	30/122 (24.6%)	RR 0.1 (0.02, 0.41)	221 fewer per 1000 (from 145 fewer to 241 fewer)	⊕OOO VERY LOW
Skin changes (grade 2-4) after RT											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/37 (43.2%)	14/44 (31.8%)	RR 1.36 (0.77, 2.40)	115 more per 1000 (from 73 fewer to 445 more)	⊕OOO VERY LOW
Mucositis (grade 2-4) after RT											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/37 (56.8%)	32/44 (72.7%)	RR 0.78 (0.56, 1.09)	160 fewer per 1000 (from 320 fewer to 65 more)	⊕OOO VERY LOW
Feeding tube required after RT											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/37 (56.8%)	28/44 (63.6%)	RR 0.89 (0.62, 1.28)	70 fewer per 1000 (from 242 fewer to 178 more)	⊕OOO VERY LOW
Feeding tube duration, mean number of days ± SD											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	206.6 ± 138.3	193.3 ± 202.7	-	MD 13.3 higher (61.35 lower to 87.95 higher)	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Former smokers	Active smokers	Relative (95% CI)	Absolute	
Hospitalisation after RT											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/37 (13.5%)	15/44 (34.1%)	RR 0.4 (0.16, 0.99)	205 fewer per 1000 (from 3 fewer to 286 fewer)	⊕OOO VERY LOW
Hospitalisation duration, mean number of days ± SD											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3.8 ± 2.2	8.2 ± 11.8	-	MD 4.4 lower (7.96 to 0.84 lower)	⊕OOO VERY LOW
Pharyngeal stricture requiring dilatation after RT											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/37 (0%)	4/44 (9.1%)	RR 0.13 (0.01, 2.37)	79 fewer per 1000 (from 90 fewer to 125 more)	⊕OOO VERY LOW
Osteoradionecrosis after RT											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/37 (2.7%)	9/44 (20.5%)	RR 0.13 (0.02, 1)	178 fewer per 1000 (from 200 fewer to 0 more)	⊕OOO VERY LOW
Incidence of larynx complications											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/180 (15%)	27/87 (31%)	RR 0.48 (0.30, 0.77)	161 fewer per 1000 (from 71 fewer to 217 fewer)	⊕OOO VERY LOW

[1] Patients 'self-allocated' to stop or continue smoking. Unclear if former and active smokers were comparable at baseline.

[2] For one study (Colasanto 2004), it is unclear when former smokers stopped smoking relative to treatment time.

[3] Unclear if the treatment received by former and active smokers was comparable.
[4] Low (<300) number of events; wide confidence intervals (encompassing no effect, significant benefit and significant harm).

Figure 1.2. Incidence of second primary tumour in former versus active smokers

	Former smokers		Active smokers			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Castigliano 1968	9	51	5	26	6.8%	0.92 [0.34, 2.46]
Gorsky 1994	13	97	23	90	24.4%	0.52 [0.28, 0.97]
Moore 1971	5	81	49	122	39.9%	0.15 [0.06, 0.37]
Silverman 1972	3	45	19	71	15.1%	0.25 [0.08, 0.79]
Silverman 1983	7	53	15	64	13.9%	0.56 [0.25, 1.28]
Total (95% CI)		**327**		**373**	**100.0%**	**0.37 [0.25, 0.53]**
Total events	37		111			

Heterogeneity: Chi² = 9.88, df = 4 (P = 0.04); I² = 60%

Test for overall effect: Z = 5.34 (P < 0.00001)

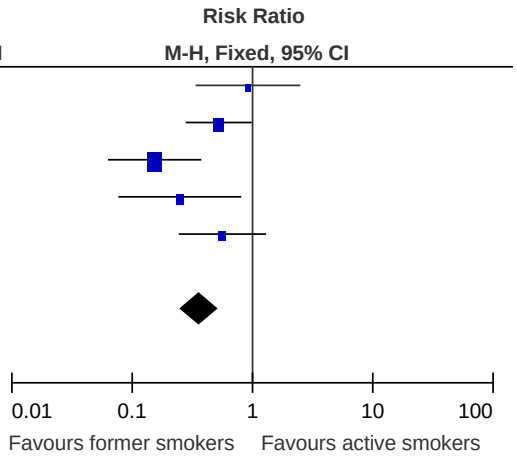


Table 1.4. GRADE evidence profile: smoking cessation before radiotherapy versus smoking cessation after radiotherapy for improving outcomes in smokers with CUADT

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Smoking cessation before RT	Smoking cessation after RT	Relative (95% CI)	Absolute	
Incidence of larynx complications											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/139 (15.8%)	5/41 (12.2%)	RR 1.3 (0.52, 3.21)	37 more per 1000 (from 59 fewer to 270 more)	⊕OOO VERY LOW

[1] Patients 'self-allocated' to stop or continue smoking. Unclear if former and active smokers were comparable at baseline.
[2] Low (<300) number of events; wide confidence intervals (encompassing no effect, significant benefit and significant harm).

Table 1.5. GRADE evidence profile: light smoking (<1 cigarette/day) versus heavier smoking during radiotherapy in smokers with CUADT

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light smoking (<1 cigarette/day)	Heavier smoking during RT	Relative (95% CI)	Absolute	
Overall mortality											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/49 (36.7%)	44/97 (45.4%)	RR 0.81 (0.53, 1.24)	86 fewer per 1000 (from 213 fewer to 109 more)	⊕OOO VERY LOW

[1] Patients 'self-allocated' to stop or continue smoking. Unclear if former and active smokers were comparable at baseline.

Table 1.6. GRADE evidence profile: smoking cessation at or before cancer diagnosis versus continued smoking after cancer diagnosis in people with CUADT

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Smoking cessation at or before cancer diagnosis	Continued smoking after cancer diagnosis	Relative (95% CI)	Absolute	
Overall mortality											
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	48/101 (47.5%)	78/101 (77.2%)	RR 0.62 (0.49, 0.78)	293 fewer per 1000 (from 170 fewer to 394 fewer)	⊕OOO VERY LOW
Tumour recurrence											
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	31/101 (30.7%)	43/101 (42.6%)	RR 0.72 (0.50, 1.04)	119 fewer per 1000 (from 213 fewer to 17 more)	⊕OOO VERY LOW
Incidence of second primary tumour											
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	14/101 (13.9%)	16/101 (15.8%)	RR 0.88 (0.45, 1.70)	19 fewer per 1000 (from 87 fewer to 111 more)	⊕OOO VERY LOW
Acute toxicity (grade 3 or above)											
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	61/101 (60.4%)	56/101 (55.4%)	RR 1.09 (0.86, 1.38)	50 more per 1000 (from 78 fewer to 211 more)	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Smoking cessation at or before cancer diagnosis**	**Continued smoking after cancer diagnosis**	**Relative (95% CI)**	**Absolute**	
Late toxicity (grade 3 or above)											
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	31/101 (30.7%)	49/101 (48.5%)	RR 0.63 (0.44, 0.9)	180 fewer per 1000 (from 49 fewer to 272 fewer)	⊕OOO VERY LOW

[1] In the smoking cessation group, smokers who quit any time prior to beginning cancer treatment were eligible for inclusion. Significant numbers (31%) had quit more than 5 years before presentation; time of quitting was not known for a further 31%.

1 Evidence tables for all included studies

2 *Systematic reviews*

Study

van Imhoff, 2015

Study type, study period

Systematic review of observational or prognostic studies. Searches were conducted on 1 March 2014. No lower date limit was specified.

Search and eligibility criteria

Inclusion criteria: studies reporting original data on the prognostic value of smoking cessation after diagnosis or after treatment on survival and recurrence in patients with oral, pharyngeal or laryngeal squamous cell carcinoma.
Exclusion criteria: studies of other head and neck subsites, such as the nasopharynx; systematic reviews, opinion papers, case reports, and animal studies.

After searching and selection, 12 articles were selected for study quality assessment. Six of these were rated as at high risk of bias (see Study quality assessment) and were excluded. The remaining six were included in the review.

Trial and patient characteristics

Overall survival was reported in three trials (total 1110 patients).
Tumour recurrence was reported in five trials (total 1440 patients).

Study	N	Design	Cancer site and T stage	Cancer therapy	Follow up	Outcomes
Al-Mamgani 2013	744	Retrospective	Larynx (glottis), T1 and T2	Radiotherapy	Up to 10 years	Survival, recurrence
Benninger 1994	63	Retrospective	Larynx (glottis), T1 and T2	Radiotherapy	Median 6.2 years	Recurrence
Colasanto 2004	76	Retrospective	Larynx (all subsites), T1 and T2	Radiotherapy	Median 16.6 years	Recurrence
Kikidis 2012	153	Prospective	Larynx (all subsites), T1 to T4	Surgery (with or without radiotherapy or chemotherapy) or chemotherapy alone	Median 3 years	Survival, recurrence
Mayne 2009	213	Prospective	Oral cavity, pharynx, larynx, CIS, T1 and T2	Surgery, radiotherapy, or both	Median 4.2 years	Survival
Ritoe 2006	402	Prospective	Larynx (all subsites), T1 to T4	Surgery, radiotherapy, or both	Median 5.5 years	Recurrence

CIS: carcinoma in situ

Intervention

Cessation of smoking after diagnosis or after treatment.

Comparison

Continued smoking after diagnosis/treatment.

3

Outcome measures and effect size

Overall survival:

Study	N	Outcome measure	Survival rate for smoking cessation, %	Survival rate for continued smoking, %	Risk difference, % (95% CI)
Al-Mamgani 2013	744	5-year survival	68	33	35 (27, 43)
Kikidis 2012	153	5-year survival	71	47	24 (6, 42)
Mayne 2009	213	4.4-year survival	87	66	21 (6, 35)

Tumour recurrence:

Study	N	Outcome measure	Survival rate for smoking cessation, %	Survival rate for continued smoking, %	Risk difference, % (95% CI)
Al-Mamgani 2013	744	5-year recurrence rate	11	34	−23 (−17, −29)
Benninger 1994	63	3-year recurrence rate	11	41	−30 (−10, −51)
Colasanto 2004	76	5-year recurrence rate	9	10	−1 (18, −17)
Kikidis 2012	153	5-year recurrence rate	29	55	−26 (−10, −44)
Ritoe 2006*	402	NR	NR	NR	NR

Results reported only as a hazard ratio of 1.46 (95% CI 0.93, 2.29) for locoregional recurrence in continued smokers.

Source of funding

Not reported.

Study quality assessment

Study quality was assessed in terms of relevance and risk of bias using a predefined checklist based on the Preferred Reporting of Items for Systematic Reviews and Meta-analyses checklist, and classified as high, moderate or low relevance and risk or bias. Studies with high risk of bias were excluded from the analysis. The remaining included studies were all rated as at moderate risk of bias; five were rated as of high relevance and one of moderate relevance.

Additional comments

1

2 ***Individual studies***

Study, country

Browman, 2002
Canada (four sites) and United States (one site).

Study type, study period

Observational cohort study.
Subjects entered into study between January 1993 and October 1996.

Number of patients

148.

Patient characteristics

Inclusion criteria: newly diagnosed squamous cell carcinoma of the head and neck involving oral cavity, hypopharnx, oropharynyx or larynx (AJCC clinical stage III or IV; ECOG status 0 to 2) recommended for radical radiotherapy and who were smokers within 12 weeks of tumour diagnosis.
Exclusion criteria: Patients undergoing any nondiagnostic surgical intervention; presence of a second primary tumour requiring treatment within the previous 6 months; any prior exposure to radiotherapy/chemotherapy; presence of distant metastatic disease.

All patients received radical radiation therapy according to the standard treatment protocols of each centre.

Mean age: 60 years (range 18-72).
Male:female: 117:31
Smoking history: mean 43 years of active smoking; mean 52 pack-years of smoking history.

Tumour site	n (%)
Oral cavity	25 (17)
Oropharynx	53 (36)
Hypopharynx	16 (11)
Larynx	54 (36)

T stage	n (%)
T1	15 (10)
T2	22 (15)
T3	87 (59)
T4	23 (16)

Tumour stage	n %
III	86 (58)
IV	62 (42)

N stage	n (%)
N0	60 (41)
N1	39 (27)
N2	40 (27)
N3	8 (5)

Intervention

Cessation of smoking during radiotherapy (n = 35), defined as complete abstention from smoking. Measured by questionnaire (administered at baseline, each week during treatment and at 13 weeks post-treatment); questionnaire results were validated against a

random sample of blood cotinine samples (correlation $R = 0.69$; $p < 0.0005$).

Comparison

Continued smoking during therapy (n = 113), defined as smoking any cigarettes during the treatment period. Measured as for intervention.

For some analyses, patients were grouped into light smokers (abstained completely or smoked an average of ≤ 1 cigarette per day ; n = 49) and heavy smokers (smoked an average of > 1 cigarette per day).

Length of follow-up

Minimum of 3 years. Patients were followed for tumour status every 3 months for the first year (beginning 13 weeks after completion of radiotherapy) and every 4 months thereafter.

Outcome measures and effect size

	Former smokers			Active smokers		
Outcome	**n**	**N**	**%**	**n**	**N**	**%**
Response to treatment*	21	35	60	70	110	64

* patients with evidence of tumour progression during radiation therapy or before 13 weeks post-treatment were classed as not responding to treatment.

	Light smokers			Heavy smokers		
Outcome	**n**	**N**	**%**	**n**	**N**	**%**
Overall survival (two years follow up)	18	49	37	44	97	45

Median survival: light smokers 42 months; heavy smokers 29 months. p = 0.07.

Source of funding

National Cancer Institute of Canada.

Risks of bias

Selection bias: unclear/unknown risks. Patients 'self-allocated' to different groups based on their willingness and ability to stop smoking. Patient characteristics according to smoking status were not reported.
Performance bias: low risk.
Attrition bias: low risk.
Detection bias: low risk.

Additional comments

Discrepancy in total patient numbers; presumably due to rounding error as in some case absolute numbers were calculated from reported percentages.

1

Study, country

Castigliano, 1968.

United States, single centre.

Study type, study period

Retrospective cohort study

Number of patients

89 (76 smokers).

Patient characteristics

Patients with a history of mouth or throat cancer who had survived without evidence of recurrent disease for at least 3 years, who came to clinic within a 4 month period.

Patients were treated with surgery (34%), radiation (34%) or a combination (32%).

Tumour site	n (%)
Oral cavity*	69 (80.2)
Tonsil	4 (4.7)
Larynx	28 (32.6)
Pharynx	1 (1.2)

*tongue; floor of mouth; buccal; palate or gingival.

Intervention

Cessation of smoking (n = 51), defined as patients who stopped smoking after the appearance of their first cancer. Determined by interview/case history.

Comparison

Non-cessation of smoking (n = 26).

Length of follow-up

Limited details reported, but patients appear to have been followed for a minimum of 3 years.

Outcome measures and effect size

	Former smokers			Active smokers		
Outcome	**n**	**N**	**%**	**n**	**N**	**%**
Incidence of a second primary cancer in a tobacco critical region*	9	51	17.6	5	26	19.2

* not clearly defined, but assumed to include lung, oesophagus and upper aerodigestive tract.

Source of funding

Not reported.

Risks of bias

Selection bias: Unclear/unknown risk. Patients 'self-allocated' to different groups based on their willingness and ability to stop smoking. Patient characteristics according to smoking status were not reported.
Performance bias: unknown/unclear risk. Blinding to cessation of smoking is unfeasible. Limited details reported of the cancer treatment received by trial participants.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

Study, country

Chen, 2011.

United States, single centre.

Study type, study period

Retrospective cohort study; included patients were referred to the centre between 1999 and 2008.

Number of patients

202.

Patient characteristics

Patients with histologically proven squamous cell carcinoma of the head and neck undergoing radiation therapy.

Primary population (n =101): patients with squamous cell carcinoma of the oral cavity, pharynx and/or larynx who smoked during radiation therapy.

Control population (n =101): head and neck cancer patients with previous smoking history who quit either before or at the time of diagnosis and therefore did not smoke during radiation therapy.

Each smoking subject was matched to a control patient based on primary disease site, age, sex, smoking history, performance status, disease stage, T stage, primary treatment and treatment dose.

Patients were treated with either primary radiotherapy (58%), or surgery in combination with postoperative radiotherapy (42%).

Median age: 55 years (active smokers); 57 years (former smokers).

Tumour site	n (%)
Oral cavity	108 (53.5)
Larynx	42 (20.8)
Tonsil	36 (17.8)
Hypopharynx	16 (7.9)

T stage	n (%)
T1	69 (34.2)
T2	37 (18.3)
T3	45 (22.3)
T4	51 (25.2)

N stage	n (%)
N0	56 (27.7)
N+	146 (72.3)

Intervention

Cessation of smoking as defined in the control population above (former smokers). Median pack-year history: 20 pack-years. 39 patients had quit within 5 years of presentation; 31 had quit more than 5 years prior; for 31 patients the time of quitting was not known.

Comparison

Continued smoking as defined in the primary population (active smokers). Median pack-year history: 40 pack-years.

Length of follow-up

Median 49 months (range 6-115).

2

Outcome measures and effect size

	Former smokers			Active smokers			
Outcome	**n**	**N**	**%**	**n**	**N**	**%**	
Overall survival (5 year follow up)	53	101	55	23	101	23	p <0.001
Disease recurrence	40	101	40	53	101	52	NR
Incidence of acute toxicity (grade 3 or above)	61	101	60	56	101	55	p = 0.74
Incidence of late toxicity (grade 3 or above)	31	101	31	49	101	49	p = 0.01
Incidence of any second cancer	14	101	14	16	101	16	P = 0.19

	Former smokers	Active smokers
Outcome	**%**	**%**
5 year disease free survival*, %	65	42
5 year locoregional control*, %	69	58
5 year distant metastasis-free survival, %	78	77
Median time to locoregional recurrence, months	12	10

* Kaplan-Meier estimates.

Source of funding

Not reported. Authors declared no conflicts of interest.

Risks of bias

Selection bias: low risk
Performance bias: low risk
Attrition bias: low risk
Detection bias: low risk

Additional comments

1

Study, country

Garces, 2007.

United States, single centre.

Study type, study period

Retrospective cohort study; April 1988 to June 2001.

Number of patients

94 eligible for analysis of outcomes in relation to smoking. 101 head and neck cancer patients in total included in the study population.

Patient characteristics

Head and neck cancer patients who were active tobacco users and received an initial consultation for treatment of nicotine dependence. Patients were included in the analysis if they had been followed up for a minimum of 6 months after consultation.

Age: mean 58.7 years
Gender: 34.7% female

Tumour site	n (%)
Oral cavity	37(36.6)
Larynx	37 (36.6)
Oropharynx	19 (18.8)
Major salivary gland	5 (5.0)
Hypopharynx	3 (3.0)

Tumour stage	n (%)
0	6 (5.9)
I	38 (37.6)
II	15 (14.9)
III	15 (14.9)
IV	22 (21.8)
Unknown	5 (5.0)

Treatment	n (%)
Surgery only	69 (69.0)
Radiation therapy only	16 (16.0)
Surgery in combination with radiation therapy	13 (13.0)
Other	2 (2.0)

Intervention

Abstaining from tobacco (measured by interview, 6 months after initial consultation for treatment of nicotine dependence)

Comparison

Using tobacco 6 months after consultation.

Length of follow-up

Median 3.7 years.

2

Outcome measures and effect size

	Former smokers			Active smokers		
Outcome	**n**	**N**	**%**	**n**	**N**	**%**
Incidence of tobacco-related second primary tumour:*						
18 months post-consultation	0	24	0	3	51	5.6
66 months post-consultation	0	7	0	7	24	28

* lung, oesophagus, oral cavity, lip, pharynx, bladder, kidney, pancreas, cervix

Source of funding

Government grant; charity grant.

Risks of bias

Selection bias: unclear/unknown risks. Patients 'self-allocated' to different groups based on their willingness and ability to stop smoking.
Performance bias: unclear/unknown risk. Patient characteristics according to smoking status not reported.
Attrition bias: high risk. Exact figures are not reported, but follow up appears to have been longer, on average, for patients in the smoking group.
Detection bias: low risk.

Additional comments

The baseline time point in this study was consultation for treatment of nicotine dependence. For some patients this took place years after their cancer diagnosis: 46.5% were seen for nicotine dependence within 3 months of cancer diagnosis; 26.7% were seen 3 months to 5 years after diagnosis and 26.7% were seen more than 5 years after diagnosis.

1

Study, country

Gorsky, 1994

Study type, study period

Retrospective cohort study.

United States, single centre.

Number of patients

403 patients included; 277 followed up for more than one year, 187 of whom were smokers.

Patient characteristics

Patients with head and neck cancer who were smokers and had at least one year of follow up data available after treatment.

Localized tumours (stages I (36% of patients) and II (28%)) were treated mainly by surgery with or without postoperative radiotherapy. Advanced tumours (stages III (29%) and IV (7%)) were treated with extensive surgery, radiotherapy and chemotherapy.

Mean age 56 years (range 24-87).
Gender: 58% male.

Tumour site	n (%)
Oral cavity*	266 (66.0%)
Oropharynx	52 (12.9%)
Nasopharynx	45 (11.2%)
Larynx	33 (8.2%)
Lip	7 (1.7%)

*tongue, floor of mouth, gingival, buccal or hard palate.

Intervention

Patients who stopped smoking for at least one year after treatment. Measured by patient interview.

Comparison

Patients who continued smoking.

Length of follow-up

Median 4 years.

Outcome measures and effect size

	Former smokers			Active smokers		
Outcome	**n**	**N**	**%**	**n**	**N**	**%**
Incidence of second primary oral/oropharyngeal cancer	13	97	13	23	90	26

Source of funding

Not disclosed.

Risks of bias

Selection bias: Unclear/unknown risk. Patients 'self-allocated' to cessation of smoking. Time of quitting relative to treatment/diagnosis is not clearly defined.
Performance bias: Unclear/unknown risk. Unclear if the treatment received by former and active smokers was comparable.
Attrition bias: Low risk

Detection bias: Low risk
Additional comments
Baseline characteristics were reported for the overall population (403 patients) and not grouped by smoking status. Only 277 patients were analysed, a subgroup of 187 smokers within that group is considered here. It is unclear if the characteristics reported for the overall population (403 patients) reflect this subgroup.

1

Study, country
Moore, 1971. United States (three centres in Louisville)
Study type, study period
Cohort study (assumed prospective). Recruitment from 1951 to 1966.
Number of patients
203.
Patient characteristics
Inclusion criteria: invasive squamous carcinoma of the oral cavity, pharynx or larynx, controlled by surgery and/or radiation for at least three years ; prior smoking. Exclusion criteria: nasopharynx or lip cancers; non-smokers.

	Active smokers	**Former smokers**
Mean age, years	58.1	60.8
Gender ratio, M:F	3.9:1	4.5:1
Mean cigarette exposure, pack/day/yr ± standard deviation	53 ± 16.8	56 ± 37.0
Cancer treatment, %		
Surgery alone	51	63
X-ray alone	28	20
Combination	21	17
Tumour site, n (%)		
Oral cavity	86 (70.5)	44 (54.3)
Larynx	22 (18.0)	33 (40.7)
Pharyngeal wall	7 (5.7)	1 (1.2)
Tonsil/anterior tonsillar pillar	7 (5.7)	3 (3.7)

Intervention
Cessation of smoking after first cancer (defined as complete cessation of smoking, determined by patient interview)
Comparison
Continued smoking after first cancer.
Length of follow-up
Mean 7.3 years (range 3-18 years)
Outcome measures and effect size

	Former smokers			**Active smokers**		
Outcome	**n**	**N**	**%**	**n**	**N**	**%**
Overall mortality	23	81	28	63	122	52
Incidence of second primary tumour*	5	81	6	49	122	40
Death from second primary tumour	2	81	2	30	122	25
	%			**%**		
5 year survival	88			90		
10 year survival	66			44		

*respiratory and upper aerodigestive tract only; tumour detected at least three years after first cancer.

Source of funding
Charity grant.
Risks of bias
Selection bias: Unclear/unknown risk. Patients 'self-allocated' to intervention/comparison by willingness/ability to quit smoking. Some baseline characteristics are listed according to smoking status; no information on tumour stage/severity at baseline. Performance bias: low risk Attrition bias: low risk Detection bias: low risk.
Additional comments

1

Study, country
Rugg, 1990. United Kingdom (single centre).
Study type, study period
Prospective cohort study (some information on smoking collected retrospectively). Patients were treated between January 1985 and May 1989.
Number of patients
41 (33 smokers).
Patient characteristics
Patients with advanced head and neck tumours receiving continuous, hyperfractionated, accelerated radiotherapy (CHART). Exclusion criteria: tumours at sites that did not involve irradiation of the oral or oropharyngeal mucosa; volume of mucosa irradiated < 20%. All patients were treated with CHART (36 fractions over a continuous 12 day period). Mean age: 61 years (range 18-83).
Intervention
Cessation of smoking from beginning of radiotherapy onwards (method of measuring smoking status not reported, presumed to be patient interview)
Comparison
Temporary abstinence from smoking during radiotherapy (complete cessation during treatment and for 4 weeks following treatment), or continued smoking during treatment.
Length of follow-up
Not reported.
Outcome measures and effect size
Mean duration of mucositis following radiotherapy: Cessation during and after radiotherapy (n = 18): 13.6 weeks Temporary abstinence or continued smoking: (n = 15): 21.0 weeks.
Source of funding
Charity and research council grants
Risks of bias
Selection bias: unclear/unknown risk. Patients 'self allocated' based on their willingness/ability to quit smoking. Baseline characteristics according to smoking status were not reported. Performance bias: low risk. Attrition bias: Unclear/unknown risk. Data not available for 24 out of 68 eligible patients Detection bias: Unclear/unknown risk. Methods for detection of presence of mucositis, and determining its complete resolution, were not reported.
Additional comments

2

Study, country
Sandoval 2009. Spain (single centre)
Study type, study period
Prospective cohort study.
Number of patients
85.
Patient characteristics
Patients with newly diagnosed, invasive carcinoma (histologically confirmed) of the oral cavity or oropharynx. Patients were treated with surgery (with or without adjuvant radiotherapy), radiotherapy (with or without chemotherapy), or other treatment (not specified).

Age (years)	n (%)
< 50	39 (26.7)
50-59	39 (26.7)
60-69	45 (30.8)
≥ 70	23 (15.8)

Gender	n (%)
Male	127 (87)
Female	19 (13)

Tumour site	n (%)
Oral cavity	115 (78.8)
Oropharynx	31 (21.2)

Treatment	n (%)
Surgery ± adjuvant radiotherapy	92 (63)
Radiotherapy ± chemotherapy	43 (29.5)
Other	11 (7.5)

Clinical stage	n (%)
Early	45 (30.8)
Advanced	101 (69.2)
IV	66 (45.2)
III	35 (24)
II	30 (20.5)
I	15 (10.3)

Intervention
Cessation of smoking at diagnosis. Measured using standardised questionnaire.

Comparison

Continued smoking after diagnosis.

Length of follow-up

Minimum 2 years

Outcome measures and effect size

	Former smokers			Active smokers		
Outcome	**n**	**N**	**%**	**n**	**N**	**%**
Incidence of recurrence	20	55	36.4	8	30	26.7
Overall mortality	27	55	49.1	13	30	43.3
Death from oral cancer	17	55	30.9	10	30	33.3

Source of funding

Governmental and charity grants

Risks of bias

Selection bias: Unclear/unknown risk. Smokers self allocated to groups according to their willingness and ability to quit smoking. Smoking status was a subgroup analysis within the study; baseline characteristics according to smoking status were not reported.
Performance bias: Low risk.
Attrition bias: Unclear/unknown risk. Limited information on follow up/treatment dropouts reported.
Detection bias: Low risk

Additional comments

1

Study, country

Silverman, 1983.
United States (single centre)

Study type, study period

Cohort study, assumed to be retrospective.
Study period not reported.

Number of patients

160 (117 tobacco users).

Patient characteristics

Biopsy-proven head and neck carcinoma; recording of tobacco usage; minimum of one year of follow up after cancer treatment.

Mean age: 58 years (25-84)
Gender: 56 % male

Tumour site	n (%)
Nasopharynx	11 (6.9)
Buccal	9 (5.6)
Tongue	53 (33.1)
Lip	4 (2.5)
Floor of munth	34 (21.3)
Gingiva	11 (6.9)
Oropharynx	22 (13.8)
Larynx	16 (10.0)

Type of treatment or tumour stage not reported.

Intervention

Cessation of smoking after first cancer. Method of measurement not reported..

Comparison

Unchanged or reduced smoking after first cancer.

Length of follow-up

Not reported.

2

Outcome measures and effect size

	Former smokers			Active smokers		
Outcome	**n**	**N**	**%**	**n**	**N**	**%**
Incidence of second primary oral/oropharyngeal cancer	7	53	13.2	15	64	23.4

Source of funding

Government grant.

Risks of bias

Selection bias: Unclear/unknown risk. Patients 'self-allocated' to groups according to willingness/ability to quit smoking.
Performance bias: Unclear/unknown risk. No details reported on cancer treatment received; it is not clear if the type of treatment was similar between former and continued smokers.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

Study, country

Silverman, 1972.
United States (single centre).

Study type, study period

Prospective cohort study.
Study period not reported.

Number of patients

174 (116 smokers).

Patient characteristics

Patients with oral carcinoma (including intraoral and oropharyngeal sites; excluding lip cancers).
Patients were treated with surgery (18%), radiation therapy (60%) or surgery in combination with radiotherapy (22%).

Intervention

Cessation of smoking after treatment. Determined by patient interview at each visit.

Comparison

Unchanged or reduced smoking after treatment.

Length of follow-up

Up to one year: 17% of patients. One to three years: 37%. Over three years: 46%.

Outcome measures and effect size

	Former smokers			Active smokers		
Outcome	**n**	**N**	**%**	**n**	**N**	**%**
Incidence of second primary oral cancer	3	45	6.7	19	71	26.8

Source of funding

Not reported

Risks of bias

Selection bias: Unclear/unknown risk. Patients 'self-allocated' to groups according to willingness/ability to quit smoking
Performance bias: Unclear/unknown risk. Limited details reported on cancer treatment received; it is not clear if the type of treatment was similar between former and continued smokers.
Attrition bias: Low risk of bias
Detection bias: Low risk of bias

Additional comments

2

Study, country

Van der Voet, 1998
Netherlands (single centre)

Study type, study period

Retrospective cohort study. January 1965 to December 1992.

Number of patients

267 (smokers only; 352 patients in total included in the study)

3

Patient characteristics

T1N0M0 glottic larynx cancer treated with primary radiotherapy.

Age	n (%)
< 55	74 (19.3)
55-64	126 (32.9)
65-74	132 (34.5)
≥ 75	51 (13.3)

Gender	n (%)
Male	348 (91.1)
Female	34 (8.9)

Tumour histology	n (%)
CIS	43 (15.8)
Grade I	111 (40.8)
Grade II	96 (35.3)
Grade 3	22 (8.1)

Intervention

Cessation of smoking, either before or after radiotherapy. Determined from patient records.

Comparison

Continued smoking during radiotherapy.

Length of follow-up

Median 89 months.

Outcome measures and effect size

Incidence of larynx complications:

Smoking status	n (%)
Former smokers	27/180 (15.0)
Continued smokers	27/87 (31.0)

Source of funding

Not reported

Risks of bias

Selection bias: Unclear/unknown risk. Smokers self allocated to groups according to their willingness and ability to quit smoking. Smoking status was a subgroup analysis within the study; baseline characteristics according to smoking status were not reported.
Performance bias: low risk
Attrition bias: low risk
Detection bias: Unclear/unknown risk. Definition of larynx complications not defined

Additional comments

Patients in the study received one of six different radiotherapy fractionation schedules; relationship between schedule and smoking status/outcome is not reported.

1

Study, country

Zevallos, 2009

United states (single centre)

Study type, study period

Retrospective cohort study

Study period not reported

Number of patients

81

Patient characteristics

Patients with laryngopharyngeal cancer who were smokers at diagnosis and were referred to a tobacco treatment programme. All patients received radiotherapy as their primary treatment modality.

Median age: 55 years.

Tumour site	Abstainers, n (%)	Continued smokers, n (%)
Nasopharynx	0 (0)	1 (3)
Oropharynx	11 (64.7)	20 (60.6)
Hypopharynx	1 (5.8	3 (9.1)
Larynx	5 (29.4)	9 (27.3)

Tumour grade/differentiation	Abstainers, n (%)	Continued smokers, n (%)
Well/moderately well	2 (11.8)	3 (9.1)
Moderate	7 (41.1)	17 (51.5)
Poor/moderately poor	7 (41.1)	8 (24.2)

T stage	Abstainers, n (%)	Continued smokers, n (%)
T0-T2	7 (41.1)	18 (54.5)
T3-T4	10 (58.9)	15 (45.5)

N stage	Abstainers, n (%)	Continued smokers, n (%)
N0	5 (29.4)	11 (33.3)
N1-N3	12 (70.6)	22 (66.7)

Intervention

Smoking cessation before radiotherapy. Measured prospectively (patient interview) for patients who enrol in the tobacco treatment programme; retrospectively collected from chart review for other patients.

Comparison

Continued smoking during radiotherapy.

Length of follow-up

Median 533 days (former smokers); 396 days (continued smokers).

Outcome measures and effect size

	Former smokers			Active smokers			
Outcome	**n**	**N**	**%**	**n**	**N**	**%**	
Incidence of skin changes (grade 2-4) after radiotherapy	16	37	43.2	14	44	31.9	
Mucositis (grade 2-4) after RT	21	37	56.8	32	44	72.8	
Feeding tube required after RT	21	37	56.8	28	44	63.6	
Hospitalisation after RT	5	37	13.5	15	44	34.1	
Pharyngeal stricture requiring dilatation after RT	0	37	0	4	44	9.1	
Osteoradionecrosis after RT	1	37	2.7	9	44	20.5	
	Days, mean ± SD			**Days, mean ± SD**			
Feeding tube duration	206.6 ± 138.3			193.3 ± 202.7			p = 0.54
Hospitalisation duration	3.8 ± 2.2			8.2 ± 11.8			p = 0.01

Source of funding

Not reported. Authors declared no conflicts of interest.

Risks of bias

Selection bias: unclear/unknown risk. Patients 'self-allocated' to quit or continue smoking. Baseline characteristics according to smoking status were reported but only for the subgroup of patients (50/83) who chose to enrol in the tobacco treatment programme. Status for possible confounders (eg alcohol use) not reported.
Performance bias: low risk
Attrition bias: low risk
Detection bias: low risk

Additional comments

1

1 Evidence search details and references

2 ***Review question in PICO format***

Population	**Intervention**	**Comparison**	**Outcomes**
Adults with cancer of the upper aerodigestive tract who are smokers at the time of diagnosis. Subgroups: • patients undergoing treatment • post-treatment • treatment type • tumour site.	Smoking cessation after cancer diagnosis	Non-cessation of smoking	• Overall survival • Progression free survival (including second primary cancers) • Tumour recurrence • Quality of life • Treatment-related morbidity

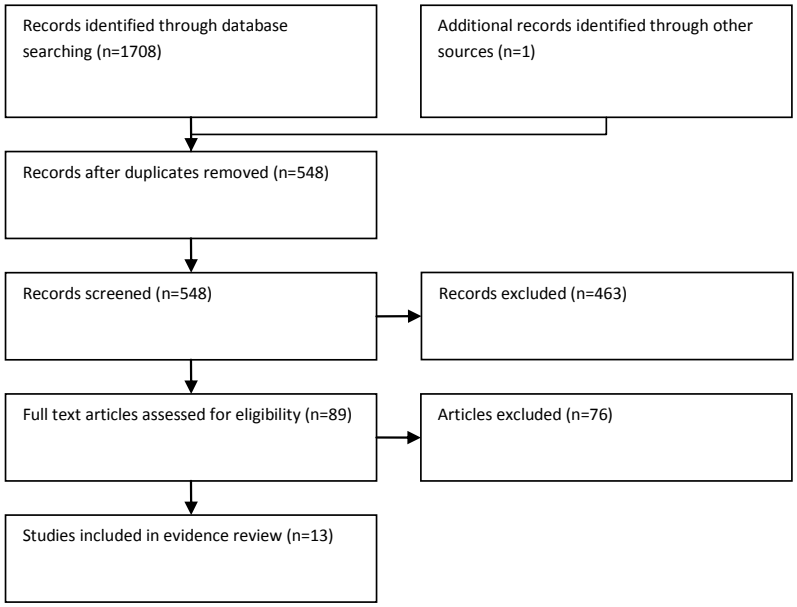
3

4 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.
Search strategies	None specified
Review strategies	The evidence tables for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Consideration will be given to the effect of delivery of smoking

	cessation interventions (use of generalist smoking cessation clinics or head and neck-specific services; specific methods used to help patients quit) and the timescale over which people stop smoking (only for the duration of treatment, or for longer periods) on the outcomes listed in the PICO.

Figure 1.3. Study flow diagram



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Reason for exclusion: Insufficient data available.

2. Investigation

Assessment of neck lumps

Clinical question: What is the most effective configuration of tests within a rapid access clinic for assessing neck lumps suspected of being cancer of the upper aerodigestive tract?

Background

The assessment of a neck lump suspected to be related to CUADT is an important part of the patient pathway. The ultimate aim is to be able to identify a cause for the swelling with the highest level of accuracy utilising the least intrusive set of investigations in the most timely fashion. There is variation in the cost, availability, and accuracy of tests and the order in which they are carried out.

Current NICE service guidance (Improving outcomes in head and neck cancers) states that patients with these neck lumps are seen in a rapid access clinic. However there is widespread variation around the country in the interpretation of this guidance. Whilst it is anticipated that a comprehensive history and examination would take place in the assessment of all patients there are a wide range of further investigations that are available in the clinic setting. These include endoscopic assessment of UADT mucosa, flexible transnasal oesophagoscopy, fine needle aspiration cytology (FNAC) and ultrasound. In addition to these 'same day' investigations many clinics offer rapid assessment with cross-sectional imaging, MRI or CT.

With regard to FNAC practice varies as to whether ultrasound is used to direct the procedure. Likewise the sample may or may not undergo immediate assessment for adequacy. Failure to obtain a definite diagnosis with FNAC may require more intrusive tissue sampling, such as core biopsy.

Evidence summary

The review identified 17 studies investigating methods of detecting malignancy in undiagnosed neck lumps.

Based on the combined results of 13 trials (total studied population: 2457) the sensitivity of fine-needle aspiration cytology (FNAC) without imaging guidance for the detection of malignancy was estimated as 0.88 (95 % confidence interval [CI] 0.85, 0.90) and the specificity as 0.92 (95% CI 0.85, 0.96). Risks of bias included a lack of clear reporting of whether patients were selected for the study in an unbiased fashion (7/13 trials) and exclusion of patients due to sample inadequacy or insufficient follow up (5/13 trials). In 6/13 trials, not all patients directly matched the population of interest to this question, or the number who did was unclear.

Combined results of two trials (185 patients) estimated the sensitivity and specificity of ultrasound (US)-guided FNAC as 0.95 (95 CI 0.83, 0.99) and 0.98 (95% CI 0.94, 0.99), respectively. Risks of bias arise from one trial not reporting how patients were selected for inclusion, whilst the second trial excluded a large proportion of eligible patients from the results (due to nondiagnostic samples or lack of results for the reference standard). Furthermore, the same trial included lesions at some sites that may not be relevant to this review question.

One trial (Pfeiffer 2007, 80 patients) reported the sensitivity and specificity of US-guided core biopsy as 0.98 (95% CI 0.90, 1.00) and 1.00 (95% CI 0.88, 1.00), respectively. It is unclear whether all patients in this trial were relevant to the review question, as no patient characteristics were reported.

One trial (Shrestha 2011, 97 patients) reported the sensitivity and specificity of CT as 0.96 (95% CI 0.88, 1.00) and 1.00 (95% CI 0.91, 1.00), respectively. There were no major bias or applicability issues identified.

No evidence was identified for test-related morbidity, time to diagnosis, or patient-reported outcomes associated with any test. No studies of combinations of tests/diagnostic pathways were identified.

Study characteristics and quality

Seventeen studies were identified as relevant to this review (see section 5 for further details). All were retrospective, with the exception of one prospective study (Shrestha 2011). Study characteristics are summarised in Table 2.1. Study quality and applicability, assessed using the QUADAS-2 checklist, are summarised in Figure 2.1~~Figure 2.1~~~~Figure 2.1~~.

Fifteen studies assessed the diagnostic accuracy of FNA in the assessment of head and neck lumps. Of these, 13 used FNA without imaging guidance, whilst two used ultrasound-guided FNA. Of the remaining two studies, one investigated ultrasound-guided core biopsy and one investigated CT. All studies assessed only one form of investigation; no combinations of tests were studied.

For 10 of the 17 studies, the authors did not report all methods used to select patients for study inclusion. Consequently, it is unclear whether these studies selected patients in an unbiased fashion. Additionally, the majority (14/17) of studies used histology results as the sole source of reference standard, and reported diagnostic accuracy results only for patients with histology results available for comparison. As not all patients would be expected to undergo the further tests necessary to obtain a biopsy for histological analysis, this introduces a further risk of bias, as results were not reported for all patients who underwent the index test. Other studies used clinical follow up/case history to obtain patients' final diagnosis if histological results were not available.

The definition of neck lumps used by each study varied, most importantly in terms of the sites being investigated. Some studies included sites that may not be relevant to this review, such as thyroid and cutaneous skin lumps. Several studies did not clearly define the ranged of sites investigated, stating only that patients with head and neck lumps/lesions were included.

Table 2.1. Characteristics of included studies

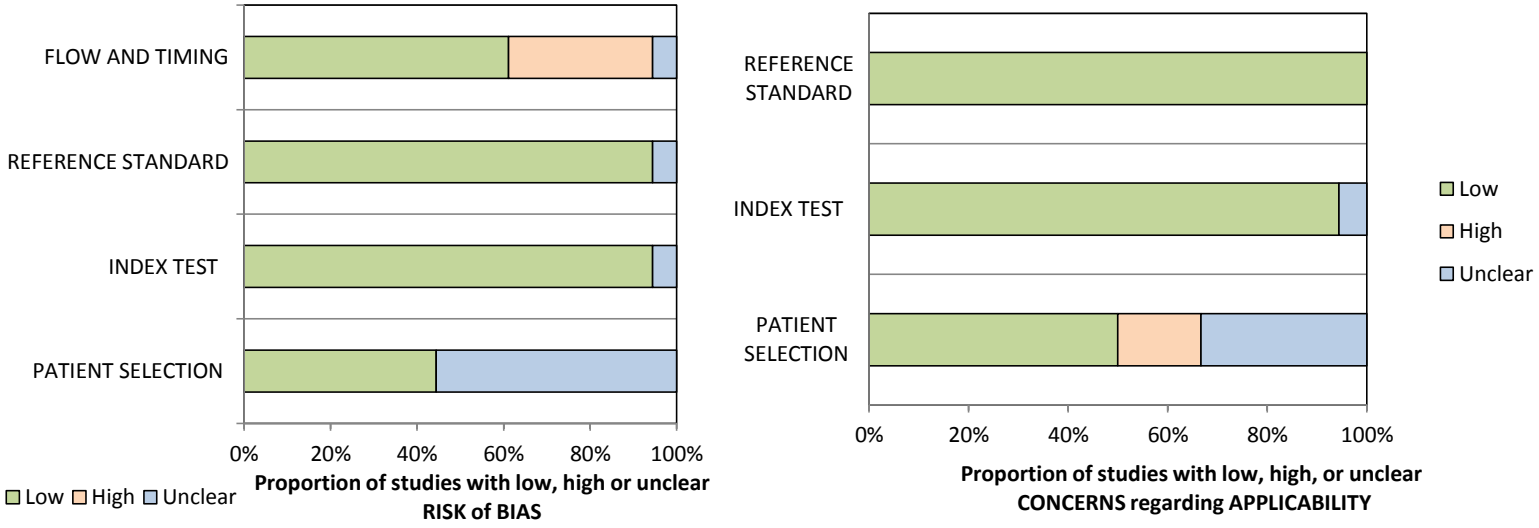
Study	Number of patients*	Inclusion criteria	Prevalence of malignancy (%)	Index test	Reference standard	Number of inadequate or nondiagnostic samples (%)
Akhavan-Moghadam 2013	65	Any non-thyroid H/N mass	40/65 (61.5)	FNAC (no imaging guidance)	Open biopsy	0 (0)
Altmann 1998	95	Any subcutaneous H/N mass	75/95 (78.9)	FNAC (no imaging guidance)	Histopathological diagnosis	14/109 (12.8)
Draper 2002	154	Patients attending a neck lump clinic	44/154 (28.6)	FNAC (no imaging guidance)	Histopathological diagnosis	49/276 (17.8)
Fulciniti 1997	206	Suspected (malignant or benign) H/N tumour	53/206 (25.7)	FNAC (no imaging guidance)	Histopathological diagnosis	12/218 (5.5)
Howlett 2007	81	Any H/N lump (non-thyroid†)	47/81 (58.0)	FNAC (no imaging guidance)	Histopathological diagnosis	77/158 (48.7)
Jandu 1999	66	Any palpable H/N lump	30/66 (45.5)	FNAC (no imaging guidance)	Histopathological diagnosis	29/95 (30.6)
Khan 2013	199	Oral cavity masses/lesions	104/199 (52.3)	FNAC (no imaging guidance)	Histopathological diagnosis	30/229 (13.1)
Kutluhan 2003	88	Any palpable H/N mass	32/88 (36.4)	FNAC (no imaging guidance)	Histopathological diagnosis	8/96 (8.3)
Murthy 1997	48	Any H/N lesion	18/48 (37.5)	FNAC (no imaging guidance)	Histopathological diagnosis	10/58 (17.2)

Study	Number of patients*	Inclusion criteria	Prevalence of malignancy (%)	Index test	Reference standard	Number of inadequate or nondiagnostic samples (%)
Raab 1998	151	Lesions of the parotid gland, submandibular gland, or level I or II neck	48/151 (31.8)	FNAC (no imaging guidance)	Clinical follow up	7/158 (4.4)
Tandon 2008	1290	Any palpable H/N mass	486/1290 (37.7)	FNAC (no imaging guidance)	Histopathological diagnosis/clinical follow up	802/2092 (38.3)
Veivers 2012	33	Lateral neck cysts	4/33 (12.1)	FNAC (no imaging guidance)	Histopathological diagnosis	4/37 (10.8)
Wu 2006	71	Any palpable H/N mass	70/71 (98.6)	FNAC (no imaging guidance)	Surgical/histopathogical diagnosis	40/111 (36.0)
Lo 2007	102	Cervical lymph nodes suspicious for malignancy	12/102 (11.8)	FNAC (with US guidance)	Histopathological diagnosis/clinical follow up	0 (0)
Robinson 1999	83	Any patients referred for H/N FNA	37/83 (44.6)	FNAC (with US guidance)	Histopathological diagnosis	45/129 (34.9)
Pfeiffer 2007	80	Any cervicofacial mass	52/80 (65.0)	Core biopsy (with US guidance)	Histopathological diagnosis/clinical follow up/laboratory studies	8/88 (9.1)
Shrestha 2011	97	Neck lesions or palpable neck masses	57/97 (58.8)	CT	Histopathological diagnosis	0 (0)

*number of patients (or in some cases the number of samples) for whom diagnostic accuracy could be calculated (i.e. patients with an adequate index test result and a final diagnosis based on the reference standard). This figure excludes inadequate/nondiagnostic samples. † The total study population also included patients with thyroid masses, but these patients were excluded from the subgroup analysis presented here.

Abbreviations: CT: computed tomography; FNAC: fine-needle aspiration cytology; H/N: head and neck; US: ultrasound.

Figure 2.1. Summary of study quality (risks of bias and concerns regarding applicability)



Outcomes

Table 2.2. Summary of the diagnostic accuracy of all tests.

Tests with evidence from multiple studies				
Test	**Number of studies**	**Total number of patients**	**Pooled sensitivity (95% CI)***	**Pooled specificity (95% CI)***
FNAC (unguided)	13	2457	0.88 (0.85, 0.90)	0.92 (0.85, 0.96)
FNAC (US-guided)	2	185	0.95 (0.83, 0.99)	0.98 (0.94, 0.99)
Tests with evidence from a single study				
Test	**Number of studies**	**Total number of patients**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Core biopsy (US-guided)	1	80	0.98 [0.90, 1.00]	1.00 [0.88, 1.00]
CT	1	97	0.96 [0.88, 1.00]	1.00 [0.91, 1.00]
*Using bivariate meta-analysis (Reitsma 2005).				
Abbreviations: CI: confidence interval; CT: computed tomography; FNAC: fine-needle aspiration cytology; US: ultrasound.				

Table 2.3. Estimated outcome from each test in 1000 patients with neck lumps (assuming 41.6% of neck lumps were malignant*)

Test	**True positive**	**False positive**	**False negative (malignancy missed)**	**True negative**
FNAC	366	47	50	537
US-guided FNAC	395	12	21	572
US-guided core biopsy	408	0	8	584
CT	399	0	17	584
*Based on the overall rate of malignancy across all studies.				
Abbreviations: CT: computed tomography; FNAC: fine-needle aspiration cytology; US: ultrasound.				

Figure 2.2. Bar charts representing estimated outcomes from each test in 1000 patients with neck lumps. A malignancy rate of 41.6% is assumed.

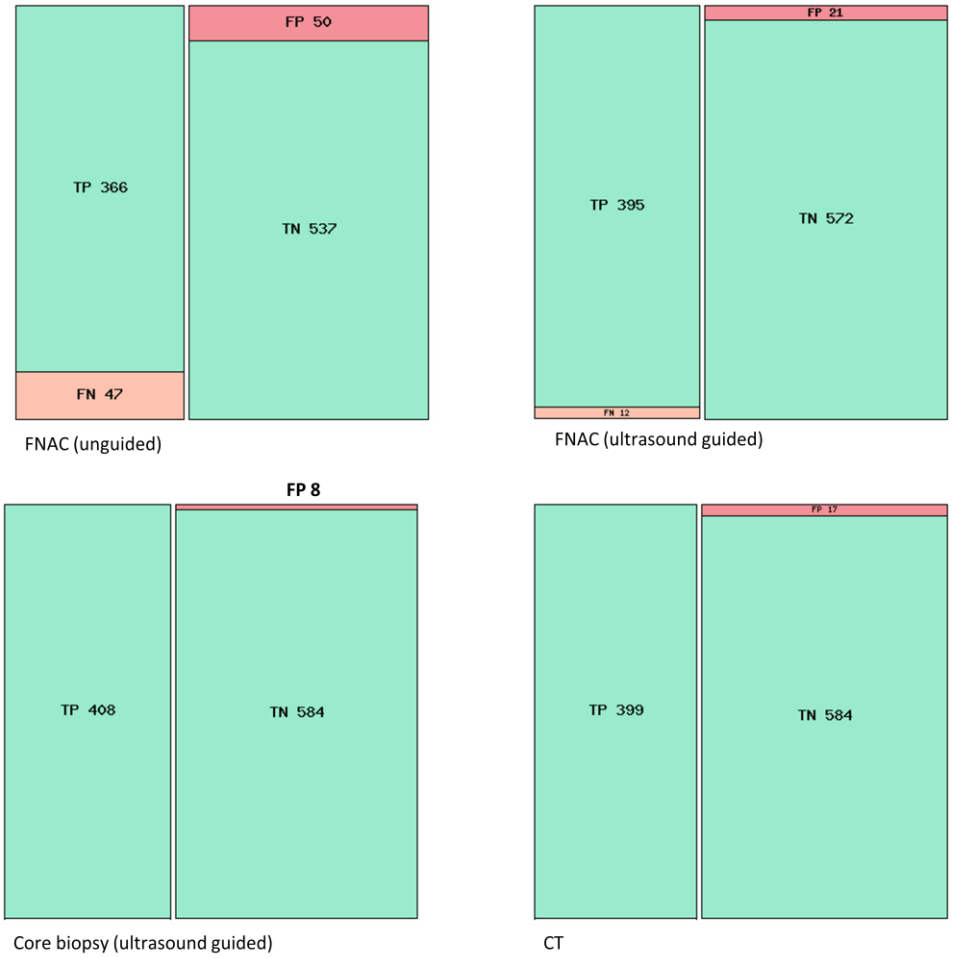
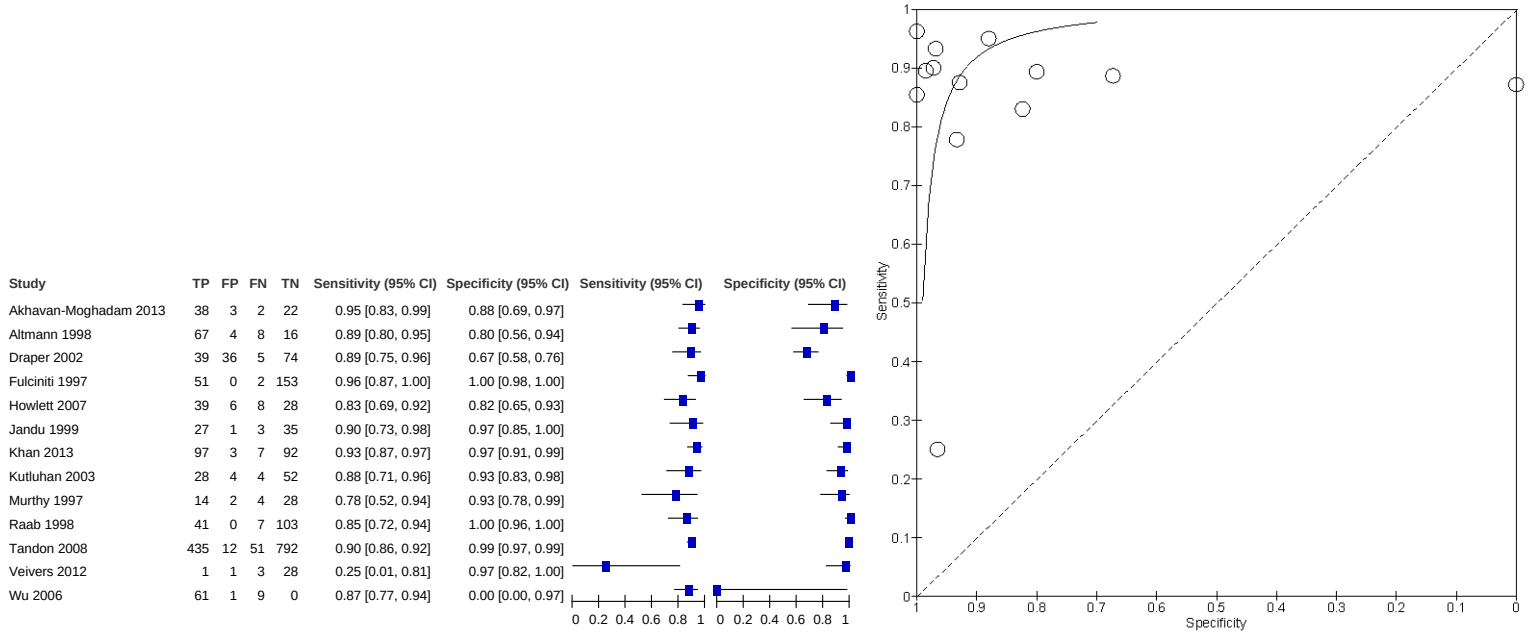
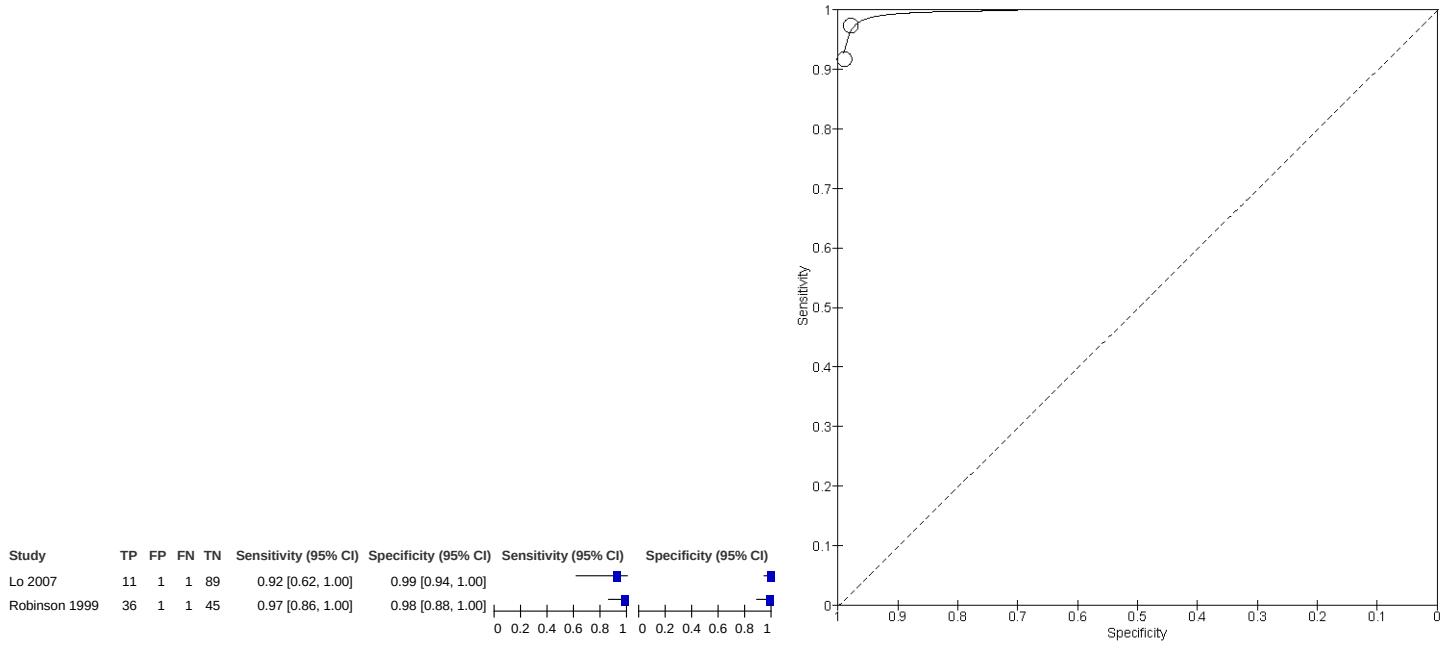


Figure 2.3. Summary of evidence for the diagnostic accuracy of FNAC (without imaging guidance). (a) forest plot of sensitivity and specificity for all identified evidence. (b) receiver operating characteristic (ROC) plot of all identified studies.



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Akhavan-Moghadam 2013	38	3	2	22	0.95 [0.83, 0.99]	0.88 [0.69, 0.97]
Altmann 1998	67	4	8	16	0.89 [0.80, 0.95]	0.80 [0.56, 0.94]
Draper 2002	39	36	5	74	0.89 [0.75, 0.96]	0.67 [0.58, 0.76]
Fulciniti 1997	51	0	2	153	0.96 [0.87, 1.00]	1.00 [0.98, 1.00]
Howlett 2007	39	6	8	28	0.83 [0.69, 0.92]	0.82 [0.65, 0.93]
Jandu 1999	27	1	3	35	0.90 [0.73, 0.98]	0.97 [0.85, 1.00]
Khan 2013	97	3	7	92	0.93 [0.87, 0.97]	0.97 [0.91, 0.99]
Kutluhan 2003	28	4	4	52	0.88 [0.71, 0.96]	0.93 [0.83, 0.98]
Murthy 1997	14	2	4	28	0.78 [0.52, 0.94]	0.93 [0.78, 0.99]
Raab 1998	41	0	7	103	0.85 [0.72, 0.94]	1.00 [0.96, 1.00]
Tandon 2008	435	12	51	792	0.90 [0.86, 0.92]	0.99 [0.97, 0.99]
Veivers 2012	1	1	3	28	0.25 [0.01, 0.81]	0.97 [0.82, 1.00]
Wu 2006	61	1	9	0	0.87 [0.77, 0.94]	0.00 [0.00, 0.97]

Figure 2.4. Summary of evidence for the diagnostic accuracy of FNAC (with US guidance). (a) forest plot of sensitivity and specificity for all identified evidence. (b) ROC plot of all identified studies.



Evidence tables for all included studies

Study, country

Akhavan-Moghadam, 2013
Iran, single centre.

Study type, study period

Retrospective cohort study.
April 2004 to April 2009.

Number of patients

65

Patient characteristics

Inclusion criteria: patients referred with non-thyroid head or neck masses.

Mean age: 40 years (range 10-82 years)

Gender	n (%)
Male	36 (55.4)
Female	29 (44.6)

Type of test(s)

FNAC

Reference standard

Open biopsy

Results

Inadequate or nondiagnostic samples: 0

Test result	Results from reference standard	
	Malignant	Benign
Malignant	38	3
Benign	2	22

Sensitivity [95% CI]: 0.95 [0.83, 0.99]
Specificity [95% CI]: 0.88 [0.69, 0.97]

Source of funding

None declared.

Comments on study quality

Risks of bias: It is unclear whether patients enrolled were a random/consecutive sample.
Concerns regarding applicability: Exact sites of masses or lesions is not reported.

Additional comments

Study, country

Altmann, 1998
Australia, single centre.

Study type, study period

Retrospective cohort study.
January 1995 to June 1997.

Number of patients

107 patients (109 aspirations performed in total)

Patient characteristics

Inclusion criteria: patients presenting with a subcutaneous head and mass, for whom final histology data was available.

Mean age 55.5 years (range 19-86 years)

Gender	n (%)
Male	74 (69)
Female	33 (31)

Site of mass or lesion	n (%)
Parotid gland	17 (16)
Thyroid	4 (4)
Other	88 (80)

Type of test(s)

FNAC

Reference standard

Final histological diagnosis

Results

Inadequate or nondiagnostic samples: 14/109

Test result	Results from reference standard	
	Malignant	Benign
Malignant	67	4
Benign	8	16

Sensitivity [95% CI]: 0.89 [0.80, 0.95]
Specificity [95% CI]: 0.80 [0.56, 0.94]

Source of funding

Not reported.

Comments on study quality

Risks of bias: no major concerns.
Concerns regarding applicability: sites of masses were reported, but a large proportion were listed in the 'other' category, with no further details given. The study included a small proportion of thyroid masses.

Additional comments

1

Study, country

Draper, 2002.
United Kingdom (single centre).

Study type, study period

Retrospective cohort study.
October 1994 to December 1999.

Number of patients

154.

Patient characteristics

Inclusion criteria: all patients attending a neck lump clinic who underwent FNAC.
Exclusion criteria: histology data not available; inadequate sample.

Gender	n (%)
Male	100 (51.8)
Female	93 (48.2)

Type of test(s)

FNAC

Reference standard

Histological analysis

Results

Inadequate or nondiagnostic samples: 49/276.

Test result	Results from reference standard	
	Malignant	Benign
Malignant	39	36
Benign	5	74

Sensitivity [95% CI]: 0.89 [0.75, 0.96]
Specificity [95% CI]: 0.67 [0.58, 0.76]

Source of funding

Not reported.

Comments on study quality

Risks of bias: Patients excluded due to a lack of histological data: 83/276.
Concerns regarding applicability: Tissue of origin for each lesion was reported, but not the location of the lump. In a minority of cases, sites of origin were not of relevance to the PICO (for example skin, thyroid).

Additional comments

2

Study, country

Fulciniti, 1997.
Italy (single centre).

Study type, study period

Retrospective cohort study.
January 1988 to December 1994.

Number of patients

218.

Patient characteristics

Inclusion criteria: patients who had undergone FNAB of a head and neck tumour.
Age range: 5-87 years.

Gender	n (%)
Male	119 (54.6)
Female	99 (45.4)

Site of mass or lesion	n (%)
Salivary glands	144 (66.1)
Oral cavity	24 (11.0)
Neck	6 (2.8)
Bone	13 (6.0)
Other	4 (1.8)

Type of test(s)

FNAB.

Reference standard

Histologic findings after surgery.

Results

Inadequate/nondiagnostic samples: 12/218.

Test result	Results from reference standard	
	Malignant	Benign
Malignant	51	0
Benign	2	153

Sensitivity [95% CI]: 0.96 [0.87, 1.00]
Specificity [95% CI]: 1.00 [0.98, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: It is unclear whether patients enrolled were a random/consecutive sample.
Concerns regarding applicability: A minority of patients (23/218) underwent investigation at sites that may not be relevant (skin, bone, "other").

Additional comments

1

Study, country

Howlett, 2007.
United Kingdom (five centres within one regional cancer network)

Study type, study period

Retrospective cohort study.
2004 inclusive.

Number of patients

158

Patient characteristics

Inclusion criteria: any patient who had undergone FNAC for a head and neck lump, including those who had more than one procedure, and for whom a histological diagnosis based on subsequent surgery was available.

Site of mass or lesion	n (%)
Neck node	50 (61.7)
Salivary gland	31 (38.3)

Type of test(s)

FNAC, unguided in “the vast majority of cases”

Reference standard

Histological results following surgery.

Results

Number of nondiagnostic FNAC tests: 77/158.

Test result	Results from reference standard	
	Malignant	Benign
Malignant	39	6
Benign	8	28

Sensitivity [95% CI]: 0.83 [0.69, 0.92]
Specificity [95% CI]: 0.82 [0.65, 0.93]

Source of funding

Not stated. No competing interests declared by the authors.

Comments on study quality

Risks of bias: a large proportion (77/158) of samples were considered inadequate/nondiagnostic.
Concerns regarding applicability: no major concerns.

Additional comments
The total study population also included patients with thyroid masses; these patients have been excluded from the analysis presented here.

1

Study, country
Jandu, 1999. United Kingdom (two centres).
Study type, study period
Retrospective cohort study. Study period not reported.
Number of patients
95.
Patient characteristics
Inclusion criteria: patients presenting with a mass in the head and neck region that was palpable and accessible to puncture Mean age 51 years (range 5-75 years). **Gender**: Male 55 (57.9); Female 40 (42.1) **Site of mass or lesion**: Salivary gland 37 (38.9); Cervical lymph node 52 (54.7); Other 6 (6.3)
Type of test(s)
FNAC
Reference standard
Final histological diagnosis
Results
Inadequate or nondiagnostic samples: 29/95 Test result: Malignant — Results from reference standard: Malignant 27, Benign 1 Test result: Benign — Results from reference standard: Malignant 3, Benign 35 Sensitivity [95% CI]: 0.90 [0.73, 0.98] Specificity [95% CI]: 0.97 [0.85, 1.00]
Source of funding
Not reported.
Comments on study quality
Risks of bias: It is unclear whether patients enrolled were a random/consecutive sample. Concerns regarding applicability: no major concerns.
Additional comments

2

Study, country
Khan, 2013 India, single centre.
Study type, study period
Retrospective cohort study. Study period not reported.
Number of patients
229 (results available for 199)
Patient characteristics
Inclusion criteria: patients presenting with any complaints relating to the oral cavity in whom the index test was performed, and for whom subsequent histopathological diagnosis was available. **Gender**: Male 147 (64.2); Female 82 (35.8) **Site of mass or lesion**: Cheek 75 (32.8); Tongue 73 (31.9); Floor of mouth 27 (11.8); Lips 19 (8.3); Gingiva 18 (7.9); Palate 17 (7.4)
Type of test(s)
FNAC
Reference standard
Histopathological diagnosis

Results

Inadequate or nondiagnostic samples: 30/229

Test result	Results from reference standard	
	Malignant	Benign
Malignant	97	3
Benign	7	92

Sensitivity [95% CI]: 0.93 [0.87, 0.97]
Specificity [95% CI]: 0.97 [0.91, 0.99]

Source of funding

Not reported.

Comments on study quality

Risks of bias: It is unclear whether patients enrolled were a random/consecutive sample.
Concerns regarding applicability: Only patients with oral lesions were included.

Additional comments

1

Study, country

Kutluhan, 2003
Turkey, single centre.

Study type, study period

Retrospective cohort study.
Study period not reported.

Number of patients

219 (results available for 96)

Patient characteristics

Inclusion criteria: patients who had undergone FNAB of palpable head and neck masses that were accessible to puncture.
Exclusion criteria: thyroid masses.

Mean age 37 years (range 7 months to 82 years).

Gender	n (%)
Male	115 (52.5)
Female	104 (47.5)

Type of test(s)

FNAB

Reference standard

Histopathologic findings observed after surgery.

Results

Insufficient sample: 8/96 samples.

Test result	Results from reference standard	
	Malignant	Benign
Malignant	28	4
Benign	4	52

Sensitivity [95% CI]: 0.88 [0.71, 0.96]
Specificity [95% CI]: 0.93 [0.83, 0.98]

Source of funding

Not reported.

Comments on study quality

Risks of bias: It is unclear whether patients included were a random/consecutive sample, and over what timescale patients were recruited.
123/219 were excluded from the study because reference standard data was not available.
Concerns regarding applicability: Exact sites of head and neck masses not reported.

Additional comments

2

Study, country

Murthy, 1997
United Kingdom (single centre).

Study type, study period

Retrospective cohort study.
April 1991 to January 1994.

Number of patients

58

Patient characteristics

Inclusion criteria: patients with lesions of the head and neck who underwent FNAC and for whom a subsequent histological diagnosis was available.

Type of test(s)

FNAC (unguided).

Reference standard

Histological diagnosis.

Results

Inadequate or nondiagnostic samples: 10/58

Test result	Results from reference standard	
	Malignant	Benign
Malignant	14	2
Benign	4	28

Sensitivity [95% CI]: 0.78 [0.52, 0.94]
Specificity [95% CI]: 0.93 [0.78, 0.99]

Source of funding

Not reported.

Comments on study quality

Risks of bias: no major concerns.
Concerns regarding applicability: no major concerns.

Additional comments

1

Study, country

Raab, 1998
United States, single centre.

Study type, study period

Retrospective cohort study.
January 1995 to April 1996.

Number of patients

158

Patient characteristics

Inclusion criteria: Patients undergoing FNA of the parotid gland, submandibular gland, or level I or II neck.
Exclusion criteria: no clinical history available; less than 6 months of follow up information available

Mean age 55 years (range 1-99 years).

Gender	n (%)
Male	82 (51.9)
Female	76 (48.1)

Site of mass or lesion	n (%)
Parotid gland	81 (51.3)
Submandibular gland	34 (21.5)
Lateral neck (level I or II)	39 (24.7)
Other	4 (2.5)

Type of test(s)

FNAC

Reference standard

Clinical follow up.

Results

Inadequate or nondiagnostic samples: 7/158

Test result	Results from reference standard	
	Malignant	Benign
Malignant	41	0
Benign	7	103

Sensitivity [95% CI]: 0.85 [0.72, 0.94]
Specificity [95% CI]: 1.00 [0.96, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: no major concerns.
Concerns regarding applicability: no major concerns.

Additional comments

1

Study, country

Tandon, 2008
United Kingdom (single centre).

Study type, study period

Retrospective cohort study.
January 1996 to December 2005.

Number of patients

1,290

Patient characteristics

Inclusion criteria: head and neck cancer patients with palpable masses from any head and neck site, including thyroid, tested with FNAC.
Exclusion criteria: image-guided FNAC; site of lump: skin; inadequate or nondiagnostic FNAC sample; definitive diagnosis based on histology or clinical follow up not available.

Site of mass or lesion	n (%)
Lymph nodes	542 (43.7)
Thyroid	222 (17.9)
Salivary gland	293 (23.6)
Not reported	183 (14.8)

Type of test(s)

FNAC

Reference standard

Histological data from surgical excision, or clinical follow up in patients not undergoing surgery.

Results

Inadequate or nondiagnostic samples: 802/2092

Test result	Results from reference standard	
	Malignant	Benign
Malignant	435	12
Benign	51	792

Sensitivity [95% CI]: 0.90 [0.86, 0.92]
Specificity [95% CI]: 0.99 [0.97, 0.99]

Source of funding

Not reported.

Comments on study quality

Risks of bias:A high number of patients were excluded from the results due to a nondiagnostic or inadequate sample, or lack of reference standard data (802 and 610 of 2702 potentially eligible patients, respectively).
Concerns regarding applicability: 17.9% of patients had a thyroid mass; for 14.8% the location of the lesion was not reported.

Additional comments

2

Study, country

Veivers, 2012
Australia, single centre.

Study type, study period

Retrospective cohort study.
2000 to 2010.

Number of patients

37.

Patient characteristics

Inclusion criteria: patients presenting to a head and neck service with a lateral neck cyst.
Exclusion criteria: clinically evident primary malignancy.

Mean age: 41,3 years.

Type of test(s)

FNAC

Reference standard

Post-surgical histology

3

Results

Inadequate or nondiagnostic samples: 4/37

Test result	Results from reference standard	
	Malignant	Benign
Malignant	1	1
Benign	3	28

Sensitivity [95% CI]: 0.25 [0.01, 0.81]
Specificity [95% CI]: 0.97 [0.82, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: It is unclear whether patients enrolled were a random/consecutive sample.
Concerns regarding applicability: no major concerns.

Additional comments

1

Study, country

Wu, 2006
United States, single centre.

Study type, study period

Retrospective cohort study.
2003 to 2004.

Number of patients

111

Patient characteristics

Inclusion criteria: patients presenting with palpable head and neck masses to a tertiary medical care centre, with surgical follow up data available.

Type of test(s)

FNAC

Reference standard

Surgical diagnosis

Results

Inadequate or nondiagnostic samples: 40/111

Test result	Results from reference standard	
	Malignant	Benign
Malignant	61	1
Benign	9	0

Sensitivity [95% CI]: 0.87 [0.77, 0.94]
Specificity [95% CI]: 0.00 [0.00, 0.97]

Source of funding

Not reported.

Comments on study quality

Risks of bias: 200 patients were potentially eligible for the study, but 40 had a nondiagnostic sample and a further 89 had no follow up data available.
Concerns regarding applicability: Of the total eligible population (n = 200) 5% had thyroid masses. The proportion of thyroid masses for the 71 analysed patients was not reported. No patient demographic data was reported.

Additional comments

2

Study, country

Lo, 2007
Taiwan, single centre.

Study type, study period

Retrospective cohort study.
January 2005 to December 2005.

Number of patients

102

Patient characteristics

Inclusion criteria: suspicious malignant cervical lymph nodes diagnosed by various imaging studies.
Exclusion criteria: patients with known primary, or with head and neck cancer diagnosed during initial clinical or imaging investigations.

Type of test(s)

Ultrasound-guided FNAB

Reference standard

Biopsy and/or clinical follow up

Results

No insufficient/nondiagnostic samples were reported.

Test result	Results from reference standard	
	Malignant	Benign
Malignant	11	1
Benign	1	89

Sensitivity [95% CI]: 0.92 [0.62, 1.00]
Specificity [95% CI]: 0.99 [0.94, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: no patient characteristics reported.
Concerns regarding applicability: no major concerns.

Additional comments

1

Study, country

Robinson, 1999
United Kingdom, single centre.

Study type, study period

Retrospective cohort study.
1996 to 1997.

Number of patients

129

Patient characteristics

Inclusion criteria: patients referred for FNA at the centre's ultrasound guided cytology clinic.
Exclusion criteria: reference standard data not available.

Type of test(s)

Ultrasound guided FNA.

Reference standard

Biopsy.

Results

Inadequate or nondiagnostic samples: 45/129

Test result	Results from reference standard	
	Malignant	Benign
Malignant	36	1
Benign	1	45

Sensitivity [95% CI]: 0.97 [0.86, 1.00]
Specificity [95% CI]: 0.98 [0.88, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: no patient baseline characteristics reported. Very limited detail of reference standard reported. 292 patients were potentially eligible for the study, but 45 had a nondiagnostic sample and a further 164 had no biopsy data available, or a biopsy was not done.
Concerns regarding applicability: Approximately 41% of the study population had lesions at sites that may not be relevant to this review (thyroid; soft tissue).

Additional comments

2

Study, country

Pfeiffer, 2007
Germany, single centre.

Study type, study period

Retrospective cohort study.
April 2003 to April 2006.

Number of patients

88

Patient characteristics

Inclusion criteria: patients with unclear cervicofacial masses.

Type of test(s)

Core needle biopsy (ultrasound-guided)

Reference standard

Final diagnosis based on secondary histologic exam, clinical follow up, or further laboratory studies.

Results

Inadequate or nondiagnostic samples: 8/88

Test result	Results from reference standard	
	Malignant	Benign
Malignant	51	0
Benign	1	28

Sensitivity [95% CI]: 0.98 [0.90, 1.00]
Specificity [95% CI]: 1.00 [0.88, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: no patient baseline/demographic characteristics reported.
Concerns regarding applicability: 38.4% of patients had a history of previous malignancy; unclear if this is representative of typical patients.

Additional comments

1

Study, country

Shrestha, 2011
India (single centre).

Study type, study period

Prospective cohort study.
2005 to 2008.

Number of patients

97

Patient characteristics

Inclusion criteria: All patients who underwent CT examinations of the neck for evaluation of neck lesions or palpable neck masses.

Gender	%
Male	66
Female	34

Type of test(s)

CT.

Reference standard

Histopathological diagnosis

Results

Test result	Results from reference standard	
	Malignant	Benign
Malignant	55	0
Benign	2	40

Sensitivity [95% CI]: 0.96 [0.88, 1.00]
Specificity [95% CI]: 1.00 [0.91, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: 100 patients were studied but relevant outcome data is only reported for 97. The reason for this discrepancy is not clear..
Concerns regarding applicability: no major concerns.

Additional comments

2

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Index Test	Reference Standard	Outcomes
Adults initially referred with undiagnosed neck lumps suspected as cancer of the upper aerodigestive tract.	• FNAC (with or without ultrasound guidance; with or without same day confirmation of sample adequacy and same day reporting of diagnosis) • Core biopsy (with or without ultrasound guidance • Flexible nasendoscopy • Flexible transnasal oesophagoscopy • MRI • CT • Ultrasound With or without same-day access to cross-sectional imaging.	Final diagnosis based on cyto/histopathology/clinical imaging and follow up	• Sensitivity • Specificity • Test-related morbidity • Time to diagnosis • Patient reported outcomes (for example patient satisfaction

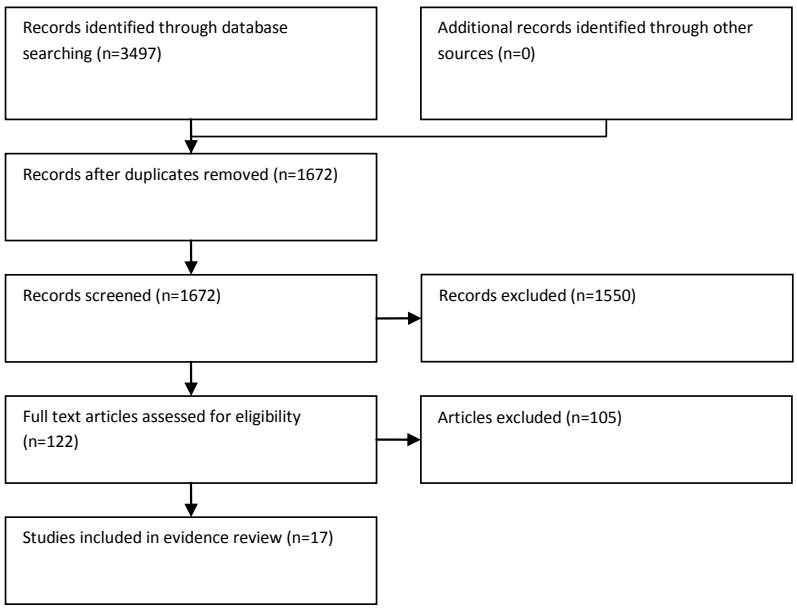
3

4 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Diagnostic test
Language	English only
Study design	Studies of diagnostic test accuracy
Status	Published studies only
Other criteria for inclusion / exclusion of studies	Inclusion criteria: sufficient data reported to calculate the total number of true positives, true negative, false positives, and false negatives for the studied test(s). Exclusion criteria: Reference standard is unclear or undefined.
Search strategies	Search from 1990 onwards. This is the date of the earliest evidence on any test included in the PICO.

Useful Search Terms	
Review strategies	The evidence table for studies of diagnostic accuracy will be used (NICE Guidelines Manual Appendix J) to extract and present data from individual studies. Sensitivity and specificity data will be pooled when appropriate. Other outcomes will be presented as risk ratios or hazard ratios. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender.

Figure 2.5. Study flow diagram



Included studies

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Altmann, C. and Clancy, D. Accuracy of fine needle aspiration cytology in patients presenting to the Princess Alexandra Hospital Combined Head and Neck Clinic. Australian Journal of Otolaryngology 1998. 3: 29-32

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Fulciniti, F., Califano, L., Zupi, A., and Vetrani, A. Accuracy of fine needle aspiration biopsy in head and neck tumors. Journal of Oral and Maxillofacial Surgery 1997. 55: 1094-1097

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Excluded studies

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Editorial/narrative review.

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Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Population not relevant to PICO.

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Burgess, C. Neck lump clinics: is on-site assessment of fine needle aspirate diagnostic adequacy cost-effective? Journal of Laryngology & Otology 2013. 127(11): 1122-1126.
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Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Individual case report.

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Reason for exclusion: Insufficient outcome data reported (conference abstract).

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Reason for exclusion: Non English publication.

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Reason for exclusion: Study design not relevant.

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Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Study design not relevant.

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Reason for exclusion: Study design not relevant.

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Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Population not relevant to PICO.

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Reason for exclusion: Insufficient outcome data available.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Study design not relevant.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Population not relevant to PICO.

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Identifying the occult primary

Clinical question: What is the most effective investigative pathway for identifying the occult primary site in patients presenting with metastatic neck disease (squamous cell carcinoma)?

Background

A small proportion of patients with head and neck cancer present with a neck lump and no clinical evidence of cancer in the UADT mucosa. Identification of the primary tumour is important to guide treatment planning and follow-up. When a primary tumour is not evident current practice involves biopsy of several mucosal sites. While there is broad consensus to perform radiological investigations prior to biopsy there is no agreement on the precise tests to be used. This may result in a delay in the diagnostic process.

Evidence summary

Narrow band imaging

Five relevant studies (Hayashi 2010, Masaki 2012, Ryu 2013, Sakai 2010, Shinozaki 2012) were identified that investigated the accuracy of narrow band imaging (NBI) for identifying an occult primary tumour of suspected upper aerodigestive tract origin, including a total of 136 patients. Based on the pooled results of these studies, the sensitivity and specificity of NBI was estimated to be 0.77 (95 % confidence interval [CI] 0.50, 0.921) and 0.84 (95% CI 0.68, 0.93), respectively. Three out of five studies were at risk of bias due to lack of clear reporting on how patients were selected; in the same three studies, it is unclear if all the patients were relevant to the review question, due to a lack of reporting of patient characteristics. All five studies reported limited details of what reference standard was used, and whether this was the same for all patients.

Cross-sectional imaging

Twenty relevant studies were identified that investigated the accuracy of various cross-sectional imaging techniques for identifying an occult primary tumour of suspected upper aerodigestive tract origin. Two systematic reviews were also identified, but as these have a broader scope than this review, they have been used as sources of study data only (refer to Section 5 for further detail).

Based on the combined results of 13 trials (Aassar 1999, Bohuslavizki 2000, Braams 1997, Freudenberg 2005, Greven 1999, Johansen 2008, Jungehulsing 2000, Miller 2008, Regelink 2002, Safa 1999, Silva 2007, Stoeckli 2003, Yabuki 2010; total studied population: 363) the sensitivity of PET was estimated as 0.78 (95 % CI 0.70, 0.84) and the specificity as 0.76 (95% CI 0.66, 0.83). There was a risk of patient selection bias in 8/13 studies, due to a lack of reporting of how patients were selected for the study (and whether a random/consecutive sample was used). There were concerns over applicability for 9/13 studies, due either to inclusion of some patients not relevant to the review question, or insufficient reporting of patient characteristics.

Based on the combined results of five trials (Freudenberg 2005, Pattani 2011, Prowse 2012, Roh 2009, Wong 2012; total studied population: 198) the sensitivity of PET-CT was estimated as 0.89 (95 % confidence interval [CI] 0.79, 0.95) and the specificity as 0.73 (95% CI 0.62, 0.82). There were

concerns over applicability for 2/5 studies, due to inclusion of a notable proportion of patients (25–33%) with non-squamous cell carcinoma histologies. Additionally, two studies did not report how patients were recruited (and whether a random/consecutive sample was used).

Based on the combined results of four trials (Freudenberg 2005, Mukherji 1996, Roh 2009, van Veen 2001; total studied population: 88) the sensitivity of CT was estimated as 0.44 (95 % confidence interval [CI] 0.30, 0.58) and the specificity as 0.75 (95% CI 0.57, 0.88). There were concerns over applicability for 2/4 studies, due to inclusion of a notable proportion of patients (25–33%) with non-squamous cell carcinoma histologies. Three out of four studies did not report the methods by which patients were recruited; it is therefore unclear whether this was carried out in unbiased manner.

One trial (van Veen 2001, 15 patients) reported the sensitivity and specificity of MRI as 0.00 (95% confidence interval (CI) 0.00, 0.71) and 0.67 (95% CI 0.35, 0.90), respectively. This evidence comes from a subgroup of patients (n = 32) within a larger trial; it is not clear how patients were selected for inclusion in the trial, or what criteria were used to select them to receive MRI or another test.

Two further trials tested a combination or mixture of imaging techniques (results reported in Tables 1 and 2).

Transoral surgery techniques

Three relevant studies were identified (Karni 2011, Mehta 2013, Patel 2013; total studied population: 85) that investigated the accuracy of transoral robotic surgery or transoral laser microsurgery for identifying an occult primary tumour of suspected upper aerodigestive tract origin. Reported values for sensitivity and specificity were 0.90–1.00 and 1.00, respectively. For all three trials, there was a risk of bias due to a lack of clear definition of the reference standard used; it is assumed patients were followed up, but it is unknown whether this was applied consistently across the cohort. Additionally, in one trial the range of tests received prior to the index test varied within the cohort. Some of these patients may be 'undertested' compared to the likely target population.

Other investigations

No evidence was identified on the diagnostic accuracy of examination under anaesthesia or nasendoscopy for the identification of an occult primary tumour of suspected upper aerodigestive tract origin.

Study characteristics and quality

Table 2.4 summarises the characteristics of all identified studies. Figure 2.6~~Figure 2.6~~~~Figure 2.6~~ summarises study quality and applicability according to the QUADAS-2 checklist.

Included studies were generally small and conducted at a single centre. Across all tests, study results were published between 1996 and 2013. Evidence on narrow band imaging and surgery is more recent; all included studies were published between 2010 and 2013.

In many studies, the information reported on patient characteristics was limited, making it difficult to assess the comparability of different study populations. Most studies reported the investigations used to attempt to identify the occult primary tumour before the index test was carried out, but the level of investigation varied between studies. This may result in differences between the study populations, as patients who have undergone more exhaustive investigation before the index test may have tumours which are more difficult to locate. Furthermore, patients in the PET and PET-CT

studies had in general undergone more exhaustive investigation before the index test than patients in studies of other cross-sectional imaging techniques. The diagnostic accuracy of different cross-sectional imaging tests therefore may not be directly comparable.

In several studies, the criteria for patient selection (and therefore whether an unbiased sample of patients was chosen) were not clear. Where the methods of patient selection were reported, all but one study used either a random or consecutive sample of patients. However, one study had 'inadequate diagnostic evaluation' as an exclusion criterion, which may have resulted in the exclusion of difficult-to-diagnose patients and therefore an overly optimistic estimate of diagnostic accuracy.

Patients with an occult primary tumour of squamous cell carcinoma (SCC) histology were included in the review protocol, but many studies included patients with SCC and other histologies. Studies were included in the review only if the majority of cases were SCC.

Most studies compared the index test with histopathological results from directed (for positive imaging results) or random (for negative imaging results) biopsies as the reference standard. Few studies reported on the length of time patients were followed up for, and whether any primary tumours were found during follow up in patients deemed 'negative' on the basis of initial investigations. None of the studies of transoral surgical investigations included a clearly specified reference standard. Reference is made to the use of histopathology and/or follow up to verify the results of the index test, but it is not clear whether this was applied consistently for every patient in the study.

Results from the three studies of transoral surgical investigations have not been pooled due to heterogeneity in the study designs, and uncertainty over some aspects of study design. It is not clear if each study used a comparable reference standard (see above), and the level of diagnostic workup, and hence the likelihood of identifying a primary tumour using the index test, varied from study to study. Furthermore, one study (Patel 2013) included patients in whom the location of the primary site was suspected (based on prior investigations) but not yet confirmed, whereas patients of this nature were excluded from the remaining two relevant studies.

Table 2.4. Characteristics of included studies

Study ID	Year	Number of patients	Tumour confirmed as SCC, %	Diagnostic work up (brackets denote an investigation that was not carried out in all patients)	Reference standard
NBI					
Hayashi	2010	46	100	CT, MRI, pharyngolaryngoscopy or white light endoscopy	Histopathology/follow up
Masaki	2012	11	100	Clinical examination	Biopsy and follow up
Ryu	2013	30	66.7	Physical examination Endoscopic examination Imaging (CT and/or MR of the head and neck)	Biopsy and/or imaging (PET-CT)
Sakai	2010	21	NR	NR	Follow up/imaging
Shinozaki	2012	28	100	White light laryngoscopy	PET-CT and/or follow up
PET					
Aassar	1999	15	93.3	Clinical examination	Biopsy Follow up
Bohuslavizki	2000	52	56.6	History Physical examination Chest radiography (Sonography) (Panendoscopy with biopsies)	Biopsy
Braams	1997	13	76.9	Physical examination CT and/or MRI	Biopsy of the oropharynx, hypopharynx, nasopharynx and upper oesophagus
Freudenberg*	2005	21	66.7	NR	Biopsy/histopathology (n=14) or follow up (n=7)
Greven	1999	13	NR	CT or MRI Panendoscopy	Panendoscopy and biopsy

Study ID	Year	Number of patients	Tumour confirmed as SCC, %	Diagnostic work up (brackets denote an investigation that was not carried out in all patients)	Reference standard
Johansen	2008	60	73	Panendoscopy of the pharynx, larynx, bronchi, oesophagus Random mucosal biopsies Tonsillectomy Chest X-ray or CT Ultrasonography of the neck CT or MRI of the head and neck	Panendoscopy/follow up
Jungehulsing	2000	27	66.7	Medical history Physical examination Chest radiography Full blood count Cervical and abdominal ultrasound Panendoscopy MRI or CT from the nasopharynx to the diaphragm with tonsillectomy for any suspicious findings	Fine needle aspiration cytology, biopsy or surgery.
Miller	2008	31	100	Endoscopy of the upper aerodigestive tract CT and/or MRI Chest X-ray	Biopsies from the tongue base and nasopharynx (directed or random); histopathologic tonsil examination
Regelink	2002	50	60	Clinical examination Fibre-optic endoscopy Contrast-enhanced MRI	Biopsy, histology
Safa	1999	14	100	Complete history (n=50) Physical examination (n=50) CT (n=30) MRI (n=30) Panendoscopy of the upper aerodigestive tract (n=45)	Panendoscopy under anaesthesia with inspection of the nasopharynx, orophaynx, hypopharynx, larynx, bronchi and oesophagus and biopsies taken from all suspected areas.
Silva	2007	25	100	Full clinical examination CT and/or MRI	Examination under anaesthesia and when necessary biopsy of the nasopharynx, tonsil and tongue base. Follow up.

Study ID	Year	Number of patients	Tumour confirmed as SCC, %	Diagnostic work up (brackets denote an investigation that was not carried out in all patients)	Reference standard
Stoeckli	2003	18	100	Transnasal fibre-endoscopy of the nasal cavity, nasopharynx, oropharynx, hypopharynx and larynx CT of the neck Chest X-ray in the postero-anterior and lateral views Fine-needle aspiration cytology of the neck metastasis	Panendoscopy with or without diagnostic tonsillectomy
Yabuki	2010	24	75	Medical history Physical examination Full blood count CT from the nasopharynx to the diaphragm MRI from the nasopharynx to the subclavia Cervical ultrasound Panendoscopy	Histological diagnosis based on direct biopsy (in patients with a positive test result) or examination under anaesthesia of the at-risk occult tumour sites (in patients with a negative test result).
PET-CT					
Freudenberg*	2005	21	66.7	NR	Biopsy/histopathology (n=14) or follow up (n=7)
Pattani	2011	23	100	Clinical examination Nasopharyngolaryngoscopy Chest radiography	Direct panendoscopy and routine speculative biopsies of the nasopharynx, tonsils, tongue base and piriform sinuses.
Prowse	2012	32	90.6	History and physical examination of the head and neck Fibreoptic transnasal endoscopy of the nasal cavity , nasopharynx, oropharynx, hypopharynx and larynx Posteroanterior and lateral chest X-rays Contrast-enhanced high-resolution CT of the neck	Biopsies from the nasopharynx, tongue base and piriform sinuses (directed or random); ipsilateral tonsillectomy.
Roh*	2009	44	75	Physical and endoscopic examination	Panendoscopy and guided biopsy of the tonsils, tongue base, nasopharynx and other sites suspected of harbouring primary tumours
Wong	2012	78	97.4	Flexible fibre optic nasendoscopy CT and/or MR Examination under anaesthesia biopsies of all suspicious sites (n = 58) Tonsillectomy (n = 30)	Histopathological diagnosis and follow up

Study ID	Year	Number of patients	Tumour confirmed as SCC, %	Diagnostic work up (brackets denote an investigation that was not carried out in all patients)	Reference standard
PET or PET-CT					
Cianchetti	2009	21	100	Complete history and physical examination Chest radiography CT and/or MRI	Biopsy
MRI					
van Veen*	2001	14	62.5	Mirror and/or endoscopic evaluation	Biopsy (directed or random) of the nasophrynx, tonsil and base of tongue.
CT					
Freudenberg*	2005	21	66.7	NR	Biopsy/histopathology (n=14) or follow up (n=7)
Mukherji	1996	17	100	Clinical examination Nasopharyngolaryngoscopy Chest radiography	Direct panendoscopy and routine speculative biopsies of the nasopharynx, tonsils, tongue base and piriform sinuses.
Roh*	2009	44	75	Physical and endoscopic examination	Panendoscopy and guided biopsy of the tonsils, tongue base, nasopharynx and other sites suspected of harbouring primary tumours
van Veen*	2001	5	62.5	Mirror and/or endoscopic evaluation	Biopsy (directed or random) of the nasophrynx, tonsil and base of tongue.
CT and MRI					
van Veen*	2001	10	62.5	Mirror and/or endoscopic evaluation	Biopsy (directed or random) of the nasophrynx, tonsil and base of tongue.
Transoral surgery					
Karni	2011	18	NR	Flexible laryngoscopy Imaging using CT or MRI	Not specified, but assumed to be histopathology/clinical follow up

Study ID	Year	Number of patients	Tumour confirmed as SCC, %	Diagnostic work up (brackets denote an investigation that was not carried out in all patients)	Reference standard
Mehta	2013	10	100	Flexible laryngoscopy Imaging using CT, MRI and/or PET-CT Examination under anaesthesia Random biopsies of the base of tongue and pharynx Tonsillectomy	Not specified, but assumed to be clinical follow up
Patel	2013	47	100	Cross-sectional imaging Physical examination Previous biopsy of the larynx or pharynx	Not specified, but assumed to be clinical follow up
*indicates studies in which more than one index test was evaluated. Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging; NBI: narrow band imaging; NR: not reported; PET: positron emission tomography; PET-CT: positron emission tomography- computed tomography; SCC: squamous cell carcinoma.					

1

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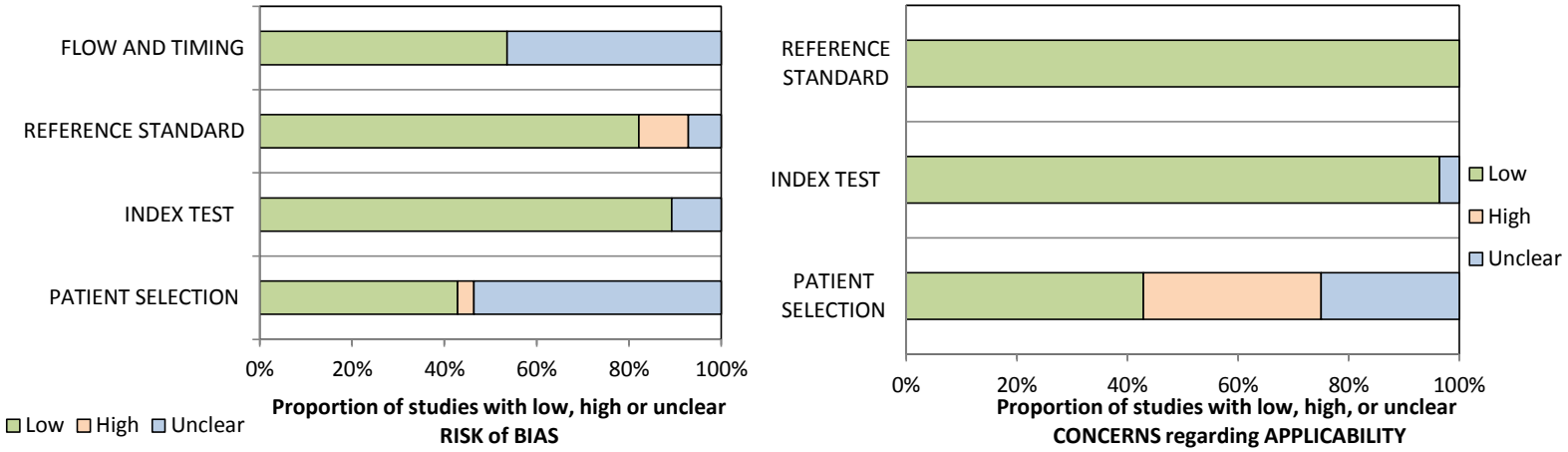
Figure 2.6. Summary of study quality (risks of bias and concerns regarding applicability)



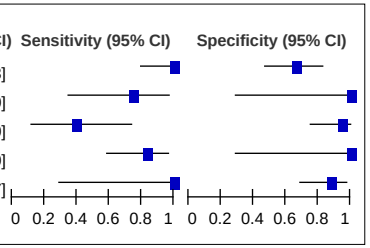
Outcomes

Table 2.5. Summary of the diagnostic accuracy of all tests.

Tests with evidence from multiple studies					
Test	**Number of studies**	**Total number of patients**	**Sensitivity [95% CI]**	**Specificity [95% CI]**	**AUC**
NBI	5	136	0.77 [0.50, 0.92]	0.83 [0.68, 0.93]	0.88
PET	13	363	0.78 [0.70, 0.84]	0.76 [0.66, 0.83]	0.78
PET-CT	5	198	0.89 [0.79, 0.95]	0.73 [0.62, 0.82]	0.89
CT	4	88	0.44 [0.30, 0.58]	0.75 [0.57, 0.88]	0.41
Transoral surgical techniques	3	85	0.90–1.00	1.00	N/A
Tests with evidence from a single study					
Test	**Number of studies**	**Total number of patients**	**Sensitivity [95% CI]**	**Specificity [95% CI]**	
PET or PET-CT	1	21	0.21 [0.05, 0.51]	0.71 [0.29, 0.96]	
MRI	1	15	0.00 [0.00, 0.71]	0.67 [0.35, 0.90]	
CT + MRI	1	9	1.00 [0.29, 1.00]	0.83 [0.36, 1.00]	
Abbreviations: AUC: area under the curve; CT: computed tomography; MRI: magnetic resonance imaging; N/A: not available; NBI: narrow band imaging; PET: positron emission tomography; PET-CT: positron emission tomography- computed tomography; SCC: squamous cell carcinoma.					

Figure 2.7. Summary of evidence for the diagnostic accuracy of NBI. (a) forest plot of sensitivity and specificity for all identified evidence. (b) receiver operating characteristic (ROC) plot of all identified studies.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hayashi 2010	16	10	0	20	1.00 [0.79, 1.00]	0.67 [0.47, 0.83]
Masaki 2012	6	0	2	3	0.75 [0.35, 0.97]	1.00 [0.29, 1.00]
Ryu 2013	4	1	6	19	0.40 [0.12, 0.74]	0.95 [0.75, 1.00]
Sakai 2010	15	0	3	3	0.83 [0.59, 0.96]	1.00 [0.29, 1.00]
Shinozaki 2012	3	3	0	22	1.00 [0.29, 1.00]	0.88 [0.69, 0.97]



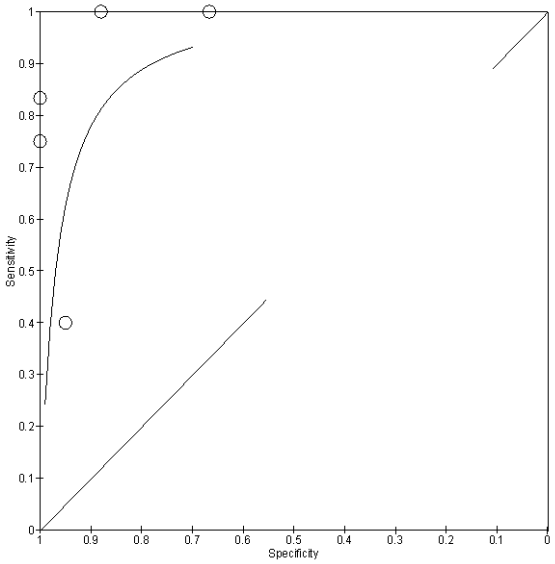
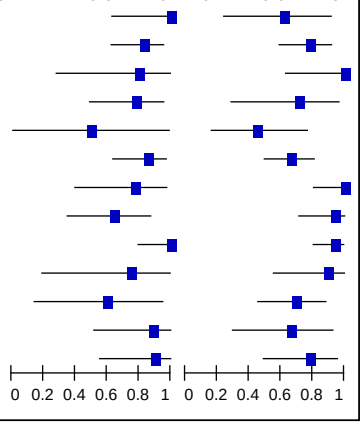


Figure 2.8. Summary of evidence for the diagnostic accuracy of PET. (a) forest plot of sensitivity and specificity for all identified evidence. (b) receiver operating characteristic (ROC) plot of all identified studies.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Aassar 1999	8	3	0	5	1.00 [0.63, 1.00]	0.63 [0.24, 0.91]
Bohuslavizki 2000	20	6	4	22	0.83 [0.63, 0.95]	0.79 [0.59, 0.92]
Braams 1997	4	0	1	8	0.80 [0.28, 0.99]	1.00 [0.63, 1.00]
Freudenberg 2005	11	2	3	5	0.79 [0.49, 0.95]	0.71 [0.29, 0.96]
Greven 1999	1	6	1	5	0.50 [0.01, 0.99]	0.45 [0.17, 0.77]
Johansen 2008	18	13	3	26	0.86 [0.64, 0.97]	0.67 [0.50, 0.81]
Jungehulsing 2000	7	0	2	17	0.78 [0.40, 0.97]	1.00 [0.80, 1.00]
Miller 2008	9	1	5	16	0.64 [0.35, 0.87]	0.94 [0.71, 1.00]
Regelink 2002	16	2	0	32	1.00 [0.79, 1.00]	0.94 [0.80, 0.99]
Safa 1999	3	1	1	9	0.75 [0.19, 0.99]	0.90 [0.55, 1.00]
Silva 2007	3	6	2	14	0.60 [0.15, 0.95]	0.70 [0.46, 0.88]
Stoeckli 2003	8	3	1	6	0.89 [0.52, 1.00]	0.67 [0.30, 0.93]
Yabuki 2010	9	3	1	11	0.90 [0.55, 1.00]	0.79 [0.49, 0.95]



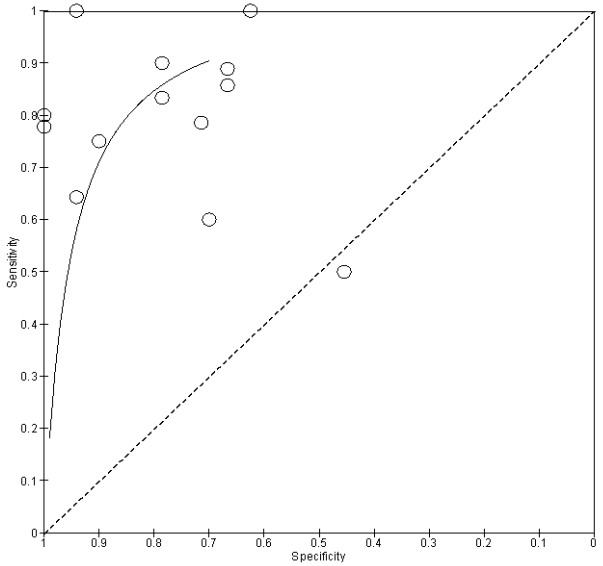
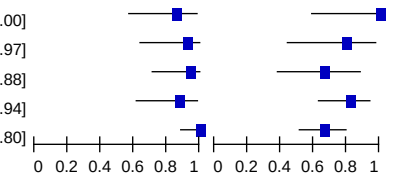


Figure 2.9. Summary of evidence for the diagnostic accuracy of PET-CT. (a) forest plot of sensitivity and specificity for all identified evidence. (b) ROC plot of all identified studies.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Freudenberg 2005	12	0	2	7	0.86 [0.57, 0.98]	1.00 [0.59, 1.00]
Pattani 2011	12	2	1	8	0.92 [0.64, 1.00]	0.80 [0.44, 0.97]
Prowse 2012	16	5	1	10	0.94 [0.71, 1.00]	0.67 [0.38, 0.88]
Roh 2009	14	5	2	23	0.88 [0.62, 0.98]	0.82 [0.63, 0.94]
Wong 2012	30	16	0	32	1.00 [0.88, 1.00]	0.67 [0.52, 0.80]



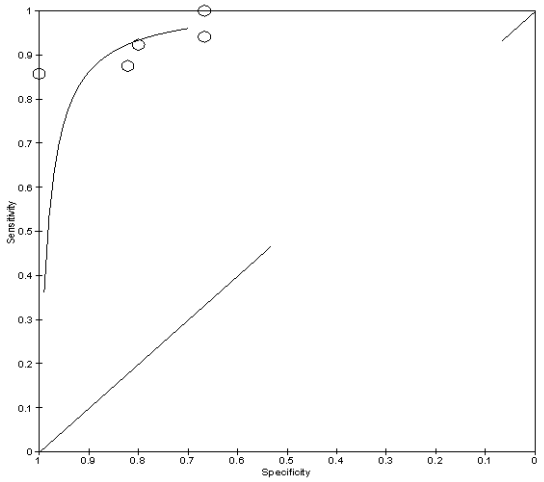
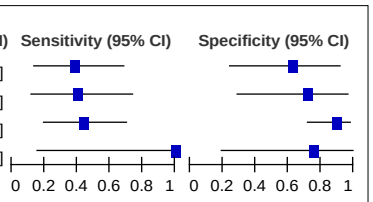


Figure 2.10. Summary of evidence for the diagnostic accuracy of CT. (a) forest plot of sensitivity and specificity for all identified evidence. (b) ROC plot of all identified studies.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Freudenberg 2005	5	3	8	5	0.38 [0.14, 0.68]	0.63 [0.24, 0.91]
Mukherji 1996	4	2	6	5	0.40 [0.12, 0.74]	0.71 [0.29, 0.96]
Roh 2009	7	3	9	25	0.44 [0.20, 0.70]	0.89 [0.72, 0.98]
van Veen 2001	2	1	0	3	1.00 [0.16, 1.00]	0.75 [0.19, 0.99]



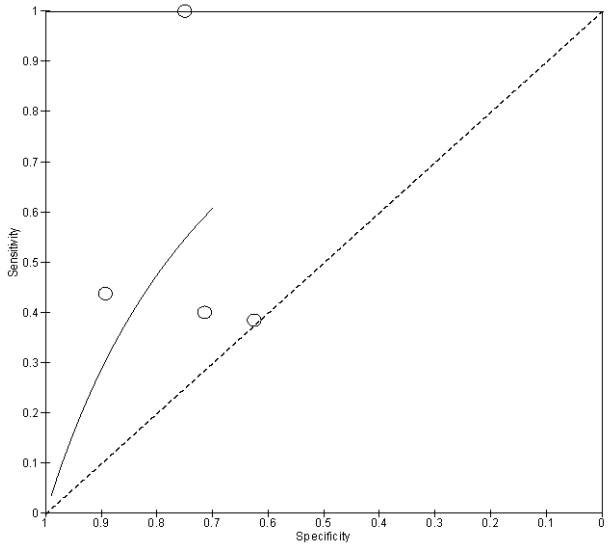
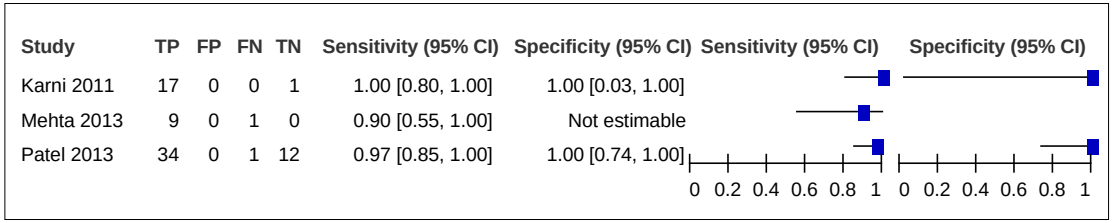


Figure 2.11. Summary of evidence for the diagnostic accuracy of transoral surgery techniques: forest plot of sensitivity and specificity for all identified evidence.



Evidence tables for all included studies

Studies of narrow band imaging

Study, country
Hayashi 2010 Japan, single centre.
Study type, study period
Retrospective cohort study. January 2003 to December 2006.
Number of patients
46
Patient characteristics
Consecutive patients with primary unknown lymph node metastasis, in whom a primary tumour could not be detected using CT, MRI, pharyngolaryngoscopy or white light endoscopy.
Type of test(s)
Narrow band imaging of the head and neck region and the cervical oesophagus
Reference standard
Histopathology/follow up
Results

Test result	**Results from reference standard**	
	Primary tumour present	**Primary tumour absent**
Test positive	16	10
Test negative	0	20

Sensitivity [95% CI]: 1.00 [0.79, 1.00]
Specificity [95% CI]: 0.67 [0.47, 0.83]

Source of funding
Not reported. Authors declared no conflicts of interest.
Comments on study quality
Risks of bias: The reference standard is not clearly defined by the study authors; it is not clear if all patients received the same reference standard. Concerns regarding applicability: no major concerns.
Additional comments

Study, country
Masaki 2012 Japan, single centre.
Study type, study period
Retrospective cohort study. September 2006 to December 2009.
Number of patients
11
Patient characteristics
Inclusion criteria: diagnosis of cervical lymph node metastasis from an unknown primary site. Exclusion criteria: history of other head and neck cancer; non-squamous cell carcinoma histology; patients whose tumours could be diagnosed on white light endoscopy without NBI examination. Diagnostic workup: clinical examination of oral cavity, pharynx and larynx.
Type of test(s)
Narrow band imaging.
Reference standard
Biopsy and follow up.
Results

Test result	**Results from reference standard**	
	Primary tumour present	**Primary tumour absent**
Test positive	6	0
Test negative	2	3

Sensitivity [95% CI]: 0.75 [0.35, 0.97]
Specificity [95% CI]: 1.00 [0.29, 1.00]

Source of funding
Not reported. Authors declared no conflicts of interest.
Comments on study quality
Risks of bias: The reference standard is not clearly defined by the study authors; it is not clear if all patients received the same reference standard. Criteria for patient selection (and whether random/consecutive) is unclear. Concerns regarding applicability: Limited detail reported on the characteristics of patients included in the study.
Additional comments

1

Study, country
Ryu 2013 Korea, single centre.
Study type, study period
Retrospective cohort study. May 2009 to May 2011.
Number of patients
30
Patient characteristics
Consecutive patients newly diagnosed with cancer of unknown primary. Prior diagnostic workup: physical and endoscopic examination, imaging (CT and/or MR of the head and neck).
Type of test(s)
Narrow band imaging.
Reference standard
Biopsy and/or imaging (PET-CT).
Results

Test result	**Results from reference standard**	
	Primary tumour present	**Primary tumour absent**
Test positive	4	1
Test negative	6	19

Sensitivity [95% CI]: 0.40 [0.12, 0.74]
Specificity [95% CI]: 0.95 [0.75, 1.00]

Source of funding
Not reported.
Comments on study quality
Risks of bias: The reference standard is not clearly defined by the study authors; it is not clear if all patients received the same reference standard. Concerns regarding applicability: no major concerns.
Additional comments

2

Study, country
Sakai 2010 Japan, single centre.
Study type, study period
Retrospective cohort study. 2006 to 2009.
Number of patients
21
Patient characteristics
Inclusion criteria: patients with cervical lymph node metastasis from an unknown primary site. Prior diagnostic workup was not reported.
Type of test(s)
Narrow band imaging.
Reference standard
Follow up/imaging.

3

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	15	0
Test negative	3	3

Sensitivity [95% CI]: 0.83 [0.59, 0.96]
Specificity [95% CI]: 1.00 [0.29, 1.00]

Source of funding

Not reported. Authors declared no conflicts of interest or financial interests.

Comments on study quality

Risks of bias: Unclear whether a consecutive/random sample of patients was studied. The reference standard is not clearly defined by the study authors; it is not clear if all patients received the same reference standard.
Concerns regarding applicability: No detail of patient characteristics reported. Diagnostic workup prior to the index test is not reported.

Additional comments

1

Study, country

Shinozaki 2012
Japan, single centre.

Study type, study period

Retrospective cohort study.
January 2003 to July 2009.

Number of patients

28

Patient characteristics

Inclusion criteria: squamous cell carcinoma (determine by cytologic examination) with an unknown primary tumour that could not be detected by white light laryngoscopy

Type of test(s)

Narrow band imaging

Reference standard

PET-CT and/or follow up

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	3	3
Test negative	0	22

Sensitivity [95% CI]: 1.00 [0.29, 1.00]
Specificity [95% CI]: 0.88 [0.69, 0.97]

Source of funding

Comments on study quality

Risks of bias: Unclear whether a consecutive/random sample of patients was studied. The reference standard is not clearly defined by the study authors; it is not clear if all patients received the same reference standard
Concerns regarding applicability: No detail of patient characteristics reported.

Additional comments

2

Studies of cross-sectional imaging techniques

Study, country

Aassar, 1999
United States, single centre.

Study type, study period

Retrospective cohort study.
Study period not reported.

Number of patients

15

Patient characteristics

Inclusion criteria: metastatic cervical adenopathy of presumed head and neck region.

Conventional diagnostic work up: Clinical examination.

Gender	n (%)
Male	13 (86.7)
Female	2 (13.3)

Histology	n (%)
Squamous cell carcinoma	14 (93.3)
Adenocarcinoma	1 (6.7)

Site of primary tumour was identified in 7/15 (46.7%) patients.

Type of test(s)

PET

Reference standard

Biopsy and follow up

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	8	3
Test negative	0	5

Sensitivity [95% CI]: 1.00 [0.63, 1.00]
Specificity [95% CI]: 0.63 [0.24, 0.91]

Source of funding

Not reported.

Comments on study quality

Risks of bias: Criteria for patient selection (and whether random/consecutive) is unclear.
Concerns regarding applicability: no major concerns.

Additional comments

One patient had two primary tumours identified by PET and both were confirmed by the reference standard; this has been counted as two true positives.

Study, country

Bohuslavizki 2000
Germany.

Study type, study period

Retrospective cohort study.
January 1997 to January 1999.

Number of patients

52

Patient characteristics

Patients presented with metastases from unknown primary sites. 44 patients had cervical metastatic adenopathy; 9 others had extracervical metastases.

Conventional diagnostic workup included history, physical examination and chest radiography. Patients with carcinoma confined to the cervical lymph nodes also underwent sonography and panendoscopy with direct biopsies.

Gender	n (%)
Male	33 (62.2)
Female	20 (37.7)

Histology	n (%)
Squamous cell carcinoma	30 (56.6)
Undifferentiated carcinoma	8 (15.1)
Adenocarcinoma	3 (5.6)
Lymphoepitheliomatous carcinoma	1 (1.9)
Unconclusive	11 (20.8)

Type of test(s)

PET.

Reference standard

Biopsy. No details given on whether directed or random, and how PET results influenced this.

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	20	6
Test negative	4	22

Sensitivity [95% CI]: 0.83 [0.63, 0.95]
Specificity [95% CI]: 0.79 [0.59, 0.92]

Source of funding

Not reported.

Comments on study quality

Risks of bias: Very limited detail of reference standard used. Criteria for patient selection (and whether random/consecutive) is unclear.
Concerns regarding applicability: Study population included non-SCC histologies and patients presenting with non-neck metastases. 28/53 patients met the population specified in the PICO.

Additional comments

One patient refused follow up biopsy and is excluded from the results.

1

Study, country

Braams 1997.
Netherlands, single centre.

Study type, study period

Retropective cohort study.
Study period not reported.

Number of patients

13

Patient characteristics

Patients referred for evaluation of metastatic lymph nodes of the neck region with an unknown primary tumour.

Mean age: 58 years (range 42-77)

Conventional diagnostic work up included physical examination, CT and/or MRI.

Gender	n (%)
Male	10 (76.9)
Female	3 (23.1)

Histology	n (%)
Squamous cell carcinoma	10 (76.9)
Other	3 (23.1)

Type of test(s)

PET.

Reference standard

Endoscopy of the oropharynx, hypopharynx, nasopharynx and upper oesophagus; suspect areas were biopsied.

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	4	0
Test negative	1	8

Sensitivity [95% CI]: 0.80 [0.28, 0.99]
Specificity [95% CI]: 1.00 [0.63, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: Criteria for patient selection (and whether random/consecutive) is unclear. Limited detail reported of the reference standard used.
Concerns regarding applicability: 23% of patients had non-SCC histologies.

Additional comments

2

Study, country

Cianchetti, 2009
United States, single centre.

Study type, study period

Retrospective cohort study.
June 1983 to December 2008.

Number of patients

21 patients underwent the index test; 236 patients included in study overall (see comments on study quality/additional comments)

Patient characteristics

Inclusion criteria: patients who presented with metastatic cervical adenopathy; an unknown primary site; squamous cell carcinoma and an upper neck presentation with the bulk of the metastatic adenopathy in level 2 or level 3. Patients were enrolled where conventional diagnostic work up failed to identify a primary tumour.
Exclusion criteria: bulk of disease in the low neck (primary lesion presumed to be below the clavicles); metastases located in the parotid tail lymph nodes; primary diagnosed before referral to the study institution; primary site detected on physical examination at the study institution; inadequate diagnostic evaluation; cervical adenopathy secondary to a previously diagnosed primary cancer; and prior treatment.

Conventional diagnostic workup prior to the index test consisted of complete history and physical examination; chest radiography; CT and/or MRI.

Gender	n (%)
Male	205 (85)
Female	31 (13)

Nodal staging	n (%)
N1	29 (12.3)
N2a	54 (22.9)
N2b	70 (29.7)
N2c	22 (9.3)
N3	55 (21.2)
NX	6 (2.5)

Mean age: 59 years (range 25-92).

Site of primary tumour was identified in 14/21 (66.7%) of patients. For the entire study population, the primary was identified in 126/236 (53.4%).

Type of test(s)

PET or PET-CT.

Reference standard

Diagnosis based on panendoscopy with directed biopsies.

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	3	2
Test negative	11	5

Sensitivity [95% CI]: 0.21 [0.05, 0.51]
Specificity [95% CI]: 0.71 [0.29, 0.96]

Source of funding

Not reported

Comments on study quality

Risks of bias: "inadequate diagnostic evaluation" was an exclusion criterion. This may have resulted in the exclusion of difficult-to-diagnose patients and an overly optimistic estimate of test performance. Furthermore it is unclear how patients were chosen to receive PET or PET-CT from the battery of tests used in the study (see additional comments).
Concerns regarding applicability: no major concerns.

Additional comments

Study participants (n = 236) received one or more of a range of tests. Of these, only the group receiving PET or PET/CT (n = 21) met the inclusion criteria for the review.

The number of patients receiving each technique (i.e. how many received PET and how many received PET-CT) was not reported.

1

Study, country

Freudenberg 2005.
Germany, single centre (assumed).

Study type, study period

Retrospective cohort study.
November 2001 to August 2003.

Number of patients

21

2

Patient characteristics

Patients with cytologically or histologically proven cervical lymph node metastases.

Details of diagnostic work up not reported.

Gender	n (%)
Male	16 (76.2)
Female	5 (23.8)

Histology	n (%)
Squamous cell carcinoma	14 (66.7)
Other	7 (33.3)

Mean age 64 years (range 46-94).

Type of test(s)

PET
PET-CT
CT

Reference standard

Histopathology (n=14) or clinical follow up for a minimum of 9 months (n=7)

Results

CT result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	5	3
Test negative	8	5

Sensitivity [95% CI]: 0.38 [0.14, 0.68]
Specificity [95% CI]: 0.63 [0.24, 0.91]

PET result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	11	2
Test negative	3	5

Sensitivity [95% CI]: 0.79 [0.49, 0.95]
Specificity [95% CI]: 0.71 [0.29, 0.96]

PET-CT result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	12	0
Test negative	2	7

Sensitivity [95% CI]: 0.86 [0.57, 0.98]
Specificity [95% CI]: 1.00 [0.59, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: Criteria for patient selection (and whether random/conscutive) is unclear. Reference standard was histopathology with or without follow up. Only 33% of patients were followed up for at least 9 months.
Concerns regarding applicability: 33% of patients had non-SCC histologies.

Additional comments

1

Study, country

Greven 1999.
United States, single centre.

Study type, study period

Prospective cohort study.
Study period note reported.

Number of patients

17 initially included; results reported for 13.

Patient characteristics

Patients with occult primary tumours in whom initial clinical evaluation of the head and neck suggested a diagnosis of squamous cell carcinoma involving neck lymph nodes from an occult primary.

Diagnostic work up: CT (n=12) or MRI (n=5), panendoscopy.

Gender	n (%)
Male	14 (82.4)
Female	3 (17.6)

2

Type of test(s)

PET

Reference standard

Panendoscopy and biopsy; either random or directed by PET results.

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	1	6
Test negative	1	5

Sensitivity [95% CI]: 0.50 [0.01, 0.99]
Specificity [95% CI]: 0.45 [0.17, 0.77]

Source of funding

Not reported.

Comments on study quality

Risks of bias: four patients excluded from analysis due to detection of primary breast carcinoma (n=1), refusal of panendoscopy and biopsy (n=2) and loss to follow up (n=1). Criteria for patient selection (and whether random/conscutive) is unclear.
Concerns regarding applicability: Included patients all had suspected squamous cell carcinoma, but the confirmed histopathological diagnosis was not reported.

Additional comments

1

Study, country

Johansen 2008.
Denmark, two centres.

Study type, study period

Prospective cohort study

Number of patients

60 included in the analysis; 67 recruited.

Patient characteristics

Inclusion criteria: cancer of unknown primary patients with a potential primary arising for the head and neck region.
Exclusion criteria: patients diagnosed with a primary tumour from a random routine biopsy before referral.

Diagnostic work up: panendoscopy of the pharynx, larynx, bronchi, oesophagus; random mucosal biopsies; tonsillectomy; chest X-ray or CT; ultrasonography of the neck; CT or MRI of the head and neck.

Median age 56.5 years (range 32-78).

Gender	n (%)
Male	48 (71.6)
Female	19 (28.4)

Histology	n (%)
Squamous cell carcinoma	44 (73)
Undifferentiated carcinoma	12 (20)
Adenosquamous carcinoma	2 (3.3)
Unspecified	2 (3.3)

Type of test(s)

PET. Full body scan (n=43) or head to umbilicus (n=21).

Reference standard

Examination under anaesthesia, panendoscopy.

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	18	13
Test negative	3	26

Sensitivity [95% CI]: 0.86 [0.64, 0.97]
Specificity [95% CI]: 0.67 [0.50, 0.81]

Source of funding

Research council.

Comments on study quality

Risks of bias: Criteria for patient selection (and whether random/consecutive) is unclear. Detailed information on diagnostic workup is reported, but it appears that in some cases several investigations were conducted after the index test. This has not been applied uniformly and could influence the estimated diagnostic accuracy by including some patients with 'easy to detect' tumours. 7 out of 67 patients were excluded from the analysis: 3 did not have a PET scan (2 abstained, one patient was ineligible due to obesity); 4 patients were deemed ineligible due to lymphoma (n=1), adenocarcinoma (n=1) or benign branchiogenic cysts (n=2).
Concerns regarding applicability: 37% of patients had non-SCC histologies.

Additional comments

1

Study, country
Jungehulsing 2000. Germany, single centre.
Study type, study period
Prospective cohort study. May 1994 to July 1998.
Number of patients
27
Patient characteristics
Patients presenting with malignant lymphadenopathy where conventional diagnostic work up did not reveal a primary tumour. Conventional diagnostic workup: medical history; physical examination; chest radiography; full blood count; cervical and abdominal ultrasound; panendoscopy; MRI or CT from the nasopharynx to the diaphragm with tonsillectomy for any suspicious findings. Site of metastasis was the cervical lymph nodes in 24 (88.9%) patients. Other sites were brain (n=1), parotid gland region (n=1) and submandibular gland tumor (n=1). Mean age 60 years (range 36-74)
Type of test(s)
PET of head and neck region and torso down to the diaphragm.
Reference standard
Fine needle aspiration cytology, biopsy or surgery.
Results

Gender	n (%)
Male	22 (81.5)
Female	5 (18.5)

Histology	n (%)
Squamous cell carcinoma	18 (66.7)
Other	9 (33.3)

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	7	0
Test negative	2	17

Sensitivity [95% CI]: 0.78 [0.40, 0.97]
Specificity [95% CI]: 1.00 [0.80, 1.00]

Source of funding
Not reported.
Comments on study quality
Risks of bias: no major concerns. Concerns regarding applicability: 33% of patients had non-SCC histologies
Additional comments

2

Study, country
Miller 2008 United States.
Study type, study period
Prospective cohort study. Study period not reported.
Number of patients
31

3

Patient characteristics

Inclusion criteria: patients with a diagnosis of an unknown primary squamous cell carcinoma of the head and neck region.

Conventional diagnostic work up: endoscopy of the upper aerodigestive tract; CT and/or MRI; chest X-ray.

Gender	n (%)
Male	27 (87.1)
Female	4 (12.9)

N Stage	n (%)
N1	10 (32.2)
N2a	7 (21.9)
N2b	3 (9.6)
N2c	2 (6.5)
N3	9 (29.0)

Type of test(s)

PET (whole body scan)

Reference standard

Diagnosis based on multiple biopsies from the tongue base and nasopharynx during panendoscopy (directed by PET results in the case of a positive scan result); histopathologic tonsil examination.

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	9	1
Test negative	5	16

Sensitivity [95% CI]: 0.64 [0.35, 0.87]
Specificity [95% CI]: 0.94 [0.71, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: no major concerns.
Concerns regarding applicability: no major concerns.

Additional comments

1

Study, country

Mukherji 1996
United States.

Study type, study period

Retrospective (assumed) cohort study.
Study period not reported.

Number of patients

17

Patient characteristics

Inclusion criteria:patients with pathologically proved squamous cell carcinoma metastatic to the cervical lymph nodes, suspected of having an occult primary tumour of the extracranial head and neck.

Conventional diagnostic work up: clinical examination; nasopharyngolaryngoscopy; chest radiography.

Characteristics of included patients not reported.

Type of test(s)

CT.

Reference standard

Direct panendoscopy and routine speculative biopsies of the nasopharynx, tonsils, tongue base and piriform sinuses.

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	4	2
Test negative	6	5

Sensitivity [95% CI]: 0.40 [0.12, 0.74]
Specificity [95% CI]: 0.71 [0.29, 0.96]

Source of funding

Not reported.

Comments on study quality
Risks of bias: Criteria for patient selection (and whether random/consecutive) is unclear. Concerns regarding applicability: No detail reported on the characteristics of patients included in the study. Very limited detail reported of the diagnostic workup each patient received before the index test.
Additional comments
All patients in the study also received FDG-SPECT, but this test is not relevant to this review. One additional patient who received MR instead of CT has been excluded from the analysis.

1

Study, country
Pattani 2011 United States, single centre.
Study type, study period
Retrospective cohort study. Study period January 2001 to December 2005.
Number of patients
23
Patient characteristics
Inclusion criteria:patients diagnosed with cervical nodal metastasis and a clinically unknown primary tumour. A finding of metastatic squamous cell carcinoma must have been made on fine-needle aspiration by a cytologist and the location of the primary remained unknown following diagnostic work up. Conventional diagnostic work up: history and physical examination of the head and neck; fibreoptic transnasal endoscopy of the nasal cavity , nasopharynx, oropharynx, hypopharynx and larynx; posteroanterior and lateral chest X-rays; contrast-enhanced high-resolution CT of the neck. Mean age 59 years (range 45-81).

Gender	n (%)
Male	18 (78.3)
Female	5 (21.7)

Histology	n (%)
N1	4 (17)
N2a	3 (13)
N2b	7 (30)
N2c	3 (13)
N3	6 (26)

Type of test(s)
PET-CT.
Reference standard
Diagnosis based on biopsies from the nasopharynx, tongue base and piriform sinuses during panendoscopy (biopsy site directed by PET-CT results in the case of a positive scan result); ipsilateral tonsillectomy.
Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	12	2
Test negative	1	8

Sensitivity [95% CI]: 0.92 [0.64, 1.00]
Specificity [95% CI]: 0.80 [0.44, 0.97]

Source of funding
Not reported.
Comments on study quality
Risks of bias: Criteria for patient selection (and whether random/consecutive) is unclear. Concerns regarding applicability: Limited detail reported on the characteristics of patients included in the study.
Additional comments

2

Study, country
Prowse, 2012 United Kingdom
Study type, study period
Retrospective cohort study. April 2008 to July 2009.
Number of patients
32.

3

Patient characteristics

Included patients were referred to the head and neck multidisciplinary team with cervical lymph node metastases from an unknown primary malignancy and had undergone PET-CT after negative clinical investigation.

Clinical investigation consisted of clinical examination, fibre-optic endoscopy and routine contrast-enhanced MRI using a dedicated head and neck imaging protocol.

Median and mean patient age: 61 years (range 39-86).

Gender	n (%)
Male	23 (71.8)
Female	9 (28.2)

Histology	n (%)
Squamous cell carcinoma	29 (90.6)
Poorly differentiated carcinoma	3 (9.4)

Site of primary tumour was identified in 17/32 (53%) patients.

Type of test(s)

PET-CT. Scanned from vertex to thigh using a two-dimensional technique. Mobile PET-CT unit used to perform scans.

Reference standard

Histology based on targeted (for PET-CT-positivecases) or non-directed (for PET-CT negative cases) biopsy.

Results

PET-CT result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	16	5
Test negative	1	10

Sensitivity [95% CI]: 0.94 [0.71, 1.00]
Specificity [95% CI]: 0.67 [0.38, 0.88]

Source of funding

Not reported; no competing interests declared.

Comments on study quality

Risks of bias: No major concerns.
Concerns regarding applicability: No major concerns. A small (<10%) proportion of patients had tumour histologies other than squamous cell carcinoma.

Additional comments

1

Study, country

Regelink 2002
Netherlands, two centres.

Study type, study period

Retrospective cohort study.
January 1994 to November 2000.

Number of patients

50

Patient characteristics

Inclusion criteria: cytologically or histologically proven cervical metastases, complete physical examination and FDG-PET.

Standard workup for an unknown primary tumour consisted of complete history (n=50), physical examination (n=50), CT (n=30), MRI (n=30) and panendoscopy of the upper aerodigestive tract (n=45).

Gender	n (%)
Male	37 (74)
Female	13 (26)

Histology	n (%)
Squamous cell carcinoma	30 (60)
Large cell carcinoma	18 (36)
Adenocarcinoma	1 (2)
Neuro-endocrine carcinoma	1 (2)

Type of test(s)

PET (whole body).

Reference standard

Panendoscopy under anaesthesia with inspection of the nasopharynx, orophaynx, hypopharynx, larynx, bronchi and oesophagus and biopsies taken from all suspected areas.

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	16	2
Test negative	0	32

Sensitivity [95% CI]: 1.00 [0.79, 1.00]
Specificity [95% CI]: 0.94 [0.80, 0.99]

Source of funding
Not reported.
Comments on study quality
Risks of bias: The level of diagnostic workup carried out before the index test was not the same for all patients. Concerns regarding applicability: 40% of patients had non-SCC histologies
Additional comments
Results for PET of the head and neck only were also reported; these were very similar to the whole body PET results and therefore have not been included separately in this review. Diagnostic results of CT and MRI were also reported, but these were grouped together into one 'imaging' category and therefore sensitivities and specificiteis of the individual tenchniques cannot be calculated.

1

Study, country
Roh 2009. Korea, single centre.
Study type, study period
Cohort study, assumed to be prospective in design. January 204 to March 2007.
Number of patients
44
Patient characteristics
Inclusion criteria: consecutive patients newly diagnosed with cervical metastases from cancer of unknown primary. Exclusion criteria: patients with a previous history of malignancies. Conventional diagnostic work up: physical and endoscopic examination.

Gender	n (%)
Male	37 (84.1)
Female	7 (15.9)

Histology	n (%)
Squamous cell carcinoma	33 (75)
Adenocarcinoma	6 (13.6)
Undifferentiated carcinoma	3 (6.8)
Salivary ductal carcinoma	1 (2.2)
Anaplastic carcinoma	1 (2.2)

N stage	
N1	6 (13.6)
N2	29 (65.9)
N3	9 (20.4)

Median age: 58 years (range 39-73)
Site of primary tumour was identified in 16/44 (%) patients.

Type of test(s)
All patients received combined PET-CT from the skull base to the upper thighs. Contrast-enhanced CT scans were also separately performed from the skull base to the upper chest.
Reference standard
Panendoscopy and guided biopsy of the tonsils, tongue base, nasopharynx and other sites suspected of harbouring primary tumours.
Results

Results for CT

CT result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	7	3
Test negative	9	25

Sensitivity [95% CI]: 0.44 [0.20, 0.70]
Specificity [95% CI]: 0.89 [0.72, 0.98]

Results for PET-CT

PET-CT result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	14	5
Test negative	2	23

Sensitivity [95% CI]: 0.88 [0.62, 0.98]
Specificity [95% CI]: 0.82 [0.63, 0.94]

Source of funding
Not reported; authors declared no conflicts of interest.
Comments on study quality
Risks of bias: no major concerns. Concerns regarding applicability: 25% of included patients had non-SCC histologies. Patients received "comprehensive work up" before index test, but it is not clear what investigations this comprised.
Additional comments

2

Study, country

Safa 1999
United States, single centre.

Study type, study period

Prospective cohort study.
January 1995 to December 1997.

Number of patients

14

Patient characteristics

Inclusion criteria: patients with a diagnosis of unknown primary cancer of the head and neck and biopsy-proven squamous cell carcinoma in a neck lymph node.

Diagnostic work up prior to index test: physical examination; chest radiography; CT (n=13) or MRI (n=1).

Gender	n (%)
Male	14 (100)
Female	0 (0)

N stage	n (%)
N2	6 (42.9)
N3	8 (57.1)

Type of test(s)

PET

Reference standard

Biopsy and follow up (median 22 months, range 16-29 months).

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	3	1
Test negative	1	9

Sensitivity [95% CI]: 0.75 [0.19, 0.99]
Specificity [95% CI]: 0.90 [0.55, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: Criteria for patient selection (and whether random/consecutive) is unclear.
Concerns regarding applicability: All included patients were male.

Additional comments

The study was conducted at a veterans' hospital; this is presumably the reason for the male-only study population.

1

Study, country

Silva 2007
UK, single centre.

Study type, study period

Prospective (assumed) cohort study.
1999 to 2003.

Number of patients

25

Patient characteristics

Inclusion criteria: patients presenting with a histologically proven metastatic squamous cell carcinoma of the neck, with no evidence of the primary malignancy detected by standard diagnostic workup.

Standard workup included full clinical examination and imaging by CT and/or MRI.

Patient characteristics were not reported.

Type of test(s)

PET.

Reference standard

Examination under anaesthesia and when necessary biopsy of the nasopharynx, tonsil and tongue base; follow up.

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	3	6
Test negative	2	14

Sensitivity [95% CI]: 0.60 [0.15, 0.95]
Specificity [95% CI]: 0.70 [0.46, 0.88]

2

Source of funding

Not reported; authors declared no conflicts of interest.

Comments on study quality

Risks of bias: Criteria for patient selection (and whether random/consecutive) is unclear. No detail reported on the characteristics of patients included in the study.
Concerns regarding applicability: no major concerns.

Additional comments

1

Study, country

Stoeckli 2003
Switzerland

Study type, study period

Prospective cohort study.
October 1999 to December 2001.

Number of patients

18

Patient characteristics

Inclusion criteria: patients with a cervical lymph node metastasis of a squamous cell carcinoma from an unknown primary.

Routine workup included transnasal fibre-endoscopy of the nasal cavity, nasopharynx, oropharynx, hypopharynx and larynx; CT of the neck; chest X-ray in the postero-anterior and lateral views; and fine-needle aspiration cytology of the neck metastasis.

Gender	n (%)
Male	15 (83.3)
Female	3 (16.7)

N category	n (%)
N1	8 (44.4)
N2a	0 (0)
N2b	8 (44.4)
N2c	1 (5.6)
N3	1 (5.6)

Median age: 53 years (range 38-86).

Type of test(s)

PET.

Reference standard

Panendoscopy with or without diagnostic tonsillectomy.

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	8	3
Test negative	1	6

Sensitivity [95% CI]: 0.89 [0.52, 1.00]
Specificity [95% CI]: 0.67 [0.30, 0.93]

Source of funding

Not reported.

Comments on study quality

Risks of bias: no major concerns.
Concerns regarding applicability: no major concerns.

Additional comments

2

Study, country

Van Veen, 2001.
Netherlands, single centre.

Study type, study period

Prospective cohort study.
1995 to 1999.

Number of patients

32; 29 investigated with one of the index tests.

3

Patient characteristics

Inclusion criteria: cytologically proven lymph node metastases from an epithelial tumour; negative mirror and/or endoscopic evaluation results.

Gender	n (%)
Male	25 (78.1)
Female	7 (21.9)

Histology	n (%)
Squamous cell carcinoma	20 (62.5)
Undifferentiated carcinoma	9 (28.1)
Adenocarcinoma	3 (9.4)

Distribution of lymph node metastases	n
Level I	0 (0)
Level II	26 (81.3)
Level III	16 (50)
Level IV	6 (18.8)
Level V	3 (9.4)

Site of primary tumour was identified in 11/32 (34%) patients.

Type of test(s)

MRI (n=14)
CT (n=5)
MRI with CT (n=10)

Reference standard

Histological findings based on directed biopsy (for positive imaging findings) or nondirected biopsy of the nasopharynx, tonsil and base of tongue.

Results

Results for patients receiving MRI

MRI result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	0	4
Test negative	3	8

Sensitivity [95% CI]: 0.0 [0.0, 0.71]
Specificity [95% CI]: 0.67 [0.0.35, 0.90]

Results for patients receiving CT

CT result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	2	1
Test negative	0	3

Sensitivity [95% CI]: 1.0 [0.16, 1.0]
Specificity [95% CI]: 0.75 [0.19, 0.99]

Results for patients receiving both MRI and CT

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	3	1
Test negative	0	5

Sensitivity [95% CI]: 1.0 [0.29, 1.0]
Specificity [95% CI]: 0.83 [0.36, 1.0]

Source of funding

Not reported.

Comments on study quality

Risks of bias: Criteria for patient selection (and whether random/consecutive) is unclear. Furthermore it is unclear how patients were chosen to receive each individual test.
Concerns regarding applicability: very small number patient numbers for each test mean the estimated sensitivities and specificities are associated with high levels of imprecision.

Additional comments

Study participants (n = 32) received one or more of a range of tests. Of these, only MRI and CT met the inclusion criteria for the review.

1

Study, country

Wong, 2012.
United Kingdom, single centre.

Study type, study period

Retrospective cohort study.
March 2004 to January 2006

Number of patients

78

2

Patient characteristics

Inclusion criteria: all patients with metastatic neck nodes due to squamous cell carcinoma and no primary identified by usual clinical assessment.

Clinical assessment prior to PET-CT included flexible fibre optic nasendoscopy (78 patients); CT and/or MR (75 patients); examination under anaesthesia biopsies of all suspicious sites (58 patients); tonsillectomy (30 patients).

Mean age: 61 years (range 34-95)

N stage	n (%)
N1	16 (20.5)
N2a	11 (14.1)
N2b	16 (20.5)
N2c	3 (3.9)
N2 (sub-classification unknown)	9 (11.5)
N3	9 (11.5)
NX	14 (17.9)

Histology	n (%)
Squamous cell carcinoma	76 (97.4)
Undifferentiated cancer	2 (2.6)

Site of primary tumour was identified in 30/78 (%) patients.

Type of test(s)

PET-CT.

Reference standard

Diagnosis based on follow up. Positive identification of primary tumour was based on histological confirmation. For PET-CT negative for primary cancer, a true negative was scored only when a minimum of 12 months of relapse free survival was achieved.

Results

PET-CT result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	30	16
Test negative	0	32

Sensitivity [95% CI]: 1.0 [0.88, 1.0]
Specificity [95% CI]: 0.67 [0.52, 0.80]

Source of funding

Not reported

Comments on study quality

Risks of bias: no major concerns.
Concerns regarding applicability: no major concerns. Some included patients had non-SCC histologies, but the proportion of these was very small (2.6%).

Additional comments

1

Study, country

Yabuki 2010
Japan, single centre

Study type, study period

Retrospective cohort study
January 1995 to December 2009.

Number of patients

24.

Patient characteristics

Inclusion criteria: patients with malignant disease of the head and neck where malignant lymphadenopathy of the neck was the only symptom and no primary site was identified by conventional diagnostic procedures.
Exclusion criteria: neck lymphadenopathy proven to be metastases from previously known carcinomas.

Conventional diagnostic procedure consisted of medical history, physical examination, full blood count, CT from the nasopharynx to the diaphragm, MRI from the nasopharynx to the subclavia, cervical ultrasound and panendoscopy (nasopharyngoscopy, laryngoscopy, gastroscopy)

Gender	n (%)
Male	21 (87.5)
Female	3 (12.5)

Histology	n (%)
Squamous cell carcinoma	18 (75)
Neuroendocrine carcinoma	2 (8.3)
Small cell carcinoma	1 (4.2)
Undifferentiated carcinoma	1 (4.2)
Suspected adenocarcinoma	1 (4.2)
Atypical cells	1 (4.2)

Type of test(s)

PET.

Reference standard

Histological diagnosis based on direct biopsy (in patients with a positive PET scan result) or EUA of the at-risk occult tumor sites (in patients with a negative PET scan result).

Results

Test result	Results from reference standard	
	Primary tumour present	Primary tumour absent
Test positive	9	3
Test negative	1	11

Sensitivity [95% CI]: 0.90 [0.55, 1.00]
Specificity [95% CI]: 0.79 [0.49, 0.95]

Source of funding

Not reported;

Comments on study quality

Risks of bias: no major concerns.
Concerns regarding applicability: 25% of study participants did not have SCC and therefore fall outside the PICO. The study has been included in the review as the majority of patients had SCC.

Additional comments

1

2

1 ***Studies of transoral surgery techniques***

Study, country
Karni 2011 United States, single centre
Study type, study period
Retrospective cohort study. 1997 to 2005
Number of patients
18
Patient characteristics
Inclusion criteria: adults (>18 years) presenting with a neck mass containing metastatic SCC. Exclusion criteria: existing evidence of a primary site based on prior diagnostic work up. Prior diagnostic work up: Flexible laryngoscopy, imaging using CT or MRI.
Type of test(s)
Examination under anaesthesia, with transoral laser microsurgery
Reference standard
Not specified, but assumed to be histopathology/clinical follow up
Results

Test result	**Results from reference standard**	
	Primary tumour present	**Primary tumour absent**
Test positive	17	0
Test negative	0	1

Sensitivity [95% CI]: 1.00 [0.80, 1.00]
Specificity [95% CI]: 1.00 [0.03, 1.00]

Source of funding
Not reported. Authors declared no funding, financial relationships or conflicts of interest
Comments on study quality
Risks of bias: Unclear whether a consecutive/random sample of patients was studied. The reference standard was not clearly defined; it is assumed patients were followed up, but it is unknown whether this was applied consistently across the cohort or whether all patients received the same reference standard. Concerns regarding applicability: no major concerns.
Additional comments

2

Study, country
Mehta 2013 United States, single centre
Study type, study period
Retrospective cohort study. 2009 to 2011
Number of patients
10.
Patient characteristics
Inclusion criteria: All patients undergoing a TORS base of tongue resection for an unknown primary tumour for whom prior diagnostic workup had failed to identify a primary mucosal site with the upper aerodigestive tract. Conventional diagnostic work up: Flexible laryngoscopy, imaging using CT, MRI and/or PET-CT, examination under anaesthesia, random biopsies of the base of tongue and pharynx, tonsillectomy.
Type of test(s)
Transoral robotic base of tongue resection,
Reference standard
Not specified, but assumed to be clinical follow up.
Results

Test result	**Results from reference standard**	
	Primary tumour present	**Primary tumour absent**
Test positive	9	0
Test negative	1	0

Sensitivity [95% CI]: 0.90 [0.55, 1.00]
Specificity [95% CI]: Not estimable, as no patients were classified as 'disease negative'.

Source of funding
Not reported.
Comments on study quality
Risks of bias: The reference standard was not clearly defined; it is assumed patients were followed up, but it is unknown whether this was applied consistently across the cohort or whether all patients received the same reference standard. Concerns regarding applicability: no major concerns.
Additional comments

1

Study, country
Patel 2013
Study type, study period
Retrospective cohort study. United States, six centres.
Number of patients
47.
Patient characteristics
Inclusion criteria: patients diagnosed with HNSCC with an unknown primary site despite prior diagnostic work up, who underwent directed biopsies with transoral robotic surgery to aid in the work up of the primary site. Conventional diagnostic work up: varied from one centre to another, but included cross-sectional imaging, physical examination or previous biopsy of larynx or pharynx.
Type of test(s)
Directed biopsies with transoral robotic surgery.
Reference standard
Not specified, but assumed to be clinical follow up.
Results

Test result	**Results from reference standard**	
	Primary tumour present	**Primary tumour absent**
Test positive	34	0
Test negative	1	12

Sensitivity [95% CI]: 0.97 [0.85, 1.00]
Specificity [95% CI]: 1.00 [0.74, 1.00]

Source of funding
Not reported.
Comments on study quality
Risks of bias: The reference standard was not clearly defined; it is assumed patients were followed up, but it is unknown whether this was applied consistently across the cohort or whether all patients received the same reference standard. Concerns regarding applicability: The range of tests received prior to the index test varied within the cohort. Some patients may have been 'undertested' compared to the likely target population.
Additional comments
From the published results, it was unclear whether a primary tumour was subsequently detected during follow up in any patients for whom the index test did not detect a primary tumour (i.e. whether any of the index test results were subsequently shown to be 'false negative'. The study authors were therefore contacted, and confirmed that a tumour had subsequently been detected in one patient in whom the index test result was negative. However, the authors stated that follow up data from two of the six centres is not available.

2

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Index Test	Reference Standard	Outcomes
Adults presenting with metastatic neck disease (squamous cell carcinoma) and clinically occult primary presumed to be of upper aerodigestive tract origin	• CT • MRI • PET CT • Examination under anaesthesia, panendoscopy, biopsy, bilateral tonsillectomy • PET • Narrow band imaging • Trans oral robotic surgery • Nasendoscopy • Combinations of the above	Identification of primary tumour site/confirmation of staging based on histopathological diagnosis/imaging/follow up	• Sensitivity • Specificity • Process-related morbidity • HRQoL • Time to diagnosis

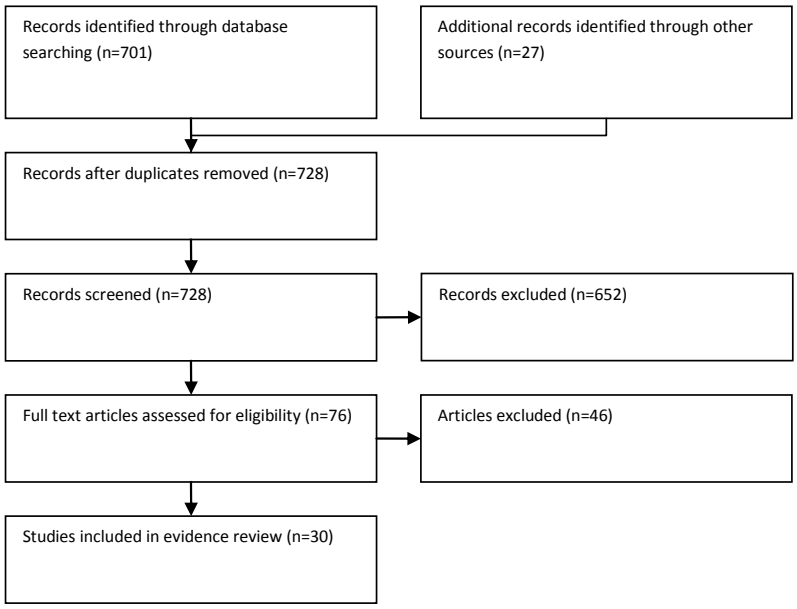
3

4 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Diagnostic test
Language	English only
Study design	Studies of diagnostic test accuracy
Status	Published data only
Other criteria for inclusion / exclusion of studies	Inclusion criteria: sufficient data reported to calculate the total number of true positives, true negative, false positives, and false negatives for the studied test(s). Exclusion criteria: Reference standard is unclear or undefined.
Search strategies	Searches will be limited to after 1995, as cross sectional imaging (CT, MRI) has been widely available only since the 1990s.
Review strategies	The evidence table for studies of diagnostic accuracy will be used (NICE Guidelines Manual Appendix J) to extract and present data from individual studies. Sensitivity and specificity data will be pooled when appropriate. Other outcomes will be presented as risk ratios or hazard ratios. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. Where possible, evidence will be analysed according to the subgroups

	specified in the PICO, and also by gender. In addition to individual tests, where possible, different combinations or sequences of tests will be compared using the outcomes listed in the PICO.

Figure 2.12. Study flow diagram



Included studies

Narrow band imaging studies

Hayashi, T., Muto, M., Hayashi, R., Minashi, K., Yano, T., Kishimoto, S., and Ebihara, S. Usefulness of narrow-band imaging for detecting the primary tumor site in patients with primary unknown cervical lymph node metastasis. Japanese Journal of Clinical Oncology 2010. 40(6): 537-541

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Cross-sectional imaging studies

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Freudenberg, L. S., Fischer, M., Antoch, G., Jentzen, W., Gutzeit, A., Rosenbaum, S. J., Bockisch, A., and Egelhof, T. Dual modality of F-18-fluorodeoxyglucose-positron emission tomography/computed tomography in patients with cervical carcinoma of unknown primary. Medical Principles and Practice 2005. 14(3): 155-160

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Systemic staging – who and how?

Background

Distant metastases are less common in CUADT than in many other cancers but their presence at diagnosis usually precludes curative treatment. Accurate systemic staging can identify patients best served by a palliative approach, often sparing them the significant morbidity of surgery or high dose radiotherapy. Staging can also detect synchronous primary cancers.

Patients with different tumour sites and stages have different risks of systemic disease. There is also debate about which imaging tests usually used for systemic staging are most accurate. There are potential harms associated with these imaging tests including radiation exposure and the discovery of incidental problems which may complicate care. There are also potential financial costs. This has resulted in variation in current practice across the UK.

Clinical question: Which patients with cancer of the upper aerodigestive tract require systemic staging?

Evidence summary

Ten studies met the criteria for the review. The National Head and Neck Cancer Audit (2011-14) included 18,968 patients; nine other studies included a total of 1,769 patients.

T stage

The value of T stage in predicting distant malignant disease was estimated based on evidence from eight studies. Five studies had an unclear risk of patient selection bias, due to a lack of reporting on the methods use to recruit patients. The applicability of six studies to the review question was unclear, either because patient characteristics were not reported, or because only certain tumour subsites were included.

For five studies, positive predictive values were reported for individual T stages. In four out of these five studies (National Head and Neck Cancer Audit, Haerle 2011, Liu 2007, Wax 2002), positive predictive values for distant metastasis were higher for patients with tumours staged as T2 or above compared to T1; in two of these studies, higher T stages (T3 and T4) were also associated with higher positive predictive values (National Head and Neck Cancer Audit, Liu 2007). Results of a fifth study (Chang 2005, 95 patients) exhibited no trend in positive predictive values according to T stage.

In an additional three studies, positive predictive values were reported according to T stage groupings: the prevalence of systemic disease in T1 and T2 patients was compared with T3 and T4 patients. One study (Chua 2009) found positive predictive values to be higher for patients with T3 or T4 disease, whilst the other two studies exhibited no trend between T1/T2 and T3/T4 patients.

N stage

The value of N stage in predicting distant malignant disease was estimated based on evidence from eight studies. Some issues with bias and applicability concerning patient selection were identified: five studies did not clearly report the methods used to recruit patients; seven studies only included certain tumour subsites, or included some patients with cancers not relevant to the review question.

Five studies (National Head and Neck Cancer Audit, Haerle 2011, Chang 2005, Liu 2007, Wax 2002) demonstrated a trend for increasing positive predictive values for distant metastasis with higher N stage. Three studies investigated positive predictive values according to N stage groupings as opposed to individual N stage categories. Two of these studies (Chua 2009, Ng 2008) showed that positive predictive values are higher for patients with N2/N3 disease than N0/N1 disease. A third study (Chan 2011) found no difference in positive predictive values between patients with N0/N2b disease and N2c/N3 disease.

Tumour site

The value of different primary tumour sites in predicting distant malignant disease was estimated based on the results of seven studies. Five studies of these studies may be only partially applicable to the review question, as they included a subgroup of the relevant population (such as a single tumour subsite) or included some patients with cancers not relevant to the review question. In addition, the criteria used for patient selection was unclear in four studies, introducing a possibility of bias in the results of these studies.

Based on data from the National Head and Neck Cancer Audit, positive predictive values for distant metastasis were highest for tumours of the hypopharynx and nasopharynx (0.086 (95% CI 0.070, 0.104) and 0.063 (95% CI 0.041, 0.093), respectively). Results from other studies are summarised in Table 2.8.

Smoking

The value of smoking status in predicting distant metastasis was investigated in one study (Chan 2011, 103 patients). There were no applicability concerns for this study, but an unclear risk of bias resulting from patient selection, for which the methods used were not reported. Positive predictive values for distant metastasis in smokers and non-smokers were 0.081 (95% CI 0.033, 0.159) and 0.063 (95% CI 0.002, 0.302), respectively.

HPV status

No evidence was identified on the predictive value of HPV status for assessing the need for systemic staging in people with cancer of the upper aerodigestive tract.

Study characteristics and quality

Five studies included patients with any cancer of the upper aerodigestive tract, three studies included nasopharyngeal cancer patients only, and the two remaining studies included other tumour subsites (oral/oropharyngeal cancers and oropharynx/hypopharynx cancer). Eight studies reported the detection of distant metastases, one of which included distant metastases and second primary tumours, and two of which reported bone metastases only. The remaining two studies reported the detection of lung malignancies only. Characteristics of the studies included in the review are summarised in Table 2.6.

Study methodological quality was assessed using QUADAS2. The majority of study aspects were assessed as at low risk of bias. In four studies (Chan 2011, Haerle 2011, Liu 2007, Ng 2008), the criteria used to select patients (and whether a random/consecutive sample was used) was unclear. In the study by Keith (2006) the exact methods used to confirm the presence of a distant malignancy were not reported. Similarly, data from the National Head and Neck Cancer Audit does not specify

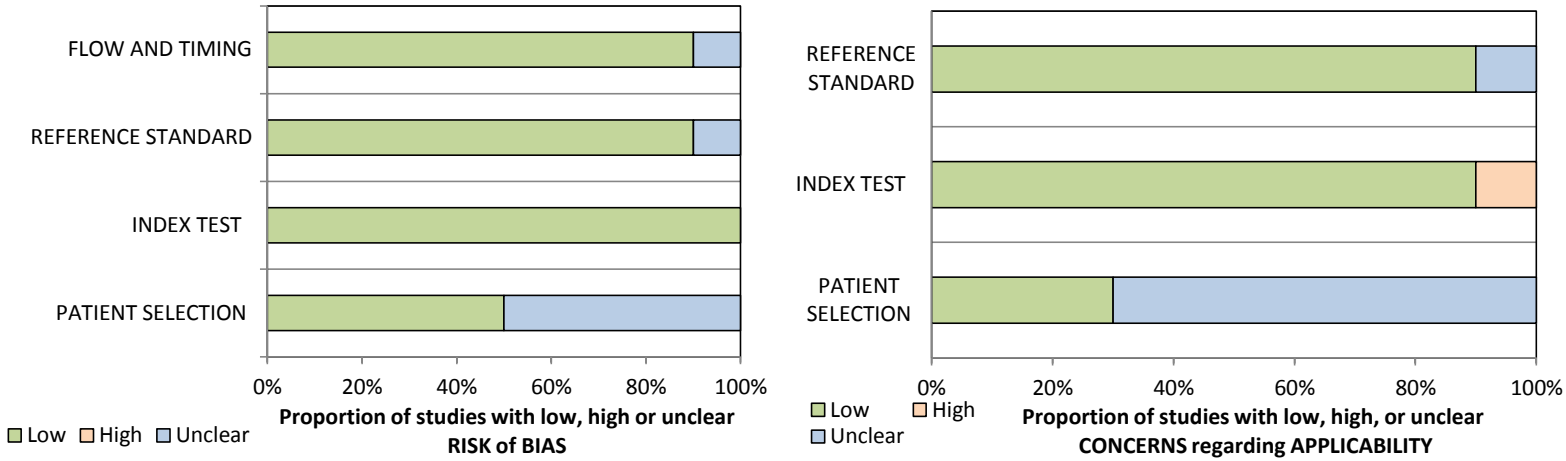
the methods used to determine M stage, or the time of determination of final M stage; given the large number of patients included, the methods used may vary between centres.

Positive and negative predictive values are calculated dependent on the prevalence of the disease or condition being tested, and therefore vary with prevalence: positive predictive values increase proportionally with the prevalence of disease in the studied population. In the studies identified, the reported prevalence of metastasis and/or secondary malignancy varied from 2.9% to 20.3%. The National Head and Neck Cancer Audit, which includes approximately 95% of UK head and neck cancer patients diagnosed between 2011 and 2014, had the lowest prevalence of any included source of evidence (2.9% of patients staged as M1). Positive predictive values estimated from other studies may therefore be overestimates when applied to UK CUADT patients.

Table 2.6. Characteristics of included studies

Study	Setting	Number of patients	Patient characteristics	Factors studied	Reference standard (workup/methods used)	Prevalence of distant malignancy, %
National Head and Neck Cancer Audit	England and Wales	18,968	Any head and neck cancer	T stage N stage Tumour site	Distant metastasis (final pretreatment M stage of M1)	2.9%
Chan 2011	Taiwan	103	Any previously untreated head and neck cancer	Smoking T stage N stage Tumour site	Distant metastasis, (MRI, PET-CT, histological findings/follow up for ≥12 months)	7.7%
Chang 2005	Taiwan	95	Newly diagnosed or recurrent nasopharyngeal carcinoma	T stage N stage	Distant metastases (imaging, clinical workup, follow up)	14.7%
Chua 2009	Singapore	78	Any nasopharyngeal carcinoma	T stage N stage	Distant metastases (PET/CT, confirmed by histology or clinical follow up).	7.6%
Haerle 2011	Switzerland	299	Newly diagnosed head and neck squamous cell carcinoma	Tumour site T stage N stage	Distant metastasis (PET/CT confirmed by histopathological or cytological work up)	11%
Keith 2006	United Kingdom	116	Oral/oropharyngeal squamous cell carcinoma	Tumour site Disease stage	Thoracic malignancy (chest CT)	3.5%
Kim 2008	Korea	564	Any cancer of the upper aerodigestive tract	Tumour site	Bone metastases, (PET, bone scan, confirmed with follow up imaging after 6 months)	3.0%
Liu 2007	Taiwan	300	Any nasopharyngeal carcinoma	T stage N stage	Bone metastases, (PET, skeletal scintigraphy, confirmed with histology and/or clinical follow up)	20.3%
Ng 2008	Taiwan	160	Previously untreated oropharynx or hypopharynx SCC	T stage N stage	Distant metastases/second primary (PET, CT confirmed pathologically or by follow up)	16.2%
Wax 2002		54	Any newly diagnosed head and neck cancer	Tumour site T stage N stage	Synchronous lung lesions (chest radiography + PET, confirmed with chest CT, bronchoscopy, and lung biopsy or bronchial washings)	18.5%

Figure 2.13. Summary of study quality (risks of bias and concerns regarding applicability)



Outcomes

Table 2.7. Positive predictive values (95 CI) for increasing T stage (A) and N stage (B) in assessing the likelihood of distant malignancy in people with cancer of the upper aerodigestive tract. 'All' represents the total proportion of patients with distant malignancy in each study. Data is shown only for studies that subdivided patients into individual T or N stage categories.

A

Study/T stage	T1	≥T2	≥T3	T4	All
DAHNO	0.008 (0.006, 0.010)	0.038 (0.035, 0.041)	0.052 (0.047, 0.057)	0.062 (0.056, 0.069)	0.029
Chang 2005	0.208 (0.072, 0.422)	0.127 (0.059, 0.227)	0.156 (0.065, 0.295)	0.133 (0.038, 0.307)	0.147
Haerle 2011	0.070 (0.015, 0.191)	0.103 (0.069, 0.146)	0.110 (0.065, 0.170)	0.111 (0.052, 0.201)	0.110
Liu 2007	0.183 (0.095, 0.304)	0.208 (0.159, 0.265)	0.265 (0.196, 0.344)	0.337 (0.237, 0.450)	0.203
Wax 2002	0.071 (0.002, 0.339)	0.222 (0.101, 0.392)	0.000 (0.000, 0.232)	0.000 (0.000, 0.285)	0.185

B

Study/N stage	N0	≥N1	≥N2	N3	All
DAHNO	0.010 (0.008, 0.012)	0.052 (0.047, 0.057)	0.057 (0.052, 0.063)	0.171 (0.135, 0.212)	0.029
Chang 2005	0.067 (0.011, 0.320)	0.163 (0.090, 0.262)	0.220 (0.123, 0.347)	0.563 (0.299, 0.802)	0.147
Haerle 2011	0.074 (0.011, 0.243)	0.099 (0.067, 0.141)	0.099 (0.064, 0.145)	0.167 (0.038, 0.414)	0.110
Liu 2007	0.000 (0.000, 0.109)	0.228 (0.179, 0.283)	0.275 (0.214, 0.342)	0.481 (0.367, 0.596)	0.203
Wax 2002	0.177 (0.068, 0.345)	0.211 (0.061, 0.456)	0.214 (0.047, 0.508)	0.375 (0.085, 0.755)	0.185

Figure 2.14. Positive predictive values for increasing T stage in assessing the likelihood of distant metastasis in people with cancer of the upper aerodigestive tract

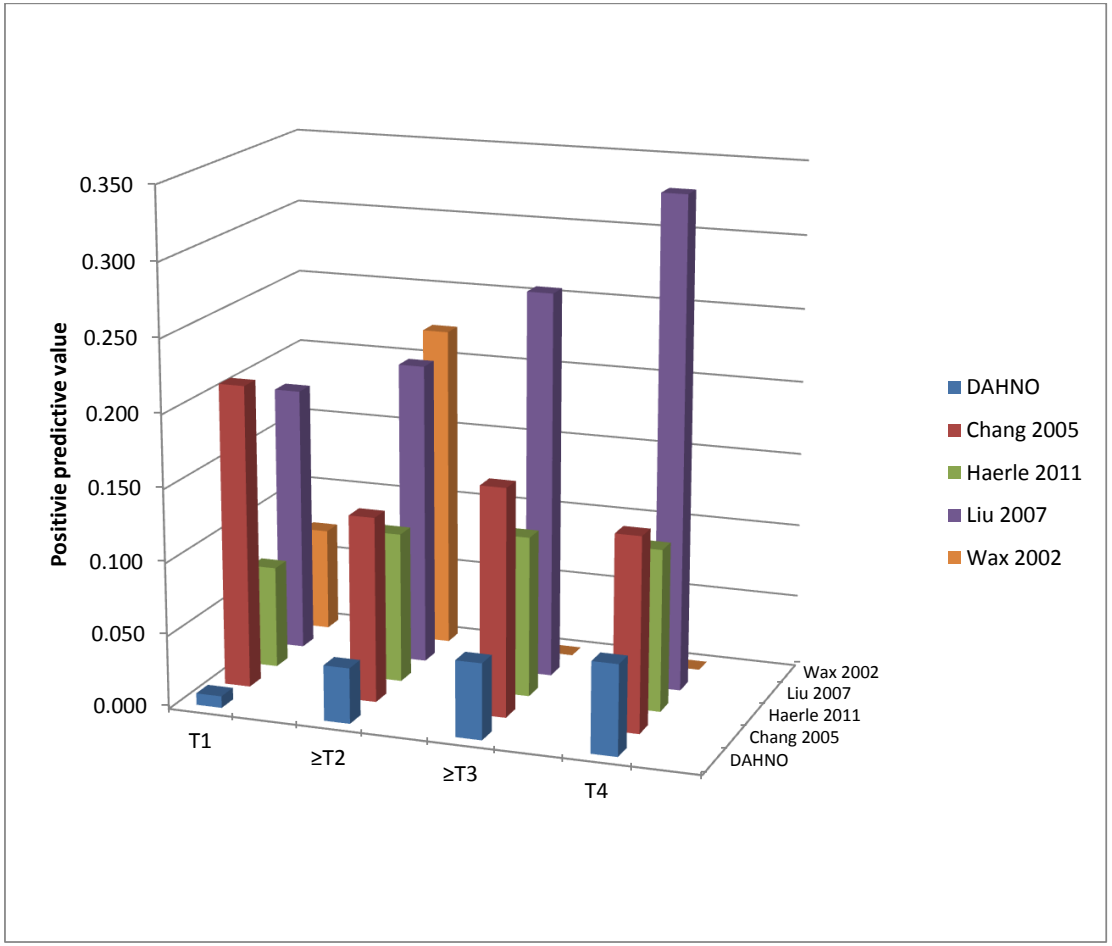


Figure 2.15. Positive predictive values for increasing N stage in assessing the likelihood of distant metastasis in people with cancer of the upper aerodigestive tract

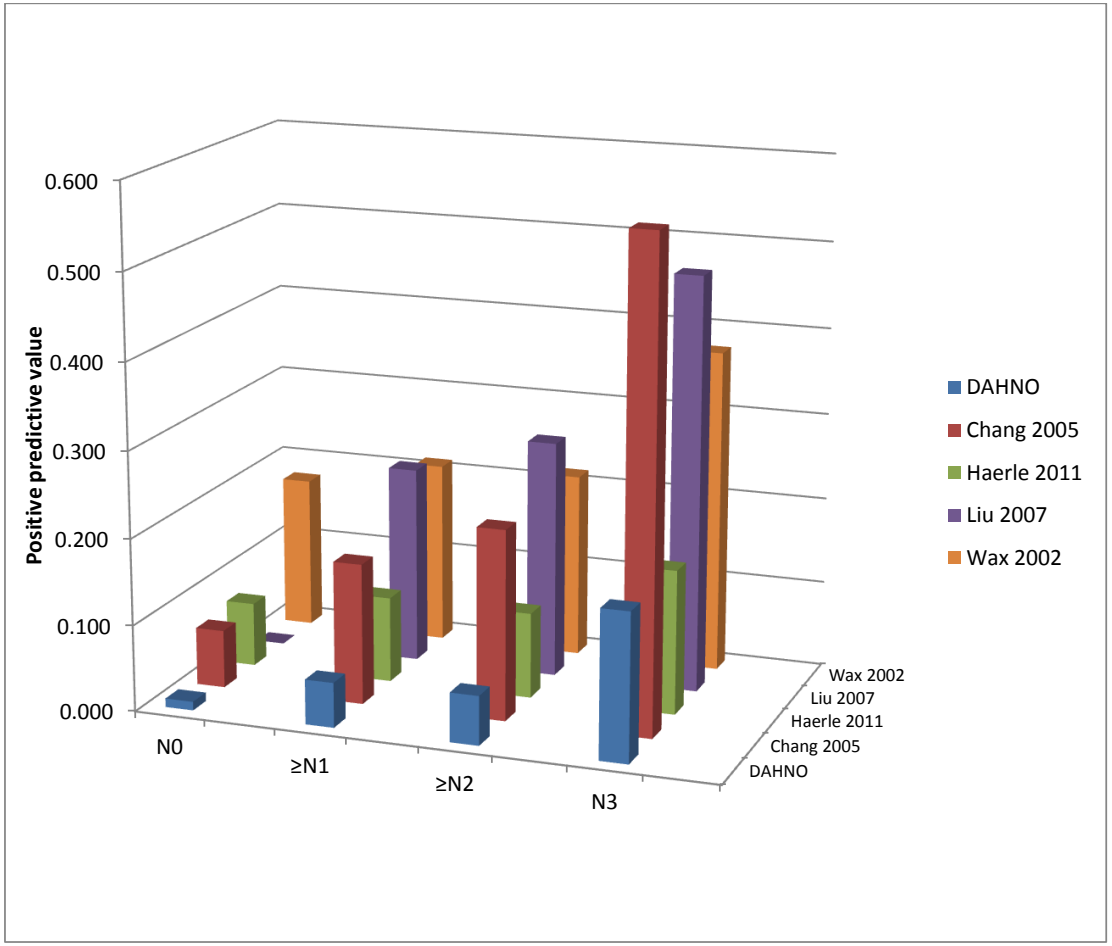


Figure 2.16. Positive predictive values for increasing T and N stage in assessing the likelihood of distant metastasis in people with cancer of the upper aerodigestive tract. Values are estimated from DAHNO, 2011-14.

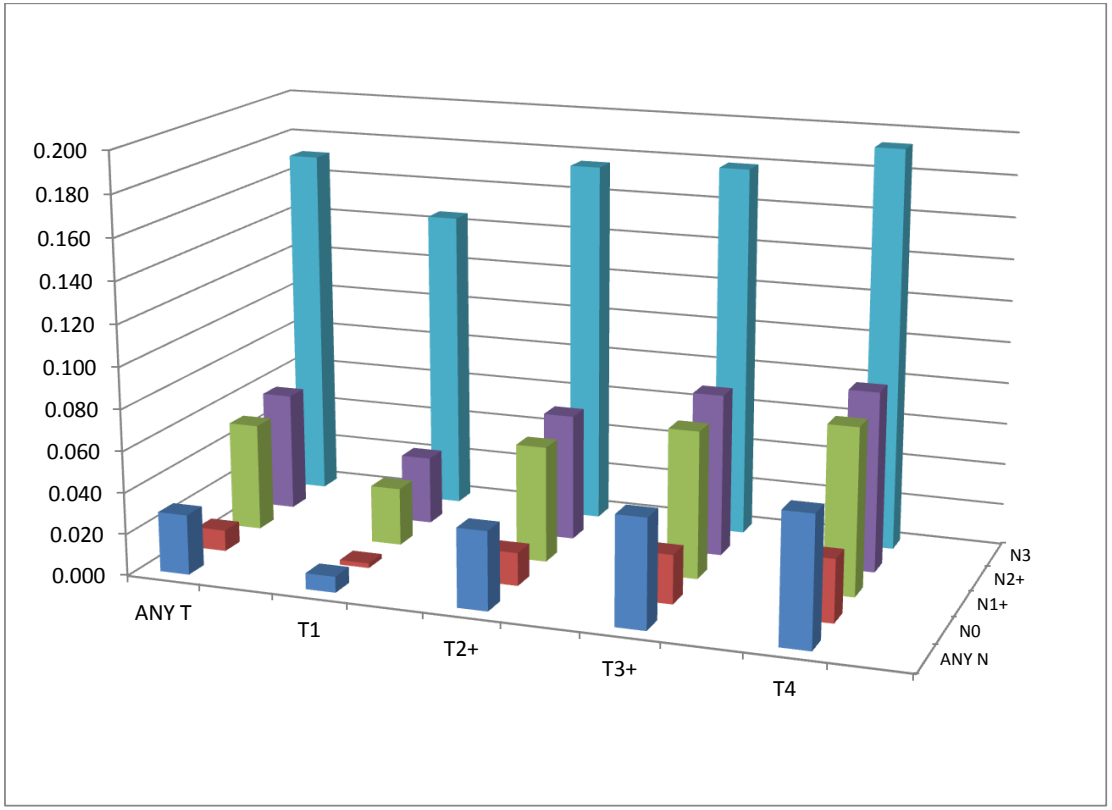


Table 2.8. Positive predictive values for tumour site in assessing the likelihood of distant metastasis/second primary cancer in people with cancer of the upper aerodigestive tract. 'All' represents the total proportion of patients with distant malignancy in each study. Dashed cells (-) indicate that no patients in the specified category were reported by the specified study.

Study/Tumour site	Hypopharynx	Larynx	Nasal cavity/paranasal sinuses	Nasopharynx	Oral cavity	Oropharynx	All
DAHNO	0.086 (0.070, 0.104)	0.023 (0.019, 0.028)	0.036 (0.023, 0.053)	0.063 (0.041, 0.093)	0.018 (0.015, 0.021)	0.032 (0.028, 0.037)	0.029
Chan 2011	0.082 (0.023, 0.196)	-	-	-	-	0.074 (0.021, 0.179)	0.077
Haerle 2011	0.158 (0.075, 0.279)	0.194 (0.082, 0.360)	-	0.286 (0.045, 0.707)	0.097 (0.022, 0.258)	0.048 (0.021, 0.092)	0.110
Keith 2006	-	-	-	-	0.013 (0.002, 0.068)	0.083 (0.019, 0.225)	0.035
Kim 2008	0.036 (0.004, 0.125)	0.010 (0.001, 0.035)	0.000 (0.000, 0.137)	0.110 (0.051, 0.198)	0.019 (0.002, 0.068)	0.010 (0.001, 0.035)	0.030
Ng 2008	0.221 (0.139, 0.323)	-	-	-	-	0.095 (0.039, 0.185)	0.162
Wax 2002	-	0.308 (0.091, 0.614)	-	-	0.313 (0.110, 0.587)	0.077 (0.002, 0.360)	0.185

Evidence tables for all included studies

Study, country

National and Head and Neck Cancer Audit, England and Wales.

Study type, study period

National database, prospectively collected data. Patients included in this dataset were diagnosed between November 2011 and October 2014.

Number of patients

18,698

Patient characteristics

Inclusion criteria: all cases of larynx, oral cavity, oropharynx, hypopharynx, nasopharynx, nasal cavity/sinus, and major salivary gland cancer registered with the database as diagnosed between November 2011 and October 2014.

Major salivary gland cancers have been excluded from this analysis as they are outside of the guideline scope.

Type of test(s)

T stage
N stage
Tumour site

Reference standard

Presence of distant metastasis, defined as any patient with a final pretreatment M stage of M1.

Results

Distant metastasis detected in 548/18,698 (2.9%) of patients.

	PPV [95% CI]	NPV[95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
Site				
Hypopharynx	0.086 [0.070, 0.104]	0.975 [0.972, 0.977]	0.18 [0.14, 0.21]	0.94 [0.94, 0.95]
Larynx	0.023 [0.019, 0.028]	0.969 [0.966, 0.972]	0.19 [0.16, 0.23]	0.76 [0.75, 0.77]
Nasal cavity and sinus	0.036 [0.023, 0.053]	0.971 [0.969, 0.974]	0.04 [0.03, 0.06]	0.97 [0.96, 0.97]
Nasopharynx	0.063 [0.041, 0.093]	0.972 [0.969, 0.974]	0.04 [0.03, 0.06]	0.98 [0.98, 0.98]
Oral cavity	0.018 [0.015, 0.021]	0.965 [0.962, 0.968]	0.21 [0.17, 0.24]	0.66 [0.65, 0.66]
Oropharynx	0.032 [0.028, 0.037]	0.973 [0.970, 0.975]	0.34 [0.30, 0.38]	0.69 [0.69, 0.70]
T stage				
T1	0.008 [0.006, 0.010]	0.962 [0.959, 0.965]	0.08 [0.06, 0.10]	0.70 [0.69, 0.71]
≥T2	0.038 [0.035, 0.041]	0.992 [0.990, 0.994]	0.92 [0.90, 0.94]	0.30 [0.29, 0.31]
≥T3	0.052 [0.047, 0.057]	0.988 [0.985, 0.990]	0.75 [0.71, 0.78]	0.60 [0.59, 0.60]
≥T4	0.062 [0.056, 0.069]	0.983 [0.981, 0.986]	0.58 [0.54, 0.62]	0.74 [0.73, 0.75]
N stage				
N0	0.010 [0.008, 0.012]	0.948 [0.943, 0.953]	0.19 [0.16, 0.23]	0.44 [0.43, 0.44]
≥N1	0.052 [0.047, 0.057]	0.990 [0.988, 0.992]	0.81 [0.77, 0.84]	0.56 [0.56, 0.57]
≥N2	0.057 [0.052, 0.063]	0.986 [0.984, 0.988]	0.68 [0.64, 0.72]	0.67 [0.66, 0.67]
≥N3	0.171 [0.135, 0.212]	0.974 [0.972, 0.976]	0.12 [0.10, 0.15]	0.98 [0.98, 0.98]

Source of funding

UK public body funded.

Comments on study quality

Risks of bias: method of determining M stage, and time of determination of final M stage, is not reported, and may vary between different cancer centres. Some patients (approximately 5%) registered with the database were excluded from the final dataset used for analysis; reasons for this are not clear.
Concerns regarding applicability: none identified..

Additional comments

Study, country

Chan, 2011. Taiwan.

Study type, study period

Prospective cohort study. Study period not reported.

Number of patients

103

Patient characteristics

Inclusion criteria:

- histological diagnosis of primary OHSCC

Exclusion criteria:

- presence of previous malignancies
- contraindications to MRI scan
- serum glucose levels of >150 mg/dl before the scheduled PET/CT scan

Mean age: 53.6 ± 9 years.

Gender	n (%)
Male	97 (94.2)
Female	6 (5.8)

Site	n (%)
Oropharynx	54 (52.4)
Hypopharynx	49 (47.6)

Site of distant metastasis (8 patients)	n
Lung only	3
Bone only	2
Distant lymph nodes only	2
Lung and distant lymph nodes	1

T-stage	n (%)
T1	15 (14.6)
T2	24 (23.3)
T3	11 (10.7)
T4	53 (51.4)

N-stage	n (%)
N0	19 (18.4)
N1	5 (4.9)
N2	65 (63.1)
N3	14 (13.6)

Type of test(s)

Smoking
T stage
N stage
Tumour site

Reference standard

Distant metastasis, diagnosis based on MRI, PET-CT and histological findings/follow up for at least 12 months.

Results

Prevalence of distant metastases in the study population: 7.7%.

Smokers	Distant metastases: Present	Absent
No	6	10
Yes	2	85

Smokers	Distant metastases: Present	Absent
Yes	2	85
No	6	10

T stage	Distant metastases: Present	Absent
T1/T2	3	94
T3/T4	5	1

T stage	Distant metastases: Present	Absent
T3/T4	5	1
T1/T2	3	94

N stage	Distant metastases: Present	Absent
N0/2b	5	59
N2c/3	3	36

N stage	Distant metastases: Present	Absent
N2c/3	3	36
N0/2b	5	59

Site	Distant metastases: Present	Absent
Oropharynx	4	50
Other	4	45

Site	Distant metastases: Present	Absent
Hypopharynx	4	45
Other	4	50

	PPV [95% CI]	NPV[95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
Smoking status				
Non-smokers	0.063 [0.002, 0.302]	0.920 [0.841, 0.967]	0.13 [0.00, 0.53]	0.84 [0.75, 0.91]
Smokers	0.081 [0.033, 0.159]	0.938 [0.354, 0.848]	0.88 [0.47, 1.00]	0.16 [0.09, 0.25]
T stage				
T1/T2	0.077 [0.016 0.209]	0.922 [0.827, 0.944]	0.38 [0.09, 0.76]	0.62 [0.52, 0.72]
T3/T4	0.078 [0.026, 0.173]	0.923 [0.912, 0.994]	0.63 [0.24, 0.91]	0.38 [0.28, 0.48]
N stage				
N0-N2b	0.078 [0.026, 0.173]	0.923 [0.791, 0.984]	0.63 [0.24, 0.91]	0.38 [0.28, 0.48]
N2c-N3	0.077 [0.016, 0.209]	0.922 [0.827, 0.974]	0.38 [0.09, 0.76]	0.62 [0.52, 0.72]
Site				
Oropharynx	0.074 [0.021, 0.179]	0.918 [0.804, 0.977]	0.50 [0.16, 0.84]	0.47 [0.37, 0.58]
Hypopharynx	0.082 [0.023, 0.196]	0.926 [0.821, 0.979]	0.50 [0.16, 0.84]	0.53 [0.42, 0.63]

Source of funding

Not reported. Authors declared no conflicts of interest.

Comments on study quality

Risks of bias: unclear whether a consecutive/random sample of patients was enrolled.
Concerns regarding applicability: none identified.

Additional comments

1

Study, country

Chang 2005, Taiwan.

Study type, study period

Prospective cohort study. May 2002 to April 2003.

Number of patients

95

Patient characteristics

Inclusion criteria: biopsy-proven primary NPC, either newly diagnosed or recurrent.

All patients underwent FDG-PET as part of their staging workup before treatment. Patients also underwent conventional staging workup; this included fibreoptic nasopharyngoscopy, complete blood count, blood biochemistry, chest X-ray, bone scan, abdominal ultrasonography, and MRI of the head and neck area.

Gender	n (%)
Male	66 (69.5)
Female	29 (30.5)

Pathologic finding	n (%)
Adenocystic cancer	1 (1.1)
Poorly differentiated squamous cell carcinoma	31 (32.6)
Undifferentiated carcinoma	63 (66.3)

T-stage	n (%)
T0-T1	24 (24.2)
T2	26 (26.3)
T3	15 (15.2)
T4	30 (30.3)

N-stage	n (%)
N0	15 (15.2)
N1	21 (21.2)
N2	43 (43.4)
N3	16 (16.2)

Type of test(s)

Assessment of T-stage
Assessment of N-stage

Reference standard

Presence of distant metastases based on imaging, clinical workup, and follow up.

Results

Prevalence of distant metastases in the study population: 14.7%.

T stage	Distant metastases: Present	Absent
Stage T0-T1	5	19
Other	9	62

T stage	Distant metastases: Present	Absent
Stage T2	2	24
Other	12	57

T stage	Distant metastases: Present	Absent
Stage T3	3	12
Other	11	69

T stage	Distant metastases: Present	Absent
Stage T4	4	26
Other	10	55

N stage	Distant metastases: Present	Absent
Stage N0	1	14
Other	13	67

N stage	Distant metastases: Present	Absent
Stage N1	0	21
Other	14	60

N stage	Distant metastases: Present	Absent
Stage N2	4	39
Other	10	42

N stage	Distant metastases: Present	Absent
Stage N3	9	7
Other	5	74

	PPV [95% CI]	NPV[95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
T stage				
T0-T1	0.208 [0.072, 0.422]	0.873 [0.773, 0.940]	0.36 [0.13, 0.65]	0.77 [0.66, 0.85]
≥T2	0.127 [0.059, 0.227]	0.792 [0.578, 0.928]	0.64 [0.35, 0.87]	0.23 [0.15, 0.34]
≥T3	0.156 [0.065, 0.295]	0.860 [0.733, 0.942]	0.50 [0.23, 0.77]	0.53 [0.42, 0.64]
≥T4	0.133 [0.038, 0.307]	0.846 [0.735, 0.924]	0.29 [0.08, 0.58]	0.68 [0.57, 0.78]
N stage				
N0	0.067 [0.011, 0.320]	0.838 [0.738, 0.911]	0.07 [0.00, 0.34]	0.83 [0.73, 0.90]
≥N1	0.163 [0.090, 0.262]	0.933 [0.680, 0.989]	0.93 [0.66, 1.00]	0.17 [0.10, 0.27]
≥N2	0.220 [0.123, 0.347]	0.972 [0.854, 0.995]	0.93 [0.66, 1.00]	0.43 [0.32, 0.55]
≥N3	0.563 [0.299, 0.802]	0.937 [0.858, 0.979]	0.64 [0.35, 0.87]	0.91 [0.83, 0.96]

Source of funding

Not reported.

Comments on study quality

Risks of bias: none identified.

Concerns regarding applicability: the study was conducted in Taiwan and includes only nasopharyngeal cancer patients. The applicability of the results to CUADT patients in the UK is therefore unclear.

Additional comments

1

Study, country

Chua 2009. Singapore.

Study type, study period

Prospective cohort study. August 2005 to May 2006.

Number of patients

78

Patient characteristics

Inclusion criteria: histologically proven primary NPC.

Gender	n (%)
Male	60 (76.9)
Female	18 (23.1)

T-stage	n (%)
T1	10 (12.9
T2	33 (42.3)
T3	21 (26.9)
T4	14 (17.9)

N-stage	n (%)
N0	16 (20.5)
N1	19 (24.4)
N2	24 (30.7)
N3	19 (24.4)

Type of test(s)

T stage

N stage

Reference standard

Presence of distant metastases based on imaging (PET/CT) and confirmed by either histology or clinical follow up.

2

Results

Prevalence of distant metastases in the study population: 7.6%.

T stage	Distant metastases: Present	Absent
T1 or T2	1	42
T3 or T4	5	30

N stage	Distant metastases: Present	Absent
N0 or N1	1	34
N2 or N3	5	38

T stage	Distant metastases: Present	Absent
T3 or T4	5	30
T1 or T2	1	42

N stage	Distant metastases: Present	Absent
N2 or N3	5	38
N0 or N1	1	34

	PPV [95% CI]	NPV[95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
T stage				
T1 or T2	0.023 [0.001, 0.123]	0.857 [0.697, 0.952]	0.17 [0.00, 0.64]	0.42 [0.30, 0.54]
T3 or T4	0.143 [0.048, 0.303]	0.977 [0.877, 0.999]	0.83 [0.36, 1.00]	0.58 [0.46, 0.70]
N stage				
N0 or N1	0.029 [0.001, 0.149]	0.884 [0.749, 0.961]	0.17 [0.00, 0.64]	0.53 [0.41, 0.65]
N2 or N3	0.116 [0.039, 0.251]	0.971 [0.851, 0.999]	0.83 [0.36, 1.00]	0.47 [0.35, 0.59]

Source of funding

Singhealth Foundation.

Comments on study quality

Risks of bias: none identified.

Concerns regarding applicability: study includes nasopharyngeal patients only and was conducted in Singapore. The applicability of the results to CUADT patients in the UK is unclear.

Additional comments

1

Study, country

Haerle 2011, Switzerland.

Study type, study period

Retrospective cohort study, January 2002 to December 2007.

Number of patients

299

Patient characteristics

Inclusion criteria: patients with newly diagnosed head and neck squamous cell carcinoma who received FDG-PET/CT for initial staging.

No patient characteristics reported, other than the tumour-associated factors included in the results.

Type of test(s)

- Tumour site
- T stage
- N stage

Reference standard

Detection of distant metastasis by PET/CT, with histopathological or cytological work up for confirmation of results.

Results

Prevalence of distant metastases in the study population: 11%.

Tumour site	Distant metastases: Present	Absent
Oral cavity	3	28
Other	26	242

Tumour site	Distant metastases: Present	Absent
Nasopharynx	2	5
Other	27	265

Tumour site	Distant metastases: Present	Absent
Oropharynx	8	160
Other	21	110

Tumour site	Distant metastases: Present	Absent
Hypopharynx	9	48
Other	20	222

Tumour site	Distant metastases: Present	Absent
Larynx	7	29
Other	22	241

Tumour site	Distant metastases: Present	Absent
Nasopharynx/ oral cavity/oropharynx	13	193
Other	16	77

Tumour site	Distant metastases: Present	Absent
Hypopharynx/larynx	16	77
Other	13	193

T stage	Distant metastases: Present	Absent
Stage T1	3	40
Other	26	230

T stage	Distant metastases: Present	Absent
Stage T2	9	92
Other	20	178

T stage	Distant metastases: Present	Absent
Stage T3	8	66
Other	21	204

T stage	Distant metastases: Present	Absent
Stage T4	9	72
Other	20	198

T stage	Distant metastases: Present	Absent
Stage T1-T2	12	132
Other	17	138

T stage	Distant metastases: Present	Absent
Stage T3-T4	17	138
Other	12	132

N stage	Distant metastases: Present	Absent
Stage N0	2	25
Other	27	245

N stage	Distant metastases: Present	Absent
Stage N1	4	36
Other N	25	234

N stage	Distant metastases: Present	Absent
Stage N2	20	194
Other N	9	76

N stage	Distant metastases: Present	Absent
Stage N3	3	15
Other N	26	255

N stage	Distant metastases: Present	Absent
Stage N0-N1	6	61
Other N	23	209

N stage	Distant metastases: Present	Absent
Stage N3-N3	23	209
Other N	6	61

	PPV [95% CI]	NPV[95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
Tumour site				
Oral cavity	0.097 [0.022, 0.258]	0.903 [0.861, 0.936]	0.10 [0.02, 0.27]	0.90 [0.85, 0.93]
Nasopharynx	0.286 [0.045, 0.707]	0.908 [0.868, 0.938]	0.07 [0.01, 0.23]	0.98 [0.96, 0.99]
Oropharynx	0.048, [0.021, 0.092]	0.840 [0.765, 0.898]	0.28 [0.13, 0.47]	0.41 [0.35, 0.47]
Hypopharynx	0.158 [0.075, 0.279]	0.917 [0.875,0.949]	0.31 [0.15, 0.51]	0.82 [0.77, 0.87]
Larynx	0.194 [0.082, 0.360]	0.916 [0.876, 0.947]	0.24 [0.10, 0.44]	0.89 [0.85, 0.93]
T stage				
T1	0.070 [0.015, 0.191]	0.898 [0.855, 0.933]	0.10 [0.02, 0.27]	0.85 [0.80, 0.89]
≥T2	0.103 [0.069, 0.146]	0.944 [0.813, 0.992]	0.93 [0.77, 0.99]	0.13 [0.09, 0.17]
≥T3	0.110 [0.065, 0.170]	0.917 [0.859, 0.956]	0.59 [0.39, 0.76]	0.49 [0.43, 0.55]
≥T4	0.111 [0.052, 0.201]	0.908 [0.862, 0.943]	0.31 [0.15, 0.51]	0.73 [0.68, 0.79]
N stage				
N0	0.074 [0.011, 0.243]	0.901 [0.859, 0.934]	0.07 [0.01, 0.23]	0.91 [0.87, 0.94]
≥N1	0.099 [0.067, 0.141]	0.926 [0.757, 0.989]	0.93 [0.77, 0.99]	0.09 [0.06, 0.13]
≥N2	0.099 [0.064, 0.145]	0.910 [0.815, 0.966]	0.79 [0.60, 0.92]	0.23 [0.18, 0.28]
≥N3	0.167 [0.038, 0.414]	0.908 [0.867, 0.939]	0.10 [0.02, 0.27]	0.94 [0.91, 0.97]

Source of funding

Not reported. Authors declared no financial disclosures or conflicts of interest.

Comments on study quality

Risks of bias: criteria for patient selection is not clear. Authors state that only high-risk (T3/4 and/or N2/3) cases were included, but the results include a notable proportion of patients with lower stage disease.

Concerns regarding applicability: no patient characteristics reported, other than tumour site and stage.

Additional comments

1

Study, country

Keith 2006, United Kingdom

Study type, study period

Prospective cohort study, June 1997 to July 2002

Number of patients

116

Patient characteristics

Inclusion criteria: patients diagnosed with oral and oropharyngeal squamous cell carcinoma undergoing thoracic CT imaging.

Gender	n (%)
Floor of mouth	30 (25.9)
Anterior tongue	22 (19.0)
Mandibular alveolus	16 (13.8)
Soft palate	11 (9.5)
Posterior tongue	11 (9.5)
Retromolar	8 (6.9)
Wall of pharynx	8 (6.9)
Tonsil	6 (5.2)
Maxillary alveolus	3 (2.6)
Buccal	1 (0.9)

T stage	n (%)
T1	19 (16)
T2	29 (25)
T3	6 (5)
T4	62 (53)

N stage	n (%)
N1	61 (53)
N2	30 (26)
N3	22 (18)
N4	3 (3)

Type of test(s)

- Tumour site
- Disease stage

Reference standard

Detection of thoracic malignancy by chest CT. Patients with abnormal CT findings were referred to the thoracic service for further management. This could involve further thoracic CT, bronchoscopy, CT-guided fine needle aspiration biopsy, or video-assisted thoracic biopsy.

Results

Prevalence of thoracic malignancy in the study population: 3.5%.

Tumour site	Thoracic malignancy: Present	Thoracic malignancy: Absent
Oral cavity	1	79
Other	3	33

Tumour site	Thoracic malignancy: Present	Thoracic malignancy: Absent
Oropharynx	3	33
Other	1	79

Stage	Thoracic malignancy: Present	Thoracic malignancy: Absent
I or II	0	33
Other	4	79

Stage	Thoracic malignancy: Present	Thoracic malignancy: Absent
III or IV	4	79
Other	0	33

	PPV [95% CI]	NPV[95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
Tumour site				
Oral cavity	0.013 [0.002, 0.068]	0.917 [0.775, 0.982]	0.25 [0.01, 0.81]	0.29 [0.21, 0.39]
Oropharynx	0.083 [0.019, 0.225]	0.988 [0.932, 0.998]	0.75 [0.19, 0.99]	0.71 [0.61, 0.79]
Disease stage				
I or II	0.000 [0.000, 0.107]	0.952 [0.881, 0.986]	0.00 [0.00, 0.60]	0.71 [0.61, 0.79]
III or IV	0.048 [0.014, 0.119]	1.000 [0.893, 1.000]	1.00 [0.40, 1.00]	0.29 [0.21, 0.39]

Source of funding

Not reported.

Comments on study quality

Risks of bias: exact work up and methods used to confirm the presence of thoracic malignancy in the case of abnormal CT findings is not clear.

Concerns regarding applicability: staging system used is not reported. Thoracic malignancy only used as reference standard; other metastatic sites not studied/reported.

Additional comments

1

Study, country

Kim 2008. Korea.

Study type, study period

Prospective cohort study. January 2001 to December 2005.

Number of patients

564

Patient characteristics

Inclusion criteria: histologically confirmed upper aerodigestive tract malignancy.

Mean age: 60.3 years.

Gender	n (%)
Male	472 (83.7)
Female	92 (16.3)

Pathologic finding	n (%)
Nasopharynx	82 (14.5)
Oropharynx	95 (16.8)
Hypopharynx	55 (9.6)
Larynx	204 (36.2)
Oral cavity	103 (18.3)
Nasal cavity/paranasal sinuses	25 (4.4)

Type of test(s)

Tumour site

Reference standard

Presence of bone metastases, imaged with PET and bone scan and confirmed with follow up imaging after 6 months

Results

Prevalence of bone metastases in the study population: 3.0%.

Tumour site	Bone metastases: Present	Bone metastases: Absent
Nasopharynx	9	73
Other	8	474

Tumour site	Bone metastases: Present	Bone metastases: Absent
Oropharynx	1	94
Other	16	453

Tumour site	Bone metastases: Present	Bone metastases: Absent
Hypopharynx	2	53
Other	15	494

Tumour site	Bone metastases: Present	Bone metastases: Absent
Larynx	3	201
Other	14	346

Tumour site	Bone metastases: Present	Bone metastases: Absent
Oral cavity	2	101
Other	15	446

Tumour site	Bone metastases: Present	Bone metastases: Absent
Nasal cavity/paranasal sinuses	0	25
Other	17	522

	PPV [95% CI]	NPV[95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
Nasopharynx	0.110 [0.051, 0.198]	0.983 [0.968, 0.993]	0.53 [0.28, 0.77]	0.87 [0.84, 0.89]
Oropharynx	0.010 [0.001, 0.057]	0.966 [0.945, 0.980]	0.06 [0.00, 0.29]	0.83 [0.79, 0.86]
Hypopharynx	0.036 [0.004, 0.125]	0.971 [0.952, 0.983]	0.12 [0.01, 0.36]	0.90 [0.88, 0.93]
Larynx	0.010 [0.001, 0.035]	0.961 [0.936, 0.979]	0.18 [0.04, 0.43]	0.63 [0.59, 0.67]
Oral cavity	0.019 [0.002, 0.068]	0.968 [0.947, 0.982]	0.12 [0.01, 0.36]	0.82 [0.78, 0.85]
Nasal cavity/paranasal sinuses	0 [0, 0.137]	0.969 [0.950, 0.982]	0.00 [0.00, 0.20]	0.95 [0.93, 0.97]

Source of funding

Ministry of Health and Welfare (Korea)

Comments on study quality

Risks of bias: none identified.
Concerns regarding applicability: no patient characteristics reported other than tumour stage, making applicability of the population difficult to assess.

Additional comments

1

Study, country

Liu 2007. Taiwan.

Study type, study period

Prospective cohort study. April 2002 to August 2005.

Number of patients

300

Patient characteristics

Inclusion criteria: histologically proven nonkeratinizing NPC.

Exclusion criteria: history of previous or synchronous second malignancy; tumour histology other than WHO type II or III; insufficient follow up data.

Gender	n (%)
Male	210 (70.0)
Female	90 (30.0)

T-stage	n (%)
T1	60 (20.0)
T2	93 (31.0)
T3	64 (21.3)
T4	83 (27.7)

N-stage	n (%)
N0	32 (10.7)
N1	68 (22.7)
N2	121 (40.3)
N3	79 (26.3)

Type of test(s)

T stage
N stage

Reference standard

Bone metastases, imaged with PET and skeletal scintigraphy and confirmed with histology and/or clinical follow up.

Results

Prevalence of distant metastases in the study population: 20.3%.

T stage	Distant metastases: Present	Absent
T1	11	49
Other	50	190

T stage	Distant metastases: Present	Absent
T2	11	82
Other	50	157

T stage	Distant metastases: Present	Absent
T3	11	53
Other	50	186

T stage	Distant metastases: Present	Absent
T4	28	55
Other	33	184

N stage	Distant metastases: Present	Absent
N0	0	32
Other	61	207

N stage	Distant metastases: Present	Absent
N1	6	62
Other	55	177

N stage	Distant metastases: Present	Absent
N2	17	104
Other	44	135

N stage	Distant metastases: Present	Absent
N3	38	41
Other	23	198

	PPV [95% CI]	NPV[95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
T stage				
T1	0.183 [0.095, 0.304]	0.792 [0.735, 0.841]	0.18 [0.09, 0.30]	0.79 [0.74, 0.84]
≥T2	0.208 [0.159, 0.265]	0.817 [0.696, 0.905]	0.82 [0.70, 0.91]	0.21 [0.16, 0.26]
≥T3	0.265 [0.196, 0.344]	0.856 [0.790, 0.908]	0.64 [0.51, 0.76]	0.55 [0.48, 0.61]
T4	0.337 [0.237, 0.450]	0.848 [0.793, 0.893]	0.46 [0.33, 0.59]	0.77 [0.71, 0.82]
N stage				
N0	0.00 [0.00, 0.109]	0.772 [0.713, 0.821]	0.00 [0.00, 0.06]	0.87 [0.82, 0.91]
≥N1	0.228 [0.179, 0.283]	1.00 [0.891, 1.00]	1.00 [0.94, 1.00]	0.13 [0.09, 0.18]
≥N2	0.275 [0.214, 0.342]	0.940 [0.874, 0.978]	0.90 [0.80, 0.96]	0.39 [0.33, 0.46]
N3	0.481 [0.367, 0.596]	0.896 [0.848, 0.933]	0.62 [0.49, 0.74]	0.83 [0.77, 0.87]

Source of funding

Hospital and university grants.

Comments on study quality

Risks of bias: unclear whether a consecutive/random sample of patients was enrolled.
Concerns regarding applicability: nasopharyngeal patients only; study conducted in Taiwan. The applicability of the results to CUADT patients in the UK is unclear.

Additional comments

1

Study, country

Ng, 2008. Taiwan.

Study type, study period

Prospective cohort study. September 2003 to March 2006.

Number of patients

160

2

Patient characteristics

Inclusion criteria:

- Patients with a pathological diagnosis of squamous cell carcinoma of the oropharynx or hypopharynx undergoing both multi-detector row computed tomography and PET for pretreatment evaluation.
- Negative results from chest radiography, liver sonography, and whole body bone scanning
- No prior treatment to the head and neck region

Gender	n (%)
Male	148 (92.5)
Female	12 (7.5)

Tumour site	n (%)
Oropharynx	74 (46.3)
Hypopharynx	86 (53.7)

Type of test(s)

Tumour site
T stage
N stage

Reference standard

Presence of distant metastases or second primary tumour, investigated with PET and CT and confirmed either pathologically or by follow up.

Results

Prevalence of distant metastases in the study population: 16.2%.

Tumour site	Distant metastases: Present	Absent
Oropharynx	7	67
Hypopharynx	19	67

Tumour site	Distant metastases: Present	Absent
Hypopharynx	19	67
Oropharynx	7	67

T stage	Distant metastases: Present	Absent
T1 or T2	9	38
T3 or T4	17	96

T stage	Distant metastases: Present	Absent
T3 or T4	17	96
T1 or T2	9	38

N stage	Distant metastases: Present	Absent
N0 or N1	4	47
N2 or N3	22	87

N stage	Distant metastases: Present	Absent
N2 or N3	22	87
N0 or N1	4	47

	PPV [95% CI]	NPV[95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
Tumour site				
Oropharynx	0.095 [0.039, 0.185]	0.779 [0.677, 0.861]	0.27 [0.12, 0.48]	0.50 [0.41, 0.59]
Hypopharynx	0.221 [0.139, 0.323]	0.905 [0.815, 0.961]	0.73 [0.52, 0.88]	0.50 [0.41, 0.59]
T stage				
T1 or T2	0.192 [0.092, 0.333]	0.850 [0.770, 0.910]	0.35 [0.17, 0.56]	0.72 [0.63, 0.79]
T3 or T4	0.150 [0.090, 0.230]	0.809 [0.667, 0.909]	0.65 [0.44, 0.83]	0.28 [0.21, 0.37]
N stage				
N0 or N1	0.078 [0.022, 0.189]	0.798 [0.711, 0.869]	0.15 [0.04, 0.35]	0.65 [0.56, 0.73]
N2 or N3	0.202 [0.131, 0.290]	0.922 [0.811, 0.978]	0.85 [0.65, 0.96]	0.35 [0.27, 0.44]

Source of funding

Hospital and National Science Council (China) grants.

Comments on study quality

Risks of bias: unclear whether a consecutive/random sample of patients was enrolled.
Concerns regarding applicability: oro/hypopharyngeal patients only; study conducted in Taiwan. The applicability of the results to CUADT patients in the UK is unclear.

Additional comments

1

Study, country

Wax 2002.

Study type, study period

Retrospective (assumed) cohort study.

Number of patients

54

Patient characteristics

Inclusion criteria: consecutive patients with a clinical diagnosis of head and neck malignancy.
Exclusion criteria: recurrent head and neck tumours, salivary gland neoplasms, malignant melanoma, thyroid neoplasms, nasopharyngeal

carcinoma, metastatic adenocarcinoma, neurogenic neoplasms, lymphoma.

Tumour site	n (%)
Oral cavity	16 (29.6)
Oropharynx	13 (24.1)
Larynx	13 (24.1)
Other	12 (22.2)

T-stage	n (%)
Tx	3 (5.6)
T1	14 (25.9)
T2	22 (40.7)
T3	3 (5.6)
T4	11 (20.4)

N-stage	n (%)
N0	34 (63.0)
N1	5 (9.3)
N2	6 (11.1)
N3	8 (14.8)

Type of test(s)

Tumour site
T stage
N stage

Reference standard

Synchronous lung lesions detected with radiography of the chest + PET and confirmed with chest CT, bronchoscopy, and lung biopsy or bronchial washings.

Results

Prevalence of distant metastases in the study population: 18.5%.

Tumour site	Distant metastases: Present	Distant metastases: Absent
Oral cavity	5	11
Other	5	33

Tumour site	Distant metastases: Present	Distant metastases: Absent
Oropharynx	1	12
Other	9	32

Tumour site	Distant metastases: Present	Distant metastases: Absent
Larynx	4	9
Other	6	35

Tumour site	Distant metastases: Present	Distant metastases: Absent
All other sites	0	12
Other	10	32

T stage	Distant metastases: Present	Distant metastases: Absent
T1	1	13
Other	9	30

T stage	Distant metastases: Present	Distant metastases: Absent
T2	8	14
Other	2	29

T stage	Distant metastases: Present	Distant metastases: Absent
T3	0	3
Other	10	40

T stage	Distant metastases: Present	Distant metastases: Absent
T4	0	11
Other	10	32

N stage	Distant metastases: Present	Distant metastases: Absent
N0	6	28
Other	4	15

N stage	Distant metastases: Present	Distant metastases: Absent
N1	1	4
Other	9	39

N stage	Distant metastases: Present	Distant metastases: Absent
N2	0	6
Other	10	37

N stage	Distant metastases: Present	Distant metastases: Absent
N3	3	5
Other	7	38

	PPV [95% CI]	NPV[95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
Tumour site				
Oral cavity	0.313 [0.110, 0.587]	0.866 [0.719, 0.956]	0.50 [0.19, 0.81]	0.75 [0.60, 0.87]
Oropharynx	0.077 [0.002, 0.360]	0.781 [0.624, 0.894]	0.10 [0.00, 0.45]	0.73 [0.57, 0.85]
Larynx	0.308 [0.091, 0.614]	0.854 [0.708, 0.944]	0.40 [0.12, 0.74]	0.80 [0.65, 0.90]
Other	0.00 [0.00, 0.265]	0.762 [0.606, 0.880]	0.00 [0.00, 0.31]	0.73 [0.57, 0.85]
T stage				
T1	0.071 [0.002, 0.339]	0.769 [0.607, 0.889]	0.10 [0.00, 0.45]	0.70 [0.54, 0.83]
≥T2	0.222 [0.101, 0.392]	0.882 [0.636, 0.985]	0.80 [0.44, 0.97]	0.35 [0.21, 0.51]
≥T3	0.00 [0.00, 0.232]	0.744 [0.579, 0.870]	0.00 [0.00, 0.31]	0.67 [0.51, 0.81]
≥T4	0.00 [0.00, 0.285]	0.762 [0.606, 0.880]	0.00 [0.00, 0.31]	0.74 [0.59, 0.86]
N stage				
N0	0.177 [0.068, 0.345]	0.790 [0.544, 0.940]	0.60 [0.26, 0.88]	0.35 [0.21, 0.51]
≥N1	0.211 [0.061, 0.456]	0.824 [0.655, 0.932]	0.40 [0.12, 0.74]	0.65 [0.49, 0.79]
≥N2	0.214 [0.047, 0.508]	0.821 [0.665, 0.925]	0.30 [0.07, 0.65]	0.74 [0.59, 0.86]
≥N3	0.375 [0.085, 0.755]	0.844 [0.705, 0.935]	0.30 [0.07, 0.65]	0.88 [0.75, 0.96]

Source of funding

Not reported.

Comments on study quality

Risks of bias: consecutive patients considered for inclusion, but a large number were excluded and reasons for this are not clear.
Concerns regarding applicability: the 'other' tumour site category included an unspecified number of patients with oesophageal or nasal septum cancer, neither of which are relevant to the review question.

Additional comments

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Index Test	Reference Standard	Outcomes
Adults with cancer of the upper aerodigestive tract Subgroups: • Newly diagnosed cancer • Recurrent cancer (within 2cm of original primary and within 3 years from primary treatment) • Unknown primary of suspected upper aerodigestive tract origin • Second primary tumour	• TN stage • Smoking status • HPV status • Tumour site	Detection of distant malignant disease and/or detection of synchronous primary	• Sensitivity • Specificity • Positive predictive value • Negative predictive value

3

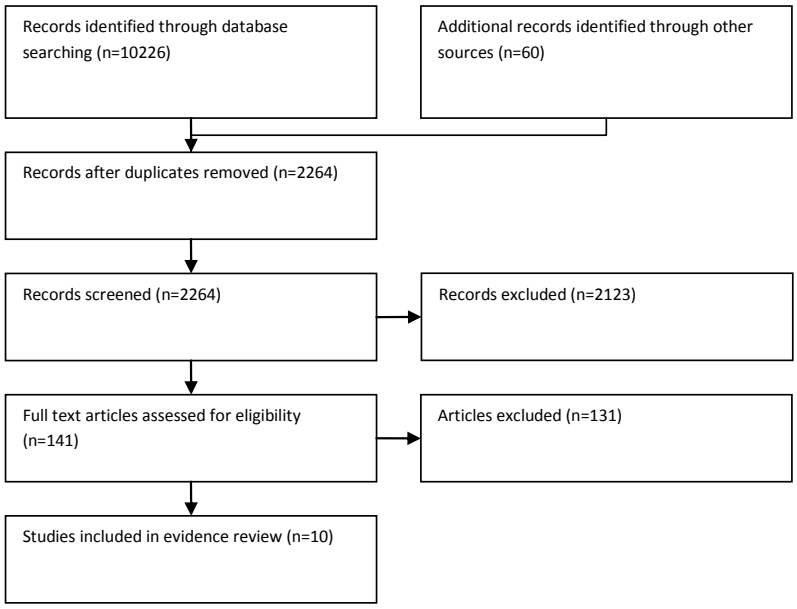
4 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Diagnostic test
Language	English only
Study design	Studies of diagnostic test accuracy
Status	Published data only
Other criteria for inclusion / exclusion of studies	Inclusion criteria: sufficient data reported to calculate the total number of true positives, true negative, false positives, and false negatives for the studied test(s). Exclusion criteria: • reference standard is unclear or undefined. • studies that exclusively report the detection of malignant disease at the primary tumour site or regional (cervical) lymph nodes.
Search strategies	None specified
Review strategies	The evidence table for studies of diagnostic accuracy will be used (NICE Guidelines Manual Appendix J) to extract and present data from individual studies. Sensitivity and specificity data will be pooled when appropriate. Other

	outcomes will be presented as risk ratios or hazard ratios. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. In addition to individual tests, where possible, different combinations or sequences of tests will be compared using the outcomes listed in the PICO.

Separate searches were conducted for the two review questions concerning systemic staging, but both databases were screened for articles relevant to either review question. The flow diagram (Figure 2.17~~Figure 2.17~~~~Figure 2.17~~) therefore shows the combined results from two database searches. Ten systematic reviews were identified as relevant to the question 'What is the most effective systemic imaging strategy for investigating cancer of the upper aerodigestive tract?' The individual studies included in each of these systematic reviews were also checked for relevance to the question 'Which patients with cancer of the upper aerodigestive tract require systemic staging?'

Figure 2.17. Study flow diagram



Included studies

National Head and Neck Cancer Audit. Data taken from:

- National Head and Neck Cancer Audit 2013, DAHNO Ninth Annual Report. July 2014. Available at: http://www.hscic.gov.uk/searchcatalogue?productid=14840&q=title%3a%22National+Head+and+Neck+Cancer+Audit%22&sort=Most+recent&size=10&page=1#top. Last accessed 2 June 2015.
- National Head and Neck Cancer Audit 2012, DAHNO Eighth Annual Report. July 2013 Available at: http://www.hscic.gov.uk/searchcatalogue?productid=11795&q=title%3a%22National+Head+and+Neck+Cancer+Audit%22&sort=Most+recent&size=10&page=1#top. Last accessed 2 June 2015.
- Michalowski, J. Health and Social Care Information Centre. Personal communication. May 2015.

Chan, S. C., Wang, H. M., Yen, T. C., Lin, C. Y., Chin, S. C., Liao, C. T., Wai, Y. Y., Wang, J. J., and Ng, S. H. (1)(8)F-FDG PET/CT and 3.0-T whole-body MRI for the detection of distant metastases and second primary tumours in patients with untreated oropharyngeal/hypopharyngeal carcinoma: a comparative study. Eur J Nucl Med Mol Imaging 2011. 38(9): 1607-1619

Chang, J. T. C. Nasopharyngeal carcinoma staging by (18)F-fluorodeoxyglucose positron emission tomography. International Journal of Radiation Oncology Biology Physics 2005. 62(2): 501-507

Chua, M. L., Ong, S. C., Wee, J. T., Ng, D. C., Gao, F., Tan, T. W., Fong, K. W., Chua, E. T., Khoo, J. B., and Low, J. S. Comparison of 4 modalities for distant metastasis staging in endemic nasopharyngeal carcinoma. Head Neck 2009. 31(3): 346-354

Haerle, S. K., Schmid, D. T., Ahmad, N., Hany, T. F., and Stoeckli, S. J. The value of F-18-FDG PET/CT for the detection of distant metastases in high-risk patients with head and neck squamous cell carcinoma. Oral Oncology 2011. 47(7): 653-659

Keith, D. J. W. The role of thoracic computed tomography in staging newly-diagnosed oral squamous cell carcinoma. British Journal of Oral and Maxillofacial Surgery 2006. 44(3): 198-202

Kim, M. R., Roh, J. L., Kim, J. S., Choi, S. H., Nam, S. Y., and Kim, S. Y. 18F-fluorodeoxyglucose-positron emission tomography and bone scintigraphy for detecting bone metastases in patients with malignancies of the upper aerodigestive tract. Oral Oncol 2008. 44(2): 148-152

Liu, F. Y., Lin, C. Y., Chang, J. T., Ng, S. H., Chin, S. C., Wang, H. M., Liao, C. T., Chan, S. C., and Yen, T. C. 18F-FDG PET can replace conventional work-up in primary M staging of nonkeratinizing nasopharyngeal carcinoma. J Nucl Med 2007. 48(10): 1614-1619

Ng, S. H., Chan, S. C., Liao, C. T., Chang, J. T., Ko, S. F., Wang, H. M., Chin, S. C., Lin, C. Y., Huang, S. F., and Yen, T. C. Distant metastases and synchronous second primary tumors in patients with newly diagnosed oropharyngeal and hypopharyngeal carcinomas: evaluation of (18)F-FDG PET and extended-field multi-detector row CT. Neuroradiology 2008. 50(11): 969-979

Wax, M. K., Myers, L. L., Gabalski, E. C., Husain, S., Gona, J. M., and Nabi, H. Positron emission tomography in the evaluation of synchronous lung lesions in patients with untreated head and neck cancer. Arch Otolaryngol Head Neck Surg 2002. 128(6): 703-707

Excluded studies identified from searches

Albuquerque, M. A. P. CT assessment of the correlation between clinical examination and bone involvement in oral malignant tumors. Brazilian Oral Research 2009. 23(2): 196-202.
Reason for exclusion: Outcomes not relevant to PICO.

Andrle, J. and Schartinger, V. H. Initial staging examinations for head and neck squamous cell carcinoma: are they appropriate? Journal of Laryngology & Otology 2009. 123(8): 885-888.
Reason for exclusion: Insufficient outcome data reported.

Bisase, B. and Kerawala, Cyrus. The role of computed tomography of the chest in the staging of early squamous cell carcinoma of the tongue. British Journal of Oral & Maxillofacial Surgery 2008. 46(5): 367-369.
Reason for exclusion: Outcomes not relevant to PICO.

Brennan, P. A., Anand, R., Ethunandan, M., Sharma, S., and Tilley, E. Keith DJ, Ong TK, Martin IC. The role of thoracic computed tomography in staging newly-diagnosed oral squamous cell carcinoma. Br J Oral Maxillofac Surg 2006;44 : 198-202. British Journal of Oral & Maxillofacial Surgery 2007. 45(3): 255-256.
Reason for exclusion: Comment on study.

Brouwer, J., Hooft, L., Hoekstra, O. S., Riphagen, I. I., Castelijns, J. A., Bree, R., and Leemans, C. R. Systematic review: accuracy of imaging tests in the diagnosis of recurrent laryngeal carcinoma after radiotherapy (Structured abstract). Head and Neck 2008. 30: 889-897.
Reason for exclusion: Outcomes not relevant to PICO.

Cacicedo, J., Del Hoyo, O., Rodeno, E., Fernandez, I., Rodriguez, O., Dolado, A., Martinez-Indart, L., Municio, J., Gomez, J., Sancho, A., de Argumedo, G. L., Alvarez, J., Gaafar, A., Espinosa, J., and Bilbao, P. Utility Of 18F-Fluorodeoxyglucose Positron Emission Tomography (PET/CT) in the Staging and Treatment Plan Evaluation of Head and Neck Squamous Cell Carcinoma. International Journal of Radiation Oncology Biology Physics 2014. 90: S552-S552.
Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

Cantrell, S. C. P. Differences in imaging characteristics of HPV-positive and HPV-negative oropharyngeal cancers: A blinded matched-pair analysis. American Journal of Neuroradiology 2013. 34(10): 2005-2009.
Reason for exclusion: Outcomes not relevant to PICO.

Castano, A. D'Ambrosi. TNM staging changes for head and neck cancer patients who underwent 18F-FDG-CT scan for radiotherapy planning. Radiotherapy and Oncology 2012. Conference(var.pagings): May.
Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

Catalano, O. A. R. Clinical impact of PET/MR imaging in patients with cancer undergoing same-day PET/CT: Initial experience in 134 patients-a hypothesis-generating exploratory study. Radiology 2013. 269(3): 857-869.
Reason for exclusion: Population not relevant to PICO.

Champion, G. A. and Piccirillo, Jay F. The impact of computed tomography on pretherapeutic staging in patients with laryngeal cancer: demonstration of the Will Rogers' phenomenon. Head & Neck 2004. 26(11): 972-976.
Reason for exclusion: Outcomes not relevant to PICO.

Chan SC, Chang JT, Wang HM, Lin CY, Ng SH, Fan KH, Chin SC, Liao CT, Yen TC., Chang, Joseph Tung-Chieh, Wang, Hung-Ming, Lin, Chien-Yu, Ng, Shu-Hang, Fan, Kang-Hsing, Chin, Shy-Chyi, Liao, Chua-Ta, and Yen, Tzu-Chen. Prediction for distant failure in patients with stage M0 nasopharyngeal carcinoma: the role of standardized uptake value. Oral Oncology 2009. 45(1): 52-58.
Reason for exclusion: Outcomes not relevant to PICO.

Chan, S. C., Chang, J. T., Lin, C. Y., Ng, S. H., Wang, H. M., Liao, C. T., Chang, C. J., Lin, S. Y., and Yen, T. C. Clinical utility of F-18-FDG PET parameters in patients with advanced nasopharyngeal carcinoma: predictive role for different survival endpoints and impact on prognostic stratification. Nuclear Medicine Communications 2011. 32(11): 989-996.
Reason for exclusion: Outcomes not relevant to PICO.

Chang MC, Chen JH, Liang JA, Yang KT, Cheng KY, Kao CH., Chen, Jin-Hua, Liang, Ji-An, Yang, Kuang-Tao, Cheng, Kai-Yuan, and Kao, Chia-Hung. Accuracy of whole-body FDG-PET and FDG-PET/CT in M staging of nasopharyngeal carcinoma: a systematic review and meta-analysis. [Review]. European Journal of Radiology 2013. 82(2): 366-373.
Reason for exclusion: Outcomes not relevant to PICO.

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King, A. D., Ma, B. B., Yau, Y. Y., Zee, B., Leung, S. F., Wong, J. K., Kam, M. K., Ahuja, A. T., and Chan, A. T. The impact of 18F-FDG PET/CT on assessment of nasopharyngeal carcinoma at diagnosis. Br J Radiol 2008. 81(964): 291-298.
Reason for exclusion: Study design not relevant.

Krabbe, C. A., Pruim, J., van der Laan, B. F., Rodiger, L. A., and Roodenburg, J. L. FDG-PET and detection of distant metastases and simultaneous tumors in head and neck squamous cell carcinoma: a comparison with chest radiography and chest CT. Oral Oncol 2009. 45(3): 234-240.
Reason for exclusion: Outcomes not relevant to PICO.

Lamarre, E. D., Batra, P. S., Lorenz, R. R., Citardi, M. J., Adelstein, D. J., Srinivas, S. M., and Scharpf, J. Role of positron emission tomography in management of sinonasal neoplasms--a single institution's experience. Am J Otolaryngol 2012. 33(3): 289-295.
Reason for exclusion: Insufficient outcome data reported.

Li TR, Du XK, Huo TL, and Zhao CL. 18F-FDG PET/CT imaging in patients with nasopharyngeal carcinoma: distant metastasis and recurrence. Journal of Chinese Clinical Medicine 2010. 5: 703-711.
Reason for exclusion: Article unavailable.

Lin Q, Zhao H, Zhao J, and Lin C. Comparison of diagnostic value between 18F-FDG PET/CT and MRI in nasopharyngeal carcinoma. Journal of Jilin University 2009. 35: 1163-1166.
Reason for exclusion: Non English publication.

Liu, F. Y., Chang, J. T., Wang, H. M., Liao, C. T., Kang, C. J., Ng, S. H., Chan, S. C., and Yen, T. C. [18F]fluorodeoxyglucose positron emission tomography is more sensitive than skeletal scintigraphy for detecting bone metastasis in endemic nasopharyngeal carcinoma at initial staging. J Clin Oncol 2006. 24(4): 599-604.
Reason for exclusion: Superseded by later study.

Loh, K. S., Brown, D. H., Baker, J. T., Gilbert, R. W., Gullane, P. J., and Irish, J. C. A rational approach to pulmonary screening in newly diagnosed head and neck cancer. Head Neck 2005. 27(11): 990-994.
Reason for exclusion: Comparison not relevant to PICO.

Mercader, V. P., Gatenby, R. A., Mohr, R. M., Fisher, M. S., and Caroline, D. F. CT surveillance of the thorax in patients with squamous cell carcinoma of the head and neck: a preliminary experience. J Comput Assist Tomogr 1997. 21(3): 412-417.
Reason for exclusion: Population not relevant to PICO.

Morrison J, Markose G, Carton AT, and Hislop WS. Thoracic computed tomography in newly diagnosed oral carcinomas. British Journal of Oral and Maxillofacial Surgery 2007. 45: e32.
Reason for exclusion: Insufficient outcome data reported.

Ng, S. H., Chan, S. C., Yen, T. C., Chang, J. T., Liao, C. T., Ko, S. F., Wang, H. M., Wai, Y. Y., Wang, J. J., and Chen, M. C. Pretreatment evaluation of distant-site status in patients with nasopharyngeal carcinoma: accuracy of whole-body MRI at 3-Tesla and FDG-PET-CT. Eur Radiol 2009. 19(12): 2965-2976.
Reason for exclusion: Insufficient outcome data reported.

Ng, S. H., Chan, S. C., Yen, T. C., Liao, C. T., Chang, J. T., Ko, S. F., Wang, H. M., Lin, C. Y., Chang, K. P., and Lin, Y. C. Comprehensive imaging of residual/ recurrent nasopharyngeal carcinoma using whole-body MRI at 3 T compared with FDG-PET-CT. Eur Radiol 2010. 20(9): 2229-2240.
Reason for exclusion: Insufficient outcome data reported.

Ng, S. H., Chan, S. C., Yen, T. C., Liao, C. T., Lin, C. Y., Tung-Chieh, Chang J., Ko, S. F., Wang, H. M., Chang, K. P., and Fan, K. H. PET/CT and 3-T whole-body MRI in the detection of malignancy in treated oropharyngeal and hypopharyngeal carcinoma. Eur J Nucl Med Mol Imaging 2011. 38(6): 996-1008.
Reason for exclusion: Insufficient outcome data reported.

Nilssen, E. L., Murthy, P., McClymont, L., and Denholm, S. Radiological staging of the chest and abdomen in head and neck squamous cell carcinoma--are computed tomography and ultrasound necessary? J Laryngol Otol 1999. 113(2): 152-154.
Reason for exclusion: Study design not relevant.

Olmi, P., Fallai, C., Colagrande, S., and Giannardi, G. Staging and follow-up of nasopharyngeal carcinoma: magnetic resonance imaging versus computerized tomography. Int J Radiat Oncol Biol Phys 1995. 32(3): 795-800.
Reason for exclusion: Insufficient outcome data reported.

Ong, T. K., Kerawala, C. J., Martin, I. C., and Stafford, F. W. The role of thorax imaging in staging head and neck squamous cell carcinoma. J Craniomaxillofac Surg 1999. 27(6): 339-344.
Reason for exclusion: Insufficient outcome data reported.

Reiner, B., Siegel, E., Sawyer, R., Brocato, R. M., Maroney, M., and Hooper, F. The impact of routine CT of the chest on the diagnosis and management of newly diagnosed squamous cell carcinoma of the head and neck. AJR Am J Roentgenol 1997. 169(3): 667-671.
Reason for exclusion: Insufficient outcome data reported.

Sigg, M. B., Steinert, H., Gratz, K., Hugenin, P., Stoeckli, S., and Eyrich, G. K. Staging of head and neck tumors: [18F]fluorodeoxyglucose positron emission tomography compared with physical examination and conventional imaging modalities. J Oral Maxillofac Surg 2003. 61(9): 1022-1029.
Reason for exclusion: Insufficient outcome data reported.

Tan, L., Greener, C. C., Seikaly, H., Rassekh, C. H., and Calhoun, K. H. Role of screening chest computed tomography in patients with advanced head and neck cancer. Otolaryngol Head Neck Surg 1999. 120(5): 689-692.
Reason for exclusion: Study design not relevant.

Teknos, T. N., Rosenthal, E. L., Lee, D., Taylor, R., and Marn, C. S. Positron emission tomography in the evaluation of stage III and IV head and neck cancer. Head Neck 2001. 23(12): 1056-1060.
Reason for exclusion: Insufficient outcome data available.

Tesche, S., Habermann, C. R., Sagowski, C., Wenzel, S., and Metternich, F. U. [The value of chest CT-scanning for staging of progressed or recurrent head and neck squamous cell carcinomas (HNSCC)]. Laryngorhinootologie 2006. 85(2): 93-98.
Reason for exclusion: Non English publication.

Veit-Haibach, P., Luczak, C., Wanke, I., Fischer, M., Egelhof, T., Beyer, T., Dahmen, G., Bockisch, A., Rosenbaum, S., and Antoch, G. TNM staging with FDG-PET/CT in patients with primary head and neck cancer. Eur J Nucl Med Mol Imaging 2007. 34(12): 1953-1962.
Reason for exclusion: Insufficient data/unclear if population is relevant to PICO.

Wang GH, Lau EW, Shakher R, Binns DS, Hogg A, and Drummond E. Clinical application of (18)F-FDG PET/CT to staging and treatment effectiveness monitoring of nasopharyngeal carcinoma (In Chinese). Ai Zheng 2007. 26: 638-642.
Reason for exclusion: Article unavailable.

Warner, G. C. and Cox, G. J. Evaluation of chest radiography versus chest computed tomography in screening for pulmonary malignancy in advanced head and neck cancer. J Otolaryngol 2003. 32(2): 107-109.
Reason for exclusion: Insufficient outcome data reported.

Xu QL, Chen F, and Wan WX. The diagnostic value of 18F-FDG PET/CT for recurrence or distant metastasis in nasopharyngeal carcinoma patients (In Chinese). Guide Chin Med 2011. 09: 341-344.
Reason for exclusion: Article unavailable.

Yen, R. F., Hong, R. L., Tzen, K. Y., Pan, M. H., and Chen, T. H. Whole-body 18F-FDG PET in recurrent or metastatic nasopharyngeal carcinoma. J Nucl Med 2005. 46(5): 770-774.
Reason for exclusion: Population not relevant to PICO.

Yi, J. S., Kim, J. S., Lee, J. H., Choi, S. H., Nam, S. Y., Kim, S. Y., and Roh, J. L. 18F-FDG PET/CT for detecting distant metastases in patients with recurrent head and neck squamous cell carcinoma. J Surg Oncol 2012. 106(6): 708-712.
Reason for exclusion: Outcomes not relevant to PICO.

Yoshida, K., Suzuki, A., Nagashima, T., Lee, J., Horiuchi, C., Tsukuda, M., and Inoue, T. Staging primary head and neck cancers with (18)F-FDG PET/CT: is intravenous contrast administration really necessary? Eur J Nucl Med Mol Imaging 2009. 36(9): 1417-1424.
Reason for exclusion: Insufficient outcome data reported.

Zhang GY, Wei WH, Li YZ, Xu T, Wu HB, and Wang QS. The role of PET-CT in diagnosing distant metastasis of nasopharyngeal carcinoma (In Chinese). Cancer Res Clin 2011. 23: 294-298.
Reason for exclusion: Article unavailable.

Clinical question: What is the most effective systemic imaging strategy for investigating cancer of the upper aerodigestive tract?

Evidence summary

The evidence summary identified 10 eligible systematic reviews and meta-analyses. All 10 reviews were directly relevant to the review question and generally well conducted (see Study Characteristics and Quality section for details). All included some assessment of study quality; 9/10 used QUADAS2 to assess study quality. On this basis, no major concerns with risks of bias or study applicability were identified for the individual studies.

Direct comparisons of test diagnostic performance: PET or PET/CT versus other diagnostic tests

Two systematic reviews included studies directly comparing the performance of PET or PET/CT to other diagnostic tests. One review (Yi 2013) compared the performance of PET or PET/CT against bone scintigraphy for detecting systemic malignant disease in people with head and neck cancer. Based on five studies of 1184 patients, the sensitivities of PET or PET/CT and bone scintigraphy were estimated as 0.85 (95% confidence intervals [CI] 0.69, 0.94) and 0.55 (95% CI 0.22, 0.84), respectively; the corresponding figures for specificity were 0.98 (95% CI 0.97, 0.99) and 0.98 (95% CI 0.97, 0.99), respectively.

One review (Xu 2012b) compared the performance of PET or PET/CT against conventional imaging for detecting distant malignancies in people with head and neck cancer. Based on eight studies of 1147 patients, the sensitivities of PET or PET/CT and conventional imaging were estimated as 0.83 (95% CI 0.76, 0.88) and 0.44 (95% CI 0.29, 0.61), respectively; the corresponding figures for specificity were 0.96 (95% CI 0.94, 0.97) and 0.96 (95% CI 0.88, 0.98) respectively. A subgroup analysis of nasopharyngeal and non-nasopharyngeal cancers was also conducted; the nasopharyngeal cancer studies used a combination of chest X-ray, abdominal ultrasound, and bone scan for conventional imaging, whereas the non-nasopharyngeal cancer studies predominantly used chest/abdominal CT. The sensitivities of conventional imaging were 0.30 (95% CI 0.19, 0.44) and 0.62 (95% CI 0.43, 0.78) for nasopharyngeal and non-nasopharyngeal cancers. Specificity of conventional imaging, and both diagnostic parameters for PET or PET/CT, were similar for the subgroups and the whole study population.

Other analyses of diagnostic accuracy (single tests)

<u>Head and neck cancer (any site)</u>

Four systematic reviews and meta-analyses (Xu 2011a, Xu 2012a, Xu 2011b, Yi 2013) investigated the diagnostic accuracy of PET/CT in people with head and neck cancer. Estimates of sensitivity and specificity were 0.88 to 0.90 and 0.95 to 0.99, respectively. One further review (Gao 2014) included recurrent head and neck cancer only, and estimated the sensitivity and specificity of PET/CT in this population to be 0.92 (95% CI 0.83, 0.96) and 0.95 (95% CI 0.91, 0.97), respectively.

Two systematic reviews and meta-analyses (Xu 2011b, Yi 2013) investigated the diagnostic accuracy of PET in people with head and neck cancer. Estimates of sensitivity and specificity were 0.81 to 0.85 and 0.95 to 0.99, respectively.

One systematic review and meta-analysis (Xu 2012b) included studies of either PET or PET/CT, and reported a single measure of diagnostic accuracy for the two techniques: sensitivity and specificity of PET or PET/CT were estimated as 0.83 (95% CI 0.76, 0.88) and 0.96 (95% CI 0.94, 0.97), respectively.

One systematic review and meta-analysis (Mcleod 2009) investigated the diagnostic accuracy of CT in people with head and neck cancer. Pooled estimates of sensitivity and specificity were 0.846 and 0.935, respectively.

Nasopharyngeal cancer

Two systematic reviews and meta-analyses (Chang 2013, Xu 2011a) investigated the diagnostic accuracy of PET/CT in people with nasopharyngeal cancer. Estimates of sensitivity were 0.88 to 0.89; both studies estimated sensitivity as 0.97.

One systematic review and meta-analysis (Shen 2014) investigated the diagnostic accuracy of PET in people with nasopharyngeal cancer. Estimates of sensitivity and specificity were 0.83 (95% CI 0.76, 0.89) and 0.95 (95% CI 0.92, 0.96), respectively.

Four systematic reviews and meta-analyses included studies of either PET or PET/CT in people with nasopharyngeal cancer, and reported a single measure of diagnostic accuracy for the two techniques (Chang 2013, Shen 2014, Vellayappan 2014, Xu 2012b). Pooled estimates of sensitivity and specificity were 0.82 to 0.87 and 0.96 to 0.98, respectively.

Study characteristics and quality

Systematic review methodological quality

All of the systematic reviews reported the databases searched to identify relevant studies, and the search terms on which their searches were based.

With the exception of one systematic review, all of the included studies addressed a clear and focussed, and relevant review question, collected studies relevant to this evidence review, used appropriate methods to generate pooled estimates of sensitivity and specificity. The remaining study (McLeod 2009) included relevant studies, but the overall purpose of the review is not clearly reported, nor are inclusion/exclusion criteria or the methods used to estimated sensitivity and specificity.

All of the systematic reviews provided at least some assessment of the methodological quality of each eligible study. Nine out of ten systematic reviews used the QUADAS system and reported either the assessment for each trial or a summary of overall study quality. In the remaining systematic review (McLeod 2009), studies are described by the review authors as all being graded as level II or level III evidence, but it is unclear what evidence assessment system these levels are based upon.

Quality of individual studies

Nine systematic reviews reported individual study quality using QUADAS. Common risks of bias highlighted included studies not reporting whether a consistent reference standard was used for all patients, and whether the reference standard results were interpreted without knowledge of the index test, and vice versa. Based on the review authors' assessment of study quality, no major applicability issues were identified.

Outcomes

Table 2.9. Summary of the diagnostic accuracy of all studied tests.

	No. of studies,	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)
Any HNC, PET/CT				
Xu 2011a	12	1276	0.88 (0.83, 0.93)	0.95 (0.94, 0.96)
Xu 2012a	7	1800	0.90 (0.83, 0.95)	0.95 (0.94, 0.96)
Xu 2011b	8	797	0.88 (0.79, 0.94)	0.95 (0.93, 0.96)
Yi 2013	10	1291	0.89 (0.73–0.96)	0.99 (0.98–0.99)
Any HNC, PET				
Xu 2011b	7	797	0.85 (0.78, 0.90)	0.95 (0.93, 0.97)
Yi 2013	9	1621	0.81 (0.68–0.96)	0.99 (0.97–1.00)
Any HNC, PET/CT or PET				
Xu 2012b	8	1147	0.83 (0.76–0.88)	0.96 (0.94–0.97)
Any HNC, CT				
Mcleod 2009	25*	4602	0.846†	0.935†
Any HNC, bone scintigraphy[§]				
Yi 2013	5	1184	0.55 (0.22–0.84)	0.98 (0.97–0.99)
Any HNC, conventional imaging[‡,§]				
Xu 2012b	8	1147	0.44 (0.29–0.61)	0.96 (0.88–0.98)
Recurrent HNC only, PET/CT				
Gao 2014	10	797	0.92 (0.83, 0.96)	0.95 (0.91, 0.97)
NPC, PET/CT				
Shen 2014	9	1061	0.89 (0.84, 0.93)	0.97 (0.96, 0.98)
Xu 2011a	6	588	0.88 (0.80, 0.94)	0.97 (0.95, 0.98)
NPC, PET				
Shen 2014	4	737	0.83 (0.76, 0.89)	0.95 (0.92, 0.96)
NPC, PET or PET/CT				
Chang 2013	8	1069	0.83 [0.77, 0.88]	0.97 [0.95, 0.98]
Shen 2014	13	1798	0.87 (0.83, 0.90)	0.96 (0.95, 0.97)
Vellayappan 2014	7	385	0.87 [0.74, 1.00]	0.98 [0.96, 1.00]
Xu 2012b	4	770	0.82 (0.72–0.89)	0.97 (0.95–0.98)
NPC, conventional imaging[‡]				
Xu 2012b	4	770	0.30 (0.19–0.44)	0.97 (0.91–0.99)

*In addition to published studies, articles also included two conference abstracts, and data from the review authors' own database.
†No 95% confidence intervals or other measures uncertainty were reported by the review authors.
‡Conventional anatomic imaging methods for nasopharyngeal cancer included chest radiography, abdominal ultrasonography, and bone scan. For other sites, conventional imaging methods were defined as chest with/without abdominal CT.
[§]Only comparative studies were included, i.e. those comparing the test to PET or PET/CT.

Table 2.10. Diagnostic accuracy of tests from studies conducting direct comparisons. Both reviews included studies of patients with any head and neck cancer.

	No. of studies	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)
Yi 2013, any HNC				
PET or PET/CT	5	1184	0.85 (0.69, 0.94)	0.98 (0.97, 0.99)
Bone scintigraphy	5	1184	0.55 (0.22, 0.84)	0.98 (0.97, 0.99)
Xu 2012b, any HNC				
PET/CT or PET	8	1147	0.83 (0.76, 0.88)	0.96 (0.94, 0.97)
Conventional imaging*	8	1147	0.44 (0.29, 0.61)	0.96 (0.88, 0.98)
Xu 2012b, NPC only				
PET/CT or PET	4	770	0.82 (0.72, 0.89)	0.97 (0.95, 0.98)
Conventional imaging*	4	770	0.30 (0.19, 0.44)	0.97 (0.91, 0.99)
Xu 2012b, non-NPC cancers only				
PET/CT or PET	4	377	0.85 (0.73, 0.93)	0.95 (0.91, 0.97)
Conventional imaging*	4	377	0.62 (0.43, 0.78)	0.93 (0.69, 0.99)
*Conventional anatomic imaging methods for nasopharyngeal cancer included chest radiography, abdominal ultrasonography, and bone scan. For other sites, conventional imaging methods were defined as chest with/without abdominal CT.				

1 Evidence tables for all included studies

Study

Chang 2013. Citation: Chang MC, Chen JH, Liang JA, Yang KT, Cheng KY, Kao CH., Chen, Jin-Hua, Liang, Ji-An, Yang, Kuang-Tao, Cheng, Kai-Yuan, and Kao, Chia-Hung. Accuracy of whole-body FDG-PET and FDG-PET/CT in M staging of nasopharyngeal carcinoma: a systematic review and meta-analysis. European Journal of Radiology 2013. 82(2): 366-373

Study type, study period

Systematic review and meta analysis of PET or PET/CT for M staging in nasopharyngeal carcinoma. Studies published between October 1996 and September 2011 were included.

Study selection criteria and analysis

Inclusion criteria:

- whole-body FDG-PET or PET/CT was used to detect distant metastasis of nasopharyngeal cancer
- histopathology analysis and/or clinical and imaging follow-up were used as the reference standard
- a 2 ×2 table could be constructed for true-positive, true-negative, false-positive, and false-negative values
- studies were based on per patient statistics

Exclusion criteria:

- studies including less than 10 patients
- non-peer-reviewed articles
- articles not published in English

When data or subsets of data were presented in more than 1 article, the authors included the article with the most details or the most recent article.

Trial characteristics

Study	Country	Imaging technique(s) used	Number of patients	Male, %	T3–T4, %	N2–N3, %	Newly diagnosed or recurrent	Prevalence of distant metastasis, %
Chang 2005	Taiwan	PET	95	69.5	47.4	62.1	Newly diagnosed (N = 85) and recurrent primary NPC (N = 10)	14.7
Liu 2006	Taiwan	PET	202	82.8	46.5	61.4	Newly diagnosed primary NPC	15
Chen 2006	Taiwan	PET/CT	70	74.3	NR	NR	Newly diagnosed (N = 20) and recurrent primary NPC (N = 50)	26.7
Liu 2007	Taiwan	PET	300	70	49.0	66.7	Newly diagnosed primary NPC	20.3
Comoretto 2008	Italy	PET/CT	63	69.8	NR	NR	Treated NPC	4.8
Chua 2009	Singapore	PET/CT	78	76.9	44.9	55.1	Newly diagnosed primary NPC	7.7
Ng 2009b	Taiwan	PET/CT	150	74	44.7	46.7	Newly diagnosed primary NPC	12
Ng 2009a	Taiwan	PET/CT	111	75.7	57.7	54.1	Newly diagnosed primary NPC	14.4

Type of test

PET or PET/CT

Reference standard

Histopathology analysis and/or clinical and imaging follow-up

Results
Five PET/CT studies (total 472 patients) and three PET studies (total 597 patients) were included. Two studies included data on both PET and PET/CT. Results for all studies: Pooled sensitivity: 0.83 [95% CI 0.77, 0.88] Pooled specificity: 0.97 [95% CI 0.95, 0.98] No separate analysis of PET and PET/CT studies reported.
Source of funding
Not reported. No potential conflicts of interest were reported by the authors.
Study quality assessment
The review authors assessed study quality using QUADAS. Selection criteria were clearly described in 7/8 studies. For all studies, it was unclear whether all patients received the same reference standard, or whether the reference standard results were interpreted with knowledge of the index test results. Study withdrawals were not explained in 5/8 studies.
Additional comments
The review authors chose not to analyse the diagnostic accuracy of PET and PET/CT separately, because (i) the review identified two studies directly comparing PET and PET/CT, both of which found no statistically significant difference between the two tests for the assessment of M stage in NPC; and (ii) meta-regression performed by the review authors suggested that the estimated diagnostic accuracy was similar for the two tests.

1

Study
Gao 2014. Citation: Gao, S. 18FDG PET-CT for distant metastases in patients with recurrent head and neck cancer after definitive treatment. A meta-analysis. Oral Oncology 2014. 50(3): 163-167
Study type, study period
Systematic review and meta-analysis of PET/CT for detecting distant metastases in patients with recurrent head and neck cancer. Searches were conducted up to 5 October 2013.
Study selection criteria and analysis
Inclusion criteria: • Studies in which PET/CT was used to evaluate distant metastases in suspected recurrent head and neck cancer patients after definitive treatment; • Histopathological analysis and /or clinical and imaging follow up were used as the reference standard; • Totals of true positives, false positives, true negatives, and false negatives were provided; • Results were based on a per-imaging analysis (as opposed to per-patient) • Studies included at least 10 patients. Exclusion criteria: • Evidence of verification bias (those that performed the reference standard only on patients with positive test results) • Studies reported only as conference abstracts or letters to the editor. The authors also state that studies from the same study group were excluded. It is not clear on what basis studies from the same group/with overlapping populations were selected, i.e. whether the largest or most recent study was given precedence. Subgroup analysis was conducted based on the initial treatment patients had received (radiotherapy or no radiotherapy). It is unclear whether this analysis was pre-planned.

2

Trial characteristics

Study	Country	No of patients (number of imaging examinations)	Initial radiotherapy	Male, %	Follow up time, months
Chen 2006	Taiwan	50 (66)	All patients	76.5	≥6
Comoretto 2008	Italy	63 (63)	All patients	69.8	≥6
Gourin 2008	USA	64 (64)	Not all patients	71.9	18 (mean)
Kao 2009	USA	80 (80)	All patients	72.5	≥11
Abgral 2009	France	91 (91)	Not all patients	85.7	≥12
Ng 2010	Taiwan	179 (179)	All patients	76	≥12
Ng 2011	Taiwan	79 (79)	All patients	88.6	≥12
Lamarre 2012	USA	31 (56)	Not all patients	56	45 (mean)
Fakhry 2012	France	37 (37)	All patients	86.5	≥6
Yi 2012	Korea	82 (82)	Not all patients	80.5	≥6

Type of test

PET/CT

Reference standard

Histopathological analysis and /or clinical and imaging follow up

Results

In total, 105 of 675 eligible patients (15.6%) had distant metastases or second primary cancers.

Analysis	Number of studies	Number of imaging examinations	Sensitivity (95% CI)	Specificity (95% CI)
All studies	10	797	0.92 (0.83, 0.96)	0.95 (0.91, 0.97)
All-radiotherapy studies	6	504	0.93 (0.80. 0.98)	0.96 (0.94, 0.98)

Pooled figures are based on total number of imaging examinations; some patients received more than one imaging examination.

Source of funding

The review authors stated that no external funding was received.

Study quality assessment

The review authors assessed study quality using QUADAS. All studies were assigned a QUADAS score of 10–12 (maximum possible score: 14). No study reported that all patients received the same reference standard regardless of the index test result, or that the reference standard was assessed without knowledge of the index test result.

Additional comments

1

Study

McLeod 2009. Citation: McLeod, N. M., Jess, A, Anand, R, Tilley, E, Higgins, B, and Brennan, P. Role of chest CT in staging of oropharyngeal cancer: a systematic review. Head & Neck 2009. 31(4): 548-555

Study type, study period

Systematic review and meta-analysis of chest CT for staging head and neck cancer. The date of last searches was not reported.

Study selection criteria and analysis

Inclusion criteria:

- Studies that contained data on chest CT either alone or in comparison with other imaging modalities, prevalence of synchronous bronchogenic primary or metastatic head and neck squamous cell carcinoma, sensitivity and specificity of chest CT for malignancy, and tumour data (T and N classification, disease stage, and primary tumour site and differentiation.

No limits were placed on study design for inclusion; data from conference abstracts was considered for inclusion. The authors also included data from their own local database, assumed to be published for the first time as part of this study.

Trial characteristics

Twenty-two published studies were identified, together with two abstracts and data from the review authors' own database. A total of 4602 patients were included.

Type of test

Chest CT

Reference standard

No details reported of the types of reference standard included.

Results

Pooled point prevalence of positive chest CT in patients with head and neck was estimated to be 7.93% (95% CI 7.10, 8.76)

Pooled sensitivity: 0.846
Pooled specificity: 0.935

2

Source of funding
Not reported.
Study quality assessment
Studies are described by the review authors as all being graded as level II or level III evidence, but it is unclear what evidence assessment system these levels are based upon.
Additional comments
The inclusion/exclusion criteria are poorly defined, as is the overall aim of the review. The title of the study refers exclusively to oropharyngeal cancer as the disease of interest, but studies of any head and neck cancer site have been included. No summary of the characteristics of individual trials is included, and citations are not provided for all of the included studies. The statistical methods used to calculate pooled estimates of diagnostic accuracy are unclear, and no measure of the uncertainty of the reported estimates, such as 95% confidence intervals, is reported.

1

Study
Shen 2014. Citation: Shen, G. and Zhang, W. Meta-analysis of diagnostic value of 18F-FDG PET or PET/CT for detecting lymph node and distant metastases in patients with nasopharyngeal carcinoma. British Journal of Radiology 2014. 87(1044): 20140296
Study type, study period
Systematic review and meta-analysis of PET or PET/CT for detecting lymph node metastasis and distant metastasis in patients with nasopharyngeal carcinoma. Databases were searched from January 1990 to June 2013.
Study selection criteria and analysis
Study inclusion criteria: • PET or PET/CT was used to assess tumour N and M staging of nasopharyngeal carcinoma • Histopathological and/or clinical and imaging follow up were used as the reference standard • Absolute numbers of true positives, false positives, true negatives, and false negatives were reported or could be calculated • At least ten patients included per study • Results based on per-patient analysis Study exclusion criteria: • Reviews, letters, case reports, and meeting abstracts When the same data were presented in more than one article, the article with most details or the most recent article was included. A number of subgroup analyses were conducted (see results below); it is not clear whether these analyses were pre-planned.

2

Trial characteristics

For M staging, 13 eligible studies were identified, including a total of 1798 patients.

Study	Country	No of patients	Newly diagnosed or recurrent	Male, %	Index test	Reference standard (follow up time, months)
Zhang 2011	China	257	Newly diagnosed	78	PET/CT	Histopathology, clinical follow up (36–60)
Xu 2011	China	41	Recurrent primary NPC	63	PET/CT	Imaging, clinical follow up (NR)
Li 2010	China	75	Newly diagnosed (22); recurrent primary NPC (53)	44	PET/CT	Histopathology, clinical follow up (NR)
Yen 2005b	Taiwan	140	Newly diagnosed (118); recurrent primary NPC (22)	69	PET	Histopathology, clinical follow up (3–6)
Ng 2009b	Taiwan	150	Newly diagnosed	74	PET/CT	Histopathology (NR)
Ng 2009a	Taiwan	111	Newly diagnosed	76	PET/CT	Histopathology, clinical follow up (>12)
Liu 2007	Taiwan	300	Newly diagnosed	70	PET	Histopathology (NR)
Liu 2006	Taiwan	202	Newly diagnosed	73	PET	Histopathology (NR)
Lin 2012	China	216	Newly diagnosed	78	PET/CT	Histopathology (NR)
Chen 2006	Taiwan	70	Newly diagnosed (20); recurrent primary NPC (50)	74	PET/CT	Imaging, clinical follow up (>6)
Chang 2005	Taiwan	95	Newly diagnosed (85); recurrent primary NPC (10)	69	PET	Imaging, clinical follow up (>6)
Chua 2009	Singapore	78	Newly diagnosed	77	PET/CT	Imaging, clinical follow up (6)
Comoretto 2010	Italy	63	Recurrent primary NPC	70	PET/CT	Imaging, clinical follow up (>6)

Type of test

PET or PET/CT

Reference standard

Histopathology, imaging, or clinical follow up

Results

Analysis	Number of studies	Number of patients	Sensitivity (95% CI)	Specificity (95% CI)
All M staging studies	13	1798	0.87 (0.83, 0.90)	0.96 (0.95, 0.97)
PET	4	737	0.83 (0.76, 0.89)	0.95 (0.92, 0.96)
PET/CT	9	1061	0.89 (0.84, 0.93)	0.97 (0.96, 0.98)

Source of funding

Government (Chinese) grants.

Study quality assessment

The review authors assessed study quality using QUADAS. All studies were assigned a QUADAS score of 10–12 (maximum possible score: 14).

None of the M staging studies reported that all patients received the same reference standard regardless of the index test result, or that the reference standard was interpreted without knowledge of the index test result. Two out of thirteen studies did not report that the index test was interpreted without knowledge of the reference standard. Nine out of thirteen studies did not report sufficient detail of any patients withdrawn from the study.

Additional comments

1

Study

Vellayappan 2014. Citation: Vellayappan, B. A., Soon, Y. Y., Earnest, A., Zhang, Q., Koh, W. Y., Tham, I. W. K., and Lee, K. M. Accuracy of F-18-flurodeoxyglucose-positron emission tomography/computed tomography in the staging of newly diagnosed nasopharyngeal carcinoma: a systematic review and meta-analysis. Radiology and Oncology 2014. 48(4): 331-338

Study type, study period

Systematic review and meta-analysis of PET/CT for staging newly diagnosed nasopharyngeal cancer. Searches included studies published up to September 2011.

Study selection criteria and analysis

Inclusion criteria:

- studies that determined the sensitivity and specificity of PET/CT for TNM staging of pre-treated (biopsy proven) nasopharyngeal cancer.
- studies comparing PET/CT to conventional staging modalities (i.e. MRI or CT scan of head and neck for T and N classifications, biopsy or clinical follow up of suspected metastases to regional lymph nodes or distant sites).

Exclusion criteria:

- studies of PET only
- for N and M classifications, studies that did not provide sufficient information to construct 2 x 2 table for sensitivity and specificity calculations

No language restrictions were applied. The most recent publication was chosen when data was presented in more than one publication.

Pre-planned subgroup analyses were done for T, N, and M classification (only M classification results are reported here).

Trial characteristics

Study	Year	N	Age, years	Male, %	Population	Reference standard
Chen	2006	20	46.3	70	Any nasopharyngeal cancer	Histological proof, or clinical follow up for 6 months
Wang	2007	18	52	60.5	Any nasopharyngeal cancer	Histological proof, or clinical follow up for 17 months (median)
King	2008	52	50	73	Stage III-IV nasopharyngeal cancer	Histological proof, or clinical follow up for 12 months
Chua	2009	78	50	76.9	Any nasopharyngeal cancer	Histological proof, or clinical follow up for 6 months
Ng	2009	150	48.1	74	Any nasopharyngeal cancer	Histological proof, or clinical follow up for 12 months
Lin	2009	41	NR	NR	Any nasopharyngeal cancer	Clinical follow up (time not specified)
Iaguru	2011	26	47.3	69.2	Any nasopharyngeal cancer	Clinical follow up (time not specified)

Type of test

PET/CT

Reference standard
Histological proof or clinical follow up
Results
Seven studies reported results for M classification (total 385 patients). Results for M classification (all studies): Pooled sensitivity: 0.87 [95% CI 0.74, 1.00] Pooled specificity: 0.98 [95% CI 0.96, 1.00]
Source of funding
Not reported. No potential conflicts of interest were disclosed.
Study quality assessment
Methodological quality was independently assessed by two study authors using QUADAS. Quality was assessed as high (QUADAS score ≥13) in three studies, moderate (QUADAS score 10–12) in seven studies, and low (QUADAS score <10) in five studies.
Additional comments

1

Study
Xu 2011a. Citation: Xu, G.-Z. ^{18}FDG-PET/CT for detecting distant metastases and second primary cancers in patients with head and neck cancer. A meta-analysis. Oral Oncology 2011. 47(7): 560-565
Study type, study period
Systematic review and meta-analysis of PET/CT for detecting distant metastases or second primary cancers in head and neck cancer patients. Searches covered 1 January 2000 to 1 March 2011.
Study selection criteria and analysis
Inclusion criteria: • Studies in which PET/CT was used to detect distant metastases and second primary cancers in patients with head and neck cancer at the time of tumour staging. • Histopathologic analysis and/or clinical and imaging follow-up were used as the reference standard. • Studies with sufficient data to allow all true positives, false positives, true negatives, and false negative to be determined. • Studies based on patient-level statistics. • Articles published in English. • At least 10 patients recruited per study. Exclusion criteria: • Studies published as conference abstracts or letter to the editor. • Studies focussing exclusively on second primary cancers. It is unclear whether the subgroup analyses performed were pre-planned.

2

Trial characteristics

Study	Country	No. of patients	Males, %	Type of staging	Reference standard (follow up time, months)
Chan 2006	Taiwan	70	74.3	Initial staging (n = 20) or restaging (n = 50)	Histopathological analysis or clinical and imaging follow up (24)
Veit-Haibach 2007	Germany	49	87.3	Initial staging	Histopathological analysis or clinical and imaging follow up (mean 13)
Kim 2007	Korea	349	76.5	Initial staging	Histopathological analysis or clinical and imaging follow up (≥6)
Gourin 2008	USA	27	93	Initial staging	Histopathological analysis or clinical and imaging follow up (≥12)
Ng 2009a	Taiwan	111	76.7	Initial staging	Histopathological analysis or clinical and imaging follow up (12)
Yoshida 2009	Taiwan	40	83.3	Initial staging	Histopathological analysis or clinical and imaging follow up (≥9)
Ng 2009b	Taiwan	150	74	Initial staging	Histopathological analysis or clinical and imaging follow up (≥12)
Chua 2009	Singapore	78	83.3	Initial staging	Histopathological analysis or clinical and imaging follow up (≥12)
Gourin 2009	USA	64	71.9	Restaging	Histopathological analysis or clinical and imaging follow up (11)
Kao 2009	USA	80	73	Restaging	Histopathological analysis or clinical and imaging follow up (11)
Ng 2010	Taiwan	179	76	Restaging	Histopathological analysis or clinical and imaging follow up (≥12)
Ng 2011	Taiwan	79	88.6	Restaging	Histopathological analysis or clinical and imaging follow up (≥12)

Type of test

PET/CT

Reference standard

Histopathological analysis or clinical and imaging follow up

Results

Twelve studies were eligible, including a total of 1276 patients.

Analysis	Number of studies	Number of patients	Sensitivity (95% CI)	Specificity (95% CI)
All studies	12	1276	0.88 (0.83, 0.93)	0.95 (0.94, 0.96)
Initial staging	8	824	0.88 (0.80, 0.94)	0.95 (0.93, 0.97)
Restaging	5	452	0.89 (0.80, 0.95)	0.95 (0.92, 0.97)
Nasopharyngeal cancer	6	588	0.88 (0.80, 0.94)	0.97 (0.95, 0.98)
All other head and neck sites	7	688	0.89 (0.80, 0.94)	0.93 (0.91, 0.95)

Source of funding

The reviews authors stated that they received no external funding for this study and declared no conflicts of interest.

Study quality assessment
The review authors assessed study quality using QUADAS. No study reported that all patients received the same reference standard, or that the results of the reference standard were interpreted without knowledge of the index test results.
Additional comments

1

Study
Xu 2011b. Citation: Xu, G.-Z. Zhu, X. Accuracy of whole-body PET and PET-CT in initial M staging of head and neck cancer: A meta-analysis. Head and Neck 2011. 33(1): 87-94.
Study type, study period
Systematic review and meta-analysis of PET or PET/CT for initial M staging in head and neck cancer patients. Databases were searched for studies published between 1 January 2000 and 31 September 2009.
Study selection criteria and analysis
Study inclusion criteria: • Whole-body PET or PET/CT was used to detect distant metastases or second primary cancer in M staging of head and neck cancer; • The reference standard was histopathologic analysis and/or clinical and imaging follow up; • The number of true positives, true negatives, false positives and false negatives was reported on could be calculated; • Studies were based on per-patient analysis Study exclusion criteria: • Less than 10 patients included; • Patients with M0 carcinoma by conventional imaging techniques. Subgroup analysis according to the imaging technique used (PET or PET/CT) was pre-planned.

2

Trial characteristics

Study	Country	No. of patients	Males, %	Prevalence of distant metastasis or second primary cancer, %	Reference standard (follow up time, months)
Teknos 2001	USA	12	100	25	Histopathological analysis or clinical and imaging follow up (24)
Chan 2006	Taiwan	20	70	10	Histopathological analysis or clinical and imaging follow up (≥6)
Veit-Haibach 2007	Germany	49	87.3	6.1	Histopathological analysis or clinical and imaging follow up (mean 13)
Kim 2007	Korea	349	76.5	11.5	Histopathological analysis or clinical and imaging follow up (≥6)
Liu 2007	Taiwan	300	70	20.3	Histopathological analysis or clinical and imaging follow up (12)
Gourin 2008	USA	27	93	18.5	Histopathological analysis or clinical and imaging follow up (12)
Ng 2008	Taiwan	160	90	16.25	Histopathological analysis or clinical and imaging follow up (12)
Krabbe 2009	Netherlands	149	68	17.4	Histopathological analysis or clinical and imaging follow up (≥6)
Ng 2009b	Taiwan	111	76.7	14.4	Histopathological analysis or clinical and imaging follow up (12)
Yoshida 2009	Japan	40	83.3	7.1	Histopathological analysis or clinical and imaging follow up (9)
Ng 2009a	Taiwan	150	74	10	Histopathological analysis or clinical and imaging follow up (12)
Chua 2009	Singapore	78	76.9	7.7	Histopathological analysis or clinical and imaging follow up (6)

Type of test

PET (studied in 7 articles and 797 patients) or PET/CT (studied in 8 articles and 795 patients)

Reference standard

Histopathological analysis or clinical and imaging follow up

Results

Analysis	Number of studies	Number of patients	Sensitivity (95% CI)	Specificity (95% CI)
PET	7	797	0.85 (0.78, 0.90)	0.95 (0.93, 0.97)
PET/CT	8	797	0.88 (0.79, 0.94)	0.95 (0.93, 0.96)

Source of funding

Not reported.

Study quality assessment

The review authors assessed study quality using QUADAS.

Additional comments

1

Study

Xu 2012a. Citation: Xu, G. Performance of whole-body PET/CT for the detection of distant malignancies in various cancers: A systematic review and meta-analysis. Journal of Nuclear Medicine 2012. 53(12): 1847-1854

Study type, study period

Systematic review and meta-analysis of PET/CT for the detection of distant malignancies in various cancers. Results from a subgroup analysis of head and neck cancer only are reported here. Databases were searched from 1 January 2000 to 30 April 2012.

Study selection criteria and analysis

Study inclusion criteria:

- PET/CT was used for the overall assessment of distant malignancies in patients with any cancer;
- Sufficient data reported to determine true positives, false positives, true negatives, and false negatives;
- Minimum sample size of 10 patients;
- Analysis performed at the patient level;
- Histopathologic analysis or clinical and imaging follow up used as the reference standard.

Exclusion criteria:

- Studies focussing exclusively on second primary cancers
- Studies from the same study group
- Studies in which the reference standard was used only for subsets of patients, based on their index test results.

Pre-planned subgroup analyses include those details in the results.

Trial characteristics (head and neck cancer studies only)

Study	Country	Stage	No. of patients	Primary or recurrent cancer	Males, %	Follow up time, months	Prevalence of distant malignancy, %
Chen 2006	Taiwan	NA	70	Primary or recurrent	74	24 (mean)	26.7
Veit-Haibach 2007	Germany	NA	49	Primary	87	13.5 (mean)	6.1
Kim 2007	Korea	I-IV	349	Primary	76	≥6	11.5
Gourin 2008	United States	III-IV	27	Primary	93	≥12	18.5
Ng 2009b	Taiwan	T1-4N0-3	111	Primary	77	12 (mean)	14.4
Yoshida 2009	Taiwan	I-IV	40	Primary	83	≥9	7.5
Ng 2009a	Taiwan	T1-4N0-3	150	Primary	74	≥12	12.0
Chua 2009	Singapore	T1-4N0-3	78	Primary	83	≥12	7.7
Gourin 2009	United States	III-IV	64	Recurrent	72	11 (mean)	15.6
Kao 2009	United States	II-IV	80	Recurrent	73	≥11	18.8
Abgral 2009	France	I-IV	91	Recurrent	86	≥12	13.2
Ng 2010	Taiwan	II-IV	179	Recurrent	76	≥12	11.7
Chan 2011	Taiwan	I-IV	103	Primary	94	≥6	17.5
Haerle 2011	Switzerland	III-IV	299	Primary	79	≥6	9.7
Ng 2011	Taiwan	II-IV	79	Recurrent	89	≥12	16.5
Lamarre 2012	United States	II-IV	31	Primary or recurrent	56	43.7 (mean)	9.0

Type of test

PET/CT

Reference standard

Histopathologic analysis or clinical and imaging follow up

Results

Sixteen head and neck cancer studies were eligible, including a total of 1800 patients.

Pooled sensitivity: 0.90 [95% CI 0.83, 0.95]
Pooled specificity: 0.95 [95% CI 0.94, 0.96]

Source of funding

Not reported. The review authors declared that they had no conflicts of interest.

Study quality assessment
The review authors assessed study quality using QUADAS. All eligible head and neck cancer studies were assigned a QUADAS score of 10–12 (maximum possible score: 14). No study reported that all patients received the same reference standard regardless of the index test result, or that the reference standard was masked to the index test result.
Additional comments

1

Study
Xu, 2012b. Citation: Xu, G., Li, Junkai, Zuo, Xiaoyan, and Li, Chunyan. Comparison of whole body positron emission tomography (PET)/PET-computed tomography and conventional anatomic imaging for detecting distant malignancies in patients with head and neck cancer: a meta-analysis. Laryngoscope 2012. 122(9): 1974-1978
Study type, study period
Systematic review and meta-analysis of PET or PET/CT compared to conventional imaging for detecting distant malignancies in people with head and neck cancer. Databases were searched for studies up to 1 January 2012.
Study selection criteria and analysis
Inclusion criteria: • Studies of head and neck cancer patients (any age, any disease stage) evaluated with whole body PET or PET/CT and conventional anatomic imaging, performed within one month of each other. • Distant metastasis/second primary cancer findings were confirmed with histopathologic analysis and/or clinical and imaging follow-up. • Studies were based on per-patient analysis. • Minimum of 10 suitable patients included in each study. Exclusion criteria: • Total numbers of true positives, false positives, true negatives, and false negatives could not be extracted. • Studies published only as a conference abstract or letter to the editor. Subgroup analysis was conducted for nasopharyngeal cancer and non-nasopharyngeal cancer. It is unclear whether this subgroup analysis was pre-planned. The authors also stated that there was insufficient data to analyse PET and PET/CT separately.

2

Trial characteristics

Eight articles identified, including a total of 1147 patients.

Study	Country	Number of patients	Primary sites	Follow up time, months	Conventional methods used
Teknos 2001	United States	12	Larynx (n =4), others (n =8)	24	Chest CT
Sigg 2003	Switzerland	56	Oropharynx (n = 8), hypopharynx (n = 6), larynx (n =5), oral cavity (n = 9), others (n = 28)	Unclear	Chest CT
Chan 2006	Taiwan	131	Nasopharynx	≥6	Chest radiography, abdominal ultrasonography, bone scan
Liu 2007	Taiwan	300	Nasopharynx	≥6	Chest radiography, abdominal ultrasonography, bone scan
Ng 2008	Taiwan	160	Oropharynx (n = 74), hypopharynx (n = 86)	≥12	Chest and abdominal CT
Krabbe 2009	Netherlands	149	Oropharynx (n = 40), hypopharynx (n = 12), larynx (n =13), oral cavity (n = 84)	Unclear	Chest CT
Ng 2009b	Taiwan	111	Nasopharynx	12	Chest radiography, abdominal ultrasonography, bone scan
Chua 2009	Singapore	78	Nasopharynx	≥12	Chest radiography, abdominal ultrasonography, bone scan

Type of test

1. Whole-body PET or PET/CT.

2. Conventional anatomic imaging methods. Conventional anatomic imaging methods for nasopharyngeal cancer included chest radiography, abdominal ultrasonography, and bone scan. For other sites, conventional imaging methods were defined as chest with/without abdominal CT.

Reference standard

Histopathologic analysis and/or clinical and imaging follow-up.

Results

Imaging method	Number of studies	Number of patients	Sensitivity (95% CI)	Specificity (95% CI)
All sites				
Whole-body PET or PET/CT	8	1147	0.83 (0.76, 0.88)	0.96 (0.94, 0.97)
Conventional anatomic imaging	8	1147	0.44 (0.29, 0.61)	0.96 (0.88, 0.98)
Nasopharyngeal cancer subgroup				
Whole-body PET or PET/CT	4	770	0.82 (0.72, 0.89)	0.97 (0.95, 0.98)
Conventional anatomic imaging	4	770	0.30 (0.19, 0.44)	0.97 (0.91, 0.99)
Non-nasopharyngeal cancer subgroup				
Whole-body PET or PET/CT	4	377	0.85 (0.73, 0.93)	0.95 (0.91, 0.97)
Conventional anatomic imaging	4	377	0.62 (0.43, 0.78)	0.93 (0.69, 0.99)

Source of funding

Not reported; authors declared no funding or conflicts of interest.

Study quality assessment
The review authors assessed study quality using QUADAS. Risks of bias: No study reported that all patients reported that patients received the same reference standard regardless of the index test result, or that the reference standard was interpreted without knowledge of reference test results. Two out of eight studies reported insufficient detail of how the index test was conducted. Applicability issues: two out of eight studies did not include a representative spectrum of patients.
Additional comments

1

Study
Yi 2013. Citation: Yi, X., Fan, Min, Liu, Yilin, Zhang, Hongting, and Liu, Shixi. 18 FDG PET and PET-CT for the detection of bone metastases in patients with head and neck cancer. A meta-analysis. Journal of Medical Imaging & Radiation Oncology 2013. 57(6): 674-679
Study type, study period
Systematic review and meta-analysis of PET or PET/CT for the detection of bone metastasis in head and neck cancer. Includes studies available up to 11 January 2013.
Study selection criteria and analysis
Inclusion criteria: • Studies of head and neck cancer patients (any disease stage, any treatment status) evaluated with whole-body PET or PET/CT. • Histopathologic analysis and/or clinical and imaging follow-up were used as the reference standard. • Total numbers of true positives, false positives, true negatives, and false negatives were available. • Studies were based on a patient-level analysis. • Studies included at least 10 patients. Exclusion criteria: • Included population overlapped with other relevant studies. • Reference standard performed only on patients with positive index test results. • Studies reported as conference abstracts or letters to the editor. • PET or PET/CT not used as the initial diagnostic modality. Five studies meeting the inclusion criteria also used bone scintigraphy to detect bone metastases. Based on the results of these studies, the diagnostic performances of PET or PET/CT and bone scintigraphy were compared.

2

Trial characteristics

17 articles identified, including a total of 2754 patients.

Study	Country	Imaging technique(s) used	Number of patients	Primary sites	Follow up time, months
Yen 2005a	Taiwan	PET	64	Nasopharynx	40.3
Chang 2005	Taiwan	PET	95	Nasopharynx	≥6
Chan 2006	Taiwan	PET	131	Nasopharynx	≥6
Liu 2007	Taiwan	PET, BS	300	Nasopharynx	≥6
Ng 2008	Taiwan	PET	160	Oropharynx (n = 74), hypopharynx (n= 86)	≥12
Kim 2008	Korea	PET, BS	564	Nasopharynx (n = 82), oropharynx (n = 95), hypopharynx (n = 55), oral cavity (n = 103), larynx (n = 204), others (n = 25)	29
Krabbe 2009	Netherlands	PET	149	Oropharynx (n= 40), hypopharynx (n = 12), larynx (n = 13), oral cavity (n = 84)	Unclear
Kim 2007	Korea	PET/CT	349	Oropharynx (n= 53), hypopharynx (n = 31), larynx (n = 112), oral cavity (n = 66)	≥6
Chua 2009	Singapore	PET, PET/CT, BS	78	Nasopharynx	≥12
Ng 2009b	Taiwan	PET/CT, BS	111	Nasopharynx	≥12
Ng 2009a	Taiwan	PET/CT	150	Nasopharynx	≥12
Abgral 2009	France	PET/CT	80	Oropharynx (n= 26), hypopharynx (n = 12), larynx (n = 27), oral cavity (n = 25), nasopharynx (n = 1)	≥12
Ng 2010	Taiwan	PET/CT	179	Nasopharynx	≥12
Chan 2011	Taiwan	PET/CT	103	Oropharynx (n = 54), hypopharynx (n = 49)	≥12
Ng 2011	Taiwan	PET/CT	79	Oropharynx (n = 54), hypopharynx (n = 49)	≥12
Yi 2012	Korea	PET/CT	82	Oropharynx (n = 7), hypopharynx (n = 11), l (n = 34), oral cavity (n = 30)	6
Chan 2012	Taiwan	PET, PET/CT	80	Any head and neck	6

Type of test

PET (9 studies, 1621 patients)
PET/CT (10 studies, 1291 patients)
Bone scintigraphy (5 studies, 1184 patients)

Reference standard

Histopathologic analysis and/or clinical imaging

Results

Imaging method	Number of studies	Number of patients	Sensitivity (95% CI)	Specificity (95% CI)
All studies				
PET	9	1621	0.81 (0.68, 0.96)	0.99 (0.97, 1.00)
PET/CT	10	1291	0.89 (0.73, 0.96)	0.99 (0.98, 0.99)
Subgroup of studies using both PET or PET/CT and bone scintigraphy				
PET or PET/CT	5	1184	0.85 (0.69, 0.94)	0.98 (0.97, 0.99)
Bone scintigraphy	5	1184	0.55 (0.22, 0.84)	0.98 (0.97, 0.99)

Source of funding

Not reported; authors declared that they received no external funding towards this study.

1

Study quality assessment
Systematic review quality: the comparison of PET or PET/CT with bone scintigraphy was not specified in the study methods, and it is therefore not clear if this analysis was pre-planned. The aims of the study are stated as assessing the use of PET or PET/CT for the detection of bone metastases, but the inclusion criteria and results do not appear to be restricted to bone metastases, but include results of studies assessing any distant metastases. The review authors assessed study quality using QUADAS. Risks of bias: No study reported that all patients reported that patients received the same reference standard regardless of the index test result, or that the reference standard was interpreted without knowledge of reference test results. 11.7% of studies reported insufficient detail of how the index test was conducted. Applicability issues: 29.4% of studies did not include a representative spectrum of patients.
Additional comments

1

2

Evidence search details and references

Review question in PICO format

Population	Intervention (Index Test)	Comparator (Reference Standard)	Outcomes
Adults with cancer of the upper aerodigestive tract who require systemic imaging Subgroups: • Tumour site • Disease stage • HPV status	• CT • Chest X-ray • Bone scan • MRI • PET-CT • PET • US • PET-MRI • Combinations of the above	Final diagnosis (based on clinical imaging/follow up/histopathology)	• Sensitivity • Specificity • Process-related morbidity • HRQoL

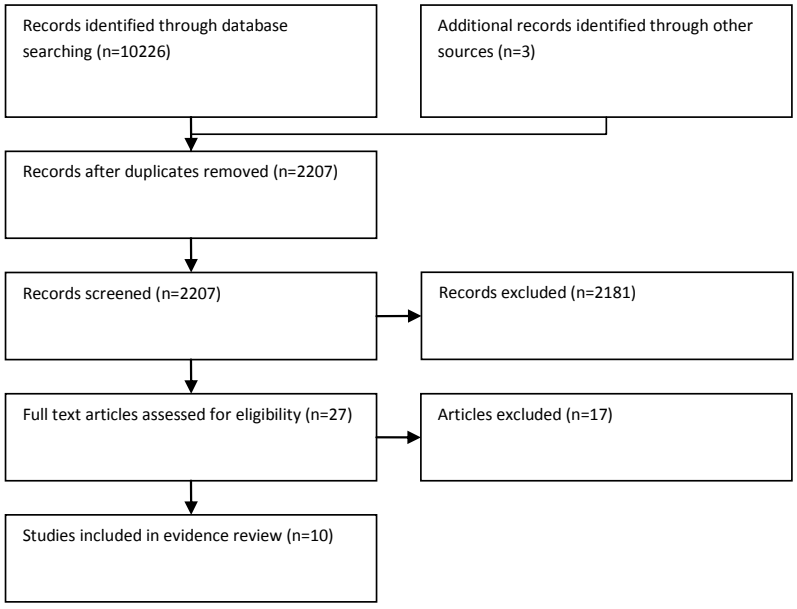
Additional review protocol details (refer to Section 10 for full review protocol)

	Details
Type of review	Diagnostic test.
Language	English only
Study design	Diagnostic accuracy studies. Conference abstracts will be excluded.
Status	Published data only
Other criteria for inclusion / exclusion of studies	For the purposes of this review, systemic imaging is defined as imaging of sites other than the primary tumour site or regional (cervical) lymph nodes. Inclusion criteria: sufficient data reported to calculate the total number of true positives, true negative, false positives, and false negatives for the studied test(s). Exclusion criteria: reference standard is unclear or undefined. Studies including non-cancer patients or cancers outside the upper aerodigestive tract will be excluded.
Search strategies	Limit search to post-1994.
Review strategies	The evidence table for studies of diagnostic accuracy will be used (NICE Guidelines Manual Appendix J) to extract and present data from individual studies. Sensitivity and specificity data will be pooled when appropriate. Other

	outcomes will be presented as risk ratios or hazard ratios. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender.

Separate searches were conducted for the two review questions concerning systemic staging, but both databases were screened for articles relevant to either review question. The flow diagram (Figure 2.18~~Figure 2.18~~~~Figure 2.18~~) therefore shows the combined results from two database searches. Ten systematic reviews were identified as relevant to the question 'What is the most effective systemic imaging strategy for investigating cancer of the upper aerodigestive tract?' The individual studies included in each of these systematic reviews were also checked for relevance to the question 'Which patients with cancer of the upper aerodigestive tract require systemic staging?'

Figure 2.18. Study flow diagram



Included studies (systematic reviews)

Chang MC, Chen JH, Liang JA, Yang KT, Cheng KY, Kao CH., Chen, Jin-Hua, Liang, Ji-An, Yang, Kuang-Tao, Cheng, Kai-Yuan, and Kao, Chia-Hung. Accuracy of whole-body FDG-PET and FDG-PET/CT in M staging of nasopharyngeal carcinoma: a systematic review and meta-analysis. European Journal of Radiology 2013. 82(2): 366-373

Gao, S. 18FDG PET-CT for distant metastases in patients with recurrent head and neck cancer after definitive treatment. A meta-analysis. Oral Oncology 2014. 50(3): 163-167

McLeod, N. M., Jess, Alex, Anand, Rajiv, Tilley, Elisabeth, Higgins, Bernie, and Brennan, Peter. Role of chest CT in staging of oropharyngeal cancer: a systematic review. [Review] [39 refs]. Head & Neck 2009. 31(4): 548-555.

Shen, G. and Zhang, W. Meta-analysis of diagnostic value of 18F-FDG PET or PET/CT for detecting lymph node and distant metastases in patients with nasopharyngeal carcinoma. British Journal of Radiology 2014. 87(1044): 20140296

Vellayappan, B. A., Soon, Y. Y., Earnest, A., Zhang, Q., Koh, W. Y., Tham, I. W. K., and Lee, K. M. Accuracy of F-18-flurodeoxyglucose-positron emission tomography/computed tomography in the staging of newly diagnosed nasopharyngeal carcinoma: a systematic review and meta-analysis. Radiology and Oncology 2014. 48(4): 331-338

Xu, G. Performance of whole-body PET/CT for the detection of distant malignancies in various cancers: A systematic review and meta-analysis. Journal of Nuclear Medicine 2012. 53(12): 1847-1854

Xu, G., Li, Junkai, Zuo, Xiaoyan, and Li, Chunyan. Comparison of whole body positron emission tomography (PET)/PET-computed tomography and conventional anatomic imaging for detecting distant malignancies in patients with head and neck cancer: a meta-analysis. Laryngoscope 2012. 122(9): 1974-1978

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3. Treatment of early stage disease

Squamous cell carcinoma of the larynx

Clinical question: What is the most effective treatment for newly diagnosed T1 or T2 carcinoma of the larynx?

Background

T1 and T2 tumours of the larynx are treated either with radiotherapy or larynx-preserving surgery. There is a lack of evidence regarding the superiority of either of these techniques over the other in terms of recurrence, survival, laryngeal function or cost effectiveness. This has resulted in variation in practice and the need for clarification.

Evidence statements

Transoral laser surgery (TLS) versus radiotherapy (RT)

Evidence came from a systematic review of observational studies (Abdurehim 2012) and four observational studies published since the review (Dinapoli 2010, Osborn 2011, Remmelts 2013, van Gogh 2012) which were used to update the meta-analyses.

Overall survival

Low quality evidence from meta-analysis of 10 observational studies including 1371 patients with stage T1a disease suggests uncertainty about whether transoral laser surgery or radiotherapy is most effective in terms of overall survival (OR 1.20; 95% CI 0.90, 1.60; OR > 1 favours TLS).

Very low quality evidence about overall survival in patients with supraglottic tumours comes from a retrospective SEER database study (Arshad 2014). 5 year overall survival was better with organ preserving surgery (not further defined) than with radiotherapy for both T1 and T2 tumours. For T1 supraglottic tumours 5 year overall survival was 53% with radiotherapy versus 65% with organ preserving surgery plus neck dissection (versus RT: HR 0.89; 95% CI 0.69, 1.15; P = 0.36) versus 76% for surgery without neck dissection (versus RT: HR 0.48; 95% CI 0.33, 0.71; P<0.001). For T2 supraglottic tumours, 5 year overall survival was 45% with radiotherapy versus 49% with organ preserving surgery plus neck dissection (HR 0.93; 95% CI 0.65, 1.3; versus RT; P = 0.67) versus 77% for surgery without neck dissection (HR 0.36; 95% CI 0.23, 0.55; versus RT; P <0.001).

Local control

Very low quality evidence from meta-analysis of 14 observational studies in 1855 patients with stage T1a disease suggests uncertainty about whether transoral laser surgery (TLS) or radiotherapy is most effective in terms of local control (OR 0.92; 95% CI 0.62, 1.36; OR > 1 favours TLS).

Subgroup analysis suggests better local control with RT than with TLS in studies that used higher dose (at least 65 Gy) radiotherapy (OR 0.64; 95% CI 0.44, 0.95; OR > 1 favours TLS). In studies that used lower dose radiotherapy (≤ 60 Gy), however, local control was better with TLS than RT (OR 1.87; 95% CI 1.06, 3.28; OR > 1 favours TLS)

Laryngeal preservation

Very low quality evidence from meta-analysis of 11 observational studies in 1442 patients with stage T1a disease suggests that laryngeal preservation is more likely following transoral laser surgery than following radiotherapy (OR 3.49; 95% CI 1.54, 7.89; OR > 1 favours TLS). Subgroup analysis indicates that this beneficial effect of TLS is limited to studies published since 2000 (OR 7.93; 95% CI 3.76, 16.71; OR > 1 favours TLS)

Voice function

Very low quality evidence from systematic reviews of observational studies in patients with stage T1a disease or stage T1-T2 disease (Spielmann 2010, van Loon 2012) suggests uncertainty about whether transoral laser surgery or radiotherapy is most effective in terms of post treatment voice function measured using maximum phonation time, air flow rate, fundamental frequency, jitter, shimmer or Voice Handicap Index.

Quality of life

Low quality evidence from a systematic review of nine observational studies in patients with T1-T2 disease (Spielmann 2010) suggests relatively good quality of life following both TLS and RT with no statistically significant differences between the two treatments.

Swallow function

Very low quality evidence from a single observational study (included in Spielmann 2010) suggests patients perceived swallow function to be better following TLS than following RT.

Treatment related mortality and morbidity

Treatment related mortality and morbidity were not reported in the included studies.

Transoral laser surgery (TLS) versus open partial laryngectomy

See Figure 3.8 to Figure 3.12.

Overall survival

Very low quality evidence from two observational studies (Mantsopoulos 2012, Puxeddu 2000) including 354 patients suggests uncertainty about whether transoral laser surgery or open partial laryngectomy is most effective in terms of overall survival (OR 7.29; 95% CI 0.39, 10.99; OR >1 favours TLS).

Disease specific survival

Very low quality evidence from three observational studies (Puxeddu 2000, Karatzanis 2010, Maurizi 2005) including 288 patients suggests that in patients with T1 laryngeal carcinoma, disease specific survival is better with transoral laser surgery than with open partial laryngectomy (OR 3.99; 95% CI 1.63, 9.74; OR >1 favours TLS). In patients with T2 laryngeal carcinoma (Mantsopoulos 2012, Karatzanis 2010) there is uncertainty about which of the treatments is the most effective (OR 1.89; 95% CI 0.72, 4.91; OR >1 favours TLS) in terms of disease specific survival.

Local control

Very low quality evidence from observational studies (Puxeddu 2000, Karatzanis 2010, Maurizi 2005, Mantsopoulos 2012) suggests that in patients with T1 glottic carcinoma local control is better with transoral laser surgery than with open partial laryngectomy (OR 2.31; 95% CI 1.17, 4.56; OR >1

favours TLS). In patients with T2 glottic carcinoma there is uncertainty about which of the treatments is the most effective (OR 0.73; 95% CI 0.34, 1.55; OR >1 favours TLS) in terms of local control.

Laryngeal preservation

Very low quality evidence from four observational studies (Puxeddu 2000, Karatzanis 2010, Maurizi 2005, Mantsopoulos 2012) suggests that laryngeal preservation is more likely with transoral laser surgery than with open partial laryngectomy (OR 3.71; 95% CI 1.87, 7.35; OR >1 favours TLS).

Voice function

A single observational study (Puxeddu 2000) reported better significantly better vocal function ($P<0.05$; measured using perceptual analysis with the Buffalo Voice Profile system), but did not provide further details.

Length of stay

A single observational study (Puxeddu 2000) provided very low quality evidence about the mean length of hospital stay: 2.1 days with transoral laser surgery versus 8.4 days with open partial laryngectomy (standard deviations not reported).

Treatment related mortality, decannulation and permanent gastrostomy rates

Low quality evidence about decannulation rates and permanent gastrostomy rates following open conservation partial laryngectomy comes from a meta-analysis of non comparative observational studies (Thomas 2012). This review included a majority of patients with stage T1-T2 disease: 79% T1-T2 and 21% T3-T4 of cases where stage was reported. Open conservation partial laryngectomy was associated with a treatment related mortality rate of 0.7%, a decannulation rate of 96% (95% CI 95%, 98%) and a permanent gastrostromy rate of 2% (95% CI 0.9%, 3.9%).

Serious complications

Very low quality evidence from 2 observational studies (Karatzanis 2010, Mantsopoulos 2012) including 344 patients suggests that serious complications are less likely with transoral laser surgery than with open partial laryngectomy (OR 0.36; 95% CI 0.14, 0.90; OR <1 favours TLS).

GRADE evidence tables and meta-analysis

Table 3.1. GRADE evidence profile: transoral laser surgery (TLS) versus radiotherapy (RT) for early stage laryngeal cancer.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TLS	RT	Relative (95% CI)	Absolute	
Overall survival (follow-up 5-139 months)											
10	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness[1]	no serious imprecision	none	556/666 (83.5%)	566/705 (80.3%)	OR 1.20 (0.90, 1.60)	27 more per 1000 (from 17 fewer to 64 more)	⊕⊕OO LOW
Disease specific survival (follow-up 5 - 139 months)											
11	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	752/766 (98.2%)	671/692 (97%)	OR 1.55 (0.75, 3.20)	11 more per 1000 (from 10 fewer to 21 more)	⊕⊕OO LOW
Local control (RT was 6-MV photons and > 65 Gy) (follow-up 5-139 months)											
8	observational studies	no serious risk of bias	no serious inconsistency[2]	no serious indirectness[1]	no serious imprecision	none	502/581 (86.4%)	481/535 (89.9%)	OR 0.64 (0.44, 0.95)	48 fewer per 1000 (from 5 fewer to 102 fewer)	⊕⊕OO LOW
Local control (RT was Co60 6-MV photons and < 60 Gy) (follow-up 5-139 months)											
6	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	374/397 (94.2%)	302/342 (88.3%)	OR 1.87 (1.06, 3.28)	51 fewer per 1000 (from 6 more to 78 more)	⊕⊕OO LOW
Progression free survival - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Treatment related mortality - not reported											
0	-	-	-	-	-	none	-	-	-	-	

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TLS	RT	Relative (95% CI)	Absolute	
Morbidity - decannulation - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Larynx preservation (pre 2000) (follow-up 5-139 months)											
3	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	166/184 (90.2%)	148/165 (89.7%)	OR 0.88 (0.38, 2.01)	12 fewer per 1000 (from 129 fewer to 49 more)	⊕⊕OO LOW
Larynx preservation (post 2000) (follow-up 5-139 months)											
8	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	562/568 (98.9%)	464/525 (88.4%)	OR 7.93 (3.76, 16.71)	100 more per 1000 (from 82 more to 108 more)	⊕⊕OO LOW
Length of stay - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Health related quality of life (Better indicated by lower values)											
9	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	-	-	Studies reported relatively good quality of life following both TLS and RT with no statistically significant differences between the two treatments	⊕⊕OO LOW
Swallow function											
1	observational studies	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	-	0%	not pooled	1 study reported patients perceived swallow function to be better following TLS than following	⊕OOO VERY

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TLS	RT	Relative (95% CI)	Absolute	
										RT.	LOW
Voice function (measured with: maximum phonation time; Better indicated by higher values)											
4	observational studies	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	55	57	-	MD 1.41 lower (3.51 lower to 0.69 higher)	⊕OOO VERY LOW
Voice function (measured with: air flow rate; Better indicated by higher values)											
3	observational studies	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	36	39	-	MD 21.46 higher (78.79 lower to 121.72 higher)	⊕OOO VERY LOW
Voice function (measured with: Fundamental frequency; Better indicated by higher values)											
7	observational studies	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	119	113	-	MD 13.89 higher (9.64 lower to 18.13 higher)	⊕OOO VERY LOW
Voice function (measured with: jitter; Better indicated by higher values)											
7	observational studies	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	168	136	-	MD 0.13 higher (0.28 lower to 0.53 higher)	⊕OOO VERY LOW
Voice function (measured with: shimmer; Better indicated by lower values)											
7	observational studies	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	168	143	-	MD 0.08 higher (0.65 lower to 0.81 higher)	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TLS	RT	Relative (95% CI)	Absolute	
Voice function (measured with: Voice Handicap Index; Better indicated by higher values)											
6	observational studies	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	194	176	-	MD 5.02 higher (2.14 lower to 12.17 higher)	⊕OOO VERY LOW

[1] T1a tumours only
[2] Considerable heterogeneity
[3] Measured patient's perception of swallow function
[4] Low number of patients

Table 3.2. GRADE evidence profile: open partial laryngectomy for early stage laryngeal cancer.

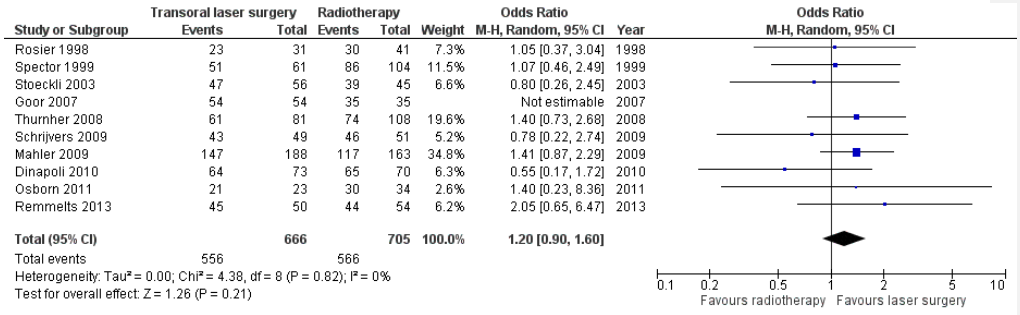
Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TLS	Open partial laryngectomy	Relative (95% CI)	Absolute	
Overall survival (follow-up 5 to 11 years)											
2	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	123/174 (70.7%)	136/180 (75.6%)	OR 7.29 (0.39, 10.99)	202 more per 1000 (from 209 fewer to 216 more)	⊕OOO VERY LOW
Disease specific survival (T1 tumours) (follow-up mean 5 years)											
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	174/182 (95.6%)	90/106 (84.9%)	OR 3.99 (1.63, 9.74)	108 more per 1000 (from 53 more to 133 more)	⊕OOO VERY

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TLS	Open partial laryngectomy	Relative (95% CI)	Absolute	
											LOW
Disease specific survival (T2 tumours) (follow-up 5 to 11 years)											
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	156/173 (90.2%)	128/138 (92.8%)	OR 1.89 (0.72, 4.91)	33 more per 1000 (from 25 fewer to 57 more)	⊕OOO VERY LOW
Local control (T1 tumours) (follow-up mean 5 years)											
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	150/167 (89.8%)	98/122 (80.3%)	OR 2.31 (1.17, 4.56)	101 more per 1000 (from 24 more to 146 more)	⊕OOO VERY LOW
Local control (T2 tumours) (follow-up 5 - 11 years)											
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	166/187 (88.8%)	141/153 (92.2%)	OR 0.73 (0.34, 1.55)	26 fewer per 1000 (from 122 fewer to 26 more)	⊕OOO VERY LOW
Larynx preservation (follow-up 5 - 11 years)											
4	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	341/355 (96.1%)	242/275 (88%)	OR 3.71 (1.87, 7.35)	85 more per 1000 (from 52 more to 102 more)	⊕OOO VERY LOW
Length of stay (Better indicated by lower values)											
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	85	-	MD 4.2 to 6.3 days longer with open surgery	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TLS	Open partial laryngectomy	Relative (95% CI)	Absolute	
Voice quality (assessed using perceptual analysis – Buffalo II Voice Profile System)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31	52	-	Single study reported better vocal function with TLS than open surgery (P <0.05; other figures not reported)	⊕OOO VERY LOW
Decannulation											
42	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	-	3955	-	96.3% [94.9 – 97.6%]	⊕OOO VERY LOW
Treatment related mortality											
23	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	1453	-	0.7 [0.7 – 0.7%]	⊕OOO VERY LOW
Permanent gastrostomy											
20	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	-	2000	-	2.0% [0.9 – 3.9%]	⊕OOO VERY LOW
Health related quality of life (swallow function) - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] Unclear whether treatment groups are from the same historical period.
[2] Considerable heterogeneity

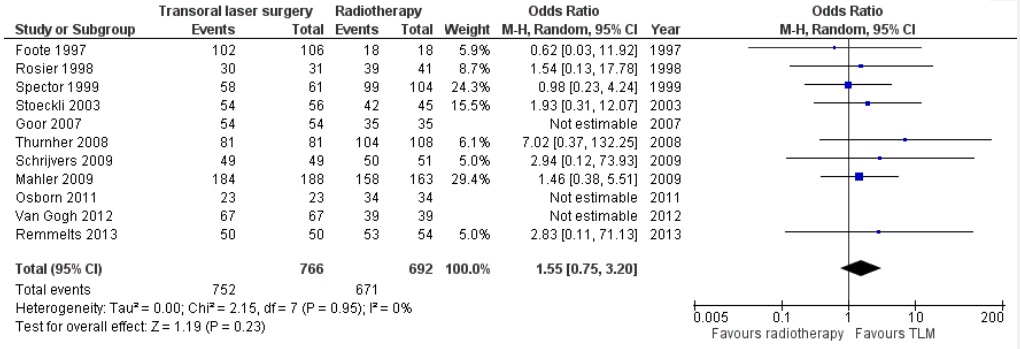
Figure 3.1. TLM versus RT, overall survival



Study or Subgroup	Transoral laser surgery Events	Total	Radiotherapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Rosier 1998	23	31	30	41	7.3%	1.05 [0.37, 3.04]	1998
Spector 1999	51	61	86	104	11.5%	1.07 [0.46, 2.49]	1999
Stoeckli 2003	47	56	39	45	6.6%	0.80 [0.26, 2.45]	2003
Goor 2007	54	54	35	35		Not estimable	2007
Thurnher 2008	61	81	74	108	19.6%	1.40 [0.73, 2.68]	2008
Schrijvers 2009	43	49	46	51	5.2%	0.78 [0.22, 2.74]	2009
Mahler 2009	147	188	117	163	34.8%	1.41 [0.87, 2.29]	2009
Dinapoli 2010	64	73	65	70	6.3%	0.55 [0.17, 1.72]	2010
Osborn 2011	21	23	30	34	2.6%	1.40 [0.23, 8.36]	2011
Remmelts 2013	45	50	44	54	6.2%	2.05 [0.65, 6.47]	2013
Total (95% CI)		**666**		**705**	**100.0%**	**1.20 [0.90, 1.60]**	
Total events	556		566				

Heterogeneity: Tau² = 0.00; Chi² = 4.38, df = 8 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)

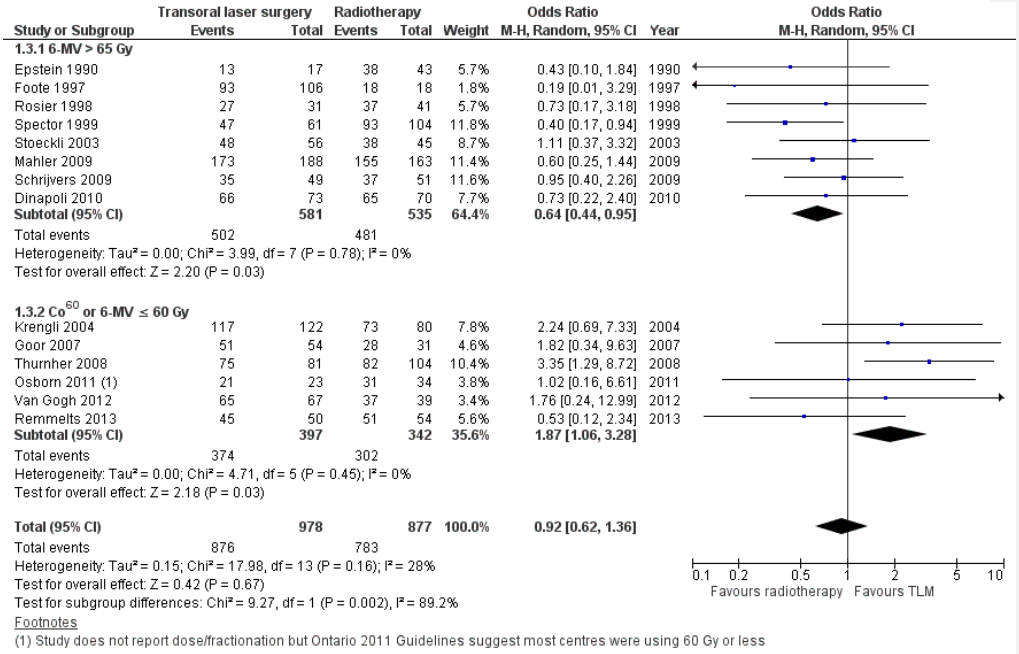
Figure 3.2. TLM versus RT, disease specific survival



Study or Subgroup	Transoral laser surgery Events	Total	Radiotherapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Foote 1997	102	106	18	18	5.9%	0.62 [0.03, 11.92]	1997
Rosier 1998	30	31	39	41	8.7%	1.54 [0.13, 17.78]	1998
Spector 1999	58	61	99	104	24.3%	0.98 [0.23, 4.24]	1999
Stoeckli 2003	54	56	42	45	15.5%	1.93 [0.31, 12.07]	2003
Goor 2007	54	54	35	35		Not estimable	2007
Thurnher 2008	81	81	104	108	6.1%	7.02 [0.37, 132.25]	2008
Schrijvers 2009	49	49	50	51	5.0%	2.94 [0.12, 73.93]	2009
Mahler 2009	184	188	158	163	29.4%	1.46 [0.38, 5.51]	2009
Osborn 2011	23	23	34	34		Not estimable	2011
Van Gogh 2012	67	67	39	39		Not estimable	2012
Remmelts 2013	50	50	53	54	5.0%	2.83 [0.11, 71.13]	2013
Total (95% CI)		**766**		**692**	**100.0%**	**1.55 [0.75, 3.20]**	
Total events	752		671				

Heterogeneity: Tau² = 0.00; Chi² = 2.15, df = 7 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)

Figure 3.3. TLM versus RT, local control by RT subgroup



Footnotes

(1) Study does not report dose/fractionation but Ontario 2011 Guidelines suggest most centres were using 60 Gy or less

Figure 3.4. TLM versus RT, larynx preservation by pre and post 2000 subgroup

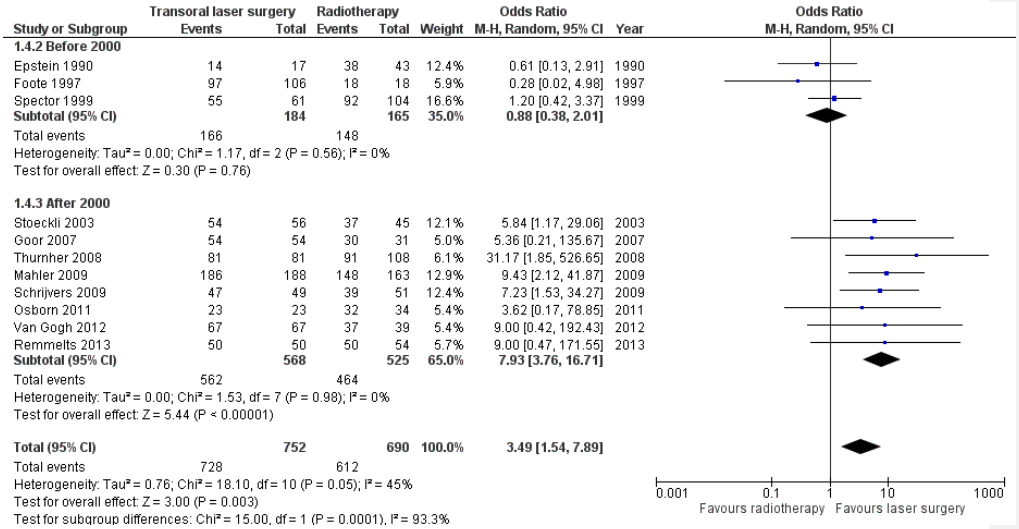


Figure 3.5. TLM versus RT, voice quality - shimmer

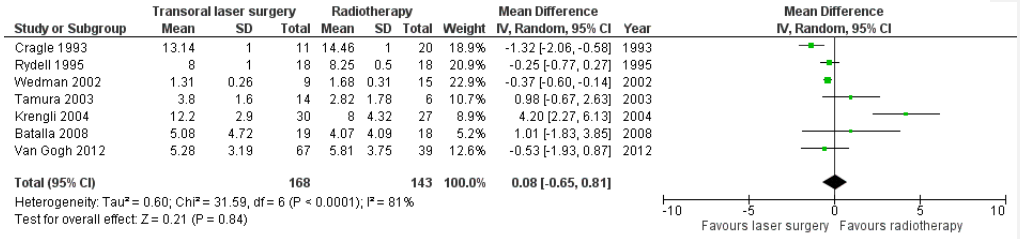


Figure 3.6. TLM versus RT, voice quality - jitter

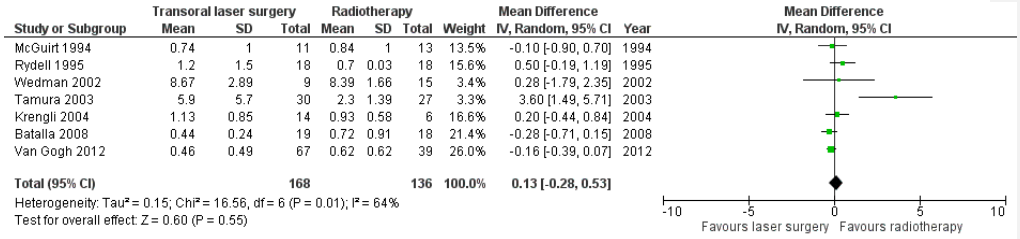


Figure 3.7. TLM versus RT, voice handicap index (VHI)

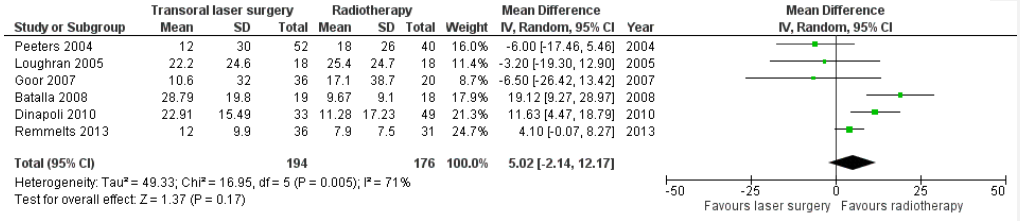


Figure 3.8. TLM versus open surgery, overall survival

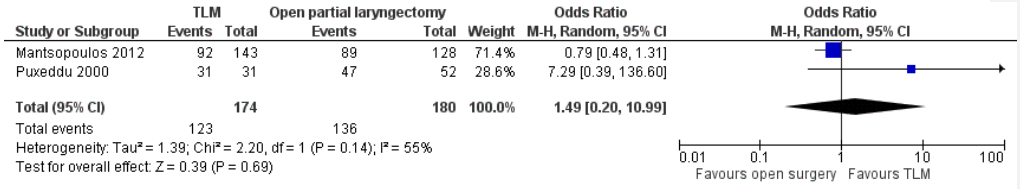


Figure 3.9. TLM versus open surgery, disease specific survival

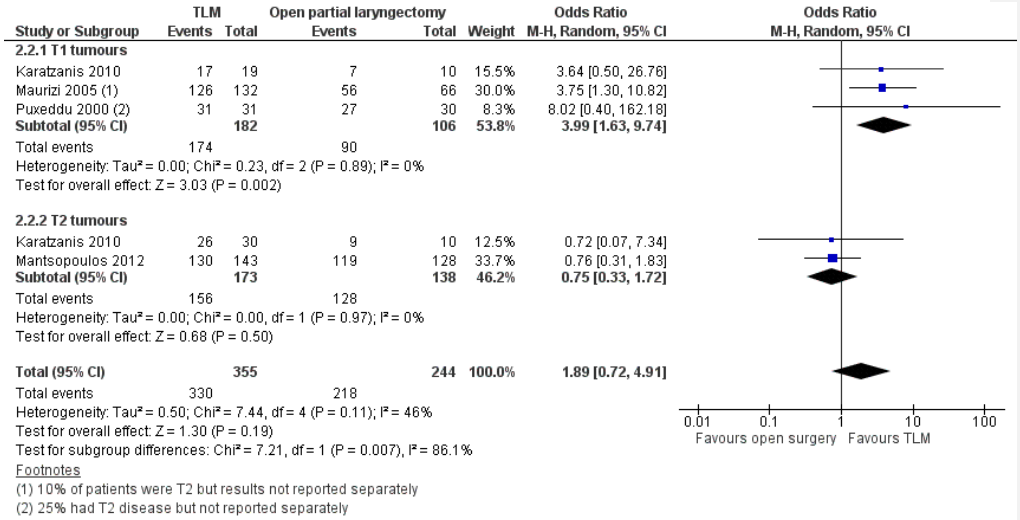


Figure 3.10. TLM versus open surgery, local control

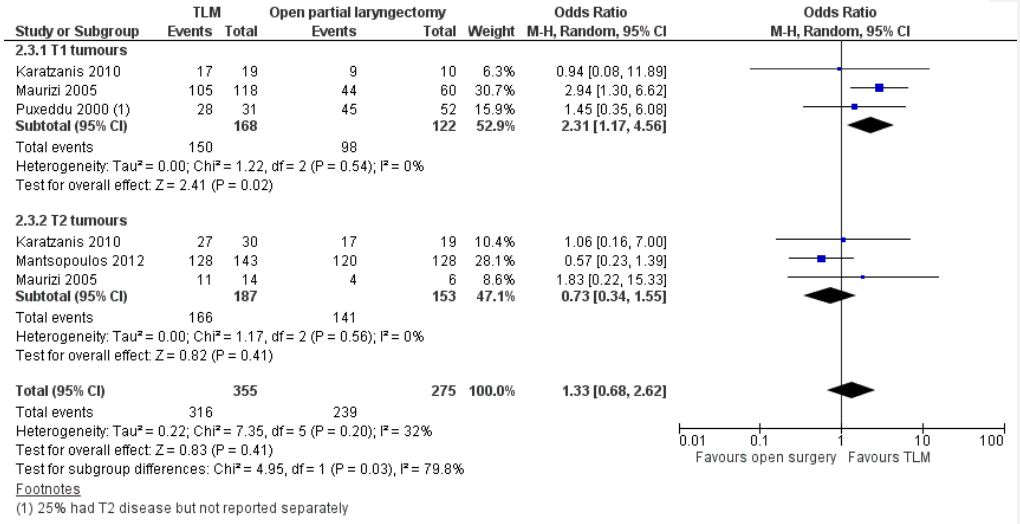


Figure 3.11. TLM versus open surgery, larynx preservation

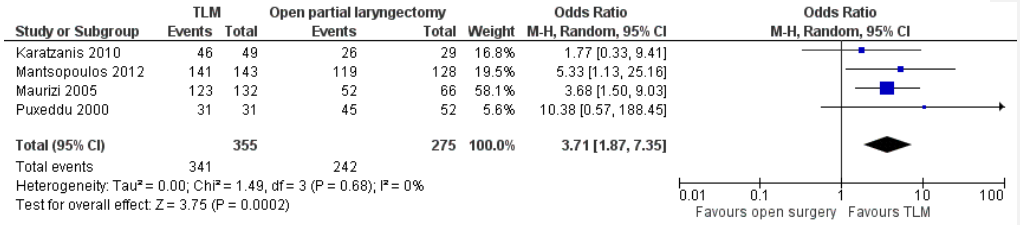
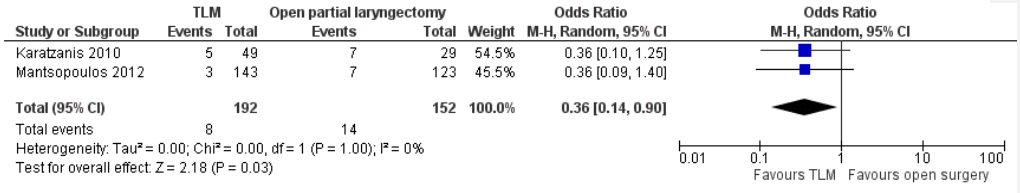


Figure 3.12. TLM versus open surgery, serious complications



Evidence tables for all included studies

Study, country

Abdurehim, Y., Hua, Z., Yasin, Y., Xukurhan, A., Imam, I., & Yuqin, F. (2012). Transoral laser surgery versus radiotherapy: systematic review and meta-analysis for treatment options of T1a glottic cancer. [Review]. Head & Neck, 34, 23-33.

Study type, study period

Systematic review of comparative studies published in 2010 or earlier

Number of patients

19 studies were included: 18 retrospective and 1 prospective. The total number of patients was 1729 (858 for TLS and 871 for RT).

Patient characteristics

T1a squamous cell carcinoma of the glottic larynx – following laryngoscopy and biopsy. 5/19 studies included a small minority of patients with T1b tumours.

Intervention

Transoral laser surgery

Comparison

Radiotherapy

Length of follow-up

Ranged from 5 months to 139 months

Outcome measures and effect size

Outcome (n studies)	TLS	RT	Pooled effect (>1 favours TLS)	Heterogeneity
Overall survival (7 studies)	426/520	427/547	OR 1.22 [95%CI 0.89, 1.66]	Not significant
Disease specific survival (8 studies)	612/626	545/565	OR 1.60 [95%CI 0.79, 3.26]	Not significant
Local control	679/765	599/680	OR 0.94 [95%CI 0.57, 1.57]	I^2 = 47% p = 0.05
Local control (high dose RT – 7 studies)	436/508	416/465	OR 0.63 [95%CI 0.42, 0.96]	Not significant
Local control (low dose RT – 3 studies)	243/257	183/215	OR 2.66 [95%CI 1.35, 5.24]	Not significant
Larynx preservation	588/612	493/563	OR 3.11 [95%CI 1.16, 8.34]	I^2 = 59% p = 0.02
Larynx preservation(studies before 2000 – N = 3)	166/184	148/165	OR 0.88 [95%CI 0.38, 2.01]	Not significant
Larynx preservation(studies after 2000 – N = 5)	422/428	345/398	OR 8.23 [95%CI 3.61,18.76]	Not significant
Maximum phonation time (4 studies)	55	57	MD -1.41 [95%CI -3.51, 0.69]	I^2 = 89% p<0.001
Air flow rate (3 studies)	36	39	MD 21.46 [95%CI -78.79, 121.72]	I^2 = 100% p<0.001
Fundamental frequency (7 studies)	119	113	MD 13.89 [95%CI -9.64, 18.13]	I^2 = 96% p<0.001
Jitter (6 studies)	101	97	MD 0.30 [95%CI -0.29, 0.90]	I^2 = 67% p = 0.01
Shimmer (6 studies)	101	104	MD 0.19 [95%CI -0.62, 1.01]	I^2 = 84% p<0.001
Voice Handicap Index (4 studies)	125	96	MD 0.21 [95%CI -0.27, 0.68]	I^2 = 79% p<0.001

Abbreviations: OR, odds ratio; MD, mean difference

For outcomes with significant heterogeneity subgroup analyses was to try to identify the source (local control and larynx preservation) or random effects models were used.

Source of funding

Not reported

Risks of bias

Selection bias: high risk (non randomised studies – allocation either unclear, by patient preference on based on clinical characteristics)
Performance bias: unclear risk 6 studies were single blind the remainder unclear
Attrition bias: unclear risk
Detection bias: unclear risk

Additional comments

Study, country

O'Hara, J., Markey, A., & Homer, J. J. (2013). Transoral laser surgery versus radiotherapy for tumour stage 1a or 1b glottic squamous cell carcinoma: systematic review of local control outcomes. Journal of Laryngology & Otology, 127, 732-738.

Study type, study period

Systematic review of observational studies published in 2011 or earlier

Number of patients

36 retrospective case series. The studies included 3815 patients T1a tumours (2507 treated with RT and 1308 with TLS). There were 738 patients with T1b tumours (544 treated with RT and 194 with TLS).

Patient characteristics

T1a glottic squamous carcinoma
T1b glottic squamous carcinoma

Intervention

Transoral laser surgery (as initial treatment)

Comparison

Radiotherapy (as initial treatment)

Length of follow-up

At least 36 months

Outcome measures and effect size

Studies of T1a tumours

Outcome (n studies)	TLS	RT
Local control at 36 months or more	1163/1308 (88.9%)	2237/2507 (89.2%)

Studies of T1b tumours

Outcome (n studies)	TLS	RT
Local control at 36 months or more	154/194 (76.8%)	468/544 (86.0%)

Source of funding

Not reported

Risks of bias

Selection bias: high risk
Performance bias: high risk
Attrition bias: unclear risk
Detection bias: unclear risk

Additional comments

Authors conclude that TLS and RT are equivalent for T1a but RT is possibly superior for T1b – however the data do not fully support this as the single arm studies are pooled using simple average – no measure of variability reported.

Study, country

Thomas, L., Drinnan, M., Natesh, B., Mehanna, H., Jones, T., & Paleri, V. (2012). Open conservation partial laryngectomy for laryngeal cancer: a systematic review of English language literature (DARE structured abstract). Cancer Treatment Reviews., 38, 203-211.

Study type, study period

Systematic review of studies published from 1980 to 2009

Number of patients

53 papers were included, with a minimum of 10 laryngectomies. N patients: T1 1134, T2 2079, T3 640 and T4 192.

Patient characteristics

Patients with laryngeal cancer (T1 – T4)

Intervention

Open partial laryngectomy

Comparison

None

Length of follow-up

At least 24 months follow up

Outcome measures and effect size

Outcome	N	Pooled estimate (95% C.I.)	Heterogeneity
Local control at 24 months or more (55 studies)	5196	89.8% [88.3, 91.2%)	I^2 = 75.6
Overall survival at 24 months or more (41 studies)	3967	79.7% [76.5, 82.8%]	I^2 = 86.2
Disease free survival at 24 months or more (28 studies)	2344	84.8% [80.6, 88.7%]	I^2 = 88.5
Decannulation rate (42 studies)	3955	96.3% [94.9, 97.6%]	I^2 = 84.1
Laryngectomy for function (29 studies)	2496	1.7% [1.2, 2.2%]	I^2 = 53.9
Laryngectomy for salvage (36 studies)	2705	6.0% [4.6, 7.6%]	I^2 = 73.4
Larynx preservation rate (39 studies)	3171	90.9% [88.8, 92.7%]	I^2 = 78.9
Permanent gastrostomy rate (20 studies)	2000	2.0% [0.9, 3.9%]	I^2 = 82.4
Laryngeal stenosis (16 studies)	1453	2.7% [1.8, 3.0%]	I^2 = 56.5
Operative mortality (23 studies)	1453	0.7 [0.7, 0.7%]	I^2 = 0

Source of funding

Not reported

Risks of bias

High risk of bias – non comparative case series

Additional comments

Study, country

Warner L, Chudasama J, Kelly C. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. [Review][Update of Cochrane Database Syst Rev. 2002;(2):CD002027; PMID: 12076435]. Cochrane Database of Systematic Reviews 2014; 12:CD002027.

Study type, study period

Systematic review of randomised trials published between 1980 and 2009

Number of patients

1 randomised trial included. N = 269 (234 with glottic laryngeal cancer).

Patient characteristics

Patients with T1-T2

Intervention

Open surgery

Comparison

Radiotherapy. (some received chemoradiotherapy but were not included the analysis)

Length of follow-up

Length of follow up not reported – but survival outcomes were reported at 5 years. The trial authors noted that follow up was poor.

Outcome measures and effect size

T1 tumours

Outcome	RT (N = 129)	Surgery (N = 76)	P
Overall survival at 5 years	91.7%	100%	No sig. difference (P not reported)
Disease free survival at 5 years	71.1%	100%	No sig. difference (P not reported)

T2 tumours

Outcome	RT (N = 129)	Surgery	P
Overall survival at 5 years	88.8%	97.4%	No sig. difference (P not reported)
Disease free survival at 5 years	60.1%	78.7%	P = 0.036

Source of funding

Freeman Hospital Trustees, Newcastle upon Tyne, UK

Risks of bias

High risk of bias: The review authors had concerns about the methodology of the included RCT. There was unclear allocation concealment, the total number of patients randomised to each arm was not reported, baseline characteristics were not reported and the groups were unbalanced in size (76 allocated to surgery and 129 to RT), there was no blinding

Additional comments

Study, country

van Loon Y., Sjogren, E. V., Langeveld, T. P., Baatenburg de Jong, R. J., Schoones, J. W., & van Rossum, M. A. (2012). Functional outcomes after radiotherapy or laser surgery in early glottic carcinoma: a systematic review. [Review]. Head & Neck, 34, 1179-1189.

Study type, study period

Systematic review of observational studies published between 1990 and 2009

Number of patients

19 studies were included. Number of patients = 1339 (1173 TLS, 166 RT)

Patient characteristics

Patients with Tis, T1 or T2 glottic carcinoma (majority of included patients had T1 tumours)

Intervention

Laser surgery

Comparison

Radiotherapy, combined laser surgery and radiotherapy

Length of follow-up

Outcome measures and effect size

Outcome	Laser surgery	Radiotherapy	LS vs. RT
Voice quality – auditory perception	5 studies found that greater resections were associated with poorer voice quality than lesser resections (but difference not statistically significant).	1 study reported 66% of patients at normal or near normal voices after RT.	One comparative study found no difference and another found voice quality better after
Voice quality – acoustic analysis	10 studies evaluated the acoustic signal. More extensive resections were associated with higher perturbation in the acoustic signal.	One small study reported high perturbation in 3/5 patients after RT.	2 comparative studies found no difference, 2 others reported greater signal perturbation with laser surgery than with RT.
Voice function – areodynamics	10 studies reported aerodynamic results: 5 found no statistical difference between aerodynamic measures after greater and lesser resection. Two reported maximum phonation time was poorer in extensive resection than in lesser resection.	Not reported	3 comparative studies reported conflicting results.
Voice function – F0	6 studies compared F0 in greater and lesser resections, 1 found higher F0 for greater resections; 3 found higher F0 with surgery compared to normal controls	1 study found 2/5 patients had lower F0 than normal after RT.	4 studies compared F0 in LS and RT: 2 reported lower F0 with RT than with LS (statistically significant in one study). The other 2 studies found similar F0 in LS and RT.
Voice function – videostroboscopy	5 studies found structural abnormalities were more likely with greater than with lesser resections. These include altered or absent mucosal wave, incomplete glottic closure, vocal fold immobility and supraglottic hyperfunction.	No results reported	One study reported structural abnormalities in 5/13 irradiated patients compared with 11/11 lasered patients.
Voice performance – VHI	Three studies reported higher (worse) VHI scores for greater than for lesser resections.	Not reported	One study compared VHI scores after RT or laser surgery- scores were higher (worse) after RT than laser surgery (but patients with more invasive tumours were selected for RT).
Quality of life	One study found that speech and social contact items on EORTC H&N 35 were significantly less affected after lesser resections than after greater resections.	Not reported	No significant differences between QOL scores on COOP/Wonca questionnaire.
Deglutition, swallowing or weight	Not reported	Not reported	Not reported

Source of funding

Grant from ZOELEON, Stichting Oncologie Holland West

Risks of bias

High risk of bias – non randomised studies (13/19 were case series, 6/19 cohort studies), – baseline differences in patients selected for RT or TLS, or for greater versus lesser TLS

Additional comments

Study, country

Spielmann, P. M., Majumdar, S., & Morton, R. P. (2010). Quality of life and functional outcomes in the management of early glottic carcinoma: a systematic review of studies comparing radiotherapy and transoral laser microsurgery. [Review]. Clinical Otolaryngology, 35, 373-382.

Study type, study period

Sytematic review of comparative observational studies published between 1970 and 2009

Number of patients

21 studies included,

Patient characteristics

Patients with T1 or T2 glottic carcinoma

Intervention

Transoral laser surgery

Comparison

Radiotherapy

Length of follow-up

Outcome measures and effect size

Outcome	TLS vs. RT
Voice quality – GRBAS scale	Seven studies compared TLS with RT: five found no statistically significant difference; two reported voice quality was better with RT but only one of these provided statistics.
Voice quality – electro acoustic analysis	Eight studies compared TLS with RT: five found no statistically significant difference; three reported significantly better voice quality with RT.
Voice performance – VHI	Seven studies compared TLS with RT: five reported no significant overall difference. One study found better overall VHI score after RT whereas another found better VHI score after TLS.
Quality of life	9 studies reported QoL outcomes covering general, head & neck specific and voice specific scales. All studies reported generally good QoL outcomes with no significant differences between TLS and RT groups
Swallow function	No comparative study measured swallow function. One study assessed patient's perception of swallow function in QoL questionnaires (EORTC QLQ H&N 35) and found better scores in the TLS group than the RT group for swallowing foods, xerostomia and tooth problems.

Source of funding

Not reported – but authors state no conflicts of interest

Risks of bias

High risk of bias – all studies were non randomised

Additional comments

Study, country

Karatzanis, A. D., Psychogios, G., Zenk, J., Waldfahrer, F., Hornung, J., Velegrakis, G. A. et al. (2010). Evaluation of available surgical management options for early supraglottic cancer. Head & Neck, 32, 1048-1055.
Germany.

Study type, study period

Retrospective observational study (1970-2004)

Number of patients

101

Patient characteristics

Patients with stage I or II supraglottic carcinoma. 90% were male, mean age 60 years (range 36 to 83 years)

Intervention

Transoral CO_2 laser microsurgery (N = 49; 19 T1, 30 T2)

Comparison

Horizontal laryngectomy (N = 29; 10 T1, 19 T2), total laryngectomy (N = 23; all T2)

Length of follow-up

Mean follow-up 5.6 years.

Outcome measures and effect size

	Laser microsurgery	Horizontal partial laryngectomy	
Permanent tracheotomy	3/49 (6.1%)	4/29 (13.7%)	
Transient tracheotomy	4/49 (8.1%)	17/29 (58.6%)	
Permanent PEG	3/49 (6.1%)	3/29 (10.3%)	
Salvage laryngectomy	3/49 (6.1%)	3/29 (10.3%)	
Major complications (bleeding, granular formation, aspiration, fistular or dyspnea)	5/49 (10.2%)	7/29 (24.1%)	P = 0.09
T1 – Death from supraglottic carcinoma	2/19	3/10	P = 0.631
T1 – Local recurrence	2/19	1/10	P = 0.924
T2 - Death from supraglottic carcinoma	4/30	4/19	P = 0.924
T2 – Local recurrence	3/30	2/19	P = 0.143

Source of funding

Not reported

Risks of bias

High risk of bias. Non randomised study. Baseline characteristics not reported by treatment group – although authors note there were no statistically significant differences. Large time period covered in study – unclear whether certain treatments were favoured at certain times.

Additional comments

Total laryngectomy data not included in this extraction (intervention not in PICO).

Study, country

Maurizi, M., Almadori, G., Plaudetti, G., De, C. E., & Galli, J. (2005). Laser carbon dioxide cordectomy versus open surgery in the treatment of glottic carcinoma: our results. Otolaryngology - Head & Neck Surgery, 132, 857-861.
Italy

Study type, study period

Retrospective observational study. 1993-2002

Number of patients

198

Patient characteristics

Patients with T1a or T2 glottic carcinoma with no involvement of the anterior commisure.

Intervention

Transoral CO_2 laser cordectomy (N = 132; T1a 118, T2 14)

Comparison

Open surgical cordectomy (N = 66; T1a 60, T2 6)

Length of follow-up

Not reported although survival outcomes were evaluated over 5 years and it is clear than many patients were not followed up for this long.

Outcome measures and effect size

	Laser microsurgery	Open surgery	
Death from glottic carcinoma	6/132 (4.5%)	10/66 (15.2%)	P = 0.04
Locoregional recurrence	16/132 (12%)	18/66 (27%)	P> 0.05
T1a Locoregional recurrence	13/118 (11.0%)	16/60 (26.7%)	N.R.
T2 Locoregional recurrence	3/14 (21.4%)	2/6 (33.3%)	N.R.
Total laryngectomy (after recurrence)	9/132 (6.8%)	14/66 (21.2%)	P<0.05

Source of funding

Not reported.

Risks of bias

High risk of bias – non randomised study. Baseline characteristics not reported for patients with T1a-T2 disease. It appears that the laser patients were more likely to have shorter follow-up (judging from the censoring marks in the survival analysis) this suggests that they may be more recently treated than the open cordectomy group.

Additional comments

Study, country

Mantsopoulos, K., Psychogios, G., Koch, M., Zenk, J., Waldfahrer, F., & Iro, H. (2012). Comparison of different surgical approaches in T2 glottic cancer. Head & Neck, 34, 73-77.
Germany

Study type, study period

Retrospective observational study. 1977-2004

Number of patients

271

Patient characteristics

Patients with T2 glottic cancer, primary treatment with surgery, 96% male, mean age 61.48 years (range 35 to 97). Anterior commisure involvement in 163/271.

Intervention

Transoral CO_2 laser surgery (N = 143)

Comparison

Vertical partial laryngectomy (N = 128)

Length of follow-up

Mean follow up 11.6 years

Outcome measures and effect size

	Transoral laser surgery (N = 143)	Partial laryngectomy (N = 128)	
Overall survival	64.5%	69.5%	P = 0.717
Disease specific survival	90.8%	92.6%	P = 0.703
Local control	89.4%	93.9%	P = 0.181
Major complications*	3/143	7/123	P = 0.271
Transient tracheotomy	1/143	23/128	P<0.001
Permanent tracheotomy	2/143	9/128	P<0.001

*requiring intensive medical treatment, blood transfusion, surgery or intensive care unit admission.

Source of funding
Not reported
Risks of bias
High risk of bias – non randomised study. Unclear whether the two groups of patients were from the same historical treatment period.
Additional comments

Study, country
Puxeddu, R., Argiolas, F., Bielamowicz, S., Satta, M., Ledda, G. P., & Puxeddu, P. (2000). Surgical therapy of T1 and selected cases of T2 glottic carcinoma: cordectomy, horizontal glottectomy and CO2 laser endoscopic resection. Tumori, 86, 277-282. Italy.
Study type, study period
1983-1997
Number of patients
83
Patient characteristics
T1 and selected T2 (without impaired vocal cord mobility) glottic carcinoma, 97% male, mean age 60.6 years. 48 T1a, 14 T1b and 21 T2. 31/83 had involvement of the anterior commissure. 52 patients had an elective neck dissection – 11 were clinically N+
Intervention
Transoral laser surgery (CO_2 laser; N = 31; 23 T1a, 4 T1b, 4 T2)
Comparison
Open partial laryngectomy: Cordectomy via thyrotomy (N = 30; 22 T1a, 8 T2) Horizontal glottectomy (N = 22; 3 T1a, 10 T1b, 9 T2)
Length of follow-up
Median 5.4 years
Outcome measures and effect size

	Transoral laser surgery (N = 31)	Cordectomy via thyrotomy (N = 30)	Horizonatal glottectomy (N = 22)	
Larynx preservation	31/31	26/30	19/22	
Overall survival	31/31	27/30	20/22	
Disease specific survival	31/31	27/30	20/22	
3 year recurrence free survival	88%	85%	86%	
Recurrence	3/31	4/30	3/22	
Mean hospitalization duration	2.1 days	7.3 days	9.8 days	
Vocal function (perceptual analysis by Buffalo III system)				Better voice quality with TLS than with open laryngeal procedures (P<0.05)

Source of funding
Not reported
Risks of bias
High risk of bias. Unbalanced baseline characteristics – more T1b-T2 disease in the horizontal glottectomy group. The authors have used transoral laser in preference to open surgery since 1994 – the open surgical group are a historically older cohort.
Additional comments

Study, country
Arshad, H., Jayaprakash, V., Gupta, V., Cohan, D. M., Ambujakshan, D., Rigual, N. R. et al. (2014). Survival Differences between Organ Preservation Surgery and Definitive Radiotherapy in Early Supraglottic Squamous Cell Carcinoma. Otolaryngology - Head & Neck Surgery, 150, 237-244. USA
Study type, study period
Population based cohort study using SEER database 1988 to 2008
Number of patients
Patient characteristics
Patients with T1-T2, N0 supraglottic carcinoma, diagnosed between 1988-2008 in the SEER database, treated with organ preservation surgery or definitive radiotherapy

Intervention

Definitive radiotherapy (N = 2278)

Comparison

Organ preservation surgery N = 354 (local tumour excision N = 118, partial/hemi laryngectomy N = 112 and supraglottic laryngectomy N = 123); For those receiving OPS, 167 had OPS plus neck dissection and 186 has OPS without neck dissection

Length of follow-up

Outcome measures and effect size

T1N0 supraglottic carcinoma

	Radiotherapy	Organ preservation surgery with neck dissection	Organ preservation surgery without neck dissection
5 year overall survival	53%	65% (HR = 0.89*, [0.69-1.15] versus RT; P = 0.36)	76% (HR = 0.48*, [0.33-0.71] versus RT; P<0.001)
5 year disease specific survival	68%	82% (HR = 0.70*, [0.48-0.99] versus RT; P = 0.05)	81% (HR = 0.61*, [0.39-0.96] versus RT; P = 0.03)

*Multivariate model adjusting for age, gender, race and tumour grade

T2N0 supraglottic carcinoma

	Radiotherapy	Organ preservation surgery with neck dissection	Organ preservation surgery without neck dissection
5 year overall survival	45%	49% (HR = 0.93*, [0.65-1.32] versus RT; P = 0.67)	77% (HR = 0.36*, [0.23-0.55] versus RT; P<0.001)
Median disease specific survival (5 yr rates not reported)	98 months	77 months (HR = 1.12*, [0.73-1.70] versus RT; P = 0.61)	122 months (HR = 0.31*, [0.17-0.57] versus RT; P<0.001)

*Multivariate model adjusting for age, gender, race and tumour grade

Source of funding

None.

Risks of bias

High risk of bias – non randomised study. Multivariate models adjusted for age, gender, race and tumour grade but other factors could lead to systematic bias between treatment groups.

Additional comments

Study, country

Dinapoli, N., Parrilla, C., Galli, J., Autorino, R., Micciche, F., Bussu, F. et al. (2010). Multidisciplinary approach in the treatment of T1 glottic cancer. The role of patient preference in a homogenous patient population. Strahlentherapie und Onkologie, 186, 607-613.
Italy

Study type, study period

Retrospective observational study. 1994 - 2001

Number of patients

134

Patient characteristics

T1 glottic carcinoma, 76.2% T1a, 93.7% male, median age 64 years. Patients were eligible for both treatments and treatment allocation was by patient choice.

Intervention

Radiotherapy (N = 70): 70 Gy at 2 Gy per fraction or 70.2 Gy at 1.8 Gy per fraction; 6 MV opposing latero-lateral photon beams

Comparison

Transoral CO_2 laser surgery (N = 73).

Length of follow-up

Median follow up not reported but survival outcomes reported up to 5 years

Outcome measures and effect size

	Radiotherapy	Laser surgery	
Overall survival	65/70	64/73	HR 1.109 [0.399 to 3.298] P = 0.798
Disease free survival	65/70	66/73	HR 0.931 [0.299 to 2.884] P = 0.898
5 year disease free survival T1a (N = 109)	97.8%	86.5%	HR 0.252 [0.079 to 1.499] P = 0.150
5 year disease free survival T1b (N = 17)	53.3%	100%	HR N.R. P = 0.07
VHI mean (SD)	11.28 (17.23)	22.91 (15.49)	P<0.0001, favours RT

Source of funding
Not reported
Risks of bias
High risk of bias – non randomised study. Unclear whether baseline characteristics were balanced between treatment groups – although there was no significant difference in age. Response bias to VH1 questionnaire: 70% of RT patients responded compared with 33% of surgery patients
Additional comments

Study, country
Osborn, H. A., Hu, A., Venkatesan, V., Nichols, A., Franklin, J. H., Yoo, J. H. et al. (2011). Comparison of endoscopic laser resection versus radiation therapy for the treatment of early glottic carcinoma. Journal of Otolaryngology: Head and Neck Surgery, 40, 200-204. Canada
Study type, study period
Retrospective observational study. 2004-2009
Number of patients
57
Patient characteristics
For the RT group: mean age 69.9 years, 85% male, 91% smokers, 29% Tis 71% T1a For the TLM group: mean age 65.4 years, 83% male, 70% smokers, 35% Tis 65% T1a
Intervention
Radiotherapy (N = 34) (dose/fractionation not reported although Ontario 2011 guideline suggests most centres used 60 Gy or less in this population)
Comparison
Transoral laser surgery (N = 23)
Length of follow-up
Mean follow up 27 months for RT, 20 months for TLS
Outcome measures and effect size

	Radiotherapy (N = 34)	Laser surgery (N = 23)	
Overall survival	88.2% (N = 30)	91.3% (N = 21)	P = 0.89
Local control	91.2% (N = 31)	91.3% (N = 21)	P = 0.72
Laryngeal preservation	94.1% (N = 32)	100% (N = 23)	P = 0.34
5 year disease free survival T1b (N = 17)			
V-RQOL score – overall	Mean 89.8 (SD 14.4)	Mean 81.4 (SD 21.3)	P = 0.228
V-RQOL score – social/emotional	Mean 89.4 (SD 20.6)	Mean 83.1 (SD 31.2)	P = 0.742
V-RQOL score – physical	Mean 90.0 (SD 12.3)	Mean 80.2 (SD 18.4)	P = 0.05

Source of funding
Authors report no financial conflicts of interest.
Risks of bias
High risk of bias – non randomised study. Very small sample size / low event rate.
Additional comments

Study, country
van Gogh, C. D., Verdonck-de Leeuw, I. M., Wedler-Peeters, J., Langendijk, J. A., & Mahieu, H. F. (2012). Prospective evaluation of voice outcome during the first two years in male patients treated by radiotherapy or laser surgery for T1a glottic carcinoma. European Archives of Oto-Rhino-Laryngology, 269, 1647-1652. The Netherlands
Study type, study period
Retrospective observational study. Patients treated over a period of 9 years.
Number of patients
106
Patient characteristics
T1aN0M0 glottic cancer, all male,
Intervention
Radiotherapy (N = 39; 57.5 to 60.0 Gy, using 2 opposing lateral fields and 6 MV photons)
Comparison
Transoral laser surgery (N = 67: CO_2 laser used for chordectomy type II)
Length of follow-up
Patients followed up for 2 years

Outcome measures and effect size

	TLM (N = 67)	RT (N = 39)	
Larynx preservation	67/67 (100%)	37/39 (95%)	OR 9.00 (0.42 to 192.42)
Disease specific survival	67/67 (100%)	39/39 (100%)	Not estimable
Jitter (at 2 years post treatment)	Mean 0.46 (SD 0.49)	Mean 0.62 (SD 0.62)	P>0.05
Shimmer (at 2 years post treatment)	Mean 5.28 (SD 3.19)	Mean 5.81 (SD 3.75)	P>0.05
Normalised noise energy at 2 years post treatment	Mean -8.39 (SD 4.23)	Mean -7.17 (SD 4.2)	P>0.05
Fundamental frequency (F0; at 2 years post treatment)	Mean 141 (SD 33)	124 (SD 29)	P = 0.027

Source of funding

Not reported

Risks of bias

High risk of bias. Non randomised observational study. The dates when treatment was given were not reported – could be different treatment eras for RT and TLM.

Additional comments

Study, country

Remmelts, A. J., Hoebers, F. J., Klop, W. M., Balm, A. J., Hamming-Vrieze, O., & van den Brekel, M. W. (2013). Evaluation of lasersurgery and radiotherapy as treatment modalities in early stage laryngeal carcinoma: tumour outcome and quality of voice. European Archives of Oto-Rhino-Laryngology, 270, 2079-2087.
The Netherlands

Study type, study period

Retrospective observational study. 2000-2008

Number of patients

N = 248

Patient characteristics

Radiotherapy group: mean age 64 years (range 39 – 89 years), 87% male, 2% Tis, 34% T1a, 17% T1b, 47% T2, all N0
Laser surgery group: mean age 67 years (range 41 – 87 years), 88% male, 26% Tis, 55% T1a, 17% T1b, 2% T2, all N0

Intervention

Radiotherapy (N = 159; 60 Gy for ≤ T1b or 70 Gy for T2 , 4MV photons)

Comparison

Transoral laser surgery (N = 89: CO_2 laser)

Length of follow-up

Radiotherapy group mean follow up 48 months, laser surgery group 44 months

Outcome measures and effect size

For T1a disease only:

	TLM (N = 50)	RT (N = 54)	
Larynx preservation	50/50	50/54	OR = 9.00 (0.47 to 171.55), P = 0.267
Overall survival	45/50	44/54	
5 year overall survival	86%	89%	P = 0.561
Disease specific survival	50/50	53/54	
5 year disease specific survival	100%	96%	P = 0.519
Local control (with initial treatment modality)	45/50	51/54	
5 year local control	81%	93%	P = 0.382
VHI	Mean 12.0 (SD 9.9)	Mean 7.9 (SD 7.5)	P = 0.06

For T1b-T2 disease only:

	TLM (N = 17)	RT (N = 102)	
Larynx preservation	15/17	88/102	P = 0.097
Overall survival	14/17	77/102	
5 year overall survival	85%	81%	P = 0.885
Disease specific survival	16/17	96/102	
5 year disease specific survival	100%	91%	P = 0.980
Local control (with initial treatment modality)	14/17	89/102	
5 year local control	78%	80%	P = 0.310
VHI (T1b)	Mean 16.7 (SD 9.0)	Mean 4.9 (SD 6.6)	P = 0.003 (favours RT)
VHI (T2)	Mean 10.0 (SD 4.2)	Mean 9.9 (SD 8.0)	N.R.

Source of funding

Not reported – but authors report no conflicts of interest

Risks of bias

High risk of bias. Significant differences between baseline T stages of the treatment groups (much more T2 in the RT group).

Additional comments

Study, country

Comert E. Comparison of early oncological results of diode laser surgery with radiotherapy for early glottic carcinoma. Otolaryngology - Head & Neck Surgery 2014; 150(5):818-823.
Turkey

Study type, study period

Retrospective observational study. 2008-2012

Number of patients

N = 140

Patient characteristics

Early glottic carcinoma
Transoral laser surgery group: N = 72; mean age 51.8 years; 39 T1, 33 T2; anterior commissure involvement 32
Radiotherapy group: N = 68; mean age 63. 1 years; 47 T1, 21 T2 ;anterior commissure involvement 23

Intervention

Radiotherapy (63 to 70 Gy from a high voltage source as opposing lateral cervical fields)

Comparison

Transoral laser surgery (gallium-aluminium-arsenide diode laser; power 4 to 9W and wavelength 980nm)

Length of follow-up

Minimum of 12 months: mean 29.3 months for TLM and 31.7 for RT

Outcome measures and effect size

Overall (T1 and T2 combined)

	TLM (N = 72)	**RT (N = 68)**	
Larynx preservation	72/72	64/68	
Locoregional recurrence	5/72	7/68	
3 year disease free survival	93.1%	89.7%	P = 0.434 (log-rank test)

Source of funding

No funding source reported.

Risks of bias

Non randomised observational study. RT group significantly older than TLM (P = 0.033). RT group tended to have more T1 disease – although not significant (P = 0.069)

Additional comments

Cannot extract T1 and T2 data separately

Study, country

Milovanovic J, Jotic A, Djukic V, Pavlovic B, Trivic A, Krejovic-Trivic S et al. Oncological and Functional Outcome after Surgical Treatment of Early Glottic Carcinoma without Anterior Commissure Involvement. Biomed Research International 2014.
Serbia

Study type, study period

prospective observational study. 2006-2007

Number of patients

N = 59

Patient characteristics

Early glottic carcinoma (Tis or T1a) with no anterior commissure involvement

Intervention

transoral laser microsurgery (N = 26) using Sharplan Lumenis 40C CO_2 laser.

Comparison

Open cordectomy (N = 33)

Length of follow-up

5 years

Outcome measures and effect size

Postoperative complications

	TLM (N = 26)	Open surgery (N = 33)
Local infection	0/26	2/33
Tracheotomy	1/26	3/33
Emphysema	0/26	2/33
Wound dehisence	0/26	2/33
Mean duration of hospitalization	3.3 days	7.5 days

Stroboscopic signs at 12 months

	TLM (N = 26)	Open surgery (N = 33)
Absent mucosal wave	6/26	11/33
Non assessable non-vibratory segment	5/21	14/33

Clinical outcomes (follow up 5 years)

	TLM (N = 26)	Open surgery (N = 33)	
Overall survival at 5 yrs	96%	91%	P>0.05 (log-rank test)
Death from any cause	1/26	3/33	
Recurrence free survival at 5 yrs	91%	92%	P>0.05 (log-rank test)
Disease recurrence	2/26	3/33	
Death from glottic cancer	0/26	1/33	

Source of funding

No funding source reported.

Risks of bias

Non randomised observational study, very small sample size

Additional comments

Study, country

Robertson SM, Yeo JC, Sabey, Robertson SM. Effects of tumor staging and treatment modality on functional outcome and quality of life after treatment for laryngeal cancer. Head & Neck 2013; 35(12):1759-1763.
UK

Study type, study period

prospective observational study. 2006-2008

Number of patients

N = 69 (with T1 disease)

Patient characteristics

Early laryngeal carcinoma (T1)

Intervention

transoral laser microsurgery (N = 43)

Comparison

Radiotherapy (N = 26)

Length of follow-up

Outcomes measured at 3 years after treatment

Outcome measures and effect size

Functional and QOL outcomes at 3 years post treatment

	TLM (N = 43)	RT (N = 26)	
median VoiSS †score (range)	20.5 (2 to 62)	15 (0 to 93)	P = 0.331
median MDADI* score (range)	88.5 (0 to 100)	85 (0 to 100)	P = 0.602
median UW-QOL‡ score (range)	100 (100-100)	100 (100-100)	P = 0.586

†Voice Symptom Scale *MD Anderson dysphagia inventory ‡University of Washington Quality of Life

Source of funding

Not reported

Risks of bias

Non randomised study – unclear whether there were baseline differences in the treatment groups

Additional comments

Study, country

Greulich, M. T., Parker, N. P., Lee, P., Merati, A. L., & Misono, S. (2015). Voice outcomes following radiation versus laser microsurgery for T1 glottic carcinoma: systematic review and meta-analysis. Otolaryngol.Head Neck Surg., 152, 811-819.UK

Study type, study period

Systematic review and meta-analysis

Number of patients

8 studies including 362 patients

Patient characteristics

T1 glottic carcinoma

Intervention

transoral laser microsurgery (N = 155)

Comparison

Radiotherapy (N = 207)

Length of follow-up

Mean follow up ranged from 21 to 60 months.

Outcome measures and effect size

	RT (N = 207)	TLM (N = 155)	Mean difference
Voice Handicap index (post treatment)	N.R.	N.R.	-5.52 (-11.40 to 0.36)

Pooled result suggests uncertainty over whether RT is superior to TLM in terms of voice handicap index.

Source of funding

Not reported

Risks of bias

Included studies were all retrospective and non-randomised. The review authors considered the characteristics of the treatment groups to be balanced.

Additional comments

Significant heterogeneity in the pooled estimate of VHI MD, unclear when the VHI was measured

Evidence search details and references

Review question in PICO format

Population	**Intervention**	**Comparison**	**Outcomes**

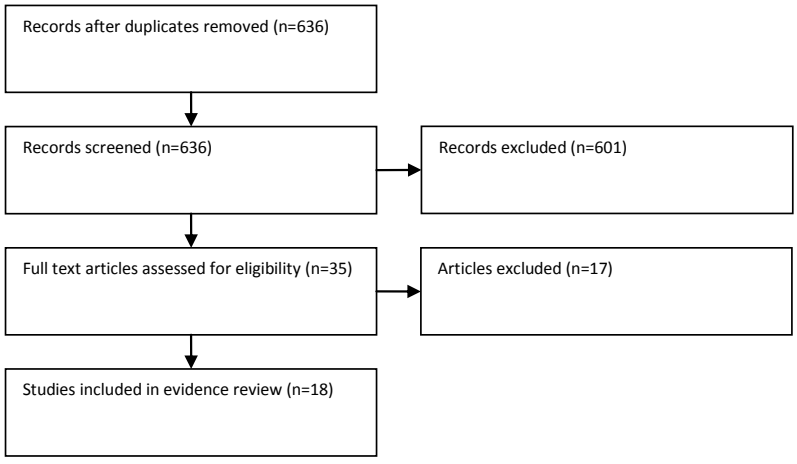
Adults diagnosed with new (T1, T2, N0) squamous cell carcinoma of the larynx
 	
Subgroups:
 	
• glottis
• supraglottis
• T1a
• T1b
• T2a
• T2b
• performance status
	• Radiotherapy
	• Larynx preserving surgery:
	  • trans oral
	  • open
		Each other	• Overall survival
			• Disease free survival
			• Tumour recurrence
			• Progression free survival
			• Treatment related mortality
			• Treatment related morbidity
			• Organ preservation rates
			• Length of stay
			• Health related quality of life
			  • Swallow function
			  • Voice quality

Additional review protocol details (refer to Section 10 for full review protocol)

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour site of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10;

	At least 75% of the included patients meet the population defined in the PICO.
Search strategies	None specified
Review strategies	The evidence tables for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. In addition to studies comparing surgery with radiotherapy, the radiotherapy regimen and type of surgery (open or trans oral) used in relevant studies will be important considerations for the review. Comparisons of different radiotherapy regimens/different surgical approaches will also be included, if these exist.

Figure 3.13. Study flow diagram



Included studies

Abdurehim, Y., Hua, Z., Yasin, Y., Xukurhan, A., Imam, I., & Yuqin, F. (2012). Transoral laser surgery versus radiotherapy: systematic review and meta-analysis for treatment options of T1a glottic cancer. Head & Neck, 34, 23-33.

Arshad, H., Jayaprakash, V., Gupta, V., Cohan, D. M., Ambujakshan, D., Rigual, N. R. et al. (2014). Survival Differences between Organ Preservation Surgery and Definitive Radiotherapy in Early Supraglottic Squamous Cell Carcinoma. Otolaryngology - Head & Neck Surgery,150, 237-244.

Comert E. Comparison of early oncological results of diode laser surgery with radiotherapy for early glottic carcinoma. Otolaryngology - Head & Neck Surgery 2014; 150(5):818-823.

Dinapoli, N., Parrilla, C., Galli, J., Autorino, R., Micciche, F., Bussu, F. et al. (2010). Multidisciplinary approach in the treatment of T1 glottic cancer. The role of patient preference in a homogenous patient population. Strahlentherapie und Onkologie, 186, 607-613.

Greulich, M. T., Parker, N. P., Lee, P., Merati, A. L., & Misono, S. (2015). Voice outcomes following radiation versus laser microsurgery for T1 glottic carcinoma: systematic review and meta-analysis. Otolaryngol.Head Neck Surg., 152, 811-819.

O'Hara, J., Markey, A., & Homer, J. J. (2013). Transoral laser surgery versus radiotherapy for tumour stage 1a or 1b glottic squamous cell carcinoma: systematic review of local control outcomes. Journal of Laryngology & Otology, 127, 732-738.

Osborn, H. A., Hu, A., Venkatesan, V., Nichols, A., Franklin, J. H., Yoo, J. H. et al. (2011). Comparison of endoscopic laser resection versus radiation therapy for the treatment of early glottic carcinoma. Journal of Otolaryngology: Head and Neck Surgery, 40, 200-204.

Mantsopoulos, K., Psychogios, G., Koch, M., Zenk, J., Waldfahrer, F., & Iro, H. (2012). Comparison of different surgical approaches in T2 glottic cancer. Head & Neck, 34, 73-77.

Maurizi, M., Almadori, G., Plaudetti, G., De, C. E., & Galli, J. (2005). Laser carbon dioxide cordectomy versus open surgery in the treatment of glottic carcinoma: our results. Otolaryngology - Head & Neck Surgery, 132, 857-861.

Karatzanis, A. D., Psychogios, G., Zenk, J., Waldfahrer, F., Hornung, J., Velegrakis, G. A. et al. (2010). Evaluation of available surgical management options for early supraglottic cancer. Head & Neck, 32, 1048-1055.

Milovanovic J, Jotic A, Djukic V, Pavlovic B, Trivic A, Krejovic-Trivic S et al. Oncological and Functional Outcome after Surgical Treatment of Early Glottic Carcinoma without Anterior Commissure Involvement. Biomed Research International 2014.

Puxeddu, R., Argiolas, F., Bielamowicz, S., Satta, M., Ledda, G. P., & Puxeddu, P. (2000). Surgical therapy of T1 and selected cases of T2 glottic carcinoma: cordectomy, horizontal glottectomy and CO2 laser endoscopic resection. Tumori, 86, 277-282.

Remmelts, A. J., Hoebers, F. J., Klop, W. M., Balm, A. J., Hamming-Vrieze, O., & van den Brekel, M. W. (2013). Evaluation of lasersurgery and radiotherapy as treatment modalities in early stage laryngeal

carcinoma: tumour outcome and quality of voice. European Archives of Oto-Rhino-Laryngology, 270, 2079-2087.

Robertson SM, Yeo JC, Sabey, Robertson SM. Effects of tumor staging and treatment modality on functional outcome and quality of life after treatment for laryngeal cancer. Head & Neck 2013; 35(12):1759-1763.

Spielmann, P. M., Majumdar, S., & Morton, R. P. (2010). Quality of life and functional outcomes in the management of early glottic carcinoma: a systematic review of studies comparing radiotherapy and transoral laser microsurgery. [Review]. Clinical Otolaryngology, 35, 373-382.

Thomas, L., Drinnan, M., Natesh, B., Mehanna, H., Jones, T., & Paleri, V. (2012). Open conservation partial laryngectomy for laryngeal cancer: a systematic review of English language literature (DARE structured abstract). Cancer Treatment Reviews., 38, 203-211.

van Gogh, C. D., Verdonck-de Leeuw, I. M., Wedler-Peeters, J., Langendijk, J. A., & Mahieu, H. F. (2012). Prospective evaluation of voice outcome during the first two years in male patients treated by radiotherapy or laser surgery for T1a glottic carcinoma. European Archives of Oto-Rhino-Laryngology, 269, 1647-1652.

van Loon Y., Sjogren, E. V., Langeveld, T. P., Baatenburg de Jong, R. J., Schoones, J. W., & van Rossum, M. A. (2012). Functional outcomes after radiotherapy or laser surgery in early glottic carcinoma: a systematic review. Head & Neck, 34, 1179-1189.

Excluded studies

Aydil, U., Akmansu, M., Kizil, Y., Yazici, O., Ustun, S., Karaloglu, F. et al. (2013). An individualised treatment algorithm for tumour stage 1 glottic squamous cell carcinoma. Journal of Laryngology & Otology, 127, 1127-1133.

Exclusion reason: results for different types of surgery (transoral and open) combined in analysis

Becker-Schiebe M, Christiansen H. Moderate hypofractionated Radiation Therapy of Glottis T1/T2-Larynx Cancer of the non inferior Normo Fractionation. Strahlenther Onkol 2014; 190(7):694-695.

Exclusion reason: commentary on Moon (2014) trial

Cabanillas, R., Rodrigo, J. P., Llorente, J. L., Suarez, V., Ortega, P., & Suarez, C. (2004). Functional outcomes of transoral laser surgery of supraglottic carcinoma compared with a transcervical approach (1). Head & Neck, 26, 653-659.

Exclusion reason: mostly T3 and does not report T1, T2 separately

Cohen, S. M., Garrett, C. G., Dupont, W. D., Ossoff, R. H., & Courey, M. S. (2006). Voice-related quality of life in T1 glottic cancer: Irradiation versus endoscopic excision. Annals of Otology, Rhinology and Laryngology, 115, 581-586.

Exclusion reason: relevant systematic review but superceeded by Spielmann et al (2010)

Goudakos, J. K., Markou, K., Nikolaou, A., Themelis, C., & Vital, V. (2009). Management of the clinically negative neck (N0) of supraglottic laryngeal carcinoma: a systematic review. European Journal of Surgical Oncology, 35, 223-229.

Exclusion reason: intervention not in PICO, also includes T3 patients

Higgins, K. M., Shah, M. D., Ogaick, M. J., & Enepekides, D. (2009). Treatment of early-stage glottic cancer: meta-analysis comparison of laser excision versus radiotherapy. [Review] [47 refs]. Journal of Otolaryngology: Head and Neck Surgery, 38, 603-612.

Exclusion reason: systematic review – evidence cited is included in the Abdurehim (2012) review

Jotic, A., Stankovic, P., Jesic, S., Milovanovic, J., Stojanovic, M., & Djukic, V. (2012). Voice quality after treatment of early glottic carcinoma. Journal of Voice, 26, 381-389.

Exclusion reason: does not report standard deviations – cannot include in meta-analysis

Wall, L. R., Ward, E. C., Cartmill, B., & Hill, A. J. (2013). Physiological Changes to the Swallowing Mechanism Following (Chemo)radiotherapy for Head and Neck Cancer: A Systematic Review. Dysphagia, 28, 481-493.

Exclusion reason: comparison(chemoRT vs. RT) not in PICO & contains only a single larynx study

Yoo, J., Lacchetti, C., Hammond, J. A., Gilbert, R. W., & Head and Neck Cancer Disease Site Group (2013). Role of endolaryngeal surgery (with or without laser) compared with radiotherapy in the management of early (T1) glottic cancer: a clinical practice guideline. Current Oncology, 20, e132-e135.

Exclusion reason: guideline – evidence cited is included in the Abdurehim (2012) review

Yoo J, Lacchetti C, Hammond. Role of endolaryngeal surgery (with or without laser) versus radiotherapy in the management of early (T1) glottic cancer: a systematic review. Head & Neck 2014; 36(12):1807-1819

Exclusion reason: systematic review – evidence cited is included in the Abdurehim (2012) review

Feng, Y., Wang, B., & Wen, S. (2011). Laser surgery versus radiotherapy for T1-T2N0 glottic cancer: a meta-analysis. [Review]. Orl; Journal of Oto-Rhino-Laryngology & its Related Specialties, 73, 336-342.

Exclusion reason: systematic review – evidence cited is included in the Abdurehim (2012) review

Ramakrishnan Y, Drinnan M, Kwong FNK, Grant DG, Mehanna H, Jones T et al. Oncologic outcomes of transoral laser microsurgery for radiorecurrent laryngeal carcinoma: A systematic review and meta-analysis of English-language literature. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck 2014; 36(2):280-285.

Exclusion reason: systematic review – recurrent disease

Trotti A, III, Trotti A. Randomized trial of hyperfractionation versus conventional fractionation in T2 squamous cell carcinoma of the vocal cord (RTOG 9512). Int J Radiat Oncol Biol Phys 2014; 89(5):958-963.

Compares RT fractionation – not RT vs. surgery

Moon SH. A prospective randomized trial comparing hypofractionation with conventional fractionation radiotherapy for T1-2 glottic squamous cell carcinomas: Results of a Korean Radiation Oncology Group (KROG-0201) study. Radiother Oncol 2014; 110(1):98-103.

Compares RT fractionation – not RT vs. surgery

Misono S, Marmor S, Yueh B, Virnig B. T1 Glottic Carcinoma: Do Comorbidities, Facility Characteristics, and Sociodemographics Explain Survival Differences across Treatment Types? Otolaryngology - Head & Neck Surgery 2015; 152(5):856-862.

Type of surgery is not reported(beyond local surgery)

Zackrisson, B., Mercke, C., Strander, H., Wennerberg, J., & Cavallin-Stahl, E. (2003). A systematic overview of radiation therapy effects in head and neck cancer. Acta Oncologica, 42, 443-461.

Exclusion reason: outdated systematic review – superceeded by the other reviews

Nakayama M, Okamoto M, Hayakawa K, Miyamoto S, Ishiyama H, Komori S et al. Clinical Outcomes of 849 Laryngeal Cancers Treated in the Past 40 Years: Are We Succeeding? Jpn J Clin Oncol 2014; 44(1):57-64.

Exclusion reason: mixed population

Additional references

Warner L, Chudasama J, Kelly C. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. [Review][Update of Cochrane Database Syst Rev. 2002;(2):CD002027; PMID: 12076435]. Cochrane Database of Systematic Reviews 2014; 12:CD002027.

Economic evidence - The most effective treatment for carcinoma of the larynx (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies).

Review question

What is the most effective treatment for newly diagnosed T1 or T2 carcinoma of the larynx?

Table 3.3. PICO table for the most effective management strategy for the clinically and radiologically N0 neck in patients with early squamous cell carcinoma of the oral cavity

Population	Intervention	Comparison	Outcomes

Adults diagnosed with new (T1, T2, N0) squamous cell carcinoma of the larynx
 	
Subgroups:
 	
• glottis
• supraglottis
• T1a
• T1b
• T2a
• T2b
• Performance status
	• Radiotherapy
	• Larynx preserving surgery:
	  • Trans oral
	  • Open
		Each other	• Overall survival
			• Disease free survival
			• Tumour recurrence
			• Progression free survival
			• Treatment related mortality
			• Treatment related morbidity
			• Organ preservation rates
			• Length of stay
			• Health related quality of life
			  • Swallow function
			  • Voice quality

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO

- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

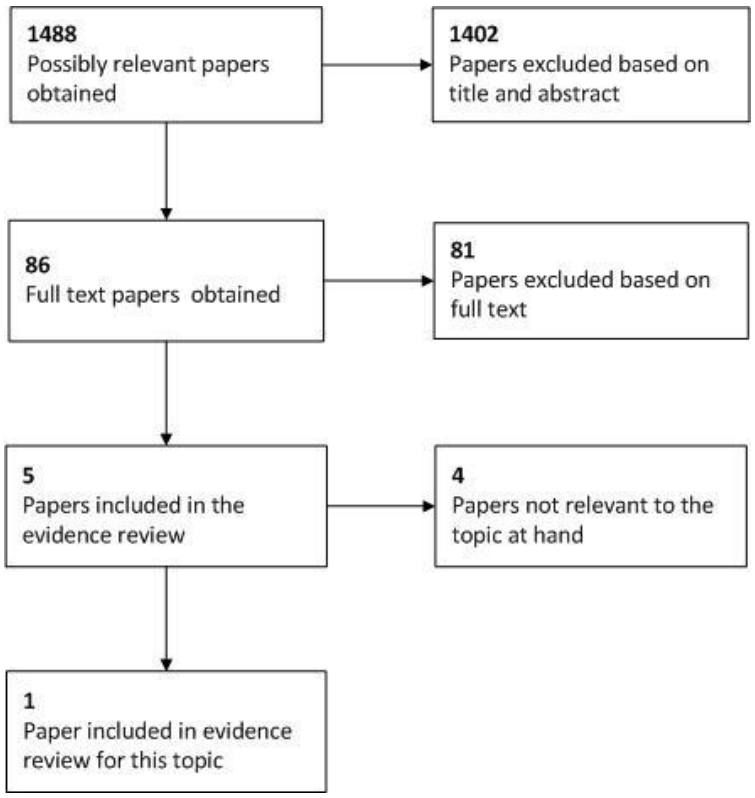
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below shows the search results and sifting process.

Figure 3.14. Summary of evidence search and sifting process for this topic



It can be seen that, in total, 1488 possibly relevant papers were identified. Of these, 1402 papers were excluded at the initial sifting stage based on the title and abstract while 86 full papers were obtained for appraisal. A further 81 papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, five papers were included in the systematic review of the economic evidence for this guideline.

One of these five papers related to the topic at hand and was thus included in the review of published economic evidence for this topic; Higgins 2011. The study included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

Quality and applicability of the included study

Higgins 2011 was deemed to be only partially applicable to the decision problem that we are evaluating because a healthcare system other than the UK was considered (Canadian study) and the discount rate did not match the NICE reference case.

Potentially serious limitations were identified with the analysis, including the use of non-comparative (single arm) studies to inform the key effectiveness data. In addition, the modelled time horizon of three years (while justified by the author) may be too short to fully capture all relevant downstream consequences.

Table 3.4. Methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		
Potentially serious limitations		HIggins 2011
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Higgins 2011 are summarised in the modified GRADE table below.

Table 3.5: Summary table showing the included evidence on the most effective treatment for newly diagnosed T1 or T2 carcinoma of the larynx.

Study	Population	Comparators:	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Higgins 2011	Patients with early stage glottis cancer (T1aN0M0).	Transoral CO_2 endolaryngeal laser excision	$2,475.65	1.663 QALYs				**Deterministic sensitivity analysis** One- and two-way sensitivity analyses were used to represent best and worst case scenarios. CO_2 laser was found to be dominant in all scenarios. Threshold analysis revealed that CO_2 laser was no longer dominant and equivalence was reached when initial laser treatment costs were increased to $4,500. Equivalence could also be reached with an increased initial laser treatment costs of $3,000 combined with a reduction in initial control probabilities to 50% or with an initial radiotherapy cost of $1,500 and an initial control probability of 0.99. Probabilistic sensitivity analysis (PSA) was not conducted.	***Partially applicable.*** The evaluation did not consider the UK health care system (Canadian health perspective). Discount rate did not match the NICE reference case of 3.5% per annum (5% applied at 3 years). ***Potentially serious limitations*** Key effectiveness inputs were based on non-comparative (single arm) studies. The modelled time horizon may also be too short to fully capture all relevant downstream consequences.
		External beam radiation	$4,965.85	1.506 QALYs	-$2,490.20	0.157 QALYs	CO_2 laser dominant		
	Comments:								

Evidence statements

The base case results of the cost-utility analysis showed that transoral laser excision was more effective and less costly than radiotherapy and was therefore considered dominant. One-way and two-way sensitivity analysis showed that transoral laser excision remained dominant under numerous best case and worst case scenarios.

However, the analysis was deemed to be only partially applicable to the decision problem in the UK setting as it was based on a Canadian health care perspective. Furthermore, some potentially serious limitations were noted including the absence of a probabilistic sensitivity analysis and the use of single-arm data to inform key inputs.

Overall, the analysis can be considered to show the potential cost-effectiveness of transoral laser resection and demonstrates some of the key trade-offs in the decision problem. However, concerns over the applicability of the results as well as some potential limitations, led to the conclusion that a de novo economic analysis was required to estimate cost-effectiveness in the UK setting.

Reference

1. Higgins, KM. What treatment for early-stage glottic carcinoma among adult patients: CO2 endolaryngeal laser excision versus standard fractionated external beam radiation is superior in terms of cost utility? *Laryngoscope* 2011; 121(1): 116-134.

Full evidence table

The full details of the study included in the evidence review are presented in the evidence table below.

Table 3.6: Full evidence table showing the included evidence on the most effective treatment for newly diagnosed T1 or T2 carcinoma of the larynx

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
Author: Higgins **Year:** 2011 **Country:** Canada **Funding:** **Comments**	**Type of analysis:** Cost-utility analysis (CUA) **Interventions** • Transoral CO_2 endolaryngeal laser excision • External beam radiation (XRT) **Model structure:** Decision tree analysis **Cycle length:** Not reported. **Time horizon:** 3 years **Perspective:** Third party payer (Ministry of Health) perspective. **Currency unit:** The costs were presented in Canadian and US dollars ($)	**Included population:** Patients with early stage glottis cancer (T1aN0M0). **Sample size:** Not reported. Per patients results are presented. **Age:** Not reported. **Gender:** Not reported. **Subgroup analysis:** Not reported.	**Source of effectiveness data:** The author reports that a detailed literature review was conducted to identify primary oncologic outcomes and secondary outcomes relating to voice and quality of life. Extensive details of this review were included in an appendix. The potential limitations of the published literature was discussed by the author, including selection bias, the use of pathologic rather than clinical staging, the inclusion of patients treated for recurrent disease and the use of non-standard therapy (such as chemotherapy). In the absence of better data, the author selected appropriate single-arm trial. A meta-analysis was then carried out (using a random effects model) to pool the evidence from multiple single-arm studies. Five year local control rates were used to determine 'first path probabilities' (i.e. initial effectiveness of treatment and whether recurrence occurs or not). The difference between reported disease-specific survival and overall survival was utilised for recurrence probability calculation. **Source of utility data:** The authors noted that there is a paucity of	**Base case** **Effectiveness (QALYs):** CO_2 laser XRT Incremental **Costs** CO_2 laser XRT Incremental **ICER (cost per QALY):** **Sensitivity analysis:** **One-way sensitivity analyses** Variations in the five-year local control probabilities were considered using best case scenarios for CO_2 laser and XRT: *Best CO_2 scenario* Incremental QALYs: Incremental costs ICER (cost per QALY): *Best XRT scenario* Incremental QALYs: Incremental costs	 1.663 1.506 0.157 $2,475.65 $4,965.85 -$2,490.20 CO_2 laser dominant 0.226 -$3,610.57 CO_2 laser dominant 0.001 -$2,238.86 CO_2 laser dominant

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
	Cost year: Price year was not reported. **Discounting:** Discount factor of 5% was applied at 3 years for both cost and utility consequences. Note that capital costs were discounted at 5% per annum (over a 7 year estimated lifespan).		quality of life data with respect to the management of early stage glottis cancer. The utility values utilised in the analysis were derived from a sample of 30 patients who were pilot-tested for a parallel radiation quality-of-life study. The patients had all received either XRT or CO_2 laser for the treatment of early stage glottic cancer. All patients had a complete response to treatment with no evidence of active disease. The Health Utilities Index Mark 3 was administered and patients were asked to assess their health on a visual analogue scale. This gave the baseline utility value for patients alive with voice box entirely intact (0.87). This health score was then adjusted to reflect further health states: 1. Alive with part of voice box intact (0.70) 2. Dead (0) 3. Alive with disease (0.307) 4. Alive without voice box (0.366) **Source of cost data:** Costs were sourced from the authors institution with both capital and operational costs included in the analysis. Capital costs were estimated assuming a useful lifespan of 7 years and 10 years for CO_2	ICER (cost per QALY): Increasing the discount rate to 15% was also reported to have no effect on the result as incremental costs remained negative. **Two-way sensitivity analyses** A further analysis considered the effect of incorporating two-way worst-case cost assumptions. The worst case for the CO_2 laser arm assumed a 2 day inpatient stay and a lower initial control rate of 0.82. The worst case for the XRT arm assumed a lower initial control rate of 0.76 and a 30% incidence of major salivary cutaneous fistula complications. Transoral CO_2 laser was again found to be dominant in all scenarios. Threshold analysis was also conducted to determine the point at which CO_2 laser dominance was lost and equivalence was reached. It was found that equivalence was reached when initial laser treatment costs were $4,500 or $3,000 when coupled with a large reduction in the initial control	

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
			laser and radiotherapy equipment respectively. Average usage for laryngeal cancer was then estimated to come up with an average capital cost per case. Operational costs were estimated using a micro-costing approach (with full details given in the appendix including the separate reporting of unit costs and quantities of resource use).	probabilities to 50%. Similarly, it was found that equivalence was also reached with an initial radiotherapy cost of $1,500 and an initial control probability of 0.99. **Probabilistic sensitivity analysis (PSA)** PSA was not conducted.	

Management of the N0 neck in T1–2 squamous cell carcinoma of the oral cavity

Clinical question: What is the most effective management strategy for the clinically and radiologically N0 neck in patients with early squamous cell carcinoma of the oral cavity?

Background

The management of the neck in early carcinoma of the oral cavity remains controversial. Elective neck dissection is commonly performed but reveals occult metastases in around 25%. Therefore the majority of neck dissections in this group are unnecessary. However identification and treatment of those with occult metastases confers a survival benefit.

Current practice in most centres is to offer a selective neck dissection but sentinel lymph node biopsy exists as an alternative. This has the potential advantage of minimising surgical morbidity but would require specific training and expertise.

Evidence statements

Elective neck dissection versus observation/ therapeutic neck dissection

Overall mortality

Low quality evidence from four randomised trials in patients with T1–2, N0 oral cancer (D'Cruz 2015, Kligerman 1994, Vandenbrouck 1980, Fakih 1989; 703 patients included in total) investigated whether elective neck dissection increases or decreases the risk of death within 3 years when compared to observation/therapeutic neck dissection. The most recent and largest trial (D'Cruz 2015, 496 patients) suggests that elective neck dissection improves overall survival (HR 0.64, 95% CI 0.45, 0.92). Across all eligible trials, the relative risk of death from any cause ranged from 0.4, 1.45 (where RR < 1 favours elective neck dissection) with a pooled estimate of RR 0.76 (95% CI 0.47, 1.23; with considerable heterogeneity).

Locoregional recurrence (recurrence in the primary site or the neck)

Moderate quality evidence from five randomised trials in patients with T1–2, N0 oral cancer (D'Cruz 2015, Kligerman 1994, Vandenbrouck 1980, Fakih 1989, Yuen 2009; 778 patients in total) suggests that elective neck dissection reduces the risk of locoregional recurrence when compared to observation. The relative risk of locoregional recurrence within 3 years of treatment ranged from 0.4 to 0.69 (where RR < 1 favours elective neck dissection) with a pooled estimate of RR 0.49 (95% CI 0.39, 0.60; with no heterogeneity). The follow up strategy to monitor the neck nodes of patients randomised to observation/therapeutic neck dissection differed in these trials. In Yuen (2009) patients received ultrasound of the neck every three months for three years; in Vandenbrouck (1980) patients received clinical follow up for 3 years; and in D'Cruz (2015) patients received physical examination and/or ultrasonography once every 4 weeks for 6 months, then every 6 weeks for the next 6 months, every 9 weeks for the next 12 months, and every 12 weeks thereafter. In the remaining trials, the follow up protocol was unclear.

Disease free survival

Moderate quality evidence from one randomised trial (D'Cruz 2015) in patients with T1–2, N0 oral cancer suggests that elective neck dissection improves disease-free survival. After a median of 39 months follow up, rates of disease free survival were 69.5% and 45.9% in patients treated with elective and therapeutic neck dissection, respectively (HR 0.45, 95% CI 0.34, 0.59).

Treatment related morbidity

Treatment-related morbidity was not directly reported in any study. In the groups of patients randomised to receive observation (with therapeutic neck dissection if nodes became clinically positive) between 31% and 47% actually received therapeutic neck dissection (D'Cruz 2015, Kligerman 1994, Vandenbrouck 1980, Fakih 1989). This suggests the overall risk of morbidity due to neck dissection in the observation group would be less than half of that in patients receiving elective neck dissection (because less than half of the observation group actually had neck dissection). It is unclear from this evidence, however, whether delaying neck dissection until nodes are clinically positive means a more morbid surgical procedure (for those patients that receive therapeutic neck dissection) than up-front elective neck dissection in patients with clinically negative nodes.

Radical versus selective neck dissection

Overall mortality

Very low quality evidence from two randomised trials (Bier 1994, Brentani 1998; 252 patients in total) suggests uncertainty about whether radical neck dissection increases or reduces the risk of death within 3 to 5 years of surgery when compared to selective neck dissection (HR 1.05; 95% CI 0.7, 1.83; where HR > 1 favours selective neck dissection). The quality of the evidence was downgraded partly for reasons of applicability: the Bier (1994) trial included an unspecified number of patients with clinically positive but mobile nodes and 38% of the patients included in Brantani (1998) had T3 or T4 disease.

Treatment related morbidity

Very low quality evidence from one randomised trial (Bretani 1998; 148 patients) indicates that treatment related morbidity is more likely following radical neck dissection than after selective neck dissection. Surgical complications (grade not reported) occurred in 41% of patients treated with radical neck dissection compared with 25% of those treated with selective neck dissection (RR 1.63; 95% CI 1.01, 2.65; where RR > 1 favours selective neck dissection).

Extent of neck dissection

Low quality evidence about the extent of neck dissection comes from a systematic review including seven observational studies of 582 patients with N0 oral cancer (Tandon 2011), which estimated the number needed to treat (NNT) for neck lymph node level. For level I the NNT was 7, that is for every seven patients receiving level I neck dissection we would expect to find one patient with histopathologically positive lymph nodes. The corresponding NNTs for levels II,III IV and V were 5, 13, 36 and 69 respectively. Tandon (2011) did not report any subgroup analysis by tumour stage, and therefore the NNTs for patients with T1 or T2 disease are not known.

Sentinel lymph node biopsy

Overall mortality, disease recurrence and treatment related morbidity

The literature searches identified no comparative evidence about the overall survival, disease recurrence or treatment related morbidity of patients treated with sentinel lymph node biopsy.

Sensitivity (false negative rate)

Low quality evidence from two systematic reviews (Govers 2013 and Yamauchi 2015, 17 observational studies (508 patients) and 12 observational studies (498 patients) respectively) estimated the diagnostic accuracy of sentinel lymph node biopsy. The pooled estimates of sensitivity were 92% (95% CI 86%, 95%) and 91% (95% CI 85%, 95%) for the studies by Govers and Yamauchi (for studies where all patients had elective neck dissection as a reference standard test), respectively. Sentinel lymph node biopsy was positive in 91–92% of the patients with a histologically positive neck node found on neck dissection, but was false negative in 8–9% of these patients.

Yamauchi (2015) also reported pooled sensitivity for studies that used different reference standards depending on the outcome of sentinel node biopsy (elective neck dissection for patients with positive nodes and clinical/radiological follow-up for those with negative sentinel nodes). In these studies, the sensitivity of sentinel node biopsy was 84% (95% CI 75%, 90%).

In the review by Govers (2013), the prevalence of positive lymph nodes in the included studies ranged from 15% to 60% with an overall average prevalence of 30%. Assuming 30% prevalence, the negative predictive value of SLNB would be 97% [95% CI 94%, 98%]. That is, 97% of patients with a negative SLNB would be true negative, but in 3% of patients SLNB would have missed a positive node that could have been otherwise detected on neck dissection. Similarly, in the review by Yamauchi (2015), the prevalence of positive lymph nodes in the included studies ranged from 9% to 60% with an overall average prevalence of 28%. Assuming 28% prevalence, the negative predictive value of SLNB would be 96% [95% CI 94%, 98%]. That is, 96% of patients with a negative SLNB would be true negative, but in 4% of patients SLNB would have missed a positive node that could have been otherwise detected on neck dissection.

A recent study not included in either systematic review (Flach 2014; N = 62) is consistent with the above results, reporting sensitivity of 80% and negative predictive value of 88% for sentinel lymph node biopsy.

Surgery plus RT versus surgery alone

Overall mortality, local recurrence and regional recurrence

Very low quality evidence about the addition of post operative radiotherapy to surgery for stage I–II oral cancer came from a systematic review of nine observational studies including 1678 patients (Brown 2012). There was uncertainty over the benefit of post operative radiotherapy in terms of overall survival or local recurrence (at the primary tumour site). However, post-operative radiotherapy consistently reduced the rate of recurrence within the neck when compared with surgery alone. Recurrence rates within the neck ranged from 2% to 14% for patients receiving post operative radiotherapy compared with 5% to 23% for those treated with surgery alone.

Chemotherapy plus locoregional therapy (surgery, radiotherapy, or surgery plus radiotherapy) versus locoregional therapy alone

Low quality evidence from a individual patient data meta analysis of 87 randomised trials (Blanchard 2011; 428 patients) suggests uncertainty over whether the addition of chemotherapy to locoregional therapy improves overall survival in patients with stage I–II squamous cell carcinoma of the oral cavity (HR = 0.90; 95% CI 0.66, 1.24; HR < 1 favours chemotherapy). There is similar uncertainty for the composite outcome of death or disease progression (HR = 0.86; 95% CI 0.64, 1.15; HR < 1 favours chemotherapy).

Study characteristics and quality

Table 3.7. Characteristics of included studies

STUDY ID	DESIGN	Site	T-stage	N-stage	N	INTERVENTION	COMPARISON	OUTCOMES MEASURED
Elective ND versus therapeutic ND								
Yuen 2009	RCT	Oral tongue (100%)	T1 (59%) T2 (41%)	N0	71	Elective ND (selective I,II,II)	Therapeutic ND	DSS, local/nodal/distant recurrence
Vandenbrouck 1980	RCT	Oral tongue (55%) Floor of mouth (45%)	T1 (20%) T2 (64%) T3 (13%)	N0	75	Elective ND (radical)	Therapeutic ND	OS, disease free survival
Kligerman 1994	RCT	Oral tongue (61%) Floor of mouth (39%)	T1 (46%) T2 (54%)	N0	67	Elective ND (supraomohyoid)	Therapeutic ND	Local/regional recurrence, OS, DSS
Fakih 1989	RCT	Oral tongue (100%)	T1 (34%) T2 (66%)	N0	70	Elective ND (radical)	Therapeutic ND	OS, disease free survival , local/nodal/distant recurrence
D'Cruz 2015	RCT	Oral tongue (85%) Buccal mucosa (14%) Floor of mouth (5%)	T1 (44%) T2 (56%)	N0	496	Elective ND (selective ipsilateral, levels I,II,II)	Therapeutic ND	OS, disease free survival
Radical ND versus selective ND								
Brentani 1998	RCT	Oral tongue (42%) Floor of mouth (33%) Retromolar (17%) Inferior gingiva (8%)	T1 (0%) T2 (61%) T3 (18%) T4 (20%)	N0	148	Radical ND	Selective ND (supraomohyoid)	Duration of hospitalization, sites of recurrence, treatment complications, OS, conversion to radical ND (in selective ND)
Bier 1994	RCT	Oral tongue (37%) Floor of mouth (21%) Retromolar (16%) Other(26%)	Not reported	N0 or movable N+	104	Radical ND	Selective ND	OS, disease free survival, local/nodal/distant recurrence

STUDY ID	DESIGN	Site	T-stage	N-stage	N	INTERVENTION	COMPARISON	OUTCOMES MEASURED
Sentinel lymph node biopsy (SLNB)								
Govers	Meta-analysis of observational studies	Oral cavity	T1-T2	N0	508	SLNB	-	Sensitivity, False negative rate
Yamauchi 2015	Meta-analysis of observational studies	Head and neck squamous cell carcinoma (proportion of oral cavity tumours not specified)	T1-T2	N0	498	SLNB		Sensitivity, False negative rate
Chemotherapy plus locoregional therapy versus locoregional therapy alone								
MACH-NC 2011	Meta-analysis of RCTs	Oral cavity	T1-T2	N0	428	Chemotherapy plus locoregional therapy	locoregional therapy alone	Overall survival, progression or death
Surgery plus post-op RT versus RT alone								
Robertson	RCT	Oral tongue (40%) Floor of mouth (43%) Retromolar (11%) Other(6%)	T1 (0%) T2 (40%) T3 (26%) T4 (31%)	N0 (57%) N1 (37%) N2 (3%)	35	Wide local excision of tumour plus neck dissection and post op radiotherapy	Radiotherapy alone: 66Gy in 33 fractions over 6.5 weeks	Overall survival, local control
Surgery plus post-op RT versus surgery alone								
Brown 2012	Systematic review of observational studies	Oral cavity	T1-T2	N0	1776	Surgery plus post-op radiotherapy	Surgery alone	Local recurrence, regional recurrence, total recurrence, salvage, overall survival
Abbreviations: DSS, disease specific survival; ND, neck dissection; OS, overall survival; RCT, randomised controlled trial								

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GRADE evidence tables

Table 3.8. GRADE evidence profile: chemotherapy plus locoregional treatment vs. locoregional treatment alone for T1-2, N0 oral cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy plus locoregional treatment	Locoregional treatment alone	Relative (95% CI)	Absolute	
Overall mortality (follow-up median 5.6 years)											
87[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	The number of events and number of patients in each group was not reported; overall N = 428		HR 0.90 (0.66, 1.24)	-	⊕⊕OO LOW
Overall mortality or disease progression (follow-up median 5.6 years)											
87[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	The number of events and number of patients in each group was not reported; overall N = 428		HR 0.86 (0.64, 1.15)	-	⊕⊕OO LOW

[1] Evidence is from a subgroup of patients with stage I-II disease in an individual patient meta-analysis of 87 trials. Unclear exactly what chemotherapy and what locoregional treatments were for this subgroup.[2] Small sample size; [3] MACH-NC individual patient data meta-analysis by site and stage (Blanchard 2011).

Table 3.9. GRADE evidence profile: elective neck dissection versus therapeutic neck dissection alone for T1-2, N0 oral cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Elective neck dissection	Therapeutic neck dissection	Relative (95% CI)	Absolute	
Overall mortality											
4[4]	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	88/344 (28.9%)	126/359 (35.1%)	RR ranged from 0.4 to 1.45	-	⊕⊕OO LOW
Disease free survival											
3[4]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	13/61 (21.3%)	33/70 (47.1%)	RR ranged from 0.79 to 1.2	-	⊕⊕OO LOW
Locoregional recurrence											
5[5]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/382 (21.7%)	182/396 (46%)	RR 0.49 (0.39, 0.60)	234 fewer per 1000 (from 184 fewer to 280 fewer)	⊕⊕⊕O MODERATE
Neck dissection rate (in therapeutic arm)											
5[5]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	375/375 (100%)	167/397(42%)	Neck dissection rate ranged from 31% to 47% in the therapeutic ND groups		⊕⊕OO LOW

[1] Unclear blinding, random sequence generation and allocation concealment; [2] Significant statistical heterogeneity; [3] Small sample size; [4]D'Cruz 2015, Fakih 1989, Kligerman 1994 and Vandenbrouck 1980.; [5] D'Cruz 2015, Fakih 1989, Kligerman 1994, Vandenbrouck 1980 and Yuen 2009

Table 3.10. GRADE evidence profile: radical neck dissection selective neck dissection alone for T1-2, N0 oral cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radical neck dissection	Selective neck dissection	Relative (95% CI)	Absolute	
Overall mortality (follow-up 3 to 5 years)											
2[4]	randomised trials	no serious risk of bias	serious[1]	Serious[3]	serious[2]	none	27/124 (21.8%)	26/128 (20.3%)	HR 1.05 (0.7, 1.83)	9 more per 1000 (from 56 fewer to 137 more)	VERY LOW
Disease free survival (follow-up 3 years)											
1[5]	randomised trials			serious[3]	serious[2]	none	?/56 (?%)	?/48 (?%)	HR 0.57 (0.29, 1.11)	-	VERY LOW
Treatment related morbidity (follow-up post operative)											
1[5]	randomised trials	serious[1]	no serious inconsistency	Serious[3]	serious[2]	none	31/75 (41.3%)	18/72 (25%)	RR 1.63 (1.01, 2.65)	157 more per 1000 (from 2 more to 413 more)	VERY LOW
Treatment related mortality (follow-up post operative)											
1[5]	randomised trials	no serious risk of bias	serious[1]	Serious[3]	serious[1]	none	2/76 (2.6%)	1/72 (1.4%)	RR 1.89 (0.18, 20.45)	12 more per 1000 (from 11 fewer to 270 more)	VERY LOW

[1] Unclear random sequence generation, allocation concealment and blinding; [2] Small sample size; [3] Bier 1994 included patients with N+ if nodes were mobile; in Brentani 1998 38% had T3-T4 disease; [4] Bier 1994 and Brentani 1998; [5] Brentani 1998;

Table 3.11. GRADE evidence profile: surgery plus radiotherapy versus radiotherapy for T1-2, N0 oral cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery plus RT	RT alone	Relative (95% CI)	Absolute	
Overall mortality											
1[3]	randomised trials		no serious inconsistency	serious[1]	serious[2]	none	8/17 (47.1%)	15/18 (83.3%)	HR 0.24 (0.1, 0.59)	484 fewer per 1000 (from 181 fewer to 669 fewer)	
Local failure (follow-up 3 years)											
1[3]	randomised trials		no serious inconsistency	serious[1]	serious[3]	none	5/17 (29.4%)	18/18 (100%)	HR 0.30 (0.11, 0.83)	-	

[1]37% of patients had N1 disease, 57% had T3-T4 disease [2] Small sample size; [3] Robertson 1998;

Table 3.12. GRADE evidence profile: sentinel lymph node biopsy versus elective neck dissection for T1-2, N0 oral cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sentinel lymph node biopsy	Elective neck dissection	Relative (95% CI)	Absolute	
Neck dissection rate (assuming only SLNB-positivepatients proceed to neck dissection)											
17[2]	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	*Assumed 100%*	-	-	VERY LOW
False negative rate											
17[2]	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	*Assumed 0%*	-	-	VERY LOW

[1] Risk of bias due to patient selection was high in 33% of the studies mostly due to inappropriate exclusion of deeply invasive tumours. Risk of bias due to index and reference tests was unclear in 71% and 81% of studies respectively. In most cases it was not clear if the index and reference standard tests were interpreted independently. [2] Govers 2013 meta-analysis.

Table 3.13. GRADE evidence profile: surgery plus radiotherapy versus surgery alone for T1-2, N0 oral cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery plus PORT	Surgery alone	Relative (95% CI)	Absolute	
Overall mortality											
6	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[1,2]	none	67/193 (34.7%)	230/979 (23.5%)	Mortality rate ranged from 17% to 46% for surgery+PORT, 16% to 34% for surgery alone		⊕OOO VERY LOW
Local recurrence											
9	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38/296 (12.8%)	152/1382 (11%)	Local recurrence rate ranged from 8% to 17% for surgery+PORT, 7% to 20% for surgery alone		⊕OOO VERY LOW
Regional recurrence (within the neck)											
7	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/198 (5.6%)	125/863 (14.5%)	Regional (neck) recurrence rate ranged from 2% to 14% for surgery+PORT, 5% to 23% for surgery alone. Regional recurrence was consistently higher with surgery alone		⊕OOO VERY LOW

[1] The baseline characteristics are not reported - unclear how patients were allocated to treatment; [2] Low event rates; [3] Brown 2012 systematic review.

Evidence tables for all included studies

Study, country

Bessell, A., Glenny, A. M., Furness, S., Clarkson, J. E., Oliver, R., Conway, D. I. et al. (2011). Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database of Systematic Reviews

Study type, study period

Systematic review of randomised trials published 1950 - 2011

Number of patients

7 RCTs were identified, including 667 patients (570 analysed)

Patient characteristics

7 RCTs were identified, including 667 patients (570 analysed) with oral cancer and 2 with oropharyngeal cancer. Tumour extent was T1-T2 in three trials (Fakih 1989; Kligerman 1994; Yuen 2009), T2-T4 in 2 trials (BHNCSG, 1998; Robertson 1998) and T1-T3 in one trial (Vandenbrouck 1980). In five trials patients were N0 (BHNCSG 1998; Fakih 1989; Kligerman 1994; Vandenbrouck 1980 and Yuen 2009), one trial included patients with N0-N2 neck nodes (Robertson 1998) and one trial did not record tumour or node stage (Bier, 1994).

Intervention

Multiple interventions and comparisons, see below.

Comparison

- **Elective versus therapeutic (delayed) neck dissection (N = 283; Fakih 1989; Kligerman 1994; Vandenbrouck 1980; Yuen 2009)**
- **Radical versus selective neck dissection (N = 252; BHNCSG 1998; Bier 1994)**
- **Surgery plus RT versus RT alone (N = 35; Robertson, 1998)**

Length of follow-up

See below

Outcome measures and effect size

	Elective neck dissection*	**Therapeutic neck dissection†**	**Effect size**	**Risk of bias**
Death from any cause - follow up ranged from 1 to 3.5 years	38/101	47/106	Fakih 1989: RR 0.74 (0.39, 1.43) Kligerman 1994: RR 0.40 (0.19, 0.84) Vandenbrouck 1980:RR 1.45 (0.89, 2.38) Pooled: RR 0.84 [0.60 to 1.18] – I^2 77%	Unclear random sequence generation in 2/3 Unclear allocation concealment in 2/3 Unclear blinding in 3/3 Incomplete outcome data in 1/3
Disease free survival - follow up ranged from 1 to 3.5 years	37/67	42/73	Fakih 1989: RR 1.20 (0.82, 1.75) Kligerman 1994: HR 0.32 (0.12, 0.84) Vandenbrouck 1980: RR 0.79 (0.51, 1.23)	
Locoregional recurrence - follow up ranged from 1 to 3.5 years	31/137	59/141	Fakih 1989: RR 0.63 (0.37,1.07) Kligerman 1994: RR 0.55 (0.27, 1.14) Yuen 2009: RR 0.42 (0.18, 0.96) Vandenbrouck 1980: RR 0.69 (0.27, 1.80) Pooled: RR 0.57 [0.40 to 0.81] – I^2 0%	Unclear random sequence generation in 3/4 Unclear allocation concealment in 3/4 Unclear blinding in 4/4 Incomplete outcome data in 1/4
Neck dissection rate	132/132	59/144	N.D. Rate in therapeutic N.D. arm Fakih 1989: 45% Kligerman 1994: 39% Yuen 2009: 31% Vandenbrouck 1980: 47%) Pooled: 41%	Not a randomised comparison
Treatment complications	-	-	-	-

*Radical neck dissection (Fakih, 1989; Vandenbrouck, 1980), selective neck dissection (Kligerman 1994; Yuen, 2009)

†Follow up was by regular utrasonography (every 3 mths for 3 years,Yuen 2009), regular clinical examination (for 3 years, Vandenbrouck 1980) or method not reported (duration 3.5 years Kligerman 1994; duration 1 year Fakih 1989).

	Radical neck dissection	Selective neck dissection	Effect size	Risk of bias
Death from any cause – follow up ranged from 3 to 5 years	27/124	26/128	BHNCSG 1998: HR 1.14 (0.70, 1.86) Bier 1994: HR 0.87 (0.41, 1.83) Pooled: HR 1.05 [0.70 to 1.83] – I^2 0%	Unclear random sequence generation in 2/2 Unclear allocation concealment in 2/2 Unclear blinding in 2/2 Incomplete outcome data in 1/2
Disease free survival	?/48	?/56	Bier 1994: HR 0.57 (0.29, 1.11)	
Disease recurrence	16/72	13/71	BHNCSG 1998: RR 1.21 (0.63, 2.33)	
Treatment related mortality	2/76	1/72	BHNCSG 1998: RR 1.89 [0.18, 20.45]	Unclear random sequence generation Unclear allocation concealment Unclear blinding
Treatment complications	31/76	18/72	BHNCSG 1998: RR 1.63 [1.01, 2.65]	

	Surgery† plus RT	RT alone	Effect size	Risk of bias
Death from any cause (N = 35; Robertson 1998)	8/17	16/18	Robertson: HR = 0.24 [0.10 to 0.59]	37% of patients had N1 disease. Differences in treatment of the primary tumour as well as the neck. Trial ended early due to excess mortality in RT only group.
Locoregional failure	5/17	18/18	Robertson: HR = 0.30 [0.11 to 0.83]	
Subcutaneous fibrosis*	5/17	2/18	Robertson: RR = 2.65 [0.59, 11.86]	
Telangiectasia*	3/17	4/18	Robertson: RR = 0.79 [0.21, 3.04]	
Oedema*	4/17	7/18	Robertson: RR = 0.61 [0.22, 1.70]	
Xerostomia*	10/17	11/18	Robertson: RR = 0.96 [0.56, 1.66]	
Trismus*	3/17	0/18	Robertson: RR = 7.39 [0.41, 133.24]	
Dysphagia*	5/17	8/18	Robertson: RR = 0.66 [0.27, 1.63]	

*Moderate or severe †Surgery included neck dissection. RT only group had no surgery to primary tumour.

Source of funding

Universities of Manchester, Dundee and Glasgow; Cochrane Oral Health Group, NIH, Central Manchester and Manchester Children's Hospitals NHS Trust.

Risks of bias

Detailed risk of bias assessment available in Cochrane review

Additional comments

Study, country

Brown, J. S. S. (2012). Systematic review of the current evidence in the use of postoperative radiotherapy for oral squamous cell carcinoma. British Journal of Oral and Maxillofacial Surgery, 50, 481-489.

Study type, study period

Systematic review of comparative studies 1998 - 2010

Number of patients

7 comparative studies analysed which included 1186 patients

Patient characteristics

Studies included patients with early stage oral squamous cell carcinoma, T1-T2 and stage 1-2 disease.

Intervention

Surgery plus post operative radiotherapy (PORT; N = 250)

Comparison

Surgery only (N = 936)

Length of follow-up

Not reported

Outcome measures and effect size

	Surgery alone	Surgery plus PORT	Effect size	Risk of bias
Local recurrence	Range 2% to 16%	Range 7% to 15%	HR 1.18	
Regional recurrence	Range 5% to 23%	Range 6% to 14%	HR 0.43	
Salvage	Range 47% to 58%	11%	N.R.	
Overall survival	Range 71% to 84%	54% to 83%	N.R.	

Source of funding

Not reported

Risks of bias

High risk of bias – non randomised study – no comparison of baseline characteristics. Authors note that higher risk patients more likely to receive PORT. Length of follow-up unclear. Methods of meta-analysis unclear.

Additional comments

Study, country
Tandon S.Munir (2011). A systematic review and Number Needed to Treat analysis to guide the management of the neck in patients with squamous cell carcinoma of the head and neck. Auris Nasus Larynx, 38, 702-709
Study type, study period
Systematic review of studies published before 2008
Number of patients
7 studies including 582 patients
Patient characteristics
Patients with oral cancer, cN0, who had at least an ipsilateral neck dissection
Intervention
Lymph node dissection level I
Comparison
Lymph node dissection level II, III, IV and V
Length of follow-up
Not reported
Outcome measures and effect size
Number needed to treat to for each case with positive lymph nodes.

Lymph node level	Oral cavity NNT
I	7
II	5
III	13
IV	36
V	69

Source of funding
No financial or material support was received by the authors.
Risks of bias
Moderate quality. Baseline characteristics not reported (beyond cN0, oral cavity cancer). Clinical/radiological staging, surgical and pathological techniques may have differed between studies.
Additional comments

Study, country
D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R et al. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. N Engl J Med 2015. India, single centre.
Study type, study period
Randomised controlled trial. January 2004 to June 2014.
Number of patients
596. This publication reports the findings in the first 500 patients who had completed at least 9 months of follow-up at the data cutoff in June 2014.
Patient characteristics

Inclusion criteria:

- aged 18 to 75 years
- histopathologically proven, invasive squamous-cell carcinoma of the oral cavity (tongue, floor of mouth, or buccal mucosa)
- tumour stage (Union for International Cancer Control) T1 (measuring ≤2 cm) or T2 (measuring >2 cm but <4 cm)
- tumour lateralized to one side of the midline
- no previous treatment
- amenable to undergoing oral excision
- no previous history of head and neck cancer.

Exclusion criteria:

- previous surgery in the head and neck region
- upper alveolar or palatal lesions
- large heterogeneous leukoplakias
- diffuse oral submucous fibrosis

All patients were evaluated for primary tumor and lymph-node involvement using physical examination and ultrasonography of the neck, and subsequently underwent oral excision of the primary tumor with adequate margins (i.e., ≥5 mm). Regardless of the intervention (see below) patients were followed once every 4 weeks for first 6 months. After that, they were followed every 6 weeks for the next 6 months,

every 8 weeks for next 12 months, and every 12 weeks thereafter.

Intervention

Elective node dissection (n = 245). Patients underwent an ipsilateral selective neck dissection with clearance of the submandibular (level I), upper jugular (level II), and midjugular (level III) nodes. In patients with metastatic nodal disease that was discovered during surgery (operative findings or frozen section), a modified neck dissection was performed with nodal clearance extended to include the lower jugular (level IV) and posterior triangle (level V) nodes.

Comparison

Therapeutic node dissection (n = 255). Patients were monitored using physical examination, with (n = 133) or without (n = 120) ultrasonography. Modified neck dissection (levels I to V) was performed only at the time of nodal relapse.

Length of follow-up

Median 39 months.

Outcome measures and effect size

	Elective surgery group (n = 245)	**Therapeutic surgery group (n = 255)**	**Unadjusted hazard ratio (95% CI)**	**Adjusted hazard ratio (95% CI)***
3-year overall survival, % (95% CI)	80.0 (74.1, 85.8)	67.5 (61.0, 73.9)	0.64 (0.45, 0.92)	0.63 (0.44, 0.90)
Total deaths	50 (20.6%)	79 (31.2%)		
3-year disease-free survival, % (95% CI)	69.5 (63.1, 76.0)	45.9 (39.4, 52.3)	0.45 (0.34, 0.59)	0.44 (0.33, 0.57)
Local or regional recurrences	52 (21.2%)	123 (48.2%)		
*After adjustment for covariates.				

Source of funding

Institutional research grant from the Tata Memorial Centre, India.

Risks of bias

No major concerns.

Additional comments

Study, country

Ebrahimi, A et al. Minimum nodal yield in oral squamous cell carcinoma: Defining the standard of care in a multicenter international pooled validation study. Ann.Surg.Oncol. 21 (9):3049-3055, 2014.
International study (Australia, Brazil, Israel, Taiwan, Germany, USA)

Study type, study period

Multi-centre observational study (9 cancer centres).
1970-2011

Number of patients

1567

Patient characteristics

cN0 oral squamous cell carcinoma, median age 55 years (range 22 to 93.2 years). 27.1% had pathological lymph node involvement, 7.7% had extracapsular spread.

Exclusion criteria

654 patients excluded for the following reasons: neoadjuvant therapy, perioperative mortality, age <20 years, missing data

Intervention

Neck dissection with nodal yield ≥ 18 (N = 1222; usually selective neck dissection, usually included levels I-III±IV)

Comparison

Neck dissection with nodal yield < 18 (N = 345; usually selective neck dissection, usually included levels I-III±IV)

Length of follow-up

Median follow-up 67 months.

Outcome measures and effect size

	Nodal yield < 18	Nodal yield ≥ 18	Hazard ratio (95% CI)*	Notes
Overall survival	?/345	?/1222	HR 1.25 (0.98, 1.60), P = 0.069	560 deaths in total
Overall survival (those treated ≥ 2000)	?	?	HR 1.48 (1.05, 2.08), P = 0.024	N = 1112
Overall survival (SND patients only)	?	?	HR 1.69 (1.22, 2.34), P = 0.002	N = 1484
Disease specific survival (DSS)	?/345	?/1222	HR 1.54 (1.10, 2.17), P = 0.012	269 SCC deaths
DSS (those treated ≥ 2000)	?	?	HR 1.84 (1.16, 2.93), P = 0.010	N = 1112
DSS (SND patients only)	?	?	HR 1.88 (1.21, 2.91), P = 0.005	N = 1484
Locoregional failure (LRF)	?/345	?/1222	HR 1.24 (0.91, 1.68), P = 0.179	309 lRFs in total
LRF (those treated ≥ 2000)	?	?	HR 1.29 (0.86, 1.95), P = 0.215	N = 1112
LRF (SND patients only)	?	?	HR 1.53 (1.04, 2.26), P = 0.032	N = 1484

*Multivariate analysis adjusting for age, sex, pT stage, pN stage, surgical margin status, ECS, time period of treatment and adjuvant therapy.

Source of funding

Not reported

Risks of bias

Unclear criteria used to select centres for inclusion. Study period dates back to 1970 (historical differences in clinical/pathological staging and treatment; although some analyses were limited to post 2000 and multivariate analysis included treatment period). No data reported on morbidity – perioperative mortality was an exclusion criterion which could bias the results in favour of more extensive surgery.

Additional comments

Study, country

Lea, J., Bachar, G., Sawka, A. M., Lakra, D. C., Gilbert, R. W., Irish, J. C. et al. (2010). Metastases to Level IIb in Squamous Cell Carcinoma of the Oral Cavity: A Systematic Review and Meta-Analysis. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck, 32, 184-190.
Included studies from Korea, Australia, Egypt, Italy and USA

Study type, study period

Systematic review. Included studies published up to March 2008.

Number of patients

N = 182 (from 5 studies)

Patient characteristics

Oral squamous cell carcinoma, clinical N0 treated with primary surgery including neck dissection, and where level IIb node status was reported. Mean age ranged from 50 to 58 years where reported.

Intervention

Neck dissection

Comparison

None

Length of follow-up

Mean follow-up ranged from 9.8 to 35 months where reported

Outcome measures and effect size

Pooled estimate for rate of level IIb metastases: 6.04% (95%CI 2.56, 9.53)

Source of funding

Not reported

Risks of bias

Low quality evidence: The systematic review did not address the quality of the individual studies. It is unclear how patients were selected for inclusion in the primary studies. The staging, surgical and pathological techniques used in the primary studies are not reported or analysed.

Additional comments

Study, country

Blanchard (2011), International

Study type, study period

Systematic review of RCTs, with individual patient meta-analysis. Trials

Number of patients

87 trials – included 428 patients with stage I or II oral cancer

Patient characteristics

Stage I-II oral cancer

Intervention

Chemotherapy plus locoregional treatment (RT, surgery or RT + surgery, see below for figures)

Comparison
Locoregional treatment (RT, surgery or RT + surgery) alone. For the oral cancer patients as a whole (stages I-IV): 46% had conventional RT, 4% hypofractionated RT, 27% surgery plus RT, 11% surgery alone and 12% other treatment.
Length of follow-up
Median follow-up 5.6 years across all trials
Outcome measures and effect size
Overall survival (stage I or II) HR 0.90 [0.66 to 1.24] Event (progression or death) free survival HR 0.86 [0.64 to 1.15]
Source of funding
Association pour la Recherche sur le Cancer (ARC No. 2015), Institut Gustave-Roussy, Ligue Nationale Contre le Cancer, Programme Hospitalier de Recherche Clinique (No. IDF 95009), Sanofi-Aventis.
Risks of bias
Moderate quality evidence: There was no separate analysis of risk of bias for the stage I-II patients. Issues with the interventions and comparison: 44% of oral cancer patients were in trials initiated before 1984. Unclear which trials included the stage I to II oral cancer patients and what chemotherapy or locoregional treatments were used for these patients. Only 428 patients with stage I-II, likely to be a source of imprecision in the effect estimate. Overall 13% of patients came from "confounded" trials where locoregional treatment (typically RT dose or duration) differed between trial arms. No adverse event outcomes reported.
Additional comments

Study, country
Govers (2013), International
Study type, study period
Systematic review of observational studies, published before November 2012
Number of patients
17 studies including 508 patients with oral cancer
Patient characteristics
Patients with clinical T1-2, N0 oral cancer
Intervention
Sentinel lymph node biopsy
Comparison
Neck dissection (in 16/17 studies, clinical follow up in 1 study)
Length of follow-up
Outcomes were measured using the surgical specimens (both SLNB and neck dissection). This review did not report survival or morbidity outcomes – follow-up length would only have been relevant in the one study that used it as a reference standard (Terada, 2010)
Outcome measures and effect size
Sensitivity 92% [95%CI 86%, 95%] Specificity assumed 100% Prevalence of positive lymph nodes ranged from 15% to 60%; overall average prevalence was 30%. Assuming 30% prevalence the negative predictive value of SLNB would be 97% [95%CI 94%, 98%]
Source of funding
Not reported
Risks of bias
Bias was assessed using QUADAS-2. Risk of bias due to patient selection was high in 33% of the studies mostly due to inappropriate exclusion of deeply invasive tumours. Risk of bias due to index and reference tests was unclear in 71% and 81% of studies respectively. In most cases it was not clear if the index and reference standard tests were interpreted independently. 29% of studies were at high risk of bias due to flow and timing issues. However there was a generally low risk of bias for all the applicability domains.
Additional comments

Study, country
Yamauchi (2015), International
Study type, study period
Systematic review of observational studies published from January 2002 to November 2012.
Number of patients
16 studies including 508 patients with oral cancer. The subgroup presented here (12 studies, 498 patients) is for studies where all patients received selective neck dissection simultaneously after SLNB, for pathological validation. In other studies, only patients who tested positive received neck dissection.
Patient characteristics
Patients with T1 or T2 head and neck squamous cell carcinoma. All studies included some oral cancer patients, but proportions of patients with disease at each tumour subsite were not reported.
Intervention
Sentinel lymph node biopsy
Comparison
Selective neck dissection
Length of follow-up
Outcomes were measured using the surgical specimens (both SLNB and neck dissection). Follow up is therefore not applicable.
Outcome measures and effect size
Sensitivity 91% (95% CI 85%, 95%) Specificity assumed 100% Prevalence of positive lymph nodes ranged from 9% to 60%; overall average prevalence was 28%. Assuming 28% prevalence the negative predictive value of SLNB would be 96% [95% CI 94%, 98%]
Source of funding
Not reported
Risks of bias
No formal assessment of study bias or applicability was reported by the review authors. The proportion of patients with oral cancer in the total study population is not clear.
Additional comments

Study, country
Flach (2014), Netherlands
Study type, study period
Prospective clinical trial (diagnostic study), 2007-2010
Number of patients
62 patients
Patient characteristics
Patients with cT1/T2 N0 oral squamous cell carcinoma. The cN0 neck was defined as negative after ultrasound guided FNAC diagnostics.
Intervention
Patients underwent sentinel lymph node biopsy with further treatment to the neck only if the sentinel node was positive (20/62, 32% of patients). The 20 SLN positive patients received: neck dissection alone (N = 11), neck dissection plus RT (N = 5) or RT alone (N = 4). Patients with negative SLN were followed up (unclear what the protocol was however).
Comparison
No comparison group
Length of follow-up
Median 4.3 years (range 0.4 to 6.4 years)
Outcome measures and effect size

Sensitivity	80% (95% CI 59, 92%)	5/42 SLN negative patients developed a cervical lymph node metastasis during follow up, after a median of 15 months (range (3.1 to 51.2 months)
Negative predictive value	88% (95% CI 74, 96%)	
Disease free survival	72.0%	
Overall survival	88.4%	
Disease specific survival	93.3%	

Source of funding
Netherlands organisation for Health Research and Development
Risks of bias
Reference standard test varied based on the SLN status. The details of follow up for SLN negative patients are not reported.
Additional comments

Evidence search details and references

Review question in PICO format

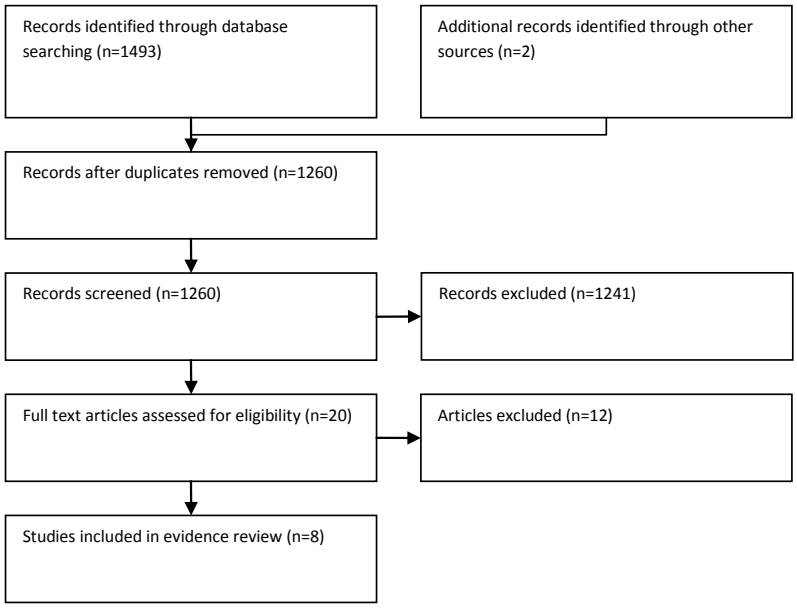
Population	**Intervention**	**Comparison**	**Outcomes**
Adults diagnosed with early (stage T1-2,N0) squamous cell carcinoma of the oral cavity undergoing curative surgery at the primary site Subgroups: • Tumour depth • Tumour sites	• Radiotherapy • Chemotherapy (induction/neo-adjuvant and concomitant) • Elective neck dissection (extent, eg levels 1-3, levels 1-4) • Other systemic therapies • Sentinel node biopsy • Active surveillance (radiology) • No treatment • Combinations of the above	Each other	• Overall survival • Disease free survival • Progression free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Organ preservation rates • Health related quality of life

Additional review protocol details (refer to Section 10 for full review protocol)

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour site of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10; At least 75% of the included patients meet the population defined in the PICO.
Search strategies	Limit search to 1994 onwards. According to the GC, this is the date of publication for the earliest evidence on this topic.

Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.

Figure 3.15. Study flow diagram



Included studies

Bessell, A., Glenny, A. M., Furness, S., Clarkson, J. E., Oliver, R., Conway, D. I. et al. (2011). Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database of Systematic Reviews.

Trials included in Bessell (2011):

Bier, J. (1994). Radical neck dissection versus conservative neck dissection for squamous cell carcinoma of the oral cavity. Recent Results in Cancer Research, Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer. 134, 1994.

Brentani, R. R., Kowalski, L. P., Soares, J. F., Torloni, H., Camargo, A. C., Pereira, R. N. et al. (1998). Results of a prospective trial on elective modified radical classical versus supraomohyoid neck dissection in the management of oral squamous carcinoma. American Journal of Surgery, 176, 422-427.

Fakih AR, Rao RS, Borges AM, Patel AR. (1989) Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. American Journal of Surgery, 158(4):309-13.

Kligerman, J., Lima, R. A., Soares, J. R., Prado, L., Dias, F. L., Freitas, E. Q. et al. (1994). Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. American Journal of Surgery, 168, 391-394.

Robertson, A. G., Soutar, D. S., Paul, J., Webster, M., Leonard, A. G., Moore, K. P. et al. (1998). Early closure of a randomized trial: surgery and postoperative radiotherapy versus radiotherapy in the management of intra-oral tumours. Clinical Oncology (Royal College of Radiologists), 10, 155-160.

Vandenbrouck C, Sancho-Garnier H, Chassagne D, Saravane D, Cachin Y, Micheau C. (1980) Elective versus therapeutic radical neck dissection in epidermoid carcinoma of the oral cavity: results of a randomized clinical trial. Cancer. 1980 Jul 15;46(2):386-90.

Yuen, A. P. W., Ho, C. M., Chow, T. L., Tang, L. C., Cheung, W. Y., Ng, R. W. M. et al. (2009). Prospective Randomized Study of Selective Neck Dissection Versus Observation for No Neck of Early Tongue Carcinoma. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck, 31, 765-772.

Blanchard, P. B. (2011). Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): A comprehensive analysis by tumour site. Radiotherapy and Oncology, 100, 33-40.

Brown, J. S. S. (2012). Systematic review of the current evidence in the use of postoperative radiotherapy for oral squamous cell carcinoma. British Journal of Oral and Maxillofacial Surgery, 50, 481-489.

Ebrahimi, A et al. Minimum nodal yield in oral squamous cell carcinoma: Defining the standard of care in a multicenter international pooled validation study. Ann.Surg.Oncol. 21 (9):3049-3055, 2014.

Govers, T. M., Hannink, G., Merkx, M. A. W., Takes, R. P., & Rovers, M. M. (2013). Sentinel node biopsy for squamous cell carcinoma of the oral cavity and oropharynx: A diagnostic meta-analysis. Oral Oncology, 49, 726-732.

Tandon S.Munir (2011). A systematic review and Number Needed to Treat analysis to guide the management of the neck in patients with squamous cell carcinoma of the head and neck. Auris Nasus Larynx, 38, 702-709.

Lea, J., Bachar, G., Sawka, A. M., Lakra, D. C., Gilbert, R. W., Irish, J. C. et al. (2010). Metastases to Level Iib in Squamous Cell Carcinoma of the Oral Cavity: A Systematic Review and Meta-Analysis. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck, 32, 184-190.

Flach, G. B., Bloemena, E., Klop, W. M., van Es, R. J., Schepman, K. P., Hoekstra, O. S. et al. (2014). Sentinel lymph node biopsy in clinically N0 T1-T2 staged oral cancer: the Dutch multicenter trial. Oral Oncol, 50, 1020-1024.

Yamauchi K, Kogashiwa Y, Nakamura T, Moro Y, Nagafuji H, Kohno N. Diagnostic evaluation of sentinel lymph node biopsy in early head and neck squamous cell carcinoma: A meta-analysis. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck 2015; 37(1):127-133.

D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R et al. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. N Engl J Med 2015. Epub ahead of print.

Excluded studies

Akhlaghi F, Akhlaghi F, Esmaeelinejad M, Shams A, Augend A. Evaluation of neo-adjuvant, concurrent and adjuvant chemotherapy in the treatment of head and neck squamous cell carcinoma: a meta-analysis. Journal of Dentistry / Tehran University of Medical Sciences 2014; 11(3):290-301.

Systematic review. Inclusion criteria and methodology unclear.

Amit M, Amit M, Yen TC, Liao CT, Chaturvedi P, Agarwal JP et al. The origin of regional failure in oral cavity squamous cell carcinoma with pathologically negative neck metastases. JAMA Otolaryngology--Head & Neck Surgery 2014; 140(12):1130-1137.

Comparison not relevant to PICO

Batstone MD. Health-related quality of life of patients treated with primary chemoradiotherapy for oral cavity squamous cell carcinoma: a comparison with surgery. The British journal of oral & maxillofacial surgery 2014; 52(2):111-117.

Intervention/comparison not relevant to PICO

Binenbaum, Y., Amit, M., Billan, S., Cohen, J. T., & Gil, Z. (2014). Minimal Clinically Important Differences in Quality of Life Scores of Oral Cavity and Oropharynx Cancer Patients. Annals of Surgical Oncology, 21, 2773-2781.

Not relevant – but may be useful for health economics model

Crombie A. Health-related quality of life of patients treated with primary chemoradiotherapy for oral cavity squamous cell carcinoma: a comparison with surgery. British Journal of Oral & Maxillofacial Surgery 2014; 52(2):111-117.

Intervention/comparison not relevant to PICO

Fasunla, A. J., Greene, B. H., Timmesfeld, N., Wiegand, S., Werner, J. A., & Sesterhenn, A. M. (2011). A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck (Provisional abstract). Oral Oncology, 47, 320-324.

Relevant systematic review but superceeded by Bessell et al (2011) systematic review

Feng Z. Selective versus comprehensive neck dissection in the treatment of patients with a pathologically node-positive neck with or without microscopic extracapsular spread in oral squamous cell carcinoma. Int J Oral Maxillofac Surg 2014; 43(10):1182-1188.

Study design not relevant

Furness, S., Glenny, A. M., Worthington, H. V., Pavitt, S., Oliver, R., Clarkson, J. E. et al. (2011). Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. Cochrane Database of Systematic Reviews.

Relevant systematic review but contains the same RCTS as the MACH-NC (2011) IPD meta-analysis – typcially trials were not restricted to oral cancer.

Glenny, A. M. F. (2010). Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. Cochrane database of systematic reviews (Online), 12, 2010.

Potentially relevant systematic review but patients in the trials tended to have advanced disease and combine patients with oral and oropharyngeal cancer. No subgroup analysis of stage I-II or N0 patients.

Huang S-F. The role of elective neck dissection in early stage buccal cancer. Laryngoscope 2015; 125(1):128-133.

Study design not relevant

Z. X. Liu, S. Y. Huang, and D. S. Zhang. High Dose Rate versus Low Dose Rate Brachytherapy for Oral Cancer - A Meta-Analysis of Clinical Trials. Plos One 8 (6), 2013.

Comparison (HDR vs. LDR brachytherapy) not in PICO

Maher NG, Maher NG, Hoffman GR. Elective neck dissection for primary oral cavity squamous cell carcinoma involving the tongue should include sublevel IIb. Journal of Oral & Maxillofacial Surgery 2014; 72(11):2333-2343.

Study design not relevant

Moore KA. Support needs and quality of life in oral cancer: a systematic review. [Review]. International Journal of Dental Hygiene 2014; 12(1):36-47.

Study design not relevant

Oliver, R. J., Clarkson, J. E., Conway, D. I., Glenny, A., Macluskey, M., Pavitt, S. et al. (2007). Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database of Systematic Reviews.

Systematic review superceeded by Bessell et al 2011

Paleri, V., Rees, G., Arullendran, P., Shoalb, T., & Krishman, S. (2005). Sentinel node biopsy in squamous cell cancer of the oral cavity and oral pharynx: A diagnostic meta-analysis. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck, 27, 739-747.

Relevant systematic review (but not restricted to oral cavity cancer) but superceeded by later systematic review

Paleri, V. S. (2008). Dissection of the submuscular recess (sublevel IIb) in squamous cell cancer of the upper aerodigestive tract: Prospective study and systematic review of the literature. Head and Neck, 30, 194-200

Potentially relevant for level IIb which is missing from Tandon (2011) analysis

Pezier, T., Nixon, I. J., Gurney, B., Schilling, C., Hussain, K., Lyons, A. J. et al. (2012). Sentinel lymph node biopsy for T1/T2 oral cavity squamous cell carcinoma--a prospective case series. Annals of Surgical Oncology, 19, 3528-3533.

Included in Govers (2013)

Ramamurthy R. A Prospective Study on Sentinel Lymph Node Biopsy in Early Oral Cancers Using Methylene Blue Dye Alone. Indian Journal of Surgical Oncology 2014; 5(3):178-183.

Study design not relevant

Sebbesen L, Sebbesen L, Bilde A, Therkildsen M, Mortensen J, Specht L et al. Three-year follow-up of sentinel node-negative patients with early oral cavity squamous cell carcinoma. Head & Neck 2014; 36(8):1109-1112.

Study design not relevant

Thompson, C. F. S. (2013). Diagnostic value of sentinel lymph node biopsy in head and neck cancer: A meta-analysis. European Archives of Oto-Rhino-Laryngology, 270, 2115-2122.

The Govers (2013) review is more up to date but the results are very similar to this study

Turner, L. M. (2013). Review of the complications associated with treatment of oropharyngeal cancer: a guide for the dental practitioner. Quintessence international (Berlin, Germany : 1985), 44, 267-279.

Oropharyngeal cancer

Wolff, K. D., Follmann, M., & Nast, A. (2012). The Diagnosis and Treatment of Oral Cavity Cancer. Deutsches Arzteblatt International, 109, 829-U38.

Clinical guideline

Economic evidence - The most effective treatment for carcinoma of the oral cavity (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies).

Review question

What is the most effective management strategy for the clinically and radiologically N0 neck in patients with early squamous cell carcinoma of the oral cavity?

Table 3.14. PICO table for the most effective management strategy for the clinically and radiologically N0 neck in patients with early squamous cell carcinoma of the oral cavity

Population	Intervention	Comparison	Outcomes
Adults diagnosed with early (stage T1-2,N0) squamous cell carcinoma of the oral cavity undergoing curative surgery at the primary site Subgroups: • Tumour depth • Tumour sites	• Radiotherapy • Chemotherapy (induction/neo-adjuvant and concomitant) • Elective neck dissection (extent, eg levels 1-3, levels 1-4) • Other systemic therapies • Sentinel node biopsy • Active surveillance (radiology) • No treatment • Combinations of the above	Each other	• Overall survival • Disease free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Health related quality of life

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO

- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

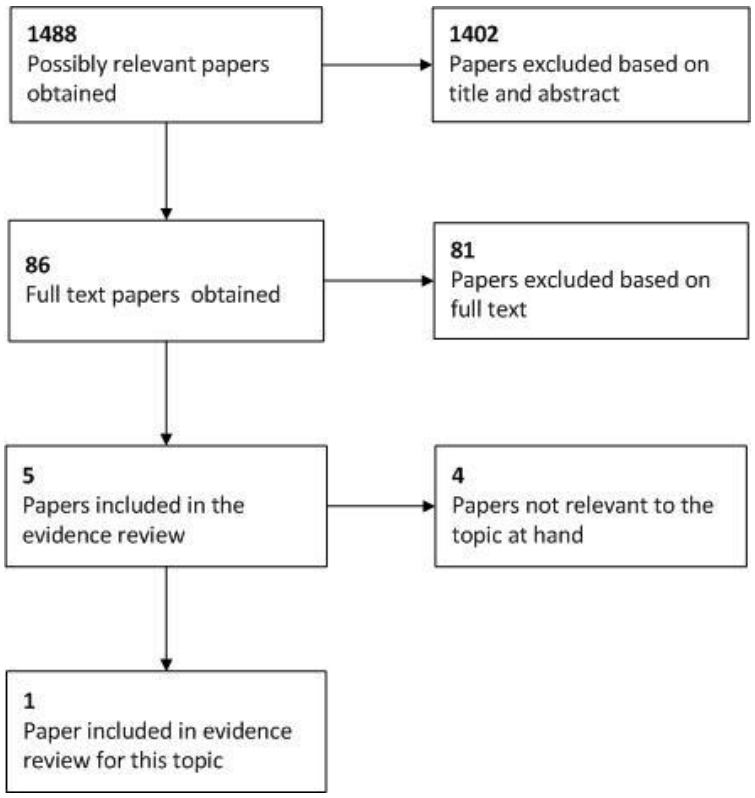
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below shows the search results and sifting process.

Figure 3.16. Summary of evidence search and sifting process for this topic



It can be seen that, in total, 1488 possibly relevant papers were identified. Of these, 1402 papers were excluded at the initial sifting stage based on the title and abstract while 86 full papers were obtained for appraisal. A further 81 papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, five papers were included in the systematic review of the economic evidence for this guideline.

One of these five papers related to the topic at hand and was thus included in the review of published economic evidence for this topic; Govers et al. 2013. The study included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

Quality and applicability of the included study

Govers et al. 2013 was deemed to be only partially applicable to the decision problem that we are evaluating because a healthcare system other than the UK was considered (Netherlands) and utility values were not directly reported by patients (as recommended by NICE). In addition, future costs and benefits were not discounted at the NICE recommended rate of 3.5% (costs were discounted at 4% and benefits at 1.5% per annum) .

A potentially serious limitation was also identified as some of the key effectiveness data (regional failure and survival rates) were based on unpublished data from an empirical study of eight head and neck oncological centres. Full details of the study or the derivation of the variables was not provided making it difficult to fully appraise. However, it should be noted that the values were adjudged to have good face validity.

Table 3.15. Methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		
Potentially serious limitations		Govers et al. 2013
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Govers et al. 2013 are summarised in the table below.

Table 3.16. Summary table showing the included evidence on the most effective management strategy for the clinically and radiologically N0 neck in patients with early squamous cell carcinoma of the oral cavity.

Study	Population	Comparators:	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Govers et al. 2013	Patients with clinical T1-2N0 oral squamous cell carcinoma.	Elective neck dissection	€9,180	3.6108 QALYs	-			**Deterministic sensitivity analysis** Variations in diagnostic accuracy, costs and regional failure rate after ND had little effect on the results. However, the results were sensitive to variations in occult metastasis and utilities. **Probabilistic sensitivity analysis (PSA)** At a threshold of €80,000 per QALY, SLNB and END were cost-effective in 66%, and 33% of the simulations, respectively. Expected value of perfect information (EVPI) was also conducted. The estimated EVPI was €997 per patient and €486,000 for the population, respectively.	***Partially applicable.*** The evaluation does not consider the UK health care system (Netherlands). Future costs and benefits were not discounted at a rate of 3.5%. Utility values were not sourced directly from patients. ***Potentially serious limitations.*** Derivation of regional failure and survival rates is unclear as they are based on unpublished data from head and neck oncological centres.
		Watchful waiting (WW)	€8,003	3.4296 QALYs	€1,177	0.1812 QALYs	€6,493 per QALY		
		Gene expression profiling (GEP) then neck dissection or WW	€11,335	3.6068 QALYs	€61	0.0183 QALYs	€3,356 per QALY		
		Sentinel lymph node biopsy (SLNB) then neck dissection or WW	€9,241	3.6291 QALYs	€2,094	-0.0223 QALYs	Dominated		
		GEP and SLNB (for positive GEP) then neck dissection or WW	€11,515	3.6114 QALYs	€2,274	-0.0177 QALYs	Dominated		
	Comments: Full incremental results are reported to determine the optimal strategy overall.								

Evidence statements

The base case results of the cost-effectiveness analysis suggested that sentinel lymph node biopsy followed by neck dissection or watchful waiting was the most effective and cost-effective strategy.

In deterministic sensitivity analysis, the result was found to be particularly sensitive to the percentage of occult metastases. Sentinel lymph node biopsy was found to remain the most cost-effective strategy with occult metastases of 11%-53%. Elective neck dissection was found to be cost-effective with occult metastases >53% and watchful waiting was found to be cost-effective with occult metastases <11%. In the probabilistic sensitivity analysis (PSA), sentinel lymph node biopsy was found to be the preferred strategy when the threshold was higher than €7,500 per QALY. At a threshold of €80,000 per QALY (recommended by the Dutch Council for Public Health and Care), SLNB and END were cost-effective in 66% and 33% of the simulations, respectively.

However, the analysis was deemed to be only partially applicable to the decision problem in the UK setting as it was based on the health care perspective of the Netherlands. The study also deviated from the NICE reference case with respect to discount rates and the use of utility data that was not directly reported by patients.

These factors coupled with the high economic importance of the topic, led to the conclusion that the study was not sufficient to address the decision problem in the UK context.

Reference

1. Govers, T. M. T. "Management of the N0 neck in early stage oral squamous cell cancer: a modeling study of the cost-effectiveness." Oral Oncology 49.8 (2013): 771-77.

Full evidence table

The full details of the study included in the evidence review are presented in the evidence table below.

Table 3.17. Full evidence table showing the included evidence on the most effective management strategy for the clinically and radiologically N0 neck in patients with early squamous cell carcinoma of the oral cavity.

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
Author: Govers et al. **Year:** 2013 **Country:** Netherlands **Funding:** **Comments**	**Type of analysis:** Cost-utility analysis **Interventions** 1. Elective neck dissection 2. Watchful waiting (WW) 3. Gene expression profiling (GEP) then neck dissection or WW 4. Sentinel lymph node biopsy (SLNB) then neck dissection or WW 5. GEP and SLNB (for positive GEP) then neck dissection or WW **Model structure:** Decision tree and Markov decision analytic model. **Cycle length:** 1 year	**Included population:** Patients with clinical T1-2N0 oral squamous cell carcinoma. **Sample size:** Not specified. Per patient outcomes are presented. **Age:** Not specified **Gender:** Not specified. **Subgroup analysis:** Not conducted.	**Source of base-line data:** The percentage of patients with occult metastases was derived from an empirical study using data from eight Dutch head and neck oncological centres (96 patients). **Source of effectiveness data:** The diagnostic accuracy data used for transition probabilities in strategies with GEP were derived from a recent Dutch multicentre study. The accuracy data of SLN biopsies were derived from a meta-analysis of 17 studies which was performed alongside the study. Data on the probability of regional failure and survival data (with and without regional failure) for patients that underwent neck dissection were derived from the empirical study of eight centres described above. WW outcomes regarding regional failure probability and survival data were derived from one center, where WW was the standard for all $cT_{1-2}N_0$ patients. This was based on 69 patients. All cause mortality data were analyzed with Kaplan–Meier	**Base case** **Effectiveness (QALYs):** Watchful waiting Elective neck dissection Sentinel node GEP GEP and SLNB **Costs** Watchful waiting Elective neck dissection Sentinel node GEP GEP and SLNB **ICER (cost per QALY) – full incremental analysis:** Watchful waiting Elective neck dissection ***Sentinel node*** GEP GEP and SLNB **Sensitivity analysis:** **Deterministic sensitivity analysis** Full results of the deterministic sensitivity analysis are not presented but the authors did report a summary of	 3.4296 3.6108 3.6291 3.6068 3.6114 €8,003 €9,180 €9,241 €11,335 €11,515 - €6,493 ***€3,356*** Dominated Dominated

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
	Time horizon: 5 years **Perspective:** Dutch health care perspective **Currency unit:** Euros (€) **Cost year:** 2011 **Discounting:** Costs were discounted at 4% per year while effects were discounted at 1.5% per year.		methods. **Source of utility data:** Utility data from the decision model of Weiss et al. 1994 were utilised in the model. Weiss et al. used expert consultation to derive disutilities in relation to WW patients without regional failure (to whom a utility of 1 was assigned). The same disutility value was assumed for patients who underwent ND after SLN and those who only underwent ND. The disutility of patients with a WW strategy after the SLN procedure was assumed to be half of the disutility of ND. GEP was assumed to have no influence on quality of life. When regional failure occurred the disutility was assumed to be independent of previous strategy because of complete neck dissection after regional failure. **Source of cost data:** Unit costs of surgery were estimated using information from the department of Otorhinolaryngology and Head and Neck Surgery of the Radboud University Nijmegen Medical Centre (RUNMC). GEP costs	their findings. Variations in diagnostic accuracy, costs and regional failure rate after ND had little effect on the results. However, the results were sensitive to variations in occult metastasis and utilities. SLNB was found to be the most cost-effective strategy when the percentage of occult was between 11% and 53%. When the percentage was above 54%, END was the most cost-effective strategy and when the percentage was 11% or lower, WW was the most cost-effective. The outcome of the model also changed when ND and SLNB disutilities were changed: • WW was found to be cost-effective when the health state following ND without regional failure was lower than 0.80. • GEP followed by SLN was found to be cost-effective when the health state following ND without regional failure was between 0.80 and 0.87. • SLNB was found to be cost-effective when the health state following ND without regional failure was between 0.88 and 0.98.	

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
			were obtained from Agendia BV (Amsterdam, Netherlands). The volume of hospital days and medical specialist hours were collected from existing registries of the RUNMC and were multiplied by reference prices from the Dutch pharmaco-economic guideline. No differences were expected in the number of hospital days for each strategy (11.8) as this is mainly determined by surgery of the primary tumor. However, hospital days were varied in the deterministic sensitivity analysis. It was assumed that patients experiencing regional failure would undergo salvage therapy with the costs of a (modified) radical neck dissection. No differences in costs were expected for follow-up between strategies and as such these costs were not included in the analysis.	• END alone was found to be cost-effective when the health state following ND was higher than 0.98. Note in these situations, the health state without regional failure after SLN always had a utility of half that of no regional failure after ND. **Probabilistic sensitivity analysis (PSA)** The authors present a cost-effectiveness acceptability curve (CEAC) for all strategies. At a threshold of €80,000 per QALY, SLNB and END were cost-effective in 66%, and 33% of the simulations, respectively. Above a threshold of €7,500/QALY, SLNB procedure appears to be the most cost-effective strategy. At or below this threshold, WW had the highest probability of being cost-effective. **Expected value of perfect information analysis (EVPI)** The value-of-information analysis demonstrated an EVPI of €997 per patient. Over 5 years the discounted population EVPI was estimated to be €486,000 (based on an estimate of 350 patients	

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
				diagnosed with cT1/T2N0 OSCC per year in the Netherlands). The EVPPI of utility values was found to be the highest at €780 per patient.	

Squamous cell carcinoma of the oropharynx (T1–T2, N0)

Clinical question: what is the optimal management of T1-2, N0 squamous cell carcinoma of the oropharynx?

Background

The incidence of carcinoma of the oropharynx is increasing as a result of Human Papillomavirus (HPV) related disease. Single modality treatment with either surgery or radiotherapy to the primary site and neck are recognised treatment approaches. Both claim excellent cure rates but the short and long term morbidity of each approach differs. There have been rapid technological advances in both surgery and radiotherapy including trans-oral laser or robotic resections and Intensity Modulated Radiation Therapy (IMRT). The addition of chemotherapy or biological therapy to radiotherapy for more advanced disease is established but its role in early stage disease is less well understood.

Evidence statements

Transoral robotic surgery (TORS) and intensity modulated radiotherapy (IMRT)

Very low quality evidence about outcome following TORS or RT for early oropharyngeal cancer (T1 or T2) comes from a systematic review of non-comparative, retrospective studies (De Almeida 2014, 20 studies, 2059 patients). The relative effectiveness of these treatments is very uncertain due to the lack of directly comparative studies.

Overall survival

Two year overall survival ranged from 82% to 94% following TORS (two studies) and from 84% to 96% following IMRT (four studies)

Disease free survival

Two year disease free survival was 79% following TORS (1 study) and ranged from 82% to 90% following IMRT (3 studies).

Adverse events

Adverse events reported following TORS included: post-operative bleeding 2.4% (6/247, 7 studies); pharyngocutaneous fistula 2.5% (10/395, 8 studies); gastrostomy placement at time of surgery 1.4% (2/139, 3 studies); gastrostomy placement at time of adjuvant therapy 30% (32/107, 3 studies); tracheostomy 12% (31/258); and hospital readmission 3% (1 patient; 1 study).

Adverse events reported following IMRT included: osteoradionecrosis of the mandible 2.6% (4/151, 3 studies); oesophageal stenosis 4.8% (4/84, 2 studies); and hospital readmission 17% (9/52, 1 study).

Locoregional treatment alone versus locoregional treatment with chemotherapy or radiotherapy

Overall survival

Low quality evidence comes from a subgroup analysis of 362 patients with stage I–II oropharyngeal cancer within an individual patient level meta-analysis (MACH-NC, Blanchard 2011). Based on this, there is uncertainty about whether adding chemotherapy to locoregional treatment (surgery or radiotherapy) improves overall survival (HR of death 0.75 [95% CI 0.56, 1.00]; HR <1 favours chemotherapy). However, mortality rates were not reported, so the absolute difference in overall survival is unclear.

Event free survival (event was death or disease progression)

Low quality evidence comes from a subgroup analysis of 362 patients with stage I–II oropharyngeal cancer within an individual patient level meta-analysis (MACH-NC, Blanchard 2011). Based on this, there is uncertainty about whether adding chemotherapy to locoregional treatment improves event free survival (HR of death or disease progression, 0.72 [95% CI 0.58, 1.02]; HR <1 favours chemotherapy). However event rates were not reported, so the absolute difference in event free survival is unclear.

Treatment related adverse events

Our searches identified no comparative studies reporting adverse events in the relevant population.

Quality of life

Very low quality evidence from one retrospective cohort study including 111 patients with early stage oropharyngeal cancer (T1–2, N0–2, M0; Ryzek et al 2014) suggests better quality of life with surgery alone than with surgery plus radiotherapy, or surgery plus chemoradiotherapy. Compared with those receiving adjuvant therapy, patients treated with surgery alone reported better QOL on scales for role function, social function, nausea, pain, financial problems, speech, social eating, mouth opening, sticky saliva, swallowing, and dry mouth.

Altered fractionation radiotherapy or IMRT versus conventional radiotherapy

Overall survival

Moderate quality evidence from a single randomised trial of 356 patients with T2–3 oropharyngeal cancer (Horiot et al, 1992), suggests uncertainty about whether hyperfractionated radiotherapy improves overall survival compared with conventionally fractionated RT. Five-year overall survival was 40% and 30% for hyperfractionated and conventionally fractionated RT respectively, but this difference was not statistically significant (p = 0.08).

Low quality evidence from a subgroup analysis of 1812 patients with stage I–II head and neck cancer within a larger individual patient level meta-analysis (MARCH, Baujat 2010; also including the Horiot 1992 data), suggests altered fractionation does not improve overall survival compared to conventional fractionation (HR for death 0.98; 95% CI 0.85, 1.14; where HR < 1 favours altered fractionation). The analysis, however, includes patients with other head and neck tumours in addition to those with oropharyngeal cancer.

Locoregional control

Moderate quality evidence from a single randomised trial of 356 patients with T2–3 oropharyngeal cancer (Horiot et al, 1992), suggests that 5 year locoregional control is better with hyperfractionated radiotherapy than with standard fractionation (59% versus 40% respectively; p = 0.02).

Quality of Life

Very low quality evidence from a retrospective cohort of 57 patients (Yao et al, 2007) suggests that patients treated with intensity modulated radiotherapy as part of their chemoradiotherapy treatment have significantly fewer problems eating or chewing compared with patients treated with conventional chemoradiotherapy.

Study characteristics and quality

Four primary studies and three systematic reviews were included. The design of each study is summarised in Table 3.18.

The meta-analyses addressed questions relevant to the review, reported their methods transparently and analysed data at the individual patient level. Only one meta-analysis (Bourhis 2006, Baujat 2010) reported the authors' assessment of study quality. Bourhis (2006) and Baujat (2010) meta-analyses covered a range of head and neck tumour sites, but included subgroup analyses of oropharyngeal cancer and stage I-II cancer.

One systematic review (De Almeida, 2014) reported outcomes in early T-stage oropharyngeal cancer but there was no meta-analysis and the individual studies included in the review were non-comparative, retrospective studies.

Table 3.18. Characteristics of included studies

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	N	INTERVENTION	COMPARISON	OUTCOMES MEASURED
Allal et al, 2003	Retrospective, non randomised study	Oropharyngeal cancer (all stages)	60	Radical radiotherapy±chemotherapy	Surgery with postoperative radiotherapy	Quality of Life
De Almeida et al (2014)	Systematic Review of non-comparative, retrospective studies	Early T stage oropharyngeal cancer	2059	Transoral Robotic Surgery	IMRT	Local Control Locoregional Control Disease specific Survival Disease Free Survival Overall Survival Adverse Events
Horiot et al (1992)	RCT	Patients with oropharyngeal cancer (excluding base of the tongue)	356	Hyperfractionated radiotherapy	Conventional radiotherapy	Locoregional control Disease free survival Overall survival Acute and late complications
MACH-NC	SRMA	Previously untreated patients with non-metastatic squamous cell carcinoma of the larynx, hypopharynx, oral cavity or oropharynx undergoing potentially curative locoregional treatment	16,192 (all tumour sites)	Locoregional treatment + chemotherapy	Locoregional treatment alone	Overall mortality; event free survival
MARCH	SRMA	Previously untreated patients with non-metastatic head and neck (oral cavity, oropharynx, hypopharynx or larynx) squamous cell carcinoma, treated with curative intent	7,073 (all tumour sites)	Hyperfractionated or accelerated radiotherapy	Standard radiotherapy	Cancer-related mortality
Yao et al (2007)	Retrospective Cohort study	Patients treated for oropharyngeal cancer	53	Intensity modulated radiotherapy	Chemoradiotherapy	Quality of Life
Ryzek et al (2014)	Cohort study	Patients treated for early stage oropharyngeal cancer	111	Surgery alone	Surgery plus RT or ChemRT	Quality of life
Abbreviations: RCT: randomised controlled trial; SRMA: systematic review and meta analysis; SCC: squamous cell carcinoma						

GRADE evidence tables

Table 3.19. GRADE evidence profile: locoregional therapy plus chemotherapy, chemoradiotherapy or radiotherapy versus locoregional therapy alone in patients with oropharyngeal cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Locoregional therapy plus chemotherapy/RT	Locoregional therapy	Relative (95% CI)	Absolute (95% CI)	
Overall Mortality (follow-up median 5.6 years)											
82[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	362 patients in total (number of patients in each arm not reported)		HR 0.75 (0.56, 1.00)	Not estimable	⊕⊕OO LOW
Event-free survival (death or disease progression) (follow-up median 5.6 years)											
82[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	362 patients in total (number of patients in each arm not reported)		HR 0.77 (0.58, 1.00)	Not estimable	⊕⊕OO LOW
Quality of life at last follow up (median EORTC-QLQ-30 Global Health status, better indicated by higher values)											
1[4]	observational study	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	51 (chemoRT); 24 (RT)	26	Not estimable	Surgery+chemoRT 66.67 (59.22, 70.91) Surgery+RT 66.67 (56.85, 72.95) Surgery alone 75.00 (62.79, 80.16)	⊕OOO VERY LOW

[1] Blanchard et al, 2011.Subgroup analysis of larger individual patient meta-analysis that included 82 comparisons in total; unclear how many of trials included patients relevant to this subgroup analysis.
[2] Absolute event rates not reported.
[3] Results for patients with stage I-II oropharyngeal cancer (unclear exactly what the T and N stage were)
[4] Ryzek et al, 2014

[5] Surgery alone group were lower risk (more T1 and N0) than the adjuvant therapy groups**Table 3.20. GRADE evidence profile: transoral robotic surgery (TORS) versus intensity-modulated radiotherapy (IMRT) for oropharyngeal carcinoma**

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TORS	IMRT	Absolute	
local control										
2[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1 study (patient numbers not reported)	1 study (patient numbers not reported)	IMRT: 96% TORS: 95%	⊕OOO VERY LOW
Locoregional control										
4[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3 studies (patient numbers not reported)	1 study (patient numbers not reported)	IMRT: 91%-96% TORS: 94%	⊕OOO VERY LOW
Disease specific survival										
5[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1 study (patient numbers not reported)	4 studies (patient numbers not reported)	IMRT: 97.7% TORS: 90%-98%	⊕OOO VERY LOW
Disease Free Survival										
4[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3 studies (patient numbers not reported)	1 study (patient numbers not reported)	IMRT: 82%-90% TORS: 79%	⊕OOO VERY LOW

Overall survival										
6[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4 studies (patient numbers not reported)	2 studies (patient numbers not reported)	IMRT: 84%-95.5% TORS: 82%-94%	⊕OOO VERY LOW

[1] **De Almeida et al, 2014. Systematic review of non-comparative, retrospective studies**
[2] **Analysis based on single-arm observational studies**

Table 3.21. GRADE evidence profile: altered fractionation radiotherapy versus conventional radiotherapy for patients with oropharyngeal cancer

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Altered fractionation radiotherapy**	**Conventional radiotherapy**	**Relative (95% CI)**	
Locoregional Control										
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	162	158	5 year locoregional control rates were significantly higher in the hyperfractionated radiotherapy arm (59% versus 40%; p = 0.02).	⊕⊕⊕O MODERATE
Overall Survival										
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	162	158	5 year OS was 40% with hyperfractionated RT and 30% with conventional RT (p = 0.08)	⊕⊕⊕O MODERATE

[1] **Horiot et al, 1992**
[2] **Population not exclusively T1-T2**

Table 3.22. GRADE evidence profile: chemoradiotherapy versus surgery plus postoperative radiotherapy in patients with oropharyngeal cancer

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy	Surgery plus postoperative radiotherapy	Relative (95% CI)	
Quality of life										
1[1]	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	40	20	No significant difference in global scores (p = 0.4)	⊕OOO VERY LOW

[1] **Allal et al, 2003**
[2] **Population not exclusively T1/T2**

Evidence tables for all included studies

Study

MACH-NC (Pignon, 2000; Pignon, 2009; Blanchard 2011)

Study type, study period

Meta-analysis of individual patient data from trials that completed patient accrual between 1965 and 2000.

Trial characteristics

Inclusion criteria:

- **Randomised trials of previously untreated patients with non-metastatic squamous cell carcinoma of the larynx, hypopharynx, oral cavity or oropharynx who had undergone a potentially curative locoregional treatment**
- **Studies of one of any three comparisons:**
  - **Chemotherapy-locoregional treatment vs. locoregional treatment plus chemotherapy**
  - **Timing of chemotherapy-neoadjuvant chemotherapy plus radiotherapy vs. concomitant or alternating radio-chemotherapy with the same drugs**
  - **Larynx preservation with neoadjuvant chemotherapy-radical surgery plus radiotherapy vs. neoadjuvant chemotherapy plus radiotherapy in responders or radical surgery and radiotherapy in non-responders**
- **Recruitment began after 1 January 1965 and ended before 31 December 2000**

Exclusion criteria:

- **Trials including only patients with squamous cell carcinoma of the nasopharynx**
- **Trial randomisation carried out using a method by which investigators may have been aware of the assigned treatment before deciding whether the patient was eligible**
- **Trial data unavailable (data required: age, sex, tumour site, TNM classification or stage, histology, performance status, treatment allocated, and date of randomisation)**

For the subgroup analysis conducted according to tumour site (Blanchard, 2011), studies were excluded if the relevant comparison(s) involved fewer than 10 patients. Patients with tumour locations other than the larynx, hypopharynx, oral cavity and oropharynx were also excluded from this analysis.

Number of trials/patients included

A total of 87 randomised trials/16, 485 patients were included in the overall meta-analysis. Because some trials had a 3-arm or 2-by-2 design, or used multiple different locoregional treatments or chemotherapies, the total number of comparisons in the meta-analysis was 105/17, 493.

For the subgroup analysis by tumour site, a total of 16,192 patients were included after application of exclusion criteria specific to this analysis.

The number of comparisons/patients for each tumour site was as follows:
Larynx: 61 comparisons/3,216 patients
Hypopharynx: 66 comparisons/2,767 patients
Oral cavity: 81 comparisons/4,331 patients
Oropharynx: 82 comparisons/5,878 patients

Intervention

Locoregional treatment plus chemotherapy.

Comparison

Locoregional treatment alone.

Patient and treatment characteristics (laryngeal tumours subgroup)

Type of locoregional treatment	n (%)
Conventional radiotherapy	1937 (60)
Hyperfractionated radiotherapy	106 (3)
Surgery + radiotherapy	729 (23)
Surgery alone	138 (4)
Other*	306 (10)

Timing of chemotherapy	n (%)
Adjuvant	623 (19)
Neoadjuvant	613 (19)
Concomitant	1980 (62)

Type of chemotherapy	n (%)
Platin + 5-fluorouracil	457 (14)
PolyCT with platin	293 (9)
PolyCT without platin	445 (14)
MonoCT with platin	770 (24)
MonoCT without platin	1251 (39)

Gender	n (%)
Male	2806 (87)
Female	410 (13)

Age category	n (%)
≤ 50 years	550 (17)
51–60 years	1188 (37)
≥ 60 years	1475 (46)
Unknown	3 (0)

Stage (UICC)	n (%)
Stage I or II	447 (14)
Stage III	1195 (37)
Stage IV	1568 (49)
Unknown	6 (0)

*trials using various locoregional treatments and for which information by patient was not available.

Patient and treatment characteristics (hypopharyngeal tumours subgroup)

Type of locoregional treatment	n (%)
Conventional radiotherapy	1114 (40)
Hyperfractionated radiotherapy	459 (17)
Surgery + radiotherapy	865 (31)
Surgery alone	116 (4)
Other*	213 (8)

Timing of chemotherapy	n (%)
Adjuvant	374 (14)
Neoadjuvant	949 (34)
Concomitant	1444 (52)

Type of chemotherapy	n (%)
Platin + 5-fluorouracil	857 (31)
PolyCT with platin	324 (12)
PolyCT without platin	538 (19)
MonoCT with platin	402 (15)
MonoCT without platin	646 (23)

Gender	n (%)
Male	2366 (86)
Female	302 (11)
Unknown	99 (4)

Age category	n (%)
≤ 50 years	610 (22)
51–60 years	990 (36)
≥ 60 years	1029 (37)
Unknown	138 (5)

Stage (UICC)	n (%)
Stage I or II	189 (7)
Stage III	834 (30)
Stage IV	1709 (62)
Unknown	35 (1)

*trials using various locoregional treatments and for which information by patient was not available.

Patient and treatment characteristics (oropharyngeal tumours subgroup)

Type of locoregional treatment	n (%)
Conventional radiotherapy	3271 (56)
Hyperfractionated radiotherapy	899 (15)
Surgery + radiotherapy	1197 (20)
Surgery alone	41 (1)
Other*	470 (8)

Timing of chemotherapy	n (%)
Adjuvant	486 (8)
Neoadjuvant	2003 (34)
Concomitant	3389 (58)

Type of chemotherapy	n (%)
Platin + 5-fluorouracil	2374 (40)
PolyCT with platin	362 (6)
PolyCT without platin	662 (11)
MonoCT with platin	799 (14)
MonoCT without platin	1681 (29)

Gender	n (%)
Male	4857 (83)
Female	906 (15)
Unknown	115 (2)

Age category	n (%)
≤ 50 years	1639 (28)
51–60 years	2155 (37)
≥ 60 years	1917 (33)
Unknown	167 (3)

Stage (UICC)	n (%)
Stage I or II	362 (6)
Stage III	1606 (27)
Stage IV	3679 (63)
Unknown	231 (4)

*trials using various locoregional treatments and for which information by patient was not available.

Outcome measures and effect size (oropharynx cancer subgroup)

	Overall mortality, number of deaths/total number of patients			Event free survival, number of events (death or disease progression)/total number of patients		
	LRT + CT	**LRT**	**HR of death [95% CI], lower values favour LRT + CT**	**LRT + CT**	**LRT**	**HR of progression or death (95% CI), lower values favour LRT + CT**
All oropharynx tumours	1981/2954	2097/2924	0.87 [0.80, 0.93]	2095/2954	2212/2924	0.86 [0.81, 0.92]
Timing of CT:						
Adjuvant	148/230	161/256	1.15 [0.92, 1.44]	153/230	169/256	1.09 [0.87, 13.6]
Neoadjuvant	715/1006	723/997	1.00 [0.90, 1.11]	755/1006	744/997	1.05 [0.94, 1.16]
Concomitant	1118/1718	1213/1671	0.78 [0.72, 0.85]	1187/1718	1299/1671	0.74 [0.69, 0.81]
Type of LRT						
Conventional radiotherapy	-	-	0.90 [0.83, 0.98]	-	-	0.86 [0.79, 0.93]
Hyperfractionated radiotherapy	-	-	0.73 [0.62, 0.86]	-	-	0.70 [0.60, 0.82]
Surgery + radiotherapy	-	-	0.88 [0.76, 1.03]	-	-	0.94 [0.81, 1.09]
Surgery alone	-	-	0.95 [0.34, 2.62]	-	-	1.08 [0.40, 2.87]
Other*	-	-	1.00 [0.81, 1.25]	-	-	1.09 [0.88, 1.35]
Type of CT:						
Platin + 5-fluorouracil	-	-	0.83 [0.75, 0.91]	-	-	0.83 [0.76, 0.91]
PolyCT	-	-	0.94 [0.81, 1.08]	-	-	0.97 [0.84, 1.12]
MonoCT with platin	-	-	0.70 [0.59, 0.84]	-	-	0.69 [0.58, 0.83]
MonoCT without platin	-	-	1.01 [0.89, 1.13]	-	-	0.93 [0.83, 1.04]
Stage (UICC)						
Stage I or II	-	-	0.75 [0.56, 1.00]	-	-	0.77 [0.58, 1.02]
Stage III	-	-	1.01 [0.88, 1.14]	-	-	0.99 [0.87, 1.12]
Stage IV	-	-	0.83 [0.77, 0.90]	-	-	0.83 [0.77, 0.89]

Cells marked (-) indicate data not reported.

Source of funding

Not reported.

Additional comments

1

Study

MARCH (Bourhis et al, 2006, Baujat, 2010).

Study type, study period

Meta-analysis of individual patient data for trials that recruited patients between 1969 and 1999.

Trial characteristics

Inclusion criteria:

- **Trials that compared conventional radiotherapy with accelerated or hyperfractionated radiotherapy, or both, in previously untreated patients with non-metastatic head and neck (oral cavity, oropharynx, hypopharynx or larynx) squamous cell carcinoma, treated with curative intent**
- **Trials where recruitment began after 1969 and ended after 1999**

Exclusion criteria:

- **Trials including mainly or exclusively nasopharyngeal carcinomas**
- **Trials that used doses per fraction higher than 2.5 Gy**

Number of trials/patients included

A total of 17 comparison/7073 patients were included.

The number of comparisons/patients for each tumour site was as follows:
Larynx: 2377 patients
Hypopharynx: 575 patients
Oral cavity: 886 patients
Oropharynx: 3079 patients

Intervention

Hyperfractionated or accelerated radiotherapy. This intervention was subdivided into three different modifications of fractionation:

- **Hyperfractionation (a higher total dose in the same overall time than in the comparison arm)**
- **Accelerated radiotherapy (the same total dose delivered as the comparison arm, but over a shorter time)**
- **Accelerated radiotherapy, but with reduced total dose**

Comparison

Conventional curative radiotherapy, defined by the authors as radiotherapy equivalent to 66 to 70 Gy, in 2 Gy fractions, for five days a week.

Patient and treatment characteristics (all tumour sites – patient characteristics by tumour site subgroups were not reported)

Gender	n (%)
Male	5782 (82)
Female	1262 (18)
Unknown	29 (0.4)

Type of altered fractionation RT	n (%)
Hyperfractionation	1350 (19)
Accelerated, same total dose	3818 (54)
Accelerated, reduced total dose	1905 (27)

Age category	n (%)
≤ 50 years	1311 (19)
51–60 years	2300 (33)
61–70 years	2346 (33)
≥ 71 years	1085 (15)
Unknown	31 (0.4)

Stage (UICC)	n (%)
Stage I	618 (9)
Stage II	1194 (17)
Stage III	2024 (29)
Stage IV	3197 (45)
Unknown	40 (0.6)

Outcome measures and effect size

	Cancer-related deaths, number of deaths/total number of patients		
	Altered frac RT	**Conventional RT**	**HR of death [95% CI], lower values favour LRT + CT**
Larynx tumours only	589/1234	557/1143	0.92 [0.82, 1.03]
Hypopharynx tumours only	232/294	223/281	0.93 [0.77,1.12]
Oral cavity tumours only	346/458	345/428	0.88 [0.76, 1.03]
Oropharynx tumours only	1086/1585	1060/1494	0.91 [0.84, 0.99]
All patients	2313/3650	2235/3423	0.92 [0.86, 0.97]
Stage			
I-II	397/950	355/862	0.99 [NS] (approx HR from forest plot)
III	639/1024	681/1000	0.82 [NS] (approx HR from forest plot)
IV	1265/1655	1189/1542	0.91 [NS] (approx HR from forest plot)

Source of funding

Not reported.

2

Additional comments
Other outcomes (all-cause mortality, locoregional control) were reported, but the results were not analysed separately for each tumour site.

1

Study, country
Horiot et al (1992) European multcentre study (28 centres in 8 countries)
Study type, study period
Randomised trial; activated February 1980 and recruitment finished April 1987
Number of patients
356 (325 patients included in the analysis)
Patient characteristics
Inclusion Aged <75 years Karnofsky performance of 60% and above T2/T3 oropharyngeal cancer Performance status and TN stages were evenly distributed between the two arms
Intervention
Hyperfractionated radiotherapy (80.5Gy in 70 fractions in 7 weeks using 2 fractions of 1.15 Gy per day)
Comparison
Conventional radiotherapy (70Gy in 35-40 fractions in 7-8 weeks)
Length of follow-up
No details
Outcome measures and effect size Locoregional Control Disease free survival Overall Survival Acute and late complications

Acute Toxicity	**Conventional Radiotherapy (158)**	**Hyperfractionated Radiotherapy (162)**
Objective Mucosal Reactions		
None	1	
Mild mucositis	13 (8%)	7 (4.5%)
Patchy mucositis	66 (42%)	47 (29%)
Diffuse mucostitis	78 (49%)	108 (66.5%)
Functional mucosal reactions		
None	1	2
Mild irritation	21 (13%)	13 (8%)
Moderate irritation	72 (45.5%)	73 (45%)
Liquid diet only	47 (30%)	48 (30%)
Oral alim. Impossible	17 (11%)	26 (16%)
Stopped <70Gy	7 (4.5%)	
Stopped <80 Gy		12 (7.5%)
Objective mucosal reactions were more severe in the hyperfractionated arm compared with the conventional radiotherapy arm (p = 0.01) **Functional mucosal reactions led to a treatment interruption in 6% of cases overall (4.5% with conventional treatment and 7.5% with hyperfractionated radiotherapy).**		

Late Toxicity	**Conventional Radiotherapy (118)**	**Hyperfractionated Radiotherapy (135)**
Grade II-III fibrosis	21	22
Grade II-III mucosal necrosis	7	12
Grade II-III oedema	15	21
No significant differences were observed between the two treatment groups for late complications with approximately 50% of patients free from grade II-III complications by 5 years post treatment.		

Locoregional Control

Nodal Control

Nodal control was achieved in 91% of patients (n = 296)
No significant difference between the treatment arms
At 5 years, 93% of N0 and 90% of N1 patients remained nodal disease free.

Locoregional control

5 year locoregional control rates were significantly higher in the hyperfractionated radiotherapy arm (59% versus 40%; p = 0.02).
In patients with an initial Karnofsky index of 90-100 locoregional control rates were significantly better in the hyperfractionated

radiotherapy arm (p<0.003).
Locoregional control was significantly better in the hyperfractionated radiotherapy arm for patients staged T3N0 (p = 0.03), T3 (p = 0.01) but not for T2 (p = 0.67).

Survival
No significant difference in overall survival was observed between the two treatment arms (p = 0.08)

Source of funding

Risks of bias

Selection bias: Unclear/unknown risk. Methods used for concealment of allocation not reported.
Performance bias: Low risk. Lack of blinding is not likely to affect any of the reported outcomes.
Attrition bias: Low risk.
Detection bias: Unclear/unknown risk. The definition and timing of measurement of some outcomes (and whether this was standardised) was not reported.

Additional comments

1

Study, country

De Almeida et al (2014)

Study type, study period

Systematic review of non-randomised studies (databases searched from their relevant start dates to September 2012)

Number of patients

20 studies

12 Transoral robotic surgery studies (n = 772 of which 502 were patients with T1 or T2 tumours)
8 IMRT studies (n = 1337 of which 1010 were patients with T1 or T2 tumours)

Patient characteristics

	TORS	**IMRT**
Chemotherapy		350/794 (44%) (5 studies)
Neck Dissection	654/687 (95%) (12 studies)	57/152 (38%) (3 studies)
N2c/N3 metastasis	<16%	<17%
Adjuvant radiotherapy	154/590 (26%)	
Adjuvant chemoradiotherapy	244/590 (41%)	

Intervention

Transoral robotic surgery

Comparison

Intensity modulated radiotherapy
- Standard fractionation or concomitant boost schemes (5 studies)
- Standard fractionation only (1 study)
- Accelerated hyperfraction (1 study)
- Not reported (1 study)

Length of follow-up

Median follow ranged from 24 months to 12.7 years across the individual studies

Outcome measures and effect size (larynx subgroup)

2 year actuarial overall survival
2 year actuarial local recurrence
Regional recurrence
Locoregional recurrence
Distant recurrence
Disease free survival
Disease specific survival
Adverse Events

	TORS	**IMRT**
2 year actuarial overall survival	82%-94% (2 studies)	84%-95.5% (4 studies)
2 year local control	95% (1 study)	96% (1 study)
Regional control	95% (1 study)	97% (1 study)
2 year Locoregional control	94% (1 study)	91%-96% (3 studies)
Distant control	97% (1 study)	87% (1 study)
Disease free survival	79% (1 study)	82%-90% (3 studies)
Disease specific survival	90%-98% (4 studies)	97.7% (1 study)
Adverse Events		

Adverse Events	TORS	IMRT
Osteoradionecrosis of the mandible		2.6% (4/151; 3 studies)
Oespohageal stenosis		4.8% (4/84; 2 studies)
Hospital readmission rate	3% (1 patient; 1 study)	17% (9/52; 1 study)
Postoperative bleeding	2.4% (6/247; 7 studies)	
Pharyngocutaneous fistula rate	2.5% (10/395; 8 studies)	
Gastrostomy tube rate	At time of Surgery: 1.4% (2/139; 3 studies) At time of adjuvant therapy30% (32/107; 3 studies)	
Tracheostomies	12% (31/258)	

Source of funding
Risks of bias
Selection bias: High risk. Non randomised, non comparative retrospective studies, no pooled analysis possible and radiotherapy regimens varied across the individual studies. Attrition bias: Low risk. Detection bias: Unclear/unknown risk.
Additional comments

Quality of Life Studies

Study, country
Allal et al (2003) Switzerland
Study type, study period
Retrospective, non randomised comparative study (1981-1998)
Aim
To compare quality of life outcomes after accelerated radiotherapy with or without chemotherapy with those obtained after surgery and postoperative radiotherapy.
Number of patients
N = 60 Radical radiotherapy ± chemotherapy = 40 Surgery with postoperative radiotherapy = 20
Patient/Study characteristics
Disease free for at least 1 year post treatment
Intervention
Radical radiotherapy ± chemotherapy
Comparison
Surgery with postoperative radiotherapy
Length of follow-up
Median follow-up Radiotherapy: 27 months (12-82 months) Surgery: 78 months (16-200 months)

Outcome measures and effect size

PSSHN function mean scores	Radiotherapy (SD)	Surgery (SD)	p
Eating in Public	84 (18)	73 (31)	0.08
Speech comprehension	95 (10)	81 (27)	0.005
Normalcy of diet	79 (19)	72 (27)	0.25

	N	Eating in Public	Speech comprehension	Normalcy of diet
T1-T2				
Radiotherapy	26	80 (20)	96 (9)	78 (21)
Surgery	13	83 (24) p = 0.7	92 (12) p = 0.27	82 (22) p = 0.056
T3-T4				
Radiotherapy	14	91 (12)	93 (12)	81 (18)
Surgery	7	54 (36) p = 0.002)	61 (35) p = 0.005	53 (25) p = 0.008

EORTC QLQ-C30 Scores
Whole Cohort

- **Global quality of life did not differ significantly (p = 0.4)**
- **Functional scales : no significant difference between the treatment groups for physical, role, emotional, cognitive or social function**
- **Symptom scales: no significant difference noted for fatigue, pain or nausea and vomiting**
- **Patients treated with surgery reported significantly more dyspnoea (p = 0.04) and appetite loss (p = 0.05)**

TI-T2 tumours
Global quality of life score did not differ significantly
Social function score was significantly better in the surgery group (p = 0.03)

T3-T4 tumours
Global quality of life score did not differ significantly
Pain symptoms score was significantly better in the radiotherapy group (p = 0.008)

Source of funding

Risks of bias

Selection bias: Unclear risk: Not randomised/retrospective comparison/group sizes different though baseline characteristics appear similar (no p values)
Performance bias: Low risk. Lack of blinding is not likely to affect any of the reported outcomes.
Attrition bias: Unclear risk.
Detection bias: Unclear/unknown risk. Potential for recall bias/selective participation to impact results/no details given on reasons for drop-outs /small sample size/vastly different follow-up times in each group

1

Study, country

Yao et al (2007) USA

Study type, study period

Retrospective comparative study

Aim

To compare health related quality of life outcomes of patients with oropharyngeal cancer treated with IMRT or CRT

Number of patients

N = 53 patients

IMRT = 26
CRT = 27

Patient/Study characteristics

Patients were drawn from the database of the Outpatients Assessment Project in which they enrolled between June 1997 and December 2005.

Patients in the IMRT group were older, had a greater percentage of stage III/IV disease and received concurrent chemotherapy compared with patients in the CRT group.

Inclusions
Oropharyngeal cancer treated with definitive radiotherapy, with or without chemotherapy and who had 12 months post treatment HRQL data available.

Exclusions
Patients treated primarily with surgery and postoperative radiotherapy

Intervention

Intensity Modulated Radiotherapy (IMRT)

Comparison

Chemoradiotherapy (CRT)

Length of follow-up

Outcome data was taken from information collected prior to treatment and at 3, 6 and 12 months after treatment

Outcome measures and effect size

HRQoL 12 months after treatment

HNCI domain	IMRT	CRT	P*	Difference	CID**	Notes
Eating	55.4	39.0	0.007	16.4	Medium	• **Significantly more patients in the CRT group had diets limited to soft foods and liquids or no oral intake (48% versus 16%, p = 0.032)**
Speech	83.2	74.3	0.059	8.9	Small	
Aesthetics	90.4	79.3	0.069	11.1	Small	
Social Disruption	86.1	78.8	0.115	7.3	Small	
*independent sample t-tests **Magnitude of difference was compared using previously derived CID's						

QoL during the first year after treatment

Mean eating score patterns	IMRT	CRT	p
Pre-treatment	78.2	79.9	N/R
3 months	34.5	34.9	N/R
6 months	42.1	31.7	N/R
12 months	55.4	34.5	0.007

Source of funding

No details

Risks of bias

Selection bias: High risk: not randomised/patients excluded if treated with IMRT during the development phase at the institution/likely that patients were selected for treatment based on likelihood of success
Performance bias: Low risk. Lack of blinding is not likely to affect any of the reported outcomes.
Attrition bias: Low risk.
Detection bias: Unclear/unknown risk – Self reporting at different time points post treatment.

Additional comments

1

Study, country

Ryzek 2014. Germany

Study type, study period

Observational study, 2011-2012

Aim

To compare health related quality of life outcomes of patients with oropharyngeal cancer treated with surgery or surgery plus adjuvant treatment

Number of patients

111

Patient/Study characteristics

Early stage oropharyngeal cancer (T1 or T2; N0-2; M0), tumour free for at least 18 months after surgery,

Intervention

Surgery alone (N = 26; neck dissection 77%)

Comparison

Surgery plus RT (N = 24; neck dissection 100%), surgery plus ChemoRT (N = 51; neck dissection 100%)

Length of follow-up

Surgery – median 2.99 years; surgery + RT median 4.44 years; surgery plus ChemoRT median 4.77 years

2

Outcome measures and effect size

	Surgery	Surgery+RT	Surgery+ChemoRT	
Median EORTC-QLQ-30 Global Health status	75.00 (62.79 to 80.16)	66.67 (56.85 to 72.95)	66.67 (59.22 to 70.91)	
Subscales of EORTC-QLQ-30 and EORTC-QLQ-H&N35	11/32 scales indicated better QOL with surgery alone (P<0.05) : role function, social function, nausea, pain, financial problems, speech, social eating, mouth opening, sticky saliva, swallowing and dry mouth.			

Source of funding

Not reported

Risks of bias

Patients treated with surgery alone were lower risk: for example they were more likely to be N0 (77%) than those treated with surgery plus RT (44%) or with surgery plus ChemoRT (10%). Patients with tumour free interval <18 months were excluded. Longer follow-up for adjuvant treatment groups

Additional comments

1

1 Evidence search details and references

2 ***Review question in PICO format***

Population	**Intervention**	**Comparison**	**Outcomes**
Adults diagnosed with new T1-2, N0 squamous cell carcinoma of the oropharynx Subgroups: • HPV status • smoking status and smoking history	• Radiotherapy • Surgery (laser, robotic) • Chemotherapy • Chemoradiotherapy • Other systemic therapies • Combinations of the above	Each other	• Overall survival • Disease free survival • Progression free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Organ preservation rates • Health related quality of life

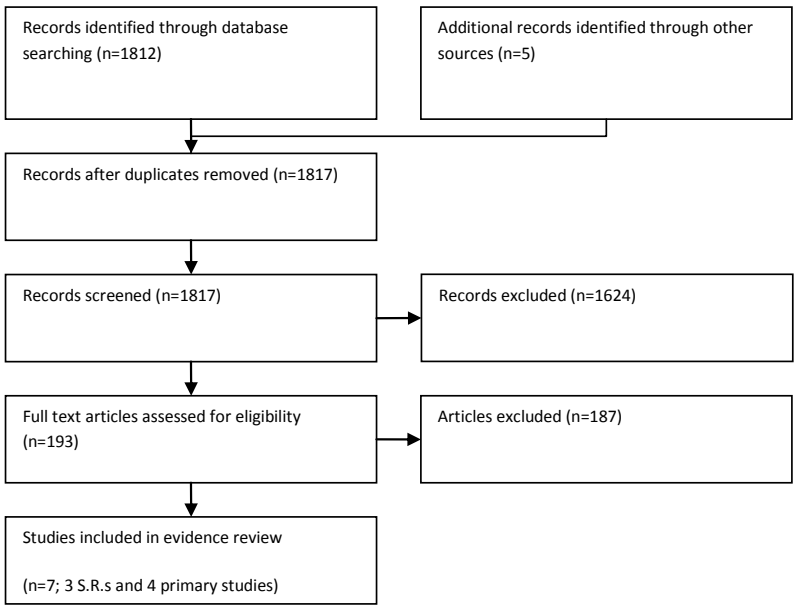
3

4 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour site of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10; At least 75% of the included patients meet the population defined in the PICO.
Search strategies	Search from 1994 onwards.
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual

	studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.

Figure 3.17. Study flow diagram



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4. Treatment of advanced disease

Squamous cell carcinoma of the larynx

Clinical question: What is the most effective treatment for newly diagnosed T3 and T4 squamous cell carcinoma of the larynx?

Background

Treatment for locally advanced (T3–T4a) carcinoma of the larynx aims to cure the patient whilst maintaining an acceptable quality of voice and swallow. A total laryngectomy offers a chance of cure and a functional swallow but the patient will need to learn alternative ways to form a voice. Cure rates can be increased by post-operative radiotherapy with or without chemotherapy/other systemic therapies but these may also have additional short and long term side effects.

An alternative is to use primary radiotherapy, usually combined with neo-adjuvant or concomitant chemotherapy (or both), reserving surgery for recurrent disease. Such larynx preservation approaches may offer equivalent cure rates to primary surgery but with variable functional outcomes.

Evidence statements

Addition of chemotherapy to locoregional therapy

Evidence about the addition of chemotherapy to locoregional therapy comes from the MACH-NC (Blanchard 2011) individual patient data meta-analysis of 61 randomised controlled trials including 3216 patients with laryngeal cancer (76% of whom had T3 or T4 disease).

High quality evidence from 47 randomised trials including 1980 patients suggests that concomitant chemotherapy and locoregional therapy improves overall survival when compared to locoregional therapy alone (HR 0.80; 95% CI 0.71, 0.90; HR<1 favours concomitant chemotherapy). This evidence suggests that for every 1000 patients treated with concomitant chemotherapy instead of locoregional therapy alone we would expect an extra 54 to be alive at five years after treatment.

There is moderate quality evidence (from 17 randomised trials including 613 patients) of uncertainty about the effect of neoadjuvant chemotherapy on overall survival. (HR 1.00; 95% CI 0.81, 1.23; HR<1 favours neoadjuvant chemotherapy).

There is moderate quality evidence (from 9 randomised trials including 623 patients) of uncertainty about the effect of adjuvant chemotherapy on overall survival. (HR 1.05; 95% CI 0.83, 1.33; HR <1 favours adjuvant chemotherapy).

Larynx preservation

Evidence about larynx preservation comes from a systematic review (Denaro 2014) including seven trials in patients with laryngeal cancer.

Neoadjuvant chemotherapy and RT versus initial surgery and RT

Moderate quality from two randomised trials including 200 patients (included in Denaro 2014), suggests that around 60% of patients treated with neoadjuvant chemotherapy and RT (instead of initial surgery then RT) had larynx preservation. Moderate quality evidence from these trials suggests that disease recurrence, however, is more likely in those treated with neoadjuvant chemotherapy than those initially treated with surgery (HR 2.08; 95% CI 1.33, 2.89; HR <1 favours neoadjuvant chemotherapy).

Neoadjuvant chemotherapy and RT versus concomitant chemoradiotherapy versus RT alone

The RTOG 91-11 trial (Forastiere 2003; including 518 patients with laryngeal cancer) provides high quality evidence about larynx preservation rates following neoadjuvant chemotherapy and radiotherapy versus concomitant chemoradiotherapy versus radiotherapy alone. This evidence suggests that larynx preservation is more likely with concomitant chemoradiotherapy, than with neoadjuvant chemotherapy plus radiotherapy or with radiotherapy alone with preservation rates of 84%, 72% and 67% respectively (P<0.001).

Radiotherapy fractionation

Moderate quality evidence from an individual patient meta-analysis of 15 randomised trials including 2377 patients with laryngeal cancer (Baujat 2010) and one subsequent randomised trial (Zackrisson 2011) suggests uncertainty over whether radiotherapy with altered fractionation improves survival compared with conventionally fractionated radiotherapy (HR 0.92; 95% CI 0.82, 1.03).

GRADE evidence tables

Table 4.1. GRADE evidence profile: locoregional treatment plus chemotherapy versus locoregional treatment alone (MACH-NC: Blanchard 2011).

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Locoregional treatment plus chemotherapy	Locoregional treatment	Relative (95% CI)	Absolute	
Event free survival[4] (neoadjuvant chemotherapy)											
17	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2,3]	no serious imprecision	none	231/338 (68.3%)	178/275 (64.7%)	HR 1.13 (0.92, 1.38)	14 fewer per 1000 (from 96 fewer to 69 more)[5]	⊕⊕⊕⊕ HIGH
Event free survival[4] (adjuvant chemotherapy)											
9	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2,3]	no serious imprecision	none	155/295 (52.5%)	169/328 (51.5%)	HR 1.06 (0.85, 1.32)	10 fewer per 1000 (from 94 fewer to 74 more)[5]	⊕⊕⊕⊕ HIGH
Event free survival[4] (concomitant chemotherapy)											
47	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2,3]	no serious imprecision	none	649/990 (65.6%)	714/990 (72.1%)	HR 0.78 (0.7, 0.87)	54 more per 1000 (from 7 more to 101 more)[5]	⊕⊕⊕⊕ HIGH
Overall survival[8] (adjuvant chemotherapy)											
9	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2,3]	serious[7]	none	138/295 (46.8%)	153/328 (46.6%)	HR 1.05 (0.83, 1.33)	1 more per 1000 (from 85 fewer to 87 more)[6]	⊕⊕⊕O MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Locoregional treatment plus chemotherapy	Locoregional treatment	Relative (95% CI)	Absolute	
Overall survival[8] (neoadjuvant chemotherapy)											
17	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2,3]	serious[7]	none	334/338 (98.8%)	319/275 (116%)	HR 1.00 (0.81, 1.23)	38 more per 1000 (from 46 fewer to 122 more)[6]	⊕⊕⊕O MODERATE
Overall survival[8] (concomitant chemotherapy)											
47	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2,3]	no serious imprecision	none	591/990 (59.7%)	630/990 (63.6%)	-	636 fewer per 1000 (from 636 fewer to 636 fewer)	⊕⊕⊕⊕ HIGH

[1] Some trials were confounded (14/61) - however sensitivity analysis excluding these trials had the same overall result.
[2] 26% of included larynx cancer patients had T0-T2 disease
[3] Some trials were pre 1980 (8/61) - however sensitivity analysis excluding these trials had the same overall result.
[4] event is disease progression or death from any cause
[5] Patients event free at 5 years after initial treatment (taken from MACH-NC - Blanchard, 2011)
[6] Patients alive at 5 years after initial treatment (taken from MACH-NC - Blanchard, 2011)
[7] confidence interval of the effect crosses both the line of no-effect and appreciable benefit or harm.
[8] event is death from any cause

Table 4.2. GRADE evidence profile: neoadjuvant chemotherapy versus surgery, both followed by RT (Denaro 2014).

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant chemo then RT	Surgery then RT	Relative (95% CI)	Absolute	
Larynx preservation											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	122/202 (60.4%)	0/198 (0%)	RR 118.72 (13.47, 824.88)	60% of patients treated with neoadjuvant chemo retained their larynx.	⊕⊕⊕O MODERATE
Overall survival[2]											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none[2]	90/202 (44.6%)	69/198 (34.8%)	HR 1.22 (0.89, 1.43)	59 more per 1000 (from 31 fewer to 110 more)	⊕⊕⊕O MODERATE
Acute toxicity (grade II mucositis)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	63/166 (38%)	40/166 (24.1%)	-	241 fewer per 1000 (from 241 fewer to 241 fewer)	⊕⊕⊕O MODERATE
Treatment related mortality											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	4/166 (2.4%)	4/166 (2.4%)	RR 1.00 (0.25, 3.93)	0 fewer per 1000 (from 18 fewer to 71 more)	⊕⊕⊕O MODERATE
Disease recurrence											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	47/202 (23.3%)	32/198 (16.2%)	HR 2.08 (1.33, 2.89)	145 more per 1000 (from 47 more to 238 more)	⊕⊕⊕O MODERATE

[1] low number of events

[2] event is death from any cause

Table 4.3. GRADE evidence profile: altered fractionation RT versus conventionally fractionated RT (MARCH meta-analysis: Baujat 2010).

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Altered fractionation RT	Conventionally fractionated RT	Relative (95% CI)	Absolute	
Overall survival[3]											
15	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	none	589/1234 (47.7%)	557/1143 (48.7%)	HR 0.92 (0.82, 1.03)	28 fewer per 1000 (from 66 fewer to 10 more)	⊕⊕⊕O MODERATE

[1] All trials including larynx cancer patients had adequate allocation concealment, random sequence generation, addressed incomplete outcome data, were free of selective reporting and other bias. All these trials were not blinded - but this is unlikely to affect the overall survival outcome.

[2] Trials using altered fractionation are grouped together - so the optimal fractionation schedule is unclear. The characteristics of the laryngeal cancer patients are not reported separately: for the overall proportion of patients with T1-T3 disease was 56%.

[3] event is death from any cause

1 Evidence tables for all included studies

Study, country

Blanchard 2011, International

Study type, study period

Systematic review (independent patient data meta-analysis),

Number of patients

3216

Patient characteristics

Type of locoregional treatment	n (%)
Conventional radiotherapy	1937 (60)
Hyperfractionated radiotherapy	106 (3)
Surgery + radiotherapy	729 (23)
Surgery alone	138 (4)
Other*	306 (10)

Timing of chemotherapy	n (%)
Adjuvant	623 (19)
Neoadjuvant	613 (19)
Concomitant	1980 (62)

Type of chemotherapy	n (%)
Platin + 5-fluorouracil	457 (14)
PolyCT with platin	293 (9)
PolyCT without platin	445 (14)
MonoCT with platin	770 (24)
MonoCT without platin	1251 (39)

Gender	n (%)
Male	2806 (87)
Female	410 (13)

Age category	n (%)
≤ 50 years	550 (17)
51–60 years	1188 (37)
≥ 60 years	1475 (46)
Unknown	3 (0)

Stage (UICC)	n (%)
Stage I or II	447 (14)
Stage III	1195 (37)
Stage IV	1568 (49)
Unknown	6 (0)

*trials using various locoregional treatments and for which information by patient was not available.

Intervention

Chemotherapy (neoadjuvant, adjuvant or concomitant) plus locoregional therapy (standard RT, hyperfractionated RT, surgery+RT, surgery or other)

Comparison

Locoregional therapy alone

Length of follow-up

Outcome measures and effect size

Overall survival

Subgroup	Total N	N deaths/N patients		HR [95%CI] of death (<1 favours LRT+chemo)	Abs benefit at 5 years (>0 favours LRT+chemo)
		LRT+CT	LRT		
Overall	3216	925/1623	949/1593	0.87 [0.80, 0.96]	
Study year before 1984	1113	-	-	0.86 [0.75, 0.99]	
1985-1990	796	-	-	0.88 [0.72, 1.07]	
After 1990	1307	-	-	0.89 [0.76, 1.04]	
LRT: standard RT	1937	-	-	0.82 [0.73, 0.92]	
LRT: hyperfract.RT	106	-	-	0.76 [0.45, 1.31]	
LRT: surgery+RT	729	-	-	0.98 [0.81, 1.19]	
LRT: surgery	138	-	-	1.08 [0.56, 2.06]	
LRT: other	306	-	-	1.03 [0.76, 1.38]	
Adjuvant chemo	623	138/295	153/328	1.05 [0.83, 1.33]	+0.1% [-8.5, 8.7]
Neoadjuvant chemo	613	?/338	?/275	1.00 [0.81, 1.23]	+3.8% [-4.6, 12.2]
Concomitant chemo	1980	591/990	630/990	0.80 [0.71, 0.90]	+5.4% [0.5, 10.3]
Platin +5-FU	457	-	-	0.87 [0.68, 1.10]	
Poly chemotherapy	738	-	-	0.97 [0.81, 1.17]	
Mono CT with platin	770	-	-	0.75 [0.61, 0.93]	
Mono CT without platin	1251	-	-	0.88 [0.76, 1.02]	
Performance status 0	1366	-	-	0.87 [0.74, 1.01]	
Performance status 1+	1000	-	-	0.82 [0.70, 0.97]	
Stage I-II	447	-	-	0.89 [0.63, 1.24]	
Stage III	1195	-	-	0.85 [0.72, 1.01]	
Stage IV	156	-	-	0.85 [0.76, 0.97]	

LRT – locoregional treatment; CT - chemotherapy

Event free survival (event was death or disease progression)

		N events/ N patients			
Subgroup	**N**	**LRT+CT**	**LRT**	**HR [95%CI] of death or progression (<1 favours LRT+chemo)**	**Absolute benefit at 5 years (>0 favours LRT+chemo)**
Overall	3216	1035/1623	1061/1593	0.88 [0.81, 0.96]	
Study year before 1984	1113	-	-	0.94 [0.82, 1.08]	
1985-1990	796	-	-	0.89 [0.74, 1.07]	
After 1990	1307	-	-	0.81 [0.70, 0.93]	
LRT: standard RT	1937	-	-	0.80 [0.72, 0.90]	
LRT: hyperfractionated RT	106	-	-	0.58 [0.34, 0.99]	
LRT: surgery+RT	729	-	-	1.03 [0.85, 1.24]	
LRT: surgery	138	-	-	1.08 [0.63, 1.85]	
LRT: other	306	-	-	1.19 [0.90, 1.58]	
Adjuvant chemo	623	155/295	169/328	1.06 [0.85, 1.32]	-1% [-9.4, 7.4]
Neoadjuvant chemo	613	231/338	178/275	1.13 [0.92, 1.38]	-1.4% [-9.6, 6.9]
Concomitant chemo	1980	649/990	714/990	0.78 [0.70, 0.87]	5.4% [0.7, 10.1]
Platin +5-FU	457			0.95 [0.75, 1.19]	
Poly chemotherapy	738			0.98 [0.82, 1.17]	
Mono CT with platin	770			0.69 [0.57, 0.83]	
Mono CT without platin	1251			0.92 [0.80, 1.06]	
Performance status 0	1366			0.84 [0.73, 0.97]	
Performance status 1+	1000			0.89 [0.76, 1.04]	
Stage I-II	447			1.01 [0.75, 1.37]	
Stage III	1195			0.80 [0.68, 0.93]	
Stage IV	156			0.88 [0.78, 1.00]	

Source of funding

Association pour la Recherche sur le Cancer (ARC No. 2015), Institut Gustave-Roussy, Ligue Nationale Contre le Cancer, Programme Hospitalier de Recherche Clinique (No. IDF 95009) and Sanofi-Aventis.

Risks of bias

The number of trials at risk of bias and sensitivity analyses excluding those biased trials are summarized below:

Bias	**N trials (total 61)**	**N patients (total 3216)**	**Results for OS when trials with this bias are excluded (HR <1 favours LRT+CT)**
Confounded	14	588	HR 0.90 [0.81, 1.00]
Old (<1980)	8	629	HR 0.89 [0.80. 0.99]
Short follow up (< 5 yrs)	16	1126	HR 0.87 [0.78, 0.97]
Small subgroups (N<40)	35	836	HR 0.88 [0.79. 0.99]
Duplicated control arm	8	532	HR 0.90 [0.81, 0.99]

Additional comments

1

Study, country

Denaro et al 2014. France

Study type, study period

Systematic review, 1991 - 2013

Number of patients

7 laryngeal cancer trials (N<1929; some trials also included hypopharyngeal cancer patients)

Patient characteristics

Stage II to IV laryngeal cancer

Intervention

Induction chemotherapy followed by radiotherapy (IC→RT), Induction chemotherapy followed by concomitant chemoradiotherapy (IC→CRT),

Comparisons

Surgery followed by radiotherapy (S→RT),Induction chemotherapy followed by concomitant chemoradiotherapy (IC→CRT)

Length of follow-up

Outcomes reported at 3 or 5 years

2

Outcome measures and effect size

INDUCTION CHEMOTHERAPY versus SURGERY (BOTH FOLLOWED BY RADIOTHERAPY)

	IC→RT		S→RT			
Outcome	**n**	**N**	**n**	**N**	**Effect [95% C.I.]**	**Trials**
Larynx preservation	122	202	0	198	RR 118.72 [13.47, 824.88]	VALCSG, GETTEC
Overall mortality	90	202	69	198	HR 1.22 [0.89, 1.43]	VALCSG, GETTEC
Disease recurrence	47	202	32	198	HR 2.08 [1.33, 2.89]	VALCSG, GETTEC
Treatment related mortality	4	166	4	166	RR 1.00 [0.25, 3.93]	VALCSG
Treatment toxicity (grade II mucositis)	63	166	40	166	RR 1.57 [1.10, 2.20]	VALCSG
Chemotherapy toxicity	27	202	-	-	-	VALCSG, GETTEC
Surgical complications	-	-	-	-	Slightly higher after chemo	VALCSG, GETTEC

IC, induction chemotherapy with platinum + 5-FU; RT, radiotherapy; S, surgery

INDUCTION CHEMOTHERAPY FOLLOWED BY RADIOTHERAPY versus CONCOMITANT CHEMORADIOTHERAPY versus RT alone

	IC→RT		CRT		RT			
Outcome	**n**	**N**	**n**	**N**	**n**	**N**	**Effect [95% C.I.]**	**Trials**
Larynx preservation	125	173	145	172	116	173	P<0.001 favours CRT	RTOG 91-11
Overall mortality	?	173	?	172	?	173	5 yr survival of 55%, 54% and 56% for IC→RT, CRT, RT (P>0.05)	RTOG 91-11*
Locoregional recurrence	?	173	?	172	?	173	5 year locoregional control 61%, 78% and 56% for IC→RT, CRT, RT (P>0.05)	RTOG 91-11
Treatment related mortality	5	173	9	172	5	173	Treatment related mortality rates: 3%, 5%, 3% for IC→RT, CRT, RT respectively	RTOG 91-11
Grade 3-4 acute toxicity	99	173	89	172	45	173	Acute toxicity rates: 57%, 52%, 26% for IC→RT, CRT, RT respectively	RTOG 91-11
Grade 3-4 late toxicity	42	173	52	172	62	173	Late toxicity rates: 24%, 30%, 36% for IC→RT, CRT, RT respectively	RTOG 91-11

IC, induction chemotherapy with platinum + 5-FU; RT, radiotherapy; CRT concomitant chemoradiotherapy
*RTOG 91-11 is included in MACH-NC for the CRT vs. RT comparison arms

DIFFERENT TYPES OF INDUCTION CHEMOTHERAPY FOLLOWED BY RADIOTHERAPY (GORTEC 2000-01, EORTC 24954-22950) – combined larynx & hypopharynx (cannot separate results)
DIFFERENT TYPES OF INDUCTION CHEMOTHERAPY FOLLOWED BY CONCOMITANT CHEMORADIOTHERAPY or immuno-radiotherapy (Posner & TREMPLIN) – combined larynx & hypopharynx (cannot separate results for TREMPLIN, for Posner not all patients were resectable)

Study	Alive & larynx preserved	Alive & functioning larynx
VALCSG	110/166	65/166 (39%)
GETTEC	15/36	N.R.
RTOG 91-11	72% to 84% (depending on treatment)	In patients with intact larynx at 1yr: 9% to 23% limited to soft foods / liquids 6% to 13% moderate or worse speech impairment

Source of funding

Not reported

Risks of bias

	VALCSG	GETTEC	RTOG 91-11
Patient inclusion criteria	Low risk of bias	Low risk (T3 patients only)	Low risk of bias
Selection bias	Unclear risk of bias	Low risk	Low risk
Performance bias	Low risk	Low risk	Low risk
Attrition bias	Low risk (<2% lost to follow up)	Low risk	Low risk
Detection bias	Low risk	Low risk	Low risk

Additional comments

1

Study

MARCH (Bourhis et al, 2006, Baujat, 2010).

Study type, study period

Meta-analysis of individual patient data for trials that recruited patients between 1969 and 1999.

Trial characteristics

Inclusion criteria:

- Trials that compared conventional radiotherapy with accelerated or hyperfractionated radiotherapy, or both, in previously untreated patients with non-metastatic head and neck (oral cavity, oropharynx, hypopharynx or larynx) squamous cell carcinoma, treated with curative intent
- Trials where recruitment began after 1969 and ended after 1999

Exclusion criteria:

- Trials including mainly or exclusively nasopharyngeal carcinomas
- Trials that used doses per fraction higher than 2.5 Gy

Number of trials/patients included

A total of 17 comparisons /7073 patients were included.

The number of comparisons/patients for each tumour site was as follows:
Larynx: 2377 patients
Hypopharynx: 575 patients
Oral cavity: 886 patients
Oropharynx: 3079 patients

Intervention

Hyperfractionated or accelerated radiotherapy. This intervention was subdivided into three different modifications of fractionation:

- Hyperfractionation (a higher total dose in the same overall time than in the comparison arm)
- Accelerated radiotherapy (the same total dose delivered as the comparison arm, but over a shorter time)
- Accelerated radiotherapy, but with reduced total dose

Comparison

Conventional curative radiotherapy, defined by the authors as radiotherapy equivalent to 66 to 70 Gy, in 2 Gy fractions, for five days a week.

Patient and treatment characteristics (all tumour sites – patient characteristics by tumour site subgroups were not reported)

Gender	n (%)
Male	5782 (82)
Female	1262 (18)
Unknown	29 (0.4)

Type of altered fractionation RT	n (%)
Hyperfractionation	1350 (19)
Accelerated, same total dose	3818 (54)
Accelerated, reduced total dose	1905 (27)

Age category	n (%)
≤ 50 years	1311 (19)
51–60 years	2300 (33)
61–70 years	2346 (33)
≥ 71 years	1085 (15)
Unknown	31 (0.4)

Stage (UICC)	n (%)
Stage I	618 (9)
Stage II	1194 (17)
Stage III	2024 (29)
Stage IV	3197 (45)
Unknown	40 (0.6)

Proportion of patients with T3-T4 disease was 56%.

Outcome measures and effect size

	Overall mortality: number of deaths/total number of patients		
	Altered frac RT	**Conventional RT**	**HR of death [95% CI], < 1 favours altered fracRT**
Larynx tumours only	589/1234	557/1143	0.92 [0.82, 1.03]
All patients	2313/3650	2235/3423	0.92 [0.86, 0.97]

Source of funding

Not reported.

Risk of bias

All trials including larynx cancer patients had adequate allocation concealment, random sequence generation, addressed incomplete outcome data , were free of selective reporting and other bias. All these trials were not blinded – but this is unlikely to affect the overall survival outcome.

Additional comments

Other outcomes (all-cause mortality, locoregional control) were reported, but the results were not analysed separately for each tumour site.

1

Study, country

ARTSCAN (Zackrisson, 2011).
Sweden (12 centres).

Study type, study period

Randomised controlled trial.
Nov 1998 to Jun 2006.

Number of patients

750 patients randomised; data available for 733.

Patient characteristics

Inclusion criteria:

- Patients aged 18 years or over
- Histologically proven squamous cell carcinoma of the oropharynx, hypopharynx, oral cavity or larynx
- Any grade/stage of tumour except T1/T2, N0 glottic carcinoma
- No distant metastases
- Previously untreated tumours considered to be treatable by a radiotherapy technique

Exclusion criteria

- Chemotherapy three months prior to or during radiotherapy
- History of previous malignant disease in the head and neck region
- Any co-existing disease or condition that could be expected to shorten the patient's life expectancy or hamper the delivery of treatment

Gender	n (%)
Male	548 (75)
Female	185 (25)

Primary tumour site	n (%)
Larynx	153 (21)
Hypopharynx	123 (17)
Oral cavity	100 (14)
Oropharynx	357 (49)

Disease stage (UICC)	n (%)
Stage I	31 (4)
Stage II	94 (13)
Stage III	203 (28)
Stage IV	405 (55)

Median patient age: 62 years (range 26–91 years)

Intervention

Accelerated radiotherapy, given as concomitant boost treatment. Gross primary tumour, clinically involved lymph nodes, and electively treated clinically uninvolved lymph nodes received 2 Gy/fraction, five fractions/week to a total dose of 46 Gy in 23 treatment days. The volume excluding elective treatment received 1.1 Gy/fraction in 20 fractions. Interfraction interval was recommended to be >7 hours and never shorter than 6 hours.

Comparison

Conventional radiotherapy. Total dose of 68 Gy during 7 weeks. The volume containing known gross primary tumour and clinically involved lymph nodes as well as elective treatment of clinically uninvolved lymph nodes received 46 Gy; the volume excluding elective treatment received 22 Gy.

Length of follow-up

Median follow up: 5.1 years (minimum 2 years).

Outcome measures and effect size (for LARYNX patients only)

Outcome	Accelerated radiotherapy	Conventional radiotherapy
Locoregional control at 2 years, % of patients	69	72
Locoregional control at 5 years, % of patients	63	70

*estimated from Kaplan-Meier survival curves.

Source of funding

Public body grants.

Risks of bias

Selection bias: Unclear/unknown risk. Methods used for randomisation and concealment of allocation not reported.
Performance bias: Low risk. Lack of blinding is not likely to affect any of the reported outcomes.
Attrition bias: Low risk.
Detection bias: Unclear/unknown risk. No definition of locoregional control reported.

Additional comments

1

Evidence search details and references

Review question in PICO format

Population	Intervention	Comparison	Outcomes

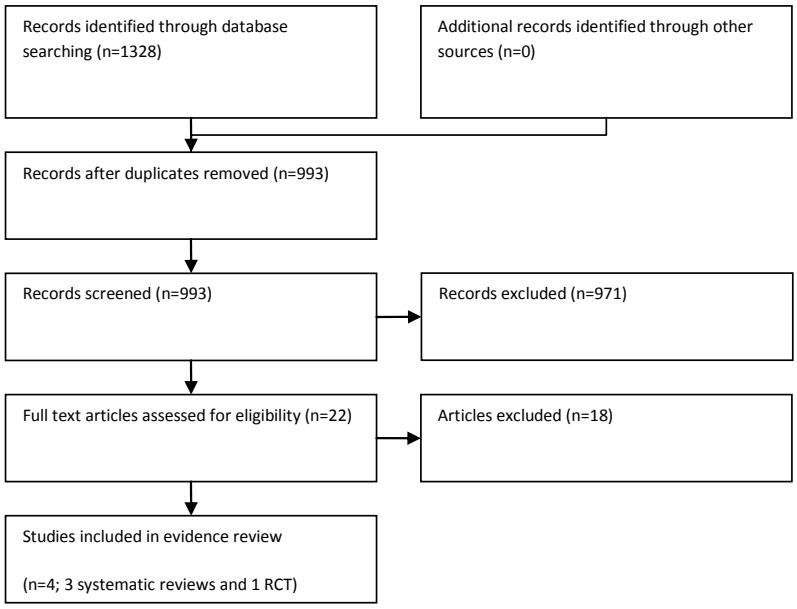
Adults with locally advanced (T3 to T4a) squamous cell carcinoma of the larynx undergoing curative treatment.
 	
Subgroups:
• glottis
• supraglottis
• subglottic
• transglottic
• stage
• performance status
• N-stage
	• Surgery (non organ sparing and organ sparing, with or without reconstruction)
	• Radiotherapy (altered fractionation)
	• Chemotherapy (induction/neo-adjuvant and concomitant)
	• Other systemic therapies (e.g. lapatinib or other EGFR antagonists)
	• Combinations of the above
		Each other	• Overall survival
			• Disease free survival
			• Progression free survival
			• Tumour recurrence
			• Treatment related mortality
			• Treatment related morbidity
			• Organ preservation rates
			• Length of stay
			• Health related quality of life
			  • swallow function
			  • voice quality

1 ***Additional review protocol details (refer to Section 10 for full review protocol)***

	Details	Additional Comments
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.	
Search strategies	Search from 1991 onwards.	This is the date of publication for the earliest evidence on this topic.
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Different chemotherapy regimens (eg induction, neo/adjuvant) and radiotherapy regimens (dose and fractionation are of particular importance) will be considered and compared where these comparisons exist.	

2

Figure 4.1. Study flow diagram



Included studies

Blanchard, P., Baujat, B., Holostenco, V., Bourredjem, A., Baey, C., Bourhis, J. et al. (2011). Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiotherapy & Oncology, 100, 33-40.

Pignon, J. P. & Bourhis, J. (2000). Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet, 355, 949-955.

Bourhis, J. O. (2006). Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet, 368, 843-854.

Denaro, N., Russi, E. G., Lefebvre, J. L., & Merlano, M. C. (2014). A systematic review of current and emerging approaches in the field of larynx preservation. Radiotherapy and Oncology, 110, 16-24.

Includes the following studies:

Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group (1991). New England Journal of Medicine, 324, 1685-1690.

Lefebvre, J. L. & Rolland, F. (2009). Phase 3 randomized trial on larynx preservation comparing sequential vs. alternating chemotherapy and radiotherapy. Journal of the National Cancer Institute, 101, 142-152.

Richard, J. M. & Sancho-Garnier, H. (1998). Randomized trial of induction chemotherapy in larynx carcinoma. Oral Oncology, 34, 224-228.

Forastiere, A. A., Zhang, Q., Weber, R. S., & Maor, M. (2013). Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. Journal of Clinical Oncology, 31, 845-852.

Pointreau, Y., Garaud, P., Chapet, S., Sire, C., Tuchais, C., Tortochaux, J. et al. (2009). Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. Journal of the National Cancer Institute, 101, 498-506.

Posner, M.R., Hershock, D.M., Blajman, C.R., Mickiewicz, E., Winquist, E., Gorbounova, V. et al. (2007). Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. New England Journal of Medicine, 357, 1705-1715.

Lefebvre, J. L., Pointreau, Y., Rolland, F., Alfonsi, M., Baudoux, A., Sire, C. et al. (2013). Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study. Journal of Clinical Oncology, 31, 853-859. **[Majority of patients had hypopharyngeal cancer – results not reported for larynx patients only]**

Prades, J.M., Lallemant, B., Garrel, R., Reyt, E., Righini C., Schmitt T. et al. (2010) Randomized phase III trial comparing induction chemotherapy followed by radiotherapy to concomitant chemoradiotherapy for laryngeal preservation in T3M0 pyriform sinus carcinoma. Acta Oto-Laryngologica, 130, 150-155. **[Pyriform sinus carcinoma patients only]**

Zackrisson, B., Nilsson, P., Kjellen, E., Johansson, K. A., Modig, H., Brun, E. et al. (2011). Two-year results from a Swedish study on conventional versus accelerated radiotherapy in head and neck squamous cell carcinoma The ARTSCAN study. Radiotherapy and Oncology, 100, 41-48.

Excluded studies (with reasons)

Bourhis, J. L. M. (2007). Individual patients' data meta-analyses in head and neck cancer. Current Opinion in Oncology, 19, 188-194. [expert review]

Budach, W. H. (1928). A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer, 6 , 2006. Article Number, 28. [No subgroup analysis for laryngeal cancer]

Elegbede AI, Rybicki LA, Adelstein DJ, Kaltenbach JA, Lorenz RR, Scharpf J et al. Oncologic and Functional Outcomes of Surgical and Nonsurgical Treatment of Advanced Squamous Cell Carcinoma of the Supraglottic Larynx. JAMA Otolaryngology-- Head & Neck Surgery 2015;epub ahead of print. [non randomised study]

Jacobi, I., van der Molen, L., Huiskens, H., van Rossum, M. A., & Hilgers, F. J. M. (2010). Voice and speech outcomes of chemoradiation for advanced head and neck cancer: a systematic review. European Archives of Oto-Rhino-Laryngology, 267, 1495-1505. [no specific subgroup analysis for this patient group]

Francis, E., Matar, N., Khoueir, N., Nassif, C., Farah, C., & Haddad, A. (2014). T4a Laryngeal Cancer Survival: Retrospective Institutional Analysis and Systematic Review. Laryngoscope, 124, 1618-1623. [includes non randomised studies]

Luo XN, Chen LS, Zhang SY, Lu ZM, Huang Y. Effectiveness of chemotherapy and radiotherapy for laryngeal preservation in advanced laryngeal cancer: a meta-analysis and systematic review. Radiol Med (Torino) 2015;epub ahead of print. [includes the same trials for laryngectomy free survival as Denaro 2014]

Ma, J., Liu, Y., Yang, X., Zhang, C., Zhang, Z., & Zhong, L. (2013). Induction chemotherapy in patients with resectable head and neck squamous cell carcinoma: a meta-analysis. World Journal of Surgical Oncology, 11, 67. [No subgroup analysis for laryngeal cancer]

Ma, J., Liu, Y., Huang, X. L., Zhang, Z. Y., Myers, J. N., Neskey, D. M. et al. (2012). Induction chemotherapy decreases the rate of distant metastasis in patients with head and neck squamous cell carcinoma but does not improve survival or locoregional control: A meta-analysis. Oral Oncology, 48, 1076-1084. [No subgroup analysis for laryngeal cancer]

McGhie, J. W. (2010). Network meta-analysis (MA) of taxane-based neoadjuvant chemotherapy (NCT) for locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). Journal of Clinical Oncology, Conference. [Abstract only]

McLaughlin, L. & Mahon, S. (2014). A Meta-Analysis of the Relationship Among Impaired Taste and Treatment, Treatment Type, and Tumor Site in Head and Neck Cancer Treatment Survivors. Oncology Nursing Forum, 41, E194-E202.

Rosenthal DI, Mohamed ASR, Weber RS, Garden AS, Sevak PR, Kies MS et al. Long-Term Outcomes After Surgical or Nonsurgical Initial Therapy for Patients With T4 Squamous Cell Carcinoma of the Larynx: A 3-Decade Survey. Cancer 2015; 121(10):1608-1619. [not randomised study]

Su, Y. X., Zheng, J. W., Zheng, G. S., Liao, G. Q., & Zhang, Z. Y. (2008). Neoadjuvant chemotherapy of cisplatin and fluorouracil regimen in head and neck squamous cell carcinoma: a meta-analysis. Chinese Medical Journal, 121, 1939-1944. [No subgroup analysis for laryngeal cancer]

Chen, H., Zhou, L., Chen, D. B., & Luo, J. F. (2011). Clinical efficacy of neoadjuvant chemotherapy with platinum-based regimen for patients with locoregionally advanced head and neck squamous cell carcinoma: an evidence-based meta-analysis. Annals of Saudi Medicine, 31, 502-512. [No subgroup analysis for laryngeal cancer]

Thomas, L., Drinnan, M., Natesh, B., Mehanna, H., Jones, T., & Paleri, V. (2012). Open conservation partial laryngectomy for laryngeal cancer: A systematic review of English language literature. Cancer Treatment Reviews, 38, 203-211. [minority of T3-T4 patients, their results are not reported separately]

Qian X, Ma C, Hoffmann TK, Kaufmann AM, Albers AE. Taxane-cisplatin-fluorouracil as induction chemotherapy for advanced head and neck cancer: a meta-analysis of the 5-year efficacy and safety. SpringerPlus 2015; 4:208. [Primary site not reported for included studies and no subgroup analysis by primary site]

Rudolph, E., Dyckhoff, G., Becher, H., Dietz, A., & Ramroth, H. (2011). Effects of tumour stage, comorbidity and therapy on survival of laryngeal cancer patients: a systematic review and a meta-analysis. European Archives of Oto-Rhino-Laryngology, 268, 165-179.

Rusthoven, K. E., Raben, D., & Chen, C. H. (2008). Improved survival in patients with Stage III-IV head and neck cancer treated with radiotherapy as primary local treatment modality. International Journal of Radiation Oncology Biology Physics, 72, 343-350. [SEER database study showing improved survival with primary RT for 1998-2004 cohort compared with 1988-1997]

Zhang L, Jiang N, Shi Y, Li S, Wang P, Zhao Y. Induction chemotherapy with concurrent chemoradiotherapy versus concurrent chemoradiotherapy for locally advanced squamous cell carcinoma of head and neck: a meta-analysis. Scientific Reports 2015; 5:10798. [Primary site not reported for included studies and no subgroup analysis by primary site]

Economic evidence - The most effective treatment for carcinoma of the larynx (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies).

Review question: What is the most effective treatment for newly diagnosed T3 and T4 squamous cell carcinoma of the larynx?

Table 4.4. PICO table

Population	Intervention	Comparison	Outcomes
Adults with locally advanced (T3to T4a) squamous cell carcinoma of the larynx undergoing curative treatment. Subgroups: • Glottis • Supraglottis • Subglottic • Transglottic • Stage • Performance status • N-stage	• Surgery (non organ sparing and organ sparing, with or without reconstruction) • Radiotherapy (altered fractionation) • Chemotherapy (induction/neo-adjuvant and concomitant) • Other systemic therapies (e.g. lapatinib or other EGFR antagonists) • Combinations of the above	Each other	• Overall survival • Disease free survival • Progression free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Organ preservation rates • Length of stay • Health related quality of life • Swallow function Voice quality

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived

- Studies that matched the population, interventions, comparators and outcomes specified in PICO
- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

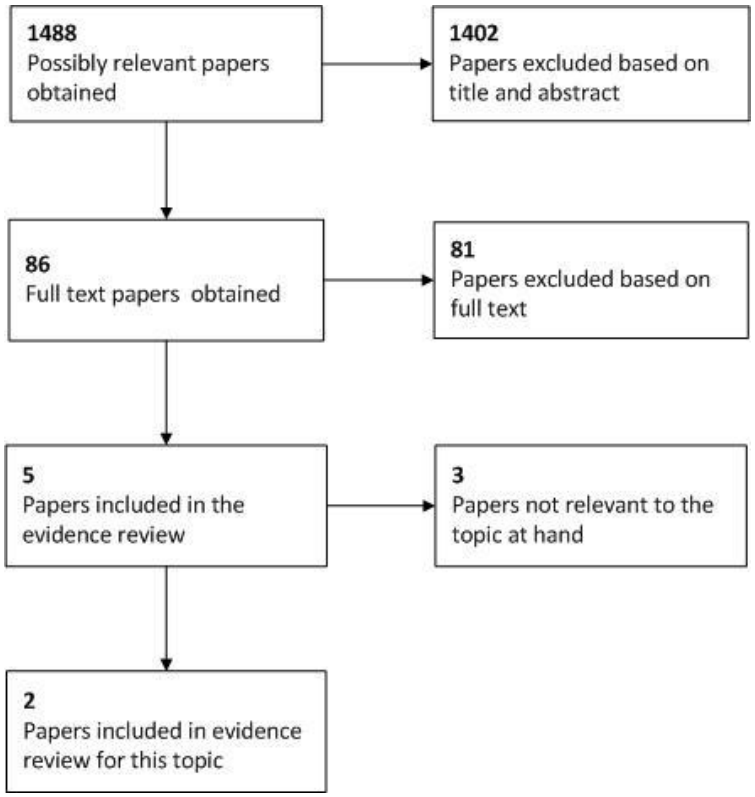
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below shows the search results and sifting process.

Figure 4.2. Summary of evidence search and sifting process for this topic



It can be seen that, in total, 1488 possibly relevant papers were identified. Of these, 1402 papers were excluded at the initial sifting stage based on the title and abstract while 86 full papers were obtained for appraisal. A further 81 papers were excluded based on the full text as they were not

applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, five papers were included in the systematic review of the economic evidence for this guideline.

Two of these five papers related to the topic at hand and were thus included in the review of published economic evidence for this topic; Liberato et al 2011 and Parthan et al 2009. The studies included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

Quality and applicability of the included studies

Liberato et al. 2011 was deemed only partially applicable to the guideline. This was primarily because it considered the Italian regional health care perspective, which differs substantially from the UK system. Also, the analysis considered all head and neck cancer patients as a combined group rather than the specific disease site that is of interest in this decision problem.

Despite being a UK based analysis that used the NHS and PSS perspective, Parthan et al. 2009 was also thought to be only partially applicable to the guideline. This was again because of the population considered in the analysis, which was a pooled cohort of head and neck cancer patients rather than the subgroup of interest here.

Minor limitations were identified in both studies. This is because both studies used data from the Tax 324 trials which demonstrate in hypopharyngeal cancers subgroups there was no significant difference in survival or progression free survival. It did however show overall significant improvements on survival when the data was not divided by sub-groups. In addition Liberato et al 2011 included data from the Tax 323 trials which were excluded from the clinical literature review.

Liberato et al 2011 concluded that the addition of docetaxel to cisplatin and fluorouracil in patients with unresectable head and neck cancer was cost effective. The reported ICERs for Tax 323 and Tax 324 were €11,822 and €6757, respectively.

Table 4.5. Methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		Liberato et al. 2011 Parthan et al. 2009
Potentially serious limitations		
Very serious limitations		

Modified GRADE table

The primary results of the analyses by Liberato et al. 2011 and Parthan et al. 2009 are summarised in the modified GRADE table below.

Table 4.6. Summary table showing the included evidence on the most effective treatment for newly diagnosed T3 and T4 squamous cell carcinoma of the larynx

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Liberato et al 2011	Hypothetical cohort of patients with stage 3/4 unresectable disease.	**Full results (Tax 323)**						**A one-way and probabilistic sensitivity analyses was conducted.** The increase of time horizon up to lifetime increased the number of quality adjusted life years and reduced the overall ICERs further. Following PSA the results for TAX 323 showed a 69% probability of cost-effectiveness at €50,000 and 99% for TAX 324	Partially applicable with minor limitations.
		TP (cisplatin and fluorouracil)	€7904	1.07	-	-	-		
		TPF (docetaxel + cisplatin and fluorouracil)	€11,753	1.40	€3849	0.33	€11,822		
		Full results (Tax 324)							
		TP (cisplatin and fluorouracil)	€12,058	1.98					
		TPF (docetaxel + cisplatin and fluorouracil)	€14,618	2.43	€2730	0.41	€6,757		
	Comments:								
Parthan et al 2009	Hypothetical cohort of patients using TPF compared	PF	£28,718	2.04				No One-way sensitivity analysis was conducted. However a probabilistic sensitivity analysis was undertaken.	Partially applicable with minor limitations.

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
	to PF as induction chemotherapy in a patient with locally advanced SCCHN	TPF	£32,440	4.12	£3721	2.09	£1782	At a willingness to pay threshold of £20,000 per QALY, the results suggest a 96.4% probability of being cost effective.	
	Comments:								

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Evidence statements

The base case results of both cost-effectiveness analyses showed that the addition of docetaxel to cisplatin and fluorouracil in patients with unresectable head and neck cancer was cost effective. Parthan et al. 2009 reported an ICER of £1,782 per QALY while Liberato et al. 2011 reported ICERs of €11,822 and €6,757 per QALY for Tax 323 and Tax 324 scenarios, respectively. Furthermore, the results of the probabilistic sensitivity analysis (PSA) showed high probabilities that the addition of docetaxel was cost-effective at the authors chosen decision thresholds (96.4% at a threshold of £20,000 per QALY in Pathan et al. 2009 and 69% and 99% at a threshold of €50,000 for the TAX 323 and TAX 324 scenarios in Liberato et al. 2011).

However, both analyses were considered to be only partially applicable to the decision problem as they considered head and neck cancers as a combined group rather than the subset of interest here (laryngeal cancer). The applicability of Liberato et al. 2011 is also reduced further as it considered the Italian healthcare perspective, which differs substantially from the UK system.

The analyses suggest that docetaxel may be a cost-effective addition to cisplatin and fluorouracil in patients with advanced head and neck cancer. However, the use of a general head and neck cancer population rather than a laryngeal cancer population limits applicability. Further disease site specific evidence is required to conclusively demonstrate cost-effectiveness.

References

2. Liberato NL, Rognoni C, Rubrichi S, Quaglini S, Marchetti M, Gorlia T, Licitra L, Vermorken JB. Adding docetaxel to cisplatin and fluorouracil in patients with unresectable head and neck cancer: a cost-utility analysis. Annals of Oncology 2012; 23(7): 1825-1832.

3. Parthan A, Posner MR, Brammer C, Beltran P, Jansen JP. Cost utility of docetaxel as induction chemotherapy followed by chemoradiation in locally advanced squamous cell carcinoma of the head and neck. Head Neck 31 (10):1255-1262, 2009.

Full evidence table

The full details of the studies included in the evidence review are presented in the evidence table below.

Table 4.7. Full evidence table showing the included evidence on the most effective treatment for newly diagnosed T3 and T4 squamous cell carcinoma of the larynx

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Liberato et al **Year:** 2011 **Country:** Italy	**Type of analysis:** Cost-effectiveness analysis using QALYs as effectiveness measure i.e. cost-utility analysis. **Model structure:** Markov state transition model **Cycle length:** 1 week **Time horizon:** 5 years (60 months) **Perspective:** Italy regional (Lombardia) health care system **Source of base-line data:** Transition probabilities were obtained from the TAX 323 and 324 clinical trial reports. Further probabilities were obtained from medical literature or from expert opinion. Transition between first line treatment and response states were derived from the two trials. **Source of effectiveness data:**	**Base case (population):** Hypothetical cohort of patients using TPF compared to PF as induction chemotherapy in a patient with locally advanced SCCHN **Sample size:** Not stated. **Age:** Not reported. **Gender:** Not reported. **Subgroup analysis:** No subgroup analyses were performed.	Docetaxel plus cisplatin and fluorouracil (TPF) was compared against cisplatin and fluorouracil alone (PF)	**Effectiveness (QALYs):** PF (TAX 323) TPF (TAX 323) PF (TAX 324) TPF (TAX 324 **Total costs:** PF (TAX 323) TPF (TAX 323) PF (TAX 324) TPF (TAX 324 **ICER (cost per QALY):** TAX 323 TAX 324 **Uncertainty:** A one-way and probabilistic sensitivity analyses was conducted. The increase of time horizon up to lifetime increased the number of quality adjusted life years and reduced the overall ICERs further. No parameters	1.07 1.40 1.84 2.25 €7904 €11753 €11888 €14618 €11822 €6757 Increase in ICER above €20000 occurs if price of docetaxel rises above €563 in the TAX 323 protocol	**Funding:** Not reported. **Comments** No conflicts of interest were reported.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	The key effectiveness data informing the model is that described above (TAX trials). These figures were not well reported in the paper. The authors report that average mortality and progression rates were estimated from the trials using the OS and progression free survival curves. **Source of utility data:** Utility data for the model was derived from the literature and adjusted if on the basis of expert opinion they changed over time. From an input table in the report it there are 17 utility values included in the model. **Source of cost data:** Costs were estimated in Italy from the Lombardia health system point of view. Data on costs were obtained form 2010 DRG reimbursement rates and official charges. The model also included costs for the most server adverse events which included febrile neutropenia; infection from chemotherapy, esophagitis, dysphagia, and odynophagia for radiotherapy and chemoradiotherapy. **Currency unit:** Euros (€) **Cost year:**			Following PSA the results showed: TAX 323 TAX 324	 69% probability of cost-effectiveness at €50,000 99% probability of cost-effectiveness at €50,000	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	2010. **Discounting:** Costs and Outcomes discounted at 3.5%					
Study 2						
Author: Parthan et al **Year:** 2009 **Country:** UK	**Type of analysis:** Cost-effectiveness analysis using QALYs as effectiveness measure i.e. cost-utility analysis. **Model structure:** Markov state transition model **Cycle length:** 3 week **Time horizon:** Lifetime **Perspective:** UK NHS perspective **Source of base-line data:** The 3 week probabilities of transition between health states for the TPF and PF arm of the model for the different steps of treatment were obtained form an additional analysis of the TAX 324 trial. **Source of effectiveness data:** The key effectiveness data informing the model is that described above (TAX 324 trial). These figures were not reported in	**Base case (population):** **Sample size:** Not stated. **Age:** Not reported. **Gender:** Not reported. **Subgroup analysis:** No subgroup analyses were performed.	Docetaxel plus cisplatin and fluorouracil (TPF) was compared against cisplatin and fluorouracil alone (PF) as induction chemotherapy for SCCHN.	**Effectiveness (QALYs):** PF TPF **Total costs:** PF TPF **ICER (cost per QALY):** TPF vs. PF **Uncertainty:** No One-way sensitivity analysis was conducted. However a probabilistic sensitivity analysis was undertaken. At a willingness to pay threshold of £20,000 per QALY, the results suggest a 96.4% probability of being cost effective.	2.04 4.12 £28,718 £32,440 £1782	**Funding:** None stated. **Comments** No conflicts of interest were declared.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	the paper. **Source of utility data:** The authors state that no direct quality of life data was found in the literature relating to SCCHN patients. The authors used TAX 323 data which used the QLQ-C30 which is a cancer disease specific instrument. The authors then used a cross walking algorithm to convert QLQ-C30 scores into EQ-5D utility scores using a trial of patients with liver metastases. **Source of cost data:** Unit costs for the model were derived from a NHS tariff and PSSRU 2006 prices. **Currency unit:** UK pound sterling (£) **Cost year:** 2006 **Discounting:** Costs and Outcomes discounted at 3.5%					

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Squamous cell carcinoma of the hypopharynx

Clinical question: What is the most effective treatment for newly diagnosed locally advanced squamous cell carcinoma of the hypopharynx (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)?

Background

Squamous cell carcinomas of the hypopharynx usually present late with metastatic spread to the neck, and have a poorer prognosis compared to other head and neck cancer subsites.

Surgery including reconstruction, usually followed by radiotherapy and concomitant chemotherapy has been the treatment of choice for many years.

Recently, the use of radiotherapy and concomitant chemotherapy with or without induction chemotherapy given to preserve structure and function has challenged this approach. This technique preserves the larynx which may become dysfunctional. If the tumour recurs salvage surgery has a high rate of complications.

Both approaches have significant treatment related morbidities as well as technical challenges.

Evidence statements

Locoregional treatment alone versus locoregional treatment with chemotherapy

High quality evidence from an individual patient level meta-analysis (Blanchard 2011; 2,767 patients, 66 comparisons) suggests that the addition of chemotherapy to locoregional treatment improves overall survival in people with advanced hypopharyngeal squamous cell carcinoma. Five-year overall survival was 29.7% and 25.8% for locoregional treatment plus chemotherapy and locoregional treatment alone, respectively (hazard ratio (HR) of death: 0.88 [95% confidence interval (CI) 0.80, 0.96]; <1 favours addition of chemotherapy); 5-year disease-free survival was 25.1% and 22.4% for locoregional treatment plus chemotherapy and locoregional treatment alone, respectively (HR of progression or death: 0.88 [95% CI 0.81, 0.96].

Altered fractionation radiotherapy versus conventional radiotherapy

High quality evidence from an individual patient level meta-analysis (Baujat 2010; 575 patients) suggests uncertainty over whether altered fractionation (either hyperfractionated or accelerated) radiotherapy reduces cancer-related deaths compared to standard radiotherapy in people with advanced hypopharnygeal squamous cell carcinoma. The risk of cancer-related death was lower for people receiving altered fractionation treatment, but the effect did not reach statistical significance (HR of cancer-related death: 0.93 [95% CI 0.77, 1.12]).

Locoregional treatment: radiotherapy versus surgery

Moderate quality evidence from one randomised controlled trial (Beauvillain 1997; 90 patients) suggests that in people with resectable advanced hypopharynx tumours, surgery and postoperative radiotherapy improves overall survival and local control compared to locoregional treatment with radiotherapy alone. Five-year overall survival was 19% and 37% for radiotherapy alone and surgery

plus radiotherapy, respectively (p = 0.04). Five-year local control was 37% and 63% for radiotherapy alone and surgery plus radiotherapy, respectively (p <0.01).

Concurrent chemoradiotherapy versus radiotherapy alone

Moderate quality evidence from a single randomised controlled trial (Bensadoun 2006; 163 patients, 40 with hypopharynx cancer) suggests uncertainty over whether chemoradiotherapy is beneficial compared to radiotherapy alone in people with stage IV hypopharyngeal cancer. After two years, overall survival was comparable between the two treatments. Concurrent chemoradiotherapy improved locoregional control (50.7% and 24.3% with concurrent chemoradiotherapy and radiotherapy alone, respectively) and disease-free survival (38% and 22% with concurrent chemoradiotherapy and radiotherapy alone, respectively), but the differences between groups did not reach statistical significance.

Chemotherapy versus surgery

Moderate quality evidence from a single randomised controlled trial (Lefevbre, 2012; 194 patients) suggests uncertainty over whether initial treatment with chemotherapy or surgery offers the most benefit to people with advanced hypopharyngeal tumours. There was no significant difference between the two treatments in terms of survival or rates of disease progression.

Chemotherapy regimen

Moderate to low quality evidence from two randomised trials (including a total of 104 patients with hypopharyngeal cancer) did not indicate any benefit to overall survival or progression-free survival from the addition of docetaxel (Posner, 2009) or vinorelbine (Rivera, 2008) to cisplatin-based chemotherapy in patients with advanced hypopharyngeal cancer.

Timing and sequence of chemoradiotherapy

Moderate quality evidence from a single randomised trial (Prades, 2010; 71 patients) suggests that in people with T3 hypopharyngeal cancer, concomitant treatment with chemotherapy and radiotherapy may improve some outcomes compared with induction chemotherapy followed by radiotherapy. After 24 months of follow up, rates of overall survival and event-free survival were comparable between the treatment groups. However, significantly more patients treated concomitantly retained their larynx one year after treatment (risk ratio 1.3 [95% CI 1.03, 1.65]).

Low quality evidence from a second randomised trial (Iro, 1997; 60 patients) suggests that concomitant treatment with chemotherapy and radiotherapy may improve overall survival compared with sequential treatment (two-year overall survival: 27% and 47% with sequential CRT and concomitant CRT respectively) in patients with non-resectable stage IV hypopharyngeal cancer.

Study characteristics and quality

Eight randomised controlled trials and two meta-analyses met the inclusion criteria for the review. The design of each study is summarised in Table 4.8. Due to differences in the studied comparisons, included populations, and reported outcomes, none of the results from the eight trials could be pooled, either with each other or by adding them to the existing meta-analyses.

Studies that were not specific to the hypopharynx (i.e. including head and neck cancers at sites other than the hypopharynx) were included only where either:

- at least 75% of the included population had hypopharynx cancer and met the other criteria defined in the PICO, or;
- subgroup analysis of patients with hypopharygeal cancer was reported or possible from the reported data, and where the number of patients with hypopharyngeal cancer was greater than 10.

Both meta-analyses addressed questions relevant to the review, reported their methods transparently, and analysed data at the individual patient level. However, only one meta-analysis (Bourhis 2006, Baujat 2010) reported the authors' assessment of study quality. Both meta-analyses covered a range of head and neck tumour sites, but included subgroup analyses of hypopharynx cancer. However, only 8% of the patients included in the MARCH meta-analysis had hypopharynx cancer.

Evidence from the randomised trials was rated as low or moderate quality. Most studies were assessed as at a low risk of bias; it was assumed that no study was blinded, but knowledge of the treatment received is not expected to influence the outcomes of interest (e.g. survival, tumour recurrence). The median study population size was 179 patients, but for studies including a range of head and neck cancers, hypopharyngeal cancers tended to be a small proportion of the total studied population. Several studies included early stage (Stage I or II) hypopharyngeal cancers, but these generally only represented a small (<20%) percentage of the total study population. In one study, 35% of patients had stage IVB hypopharyngeal cancer (i.e. more advanced disease than the population of interest).

Table 4.8. Characteristics of included studies

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	N	INTERVENTION	COMPARISON	OUTCOMES MEASURED
Beauvillain, 1997	RCT	T3 or T4, N0–N3 resectable hypoharyngeal SCC; neoadjuvant chemotherapy prior to locoregional treatment	90	Locoregional treatment = radiotherapy	Locoregional treatment = surgery followed by postoperative radiotherapy	Local control; overall survival
Bensadoun 2006 (FNCLC-GORTEC)	RCT	Unresectable stage IV oropharynx or hypopharynx SCC	163 (all tumour sites)	Concurrent chemoradiotherapy	Radiotherapy alone	Treatment response; overall survival; cancer-specific survival; locoregional control
EORTC 24891 (Lefebvre 2012, Lefebvre 1996)	RCT	Hypopharynx SCC, stage T2, T3 or T4, suitable for surgery	194	Chemotherapy	Surgery	Overall survival; progression free survival; locoregional control; larynx preservation
Iro, 1997	RCT	Non-resectable SCC of the hypopharynx (stage IV)	60	Sequential chemotherapy	Concomitant chemotherapy	Overall survival; treatment toxicity; treatment response
TAX324 (Posner, 2007, Posner, 2009)	RCT	Stage III or IV SCC of the oral cavity, larynx, oropharynx, or hypopharynx	501 (all tumour sites)	Docetaxel, cisplatin and fluorouracil as induction chemotherapy	Cisplatin and fluorouracil as induction chemotherapy	Overall survival; progression free survival
Rivera 2008	RCT	Head and neck SCC, stage III, IVA or IVB	206 (all tumour sites)	Vinorelbine, cisplatin and uracil-tegafur as induction chemotherapy	Cisplatin and FU as induction chemotherapy	Overall survival
Prades 2010	RCT	Previously untreated T3 pyriform sinus squamous cell carcinoma with fixed hemilarynx	71	Concomitant chemoradiotherapy	Induction chemotherapy followed by radiotherapy	Larynx preservation; local control; incidence of metastases; overall survival; treatment related morbidity

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	N	INTERVENTION	COMPARISON	OUTCOMES MEASURED
Zackrisson 2011	RCT	Previously untreated SCC of the oral cavity, larynx, oropharynx, or hypopharynx (any stage)suitable for radiotherapy treatment	733 (all tumour sites)	Accelerated radiotherapy	Conventional radiotherapy	Locoregional control
MACH-NC	SRMA	Previously untreated patients with non-metastatic squamous cell carcinoma of the larynx, hypopharynx, oral cavity or oropharynx undergoing potentially curative locoregional treatment	16,192 (all tumour sites)	Locoregional treatment + chemotherapy	Locoregional treatment alone	Overall mortality; event free survival
MARCH	SRMA	Previously untreated patients with non-metastatic head and neck (oral cavity, oropharynx, hypopharynx or larynx) squamous cell carcinoma, treated with curative intent	7,073 (all tumour sites)	Hyperfractionated or accelerated radiotherapy	Standard radiotherapy	Cancer-related mortality
Abbreviations: RCT: randomised controlled trial; SRMA: systematic review and meta analysis; SCC: squamous cell carcinoma						

GRADE evidence tables

Table 4.9. GRADE evidence profile: locoregional treatment with chemotherapy versus locoregional treatment for treatment of hypopharyngeal SCC

Quality assessment							No of patients		Effect		Quality
No of comparisons[1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Locoregional treatment with chemotherapy	Locoregional treatment without chemotherapy	Relative (95% CI)	Absolute	
Overall mortality											
66	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	953/1380 (69.1%)	1001/1387 (72.2%)	HR 0.88 (0.80, 0.96)	46 fewer per 1000 (from 15 fewer to 81 fewer)	⊕⊕⊕⊕ HIGH
Death or disease progression											
66	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1033/1380 (74.9%)	1077/1387 (77.6%)	HR 0.88 (0.81, 0.96)	44 fewer per 1000 (from 14 fewer to 74 fewer)	⊕⊕⊕⊕ HIGH

CI: confidence interval; HR: hazard ratio.

[1] Figures are from a subgroup analysis of patients with hypopharynx cancer (Blanchard, 2011) within a larger meta-analysis (Pignon, 2009). Some trials had a 3-arm or 2-by-2 design, or used multiple different locoregional treatments or chemotherapies, and hence were counted as more than one comparison.

Table 4.10. GRADE evidence profile: altered fractionation radiotherapy versus conventional radiotherapy for treatment of hypopharyngeal SCC

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Altered fractionation RT	Conventional RT	Relative (95% CI)	Absolute	
Cancer-related deaths											
17[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	232/294 (78.9%)	223/281 (79.4%)	HR 0.93 (0.77, 1.12)	24 fewer per 1000 (from 90 fewer to 36 more)	⊕⊕⊕⊕ HIGH

CI: confidence interval; HR: hazard ratio; RT: radiotherapy.

[1.] Figures represent a subgroup of patients with hypopharynx cancer within a larger meta-analysis (Bourhis, 2006; Baujat, 2010) that included other head and neck cancer sites. Seventeen studies in total were included; the number of these studies that included hypopharynx tumours was not specified.

Table 4.11. GRADE evidence profile: locoregional treatment with radiotherapy versus locoregional treatment with surgery followed by postoperative radiotherapy in advanced hypopharnx cancer

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Locoregional treatment with radiotherapy	Locoregional treatment with surgery followed by postoperative radiotherapy	Absolute	
5-year local control, Kaplan-Meier estimates (follow-up mean 92 months)										
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	45	45	39% and 63% for radiotherapy alone and radiotherapy + surgery, respectively. P <0.01.	⊕⊕⊕O MODERATE
Overall survival, Kaplan-Meier estimates (follow-up mean 92 months)										
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	45	45	5-year OS: RT 19%, S + RT 37%; Median OS, months: RT 20, S + RT 40; P = 0.04	⊕⊕⊕O MODERATE

OS: overall survival; RT: radiotherapy; S: surgery.

[1] Beauvillain, 1997
[2] Downgraded due to small study population.

Table 4.12. GRADE evidence profile: concurrent chemoradiotherapy versus radiotherapy alone in stage IV hypopharynx SCC

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Concurrent chemoradiotherapy	Radiotherapy alone	Relative (95% CI)	Absolute	
Complete response at treatment end (follow-up median 45 months)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious imprecision	serious[2]	none	11/20 (55%)	9/20 (45%)	RR 1.22 (0.65, 2.29)	99 more per 1000 (from 158 fewer to 580 more)	⊕⊕⊕O MODERATE
Overall survival, Kaplan-Meier estimates (follow-up median 45 months)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	**Outcome** / **ChemoRT** / **RT alone**: 2-year OS, % — 21.5 — 21.7 — NS; Median OS, months — 12 — 9 — NS		⊕⊕⊕O MODERATE
Locoregional control, Kaplan-Meier estimates (follow-up median 45 months)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	Rate of locoregional control at 2 years: 50.7% and 24.3% with concurrent chemoradiotherapy and radiotherapy alone, respectively		⊕⊕⊕O MODERATE
Disease free survival, Kaplan-Meier estimates (follow-up median 45 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	Rate of disease-free survival at 2 years: 38% and 22% with concurrent chemoradiotherapy and radiotherapy alone, respectively		⊕⊕⊕O MODERATE

CI: confidence interval; NS: not significant; OS: overall survival; RT: radiotherapy.

[1] Bensadoun 2006
[2] Small study population.

1 **Table 4.13. GRADE evidence profile: chemotherapy versus surgery in stage IV hypopharynx SCC**

Quality assessment							No of patients		Effect				Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy	Surgery	Relative (95% CI)	Absolute			
Overall survival (follow-up median 10.5 years)													
1[1,2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	94	100	HR 0.88 (0.65, 1.19)		Surgery (n = 94)	Chemotherapy (n = 100)	⊕⊕⊕O MODERATE
										Median OS, years (95% CI)	2.1 (1.8, 4.2)	3.67 (2.3, 4.7)	
										5-year overall survival, % (95% CI)	32.6 (23.0, 42.1)	38.0 (28.4, 47.6)	
										10-year overall survival, % (95% CI)	13.8 (6.1, 21.6)	13.1 (5.6, 20.6)	
Progression free survival (follow-up median 10.5 years)													
1[1,2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	94	100	HR 0.83 (0.62, 1.12)		Surgery (n = 94)	Chemotherapy (n = 100)	⊕⊕⊕O MODERATE
										Median progression-free survival, years (95% CI)	1.4 (1.1, 2.1)	1.8 (1.3, 3.0)	
										5-year event-free rate, % (95% CI)	24.1 (15.4, 32.9)	26.8 (18.1, 35.5)	
										10-year event-free rate, % (95% CI)	6.7 (1.2, 12.1)	8.6 (2.3, 14.9)	
Incidence of locoregional failure (follow-up median 10.5 years)													
1[1,2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	29/94 (30.9%)	33/100 (33%)	RR 0.93 (0.62, 1.41)	23 fewer per 1000 (from 125 fewer to 135 more)			⊕⊕⊕O MODERATE
5-year survival with preserved larynx (follow-up median 10.5 years)													
1[1,2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	100	-	Out of 37 patients who were alive after 5 years in the chemotherapy arm, 22 had retained a normal larynx.			⊕⊕⊕O MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy	Surgery	Relative (95% CI)	Absolute	
Incidence of distant failure at last follow up (follow-up median 10.5 years)											
1[1,2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	34/94 (36.2%)	28/100 (28%)	RR 1.46 (0.79, 2.67)	82 more per 1000 (from 45 fewer to 229 more)	⊕⊕⊕O MODERATE

CI: confidence interval; HR: hazard ratio; RR: risk ratio.

[1] Lefebvre 2012
[2] Lefebvre 2006
[3] 95% CI around the effect includes values corresponding to appreciable benefit and no effect
[4] 95% CI around the effect includes values corresponding to appreciable harm and no effect

Table 4.14. GRADE evidence profile: concomitant chemoRT versus induction chemotherapy followed by RT for advanced hypopharynx SCC

Quality assessment							No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Concomitant chemoRT	Induction chemo followed by RT	Relative (95% CI)	Absolute		
Overall survival (follow-up median 24 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	37	34	**Outcome**	**Concomitant chemoRT**	**Induction chemo (**	⊕⊕⊕O MODERATE
									Estimated 1-year overall survival, %	71	76	
									Estimated 2-year overall survival, %	47	51	
Event free survival (follow-up mean 24 months)												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	37	34	**Outcome**	**Concomitant chemoRT**	**Induction chemo**	⊕⊕⊕O MODERATE
									Estimated 1-year event free survival, %	68	58	
									Estimated 2-year event-free survival, %	36	38	
Larynx preservation at 1 year												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	34/37 (91.9%)	24/34 (70.6%)	RR 1.3 (1.03, 1.65)	212 more per 1000 (from 21 more to 459 more)		⊕⊕⊕O MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Concomitant chemoRT	Induction chemo followed by RT	Relative (95% CI)	Absolute	
Incidence of local failure at 2 years											
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	2/37 (5.4%)	7/34 (20.6%)	RR 0.26 (0.06, 1.18)	152 fewer per 1000 (from 194 fewer to 37 more)	⊕⊕⊕O MODERATE
Neutropenia											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	12/37 (32.4%)	7/34 (20.6%)	RR 1.58 (0.7, 3.53)	119 more per 1000 (from 62 fewer to 521 more)	⊕⊕⊕O MODERATE
Febrile neutropenia											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/37 (5.4%)	1/34 (2.9%)	RR 1.84 (0.17, 19.36)	25 more per 1000 (from 24 fewer to 540 more)	⊕⊕⊕O MODERATE
Mucositis, grade 2-4											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	24/37 (64.9%)	28/34 (82.4%)	RR 0.79 (0.59, 1.05)	173 fewer per 1000 (from 338 fewer to 41 more)	⊕⊕⊕O MODERATE
Vomiting/nausea											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/37 (54.1%)	18/34 (52.9%)	RR 1.02 (0.66, 1.58)	11 more per 1000 (from 180 fewer to 307 more)	⊕⊕⊕O MODERATE
Renal toxic effects											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/37 (5.4%)	0/34 (0%)	RR 4.61 (0.23, 92.63)	Not estimable	⊕⊕⊕O MODERATE
Toxic death											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1/37 (2.7%)	1/34 (2.9%)	RR 0.92 (0.06, 14.12)	2 fewer per 1000 (from 28 fewer to 386 more)	⊕⊕⊕O MODERATE

CI: confidence interval; RR: risk ratio; RT: radiotherapy.

[1] Small population size
[2] Prades, 2010
[3] 95% CI includes values corresponding to appreciable benefit and no effect

Table 4.15. GRADE evidence profile: sequential chemoradiotherapy versus concomitant chemoradiotherapy in non-resectable SCC of the hypopharynx (stage IV)

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential CRT	Concomitant CRT	Absolute	
Overall survival										
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	28	32	Two-year overall survival: 27% and 47% with sequential CRT and concomitant CRT, respectively	⊕⊕OO LOW
Complete remission achieved										
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	28	32	Complete remission achieved: 49% and 57% with sequential CRT and concomitant CRT, respectively	⊕⊕OO LOW
Incidence of mucositis										
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	28	32	Incidence of mucositis: 4% and 32% with sequential CRT and concomitant CRT, respectively	⊕⊕OO LOW

CRT: chemoradiotherapy.

[1] Iro, 1997

[2] Several important aspects of study methodology (Methods used for randomisation, patient baseline characteristics, concealment of allocation, and length of follow up) were not reported. 98 patients were randomised, but only 60 went on to receive treatment. The reasons for this are not explained.

[3] Small study population

Table 4.16. GRADE evidence profile: induction chemotherapy (5-FU and cisplatin) with docetaxel (TPF) versus induction chemotherapy without docetaxel (PF) in stage III or IV hypopharynx SCC

Quality assessment							No of patients		Effect				Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Induction chemotherapy (5-FU and cisplatin) with docetaxel	Induction chemotherapy without docetaxel	Relative (95% CI)	Absolute			
Overall survival (follow-up median 42 months)													
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	43	34	HR 0.67 (0.37, 1.20)		TPF (n = 43)	PF (n = 34)	⊕⊕⊕O MODERATE
										Median OS, months	32	20	
										Estimated 3-year OS, %	49	35	
Progression-free survival (follow-up median 42 months)													
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	43	34	HR 0.76 (0.44, 1.32)		TPF (n = 43)	PF (n = 34)	⊕⊕⊕O MODERATE
										Median PFS, months	16	11	
										Estimated 3-year PFS, %	38	32	

5-FU: 5-fluoruracil; CI: confidence interval; HR: hazard ratio.

[1] Posner, 2009

[2] 95% CI includes values corresponding to appreciable benefit and no effect

Table 4.17. GRADE evidence profile: comparison of induction chemotherapy regimens in Stages III-IVB hypopharynx SCC

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Induction chemotherapy with vinorelbine, cisplatin and uracil-tegafur (UFTVP)	Induction chemotherapy with cisplatin and 5-FU (PF)	Absolute	
Overall survival (follow-up median 64 months)										
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	15	16	5-year OS: 43% and 29% with UFTVP and PF, respectively. P = 0.26.	⊕⊕OO LOW

5-FU: 5-fluoruracil; OS: overall survival.

[1] 38% of included patients had stage IVB tumours or tumours of an unreported stage.
[2] Overall number of patients is small
[3] Rivera, 2008

Table 4.18. GRADE evidence profile: accelerated radiotherapy versus conventional radiotherapy in hypopharynx SCC

Quality assessment							No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated radiotherapy	Conventional radiotherapy	Absolute			
Locoregional control (follow-up median 5.1 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	66	67	Outcome	Accelerated radiotherapy	Conventional radiotherapy	⊕⊕⊕O MODERATE
									Locoregional control at 2 years, % of patients	41	46	
									Locoregional control at 5 years, % of patients	41	43	

1.Zackrisson, 2011
2.Small population size

Evidence tables for all included studies

Individual studies

Study, country

Beauvillain, 1997.
France, number of centres not reported.

Study type, study period

Randomised trial, 1985 to 1989.

Number of patients

92 patients randomised; results evaluable for 90.

Patient characteristics

Inclusion criteria:
< 70 years of age
T3 or T4, N0–N3 resectable hypoharyngeal SCC
Performance status ≤2

All patients received three courses of neoadjuvant chemotherapy prior to (randomised) locoregional treatment (randomisation was done prior to chemotherapy treatment).

All patients' tumours were located in the pyriform sinus.
Mean age 55 years (range 35 to 69 years)

Gender	n (%)
Male	90 (100)
Female	0 (0)

T Stage	n (%)
T3	86 (95.6)
T4	4 (4.4)

N stage	n (%)
N0	27 (30.0)
N1	12 (13.3)
N2	39 (43.3)
N3	12 (13.3)

Intervention

Locoregional treatment = radiotherapy. Seventy to 75 Gy dose to tumour and involved nodes; 50 to 60 Gy to non-involved nodes. All patients received 2 Gy per fraction, five fractions per week.

Comparison

Locoregional treatment = surgery followed by postoperative radiotherapy. Total larngopharyngectomy plus unilateral or bilateral radical or conservative lymph node dissection. Fifty to 60 Gy dose to tumour bed; 60 to 70 Gy to involved nodes. All patients received 2 Gy per fraction, five fractions per week.

Length of follow-up

Mean 92 months (range 64 to 115 months)

Outcome measures and effect size

	RT (n = 44)	S + RT (n = 46)	
Rate of 5-year local control*	39%	63%	P < 0.01
Rate of 5-year overall survival*	19%	37%	P = 0.04
Median overall survival, months	20	40	

*estimated by the Kaplan-Meier method.

Source of funding

Not reported.

Risks of bias

Selection bias: Unclear/unknown risk. Methods used for randomisation and concealment of allocation not reported.
Performance bias: Low risk. Lack of blinding is not likely to affect any of the reported outcomes
Attrition bias: Low risk.
Detection bias: Unclear/unknown risk. Definition of local control not reported.

Additional comments

Study, country

Bensadoun 2006 (FNCLC-GORTEC)
France, eight centres.

Study type, study period

Randomised controlled trial.
Nov 1997 to Mar 2002.

Number of patients

171 patients recruited, results evaluable for 163.

Patient characteristics

Inclusion criteria:
Age 18 to 75 years
Strictly unresectable not previously treated stage IV SCC of the oropharynx or hypopharynx
No evidence of distant metastases
Karnofsky performance score ≥60

Median age: 54 years (range 38 to 76 years)

Gender	n (%)
Male	144 (88.3)
Female	19 (11.7)

Primary tumour site	n (%)
Hypopharynx	40 (24.5)
Oropharynx	123 (75.5)

T stage	n (%)
T3	54 (33.1)
T4	109 (66.9)

N stage	n (%)
N0	23 (14.1)
N1	16 (9.8)
N2b	34 (20.9)
N2c	60 (36.8)
N3	30 (18.4)

Intervention

Concurrent chemotherapy and radiotherapy: radiotherapy (given to the same schedule as the comparison group) given concurrently with three courses of cisplatinum + 5-fluorouracil. Each chemotherapy course consisted of 100 mg/m^2 of CP on day 1 (intravenous infusion 1 mg/min in the afternoon, irrespective of radiation timing) followed by a 5 day continuous infusion of 5-FU (750mg/m^2/day at first course; 430 mg/m^2/day at second and third courses) beginning at the end of CP infusion.

Comparison

Radiotherapy: five days per week for seven weeks. Twice per day irradiation of the primary and satellite nodes (1.2 Gy per fraction, minimum 6 hour interval between fractions). At 57.6 Gy (48th fraction) the fields were reduced to include the primary only.

Total dose (hypopharynx): 75.6 Gy (63 fractions/44 days).
Total dose (oropharynx): 80.4 Gy (67 fractions/46 days).

Length of follow-up

50 months and 40 months for the chemoradiotherapy and radiotherapy treatment arms, respectively (difference not statistically significant, p = 0.74)

Outcome measures and effect size – hypopharynx tumour subgroup

Outcome	ChemoRT	RT alone
Incidence of complete response at the end of treatment	11/20 (50)	9/20 (45)
Estimated overall survival at 24 months, %	21.5	21.7
Estimated median overall survival, MONTHS	12	9
Specific survival related to pharyngeal cancer at 24 months, %	23.7	23.5
Disease free survival at 24 months , %	38	22
Rate of locoregional control at 24 months, %	50.7	24.3

Differences between treatment groups were not significant for any outcome.

Source of funding

Not reported.

Risks of bias

Selection bias: Unclear/unknown risk. Methods used for concealment of allocation not reported.
Performance bias: Low risk. Lack of blinding is not likely to affect any of the reported outcomes.
Attrition bias: Low risk.
Detection bias: Unclear/unknown risk. The definition and timing of measurement of some outcomes (and whether this was standardised) was not reported.

Additional comments

1

Study, country

EORTC 24891 (Lefebvre 2012, Lefebvre 1996)
France (six centres), Italy (two centres), Switzerland (one centre), Belgium (one centre), and the Netherlands (one centre).

Study type, study period

Randomised controlled trial.
Mar 1986 to Dec 1993.

Number of patients

202 patients randomised, 194 patients with analysable results.

2

Patient characteristics

Inclusion criteria:

- Age: 18-75 years
- Histologically proven SCC of the piriform sinus or hypopharyngeal aspect of the aryepiglottic fold
- AJCC/UICC stages T2–T4 N0-2b necks
- Hypopharynx tumours had to be operable at the first attempt and suitable for only classical total laryngectomy with partial pharyngectomy

Exclusion criteria:

- Previous treatment in the head and neck
- Any distant metastases or another cancer (except in situ carcinoma of the cervix and adequately treated basal or squamous cell carcinoma of the skin)
- Patients with either a possibility of functional surgery or of extended surgery requiring a plastic procedure for pharyngeal closure
- Any medical condition incompatible with surgery under general anaesthesia or with cisplatin/5-FU

Median age 55.6 years (range 35.8 to 70.4 years)

Gender	n (%)
Male	186 (96)
Female	8 (4)

Primary tumour subsite	n (%)
Pyriform sinus	152 (78)
Aryepiglottic fold	42 (22)

Disease stage (AJCC)	n (%)
Stage II	13 (6)
Stage III	110 (57)
Stage IV	71 (37)

Intervention

Surgery: total laryngectomy with partial pharyngectomy and radical neck dissection, followed by postoperative irradiation.

Comparison

Chemotherapy: cisplatin (100 mg/m^2) intravenously (iv) as a single injection after an iv bolus of 12.5 g mannitol; fluorouracil infusion of 1000 mg/m^2 per day in 2 L of 5% dextrose in 0.45% NaCl infusion over 5 days. Up to three cycles of treatment, depending on response (non-responders were treated with surgery). Patients with a complete response to chemotherapy were treated with irradiation after the third chemotherapy cycle.

Length of follow-up

Median 10.5 years.

Outcome measures and effect size

	Surgery (n = 94)	Chemotherapy (n = 100)	
Median overall survival*, years	2.1 (1.8, 4.2)	3.67 (2.3, 4.7)	HR = 0.88 (95% CI 0.65, 1.19)
5-year overall survival, % (95% CI)	32.6 (23.0, 42.1)	38.0 (28.4, 47.6)	
10-year overall survival, % (95% CI)	13.8 (6.1, 21.6)	13.1 (5.6, 20.6)	
Median progression-free survival*†, years	1.4 (1.1, 2.1)	1.8 (1.3, 3.0)	HR = 0.83 (95% CI 0.62, 1.12)
5-year event-free rate†, % (95% CI)	24.1 (15.4, 32.9)	26.8 (18.1, 35.5)	
10-year event-free rate†, % (95% CI)	6.7 (1.2, 12.1)	8.6 (2.3, 14.9)	
Incidence of locoregional failure at last follow up	29	33	P = 0.75
Incidence of distant failure at last follow up	34	28	P = 0.22
5-year survival with preserved larynx	N/A	21.9%‡	

*estimated by the Kaplan-Meier method.
†including second cancer as an event.
‡22 out of 37 patients in the chemotherapy arm who were alive after 5 years had retained a normal larynx.

Source of funding

Various public health service grants.

Risks of bias

Selection bias: Unclear/unknown risk. Methods used for concealment of allocation not reported.
Performance bias: Low risk
Attrition bias: Low risk
Detection bias: Unclear/unknown risk. Definitions of progression and locoregional failure not reported.

Additional comments

Study, country
Iro, 1997. Germany (single centre).
Study type, study period
Randomised controlled trial. Study period not reported.
Number of patients
98 randomised; data analysed for 60.
Patient characteristics
Inclusion criteria: Patients with advanced, non-resectable SCC of the hypopharynx (UICC stage IV). No patient baseline characteristics reported.
Intervention
Sequential chemoradiotherapy: cisplatin (25 mg/m^2/day for 5 days) and 5-fluorouracil (750 mg/m^2/day for 5 days) followed by G-CSF for 6 days. Two courses, the second of which began at day 14. Chemotherapy was followed by external beam radiotherapy (70 Gy dose to primary lesion; 60 Gy dose to the neck).
Comparison
Concomitant chemoradiotherapy: doses of chemotherapeutic agents as above, but with a three week interval between courses.
Length of follow-up
Not reported.
Outcome measures and effect size

	Sequential CRT (n = 28)	**Concomitant CRT (n = 32)**
Two-year overall survival	27%	47%
Complete remission achieved	49%	57%
Incidence of mucositis	4%	32%

Source of funding
Foundation grant.
Risks of bias
Selection bias: Unclear/unknown risk. Methods used for randomisation, patient baseline characteristics, and concealment of allocation were not reported. Performance bias: Low risk. Attrition bias: Unclear/unknown risk. 98 patients were randomised, but only 60 went on to receive treatment. The reasons for this are not explained. Length of follow up was not reported. Detection bias: Unclear/unknown risk. The timing of measurement of some outcomes (and whether this was standardised) was not reported.
Additional comments

1

Study, country
TAX324 (Posner, 2007, Posner, 2009). International (55 centres in the United States, Argentina, Canada, and Europe)
Study type, study period
Randomised controlled trial. May 1999 to Dec 2003.
Number of patients
501 patients randomised.

2

Patient characteristics

Inclusion criteria:
Measurable, non-metastatic, histologically proven stage III or IV SCC of the oral cavity, larynx, oropharynx, or hypopharynx
Tumour deemed to be unresectable or of low surgical curability.
Age >18 years
WHO performance status of 0 or 1.

Exclusion criteria
Any previous chemotherapy or radiotherapy
Other active cancer or cancer diagnosis within the preceding 5 years
Any previous definitive surgery for SCC of the head and neck
Severe weight loss (>20% body weight) in the preceding 3 months

Median age 55 years (range 33 to 82 years).

Gender	n (%)
Male	419 (83.6)
Female	82 (16.4)

Primary tumour site	n (%)
Hypopharynx	77 (15.4)
Larynx	89 (17.8)
Oral cavity	71 (14.2)
Oropharynx	263 (52.5)
Other	1 (0.2)

N stage	n (%)
N0	77 (15.4)
N1	102 (20.4)
N2	251 (50.1)
N3	70 (14.0)
NX	1 (0.2)

T stage	n (%)
T1	22 (4.4)
T2	99 (19.8)
T3	162 (32.3)
T4	217 (43.3)
TX	1 (0.2)

Overall stage	n (%)
Stage III	87 (17.4)
Stage IV	413 (82.4)
Unknown	1 (0.2)

Reason for inoperability	n (%)
Technical unresectability	176 (35.1)
Low surgical curability	153 (30.5)
Organ preservation	172 (34.3)

After induction chemotherapy (see intervention/comparison), all patients received chemoradiotherapy beginning 3 to 8 weeks after the start of the third cycle of induction chemotherapy. Weekly carboplatin at an area under the curve of 1.5 was given as intravenous (i.v.) infusion during a 1-hour period, for a maximum of seven weekly doses during the course of radiotherapy. Radiotherapy was administered to the primary tumour at a total dose of 70 to 74 Gy in fractions of 2 Gy per day, 5 days per week. Involved lymph nodes received a dose of 60 to 74 Gy; uninvolved lymph nodes received at least 50 Gy.

Intervention

Induction chemotherapy with docetaxel, cisplatin and fluorouracil. Docetaxel (75 mg/m^2) was administered as administered as a 1-hour i.v. infusion, followed by i.v. cisplatin (100 mg/m^2) administered during a period of 0.5 to 3 hours. After completion of the cisplatin infusion, fluorouracil (1000 mg/m^2) was administered as a continuous 24-hour infusion for 4 days.

Induction chemotherapy was given every 3 weeks for three cycles, but stopped early in the event of disease progression, unacceptable toxic effects, withdrawal of consent by the patient, or a reduction of <25% in tumour size after cycle 2.

Comparison

Induction chemotherapy with cisplatin and fluorouracil. Cisplatin was administered as for the intervention group; fluorouracil was administered as for the intervention group, except the duration of administration was 5 days.

Length of follow-up

Minimum 24 months, median 42 months.

Outcome measures and effect size (hypopharynx tumour subgroup)

	TPF (n = 43)	PF (n = 34)	Hazard ratio (95% CI)	P value
Median overall survival, months	32	20	0.67 (0.37, 1.20)	0.18
Estimated 3-year overall survival, %	49	35		
Median progression free survival, months	16	11	0.76 (0.44, 1.32)	0.34
Estimated 3-year progression free survival, %	38	32		

Source of funding

Sanofi-Aventis.

Risks of bias

Selection bias: Low risk
Performance bias: Low risk. Study was not blinded, but lack of blinding is unlikely to affect assessment of outcome
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

Results are based on available subgroup analyses by tumour site. This data was not available for all outcomes/sites.

1

Study, country

Prades, 2010.
France (four centres).

Study type, study period

Randomised controlled trial.
Jun 2001 to Jun 2003.

Number of patients

75 patients randomised; four later considered ineligible (all due to metastatic disease) and therefore data is available for 71 patients.

Patient characteristics

Inclusion criteria:

- Histologically proven, non-metastatic, previously untreated T3 pyriform sinus squamous cell carcinoma with fixed hemilarynx
- Performance status ≤1
- Normal organ function as determined by absolute neutrophil count, platelet count, and calculated creatinine clearance

Exclusion criteria:

- T1, T2 or T4 disease
- Metastatic disease

Gender	n (%)
Male	68 (96)
Female	3 (4)

N stage	n (%)
N0	20 (28)
N1	19 (27)
N2	22 (31)
N3	10 (14)

Median age: 59 years (intervention group); 56 years (comparison group).

Intervention (n = 34)

Concomitant chemoradiotherapy. Intravenous (i.v.) cisplatin (100 mg/m^2 on days 1, 22, and 43) was administered concomitantly with conventional radiotherapy (35 fractions of 2 Gy each over a 7 week period to the primary tumour (50 Gy) and pathologically-positiveneck lymph nodes (20 Gy); lymph nodes were irradiated according to pathological findings of pretreatment neck dissection).

Comparison (n = 37)

Induction chemotherapy followed by radiotherapy. Intravenous (i.v.) cisplatin (100 mg/m^2) on day 1 and fluorouracil (1000 mg/m^2/day) by continuous infusion on days 1–5 for two courses after 3 weeks. After induction chemotherapy patients underwent full endoscopic examination and CT imaging. If a complete response or partial response (>80%) was identified for the primary tumour, the patient was offered conventional radiotherapy (35 fractions of 2 Gy each over a 7 week period to the primary tumour (50 Gy) and pathologically-positiveneck lymph nodes (20 Gy); lymph nodes were irradiated according to pathological findings of pretreatment neck dissection).

Length of follow-up

Median 24 months.

Outcome measures and effect size

Outcome	Concomitant chemoRT (intervention, n = 37))	Induction chemo (comparison, n = 34)	
Larynx preservation at 1 year, n (%)	34 (92)	24 (71)	P = 0.03
Larynx preservation at 2 years, n (%)	34 (92)	23 (68)	P = 0.016
Rate of local control at 2 years, %	81	62	
Incidence of local failure at 2 years, n (%)	2 (3)	7 (10)	
Distant metastases at 2 years, %	19	38	
Estimated 1-year overall survival*, %	71	76	
Estimated 2-year overall survival*, %	47	51	
Estimated 1-year event† free survival*, %	68	58	
Estimated 2-year event†-free survival*, %	36	38	
Incidence of treatment-related toxicities, n (%):			
Neutropaenia	12 (35)	7 (21)	
Febrile neutropaenia	2 (6)	1 (3)	
Mucositis, grade 2-4	24 (71)	28 (82)	
Vomiting/nausea	20 (59)	18 (53)	
Renal toxic effect	2 (6)	0 (0)	
Toxic death	1 (3)	1 (3)	

*estimated from Kaplan-Meier survival curves.
†locoregional recurrent disease, metastases or death.

Source of funding

Not reported. Authors report no conflicts of interest.

Risks of bias
Selection bias: Unclear/unknown risk. Methods used for randomisation and concealment of allocation not reported. Performance bias: Low risk. Lack of blinding is not likely to affect any of the reported outcomes. Attrition bias: Low risk. Detection bias: Unclear/unknown risk. The definition and timing of measurement of some outcomes (and whether this was standardised) was not reported.
Additional comments

1

Study, country
Rivera, 2008. Spain (two centres)
Study type, study period
Randomised controlled trial Jun 1997 to Nov 2001.
Number of patients
206 patients randomised and included in the study.
Patient characteristics
Inclusion criteria: • Histological diagnosis of squamous cell carcinoma of the head and neck, stage III, IVA or IVB. • Age 18–75 years • ECOG performance status ≤2 • Adequate neutrophil and platelet counts; adequate hepatic and renal function • No previous tumour other than cervical, basal or squamous cell cancer of the skin within 5 years of study entry Exclusion criteria: • Any previous chemotherapy or radiotherapy • Cardiac disease or other serious concomitant illness

Primary tumour site	n (%)
Larynx	104 (51)
Hypopharynx	31 (15)
Oral cavity	18 (9)
Oropharynx	45 (22)
Not reported	8 (4)

Disease stage	n (%)
Stage III	76 (37)
Stage IVA	50 (24)
Stage IVB	73 (35)
Not reported	7 (3)

Median age: 60 years (UFTVP arm); 56 years (PF arm)

Intervention
Vinorelbine, cisplatin and uracil-tegafur (UFT) as induction chemotherapy (UFTVP). Cisplatin 100 mg/m^2 i.v. day 1, vinorelbine 25 mg/m^2 i.v. days 1 and 8, and UFT 200 mg/m^2 p.o. days 1 through 21 every 21 days, for four cycles. Treatment was performed on an outpatient basis. Treatment was immediately discontinued upon evidence of tumour progression or excessive toxicity.
Comparison
Cisplatin and 5-FU as induction chemotherapy (PF). Doses not reported in the study methods; inferred to be cisplatin 100 mg/m^2 i.v. on day 1 and 5-FU 1,000 mg/m^2 continuous i.v. infusion from day 1 through day 5, every 21 days. Treatment was performed on an inpatient basis.
Length of follow-up
Median 64 months (range 33–89 months).
Outcome measures and effect size (hypopharynx tumour subgroup)
5 year overall survival = 43 % (UFTVP) vs. 29% (PF). P = 0.26.
Source of funding
Not reported.
Risks of bias
Selection bias: Low risk Performance bias: Unclear/unknown risk. Lack of blinding is not likely to affect any of the reported outcomes. However, UFTVP and PF patients received treatment as outpatients and inpatients respectively. Whether patients therefore received the same overall standard of care is unclear. Attrition bias: Low risk Detection bias: Low risk
Additional comments

2

Study, country

ARTSCAN (Zackrisson, 2011).
Sweden (12 centres).

Study type, study period

Randomised controlled trial.
Nov 1998 to Jun 2006.

Number of patients

750 patients randomised; data available for 733.

Patient characteristics

Inclusion criteria:

- Patients aged 18 years or over
- Histologically proven squamous cell carcinoma of the oropharynx, hypopharynx, oral cavity or larynx
- Any grade/stage of tumour except T1/T2, N0 glottic carcinoma
- No distant metastases
- Previously untreated tumours considered to be treatable by a radiotherapy technique

Exclusion criteria

- Chemotherapy three months prior to or during radiotherapy
- History of previous malignant disease in the head and neck region
- Any co-existing disease or condition that could be expected to shorten the patient's life expectancy or hamper the delivery of treatment

Gender	n (%)
Male	548 (75)
Female	185 (25)

Primary tumour site	n (%)
Larynx	153 (21)
Hypopharynx	123 (17)
Oral cavity	100 (14)
Oropharynx	357 (49)

Disease stage (UICC)	n (%)
Stage I	31 (4)
Stage II	94 (13)
Stage III	203 (28)
Stage IV	405 (55)

Median patient age: 62 years (range 26–91 years)

Intervention

Accelerated radiotherapy, given as concomitant boost treatment. Gross primary tumour, clinically involved lymph nodes, and electively treated clinically uninvolved lymph nodes received 2 Gy/fraction, five fractions/week to a total dose of 46 Gy in 23 treatment days. The volume excluding elective treatment received 1.1 Gy/fraction in 20 fractions. Interfraction interval was recommended to be >7 hours and never shorter than 6 hours.

Comparison

Conventional radiotherapy. Total dose of 68 Gy during 7 weeks. The volume containing known gross primary tumour and clinically involved lymph nodes as well as elective treatment of clinically uninvolved lymph nodes received 46 Gy; the volume excluding elective treatment received 22 Gy.

Length of follow-up

Median follow up: 5.1 years (minimum 2 years).

Outcome measures and effect size (hypopharynx tumour subgroup)

Outcome	Accelerated radiotherapy	Conventional radiotherapy
Locoregional control at 2 years, % of patients	41	46
Locoregional control at 5 years, % of patients	41	43

*estimated from Kaplan-Meier survival curves.

Source of funding

Public body grants.

Risks of bias

Selection bias: Unclear/unknown risk. Methods used for randomisation and concealment of allocation not reported.
Performance bias: Low risk. Lack of blinding is not likely to affect any of the reported outcomes.
Attrition bias: Low risk.
Detection bias: Unclear/unknown risk. No definition of locoregional control reported.

Additional comments

1 *Meta-analyses*

Study

MACH-NC (Pignon, 2000; Pignon, 2009; Blanchard 2011)

Study type, study period

Meta-analysis of individual patient data from trials that completed patient accrual between 1965 and 2000.

Trial characteristics

Inclusion criteria:

- Randomised trials of previously untreated patients with non-metastatic squamous cell carcinoma of the larynx, hypopharynx, oral cavity or oropharynx who had undergone a potentially curative locoregional treatment
- Studies of one of any three comparisons:
  - Chemotherapy-locoregional treatment vs. locoregional treatment plus chemotherapy
  - Timing of chemotherapy-neoadjuvant chemotherapy plus radiotherapy vs. concomitant or alternating radio-chemotherapy with the same drugs
  - Larynx preservation with neoadjuvant chemotherapy-radical surgery plus radiotherapy vs. neoadjuvant chemotherapy plus radiotherapy in responders or radical surgery and radiotherapy in non-responders
- Recruitment began after 1 January 1965 and ended before 31 December 2000

Exclusion criteria:

- Trials including only patients with squamous cell carcinoma of the nasopharynx
- Trial randomisation carried out using a method by which investigators may have been aware of the assigned treatment before deciding whether the patient was eligible
- Trial data unavailable (data required: age, sex, tumour site, TNM classification or stage, histology, performance status, treatment allocated, and date of randomisation)

For the subgroup analysis conducted according to tumour site (Blanchard, 2011), studies were excluded if the relevant comparison(s) involved fewer than 10 patients. Patients with tumour locations other than the larynx, hypopharynx, oral cavity and oropharynx were also excluded from this analysis.

Number of trials/patients included

A total of 87 randomised trials/16, 485 patients were included in the overall meta-analysis. Because some trials had a 3-arm or 2-by-2 design, or used multiple different locoregional treatments or chemotherapies, the total number of comparisons in the meta-analysis was 105/17, 493.

For the subgroup analysis by tumour site, a total of 16,192 patients were included after application of exclusion criteria specific to this analysis.

The number of comparisons/patients for each tumour site was as follows:
Larynx: 61 comparisons/3,216 patients
Hypopharynx: 66 comparisons/2,767 patients
Oral cavity: 81 comparisons/4,331 patients
Oropharynx: 82 comparisons/5,878 patients

Intervention

Locoregional treatment plus chemotherapy.

Comparison

Locoregional treatment alone.

Patient and treatment characteristics (hypopharyngeal tumours subgroup)

Type of locoregional treatment	n (%)
Conventional radiotherapy	1114 (40)
Hyperfractionated radiotherapy	459 (17)
Surgery + radiotherapy	865 (31)
Surgery alone	116 (4)
Other*	213 (8)

Timing of chemotherapy	n (%)
Adjuvant	374 (14)
Neoadjuvant	949 (34)
Concomitant	1444 (52)

Type of chemotherapy	n (%)
Platin + 5-fluorouracil	857 (31)
PolyCT with platin	324 (12)
PolyCT without platin	538 (19)
MonoCT with platin	402 (15)
MonoCT without platin	646 (23)

Gender	n (%)
Male	2366 (86)
Female	302 (11)
Unknown	99 (4)

Age category	n (%)
≤ 50 years	610 (22)
51–60 years	990 (36)
≥ 60 years	1029 (37)
Unknown	138 (5)

Stage (UICC)	n (%)
Stage I or II	189 (7)
Stage III	834 (30)
Stage IV	1709 (62)
Unknown	35 (1)

*trials using various locoregional treatments and for which information by patient was not available.

Outcome measures and effect size (hypopharyngeal tumours subgroup)

	Overall mortality, number of deaths/total number of patients			Event free survival, number of events (death or disease progression)/total number of patients		
	LRT + CT	**LRT**	**HR of death [95% CI], lower values favour LRT + CT**	**LRT + CT**	**LRT**	**HR of progression or death (95% CI), lower values favour LRT + CT**
All hypopharynx tumours	958/1380	1001/1387	0.88 [0.80, 0.96]	1033/1380	1077/1387	0.88 [0.81, 0.96]
Timing of CT:						
Adjuvant	117/195	109/179	1.06 [0.82, 1.38]	122/195	118/179	0.97 [0.75, 1.25]
Neoadjuvant	330/465	356/484	0.88 [0.75, 1.02]	363/465	380/484	0.94 [0.81, 1.09]
Concomitant	511/720	536/724	0.85 [0.75, 0.96]	548/720	579/724	0.83 [0.73, 0.93]
Type of LRT						
Conventional radiotherapy	-	-	0.83 [0.72, 0.95]	-	-	0.80 [0.70, 0.91]
Hyperfractionated radiotherapy	-	-	0.85 [0.67, 1.07]	-	-	0.82 [0.66, 1.02]
Surgery + radiotherapy	-	-	1.02 [0.86, 1.21]	-	-	1.04 [0.88, 1.22]
Surgery alone	-	-	0.46 [0.23, 0.94]	-	-	0.45 [0.24, 0.86]
Other*	-	-	0.86 [0.62, 1.18]	-	-	1.10 [0.81, 1.50]
Type of CT:						
Platin + 5-fluorouracil	-	-	0.84 [0.71, 0.98]	-	-	0.90 [0.77, 1.05]
PolyCT	-	-	1.03 [0.88, 1.21]	-	-	1.02 [0.87, 1.19]
MonoCT with platin	-	-	0.78 [0.61, 0.99]	-	-	0.80 [0.64, 1.02]
MonoCT without platin	-	-	0.82 [0.68, 0.99]	-	-	0.73 [0.61, 0.88]
Stage (UICC)						
Stage I or II	-	-	1.01 [0.60, 1.70]	-	-	0.90 [0.55, 1.45]
Stage III	-	-	0.94 [0.77, 1.13]	-	-	0.95 [0.79, 1.13]
Stage IV	-	-	0.84 [0.75, 0.94]	-	-	0.83 [0.74, 0.93]

Cells marked (-) indicate data not reported.

Source of funding

Not reported.

Additional comments

1

Study

MARCH (Bourhis et al, 2006, Baujat, 2010).

Study type, study period

Meta-analysis of individual patient data for trials that recruited patients between 1969 and 1999.

Trial characteristics

Inclusion criteria:

- Trials that compared conventional radiotherapy with accelerated or hyperfractionated radiotherapy, or both, in previously untreated patients with non-metastatic head and neck (oral cavity, oropharynx, hypopharynx or larynx) squamous cell carcinoma, treated with curative intent
- Trials where recruitment began after 1969 and ended after 1999

Exclusion criteria:

- Trials including mainly or exclusively nasopharyngeal carcinomas
- Trials that used doses per fraction higher than 2.5 Gy

Number of trials/patients included

A total of 17 comparison/7073 patients were included.

The number of comparisons/patients for each tumour site was as follows:
Larynx: 2377 patients
Hypopharynx: 575 patients
Oral cavity: 886 patients
Oropharynx: 3079 patients

Intervention

Hyperfractionated or accelerated radiotherapy. This intervention was subdivided into three different modifications of fractionation:

- Hyperfractionation (a higher total dose in the same overall time than in the comparison arm)
- Accelerated radiotherapy (the same total dose delivered as the comparison arm, but over a shorter time)
- Accelerated radiotherapy, but with reduced total dose

Comparison

Conventional curative radiotherapy, defined by the authors as radiotherapy equivalent to 66 to 70 Gy, in 2 Gy fractions, for five days a week.

Patient and treatment characteristics (all tumour sites – patient characteristics by tumour site subgroups were not reported)

Gender	n (%)
Male	5782 (82)
Female	1262 (18)
Unknown	29 (0.4)

Type of altered fractionation RT	n (%)
Hyperfractionation	1350 (19)
Accelerated, same total dose	3818 (54)
Accelerated, reduced total dose	1905 (27)

Age category	n (%)
≤ 50 years	1311 (19)
51–60 years	2300 (33)
61–70 years	2346 (33)
≥ 71 years	1085 (15)
Unknown	31 (0.4)

Stage (UICC)	n (%)
Stage I	618 (9)
Stage II	1194 (17)
Stage III	2024 (29)
Stage IV	3197 (45)
Unknown	40 (0.6)

Outcome measures and effect size - hypopharynx tumour subgroup

	Cancer-related deaths, number of deaths/total number of patients		
	Altered frac RT	**Conventional RT**	**HR of death [95% CI], lower values favour LRT + CT**
Hypopharynx tumours only	232/294	223/281	0.93 [0.77,1.12]
All patients	2313/3650	2235/3423	0.92 [0.86, 0.97]

Source of funding

Not reported.

Additional comments

Other outcomes (all-cause mortality, locoregional control) were reported, but the results were not analysed separately for each tumour site.

1

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Intervention	Comparison	Outcomes
Adults diagnosed with stage 3 or 4a carcinoma of the hypopharynx undergoing curative treatment Subgroups: Tumour stage	• Surgery (non organ sparing and organ sparing, with or without reconstruction) • Radiotherapy (altered fractionation) • Chemotherapy (induction/neo-adjuvant and concomitant) • Other systemic therapies (e.g. lapatinib, EGFR antagonists) • Combinations of above •	Each other	• Overall survival • Disease free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Organ preservation rates • Health related quality of life

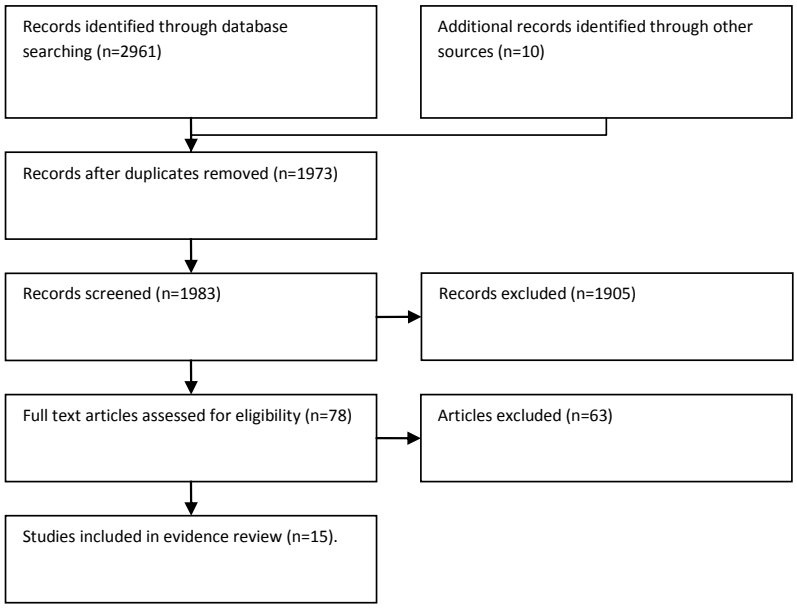
3

1 ***Additional review protocol details***

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the hypopharynx but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site and subgroup analysis of patients with hypopharynx cancer is possible, and where the number of patients in this category is ≥10; At least 75% of the included patients meet the population defined in the PICO. Evidence on cetuximab will not be considered under the 'other systemic therapies' category of interventions, as cetuximab is covered by NICE TA145 and TA172.
Search strategies	Search from 1995 onwards. According to the GC, this is the earliest date of publication for relevant studies of the interventions in the PICO. Any earlier studies that exist would not be relevant to current clinical practice.
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.

2

Figure 4.3. Study flow diagram



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Zackrisson, B., Mercke, C., Strander, H., Wennerberg, J., and Cavallin-Stahl, E. A systematic overview of radiation therapy effects in head and neck cancer. Acta Oncol 2003. 42: 443-461.
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Economic evidence - What is the most effective treatment for newly diagnosed locally advanced squamous cell carcinoma of the hypopharynx?

Review question: What is the most effective treatment for newly diagnosed locally advanced squamous cell carcinoma of the hypopharynx (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)?

Table 4.19: PICO table for the most effective treatment for newly diagnosed locally advanced squamous cell carcinoma of the hypopharynx

Population	Intervention	Comparison	Outcomes
Adults diagnosed with stage 3 or 4a carcinoma of the hypopharynx undergoing curative treatment	• Surgery • Chemotherapy • Radiotherapy	Each other	• Overall survival • Disease free survival • Treatment-related morbidity • Health-related quality of life including patient reported outcomes.

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO
- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

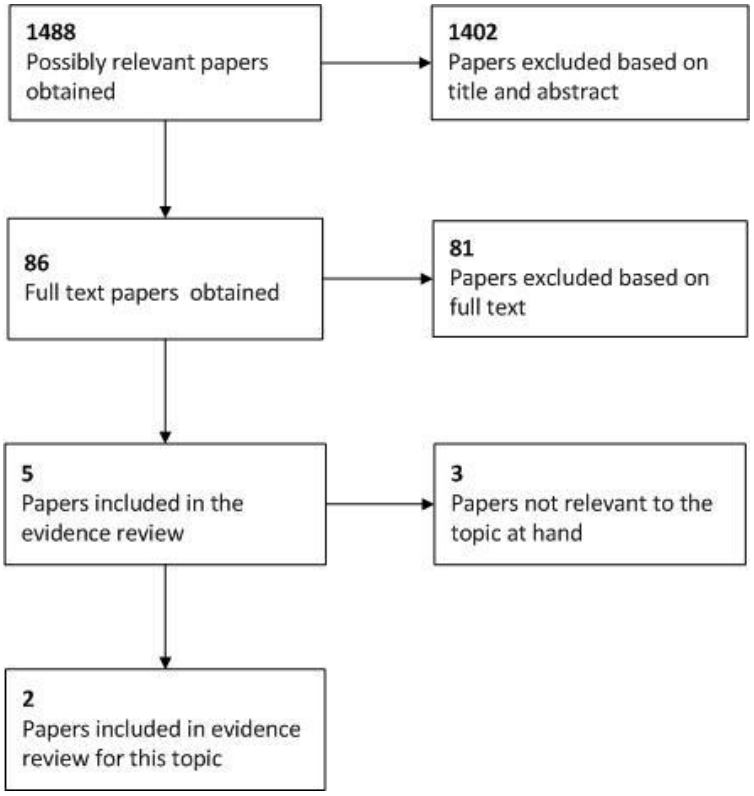
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below shows the search results and sifting process.

Figure 4.4. Summary of evidence search and sifting process for this topic



It can be seen that, in total, 1488 possibly relevant papers were identified. Of these, 1402 papers were excluded at the initial sifting stage based on the title and abstract while 86 full papers were obtained for appraisal. A further 81 papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, five papers were included in the systematic review of the economic evidence for this guideline.

Two of these five papers related to the topic at hand and were thus included in the review of published economic evidence for this topic; Liberato et al 2011 and Parthan et al 2009. The studies included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

Quality and applicability of the included studies

Liberato et al. 2011 was deemed only partially applicable to the guideline. This was primarily because it considered the Italian regional health care perspective, which differs substantially from the UK system. Also, the analysis considered all head and neck cancer patients as a combined group rather than the specific disease site that is of interest in this decision problem.

Despite being a UK based analysis that used the NHS and PSS perspective, Parthan et al. 2009 was also thought to be only partially applicable to the guideline. This was again because of the population considered in the analysis, which was a pooled cohort of head and neck cancer patients rather than the subgroup of interest here.

Minor limitations were identified in both studies. This is because both studies used data from the Tax 324 trials which demonstrate in hypopharyngeal cancers subgroups there was no significant difference in survival or progression free survival. It did however show overall significant improvements on survival when the data was not divided by sub-groups. In addition Liberato et al 2011 included data from the Tax 323 trials which were excluded from the clinical literature review.

Liberato et al 2011 concluded that the addition of docetaxel to cisplatin and fluorouracil in patients with unresectable head and neck cancer was cost effective. The reported ICERs for Tax 323 and Tax 324 were €11,822 and €6757, respectively.

Table 4.20. Methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		Liberato et al. 2011 Parthan et al. 2009
Potentially serious limitations		
Very serious limitations		

Modified GRADE table

The primary results of the analyses by Liberato et al. 2011 and Parthan et al. 2009 are summarised in the modified GRADE table below.

Table 4.21: Summary table showing the included evidence on the most effective treatment for newly diagnosed T3 and T4 squamous cell carcinoma of the hypopharynx

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Liberato et al 2011	Hypothetical cohort of patients with stage 3/4 unresectable disease.	**Full results (Tax 323)**						**A one-way and probabilistic sensitivity analyses was conducted.** The increase of time horizon up to lifetime increased the number of quality adjusted life years and reduced the overall ICERs further. Following PSA the results for TAX 323 showed a 69% probability of cost-effectiveness at €50,000 and 99% for TAX 324	Partially applicable with minor limitations.
		TP (cisplatin and fluorouracil)	€7904	1.07	-	-	-		
		TPF (docetaxel + cisplatin and fluorouracil)	€11,753	1.40	€3849	0.33	€11,822		
		Full results (Tax 324)							
		TP (cisplatin and fluorouracil)	€12,058	1.98					
		TPF (docetaxel + cisplatin and fluorouracil)	€14,618	2.43	€2730	0.41	€6,757		
	Comments:								
Parthan et al 2009	Hypothetical cohort of patients using TPF compared	PF	£28,718	2.04				No One-way sensitivity analysis was conducted. However a probabilistic sensitivity analysis was undertaken.	Partially applicable with minor limitations.

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
	to PF as induction chemotherapy in a patient with locally advanced SCCHN	TPF	£32,440	4.12	£3721	2.09	£1782	At a willingness to pay threshold of £20,000 per QALY, the results suggest a 96.4% probability of being cost effective.	
	Comments:								

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Evidence statements

The base case results of both cost-effectiveness analyses showed that the addition of docetaxel to cisplatin and fluorouracil in patients with unresectable head and neck cancer was cost effective. Parthan et al. 2009 reported an ICER of £1,782 per QALY while Liberato et al. 2011 reported ICERs of €11,822 and €6,757 per QALY for Tax 323 and Tax 324 scenarios, respectively. Furthermore, the results of the probabilistic sensitivity analysis (PSA) showed high probabilities that the addition of docetaxel was cost-effective at the authors chosen decision thresholds (96.4% at a threshold of £20,000 per QALY in Pathan et al. 2009 and 69% and 99% at a threshold of €50,000 for the TAX 323 and TAX 324 scenarios in Liberato et al. 2011).

However, both analyses were considered to be only partially applicable to the decision problem as they considered head and neck cancers as a combined group rather than the subset of interest here (hypopharyngeal cancer). The applicability of Liberato et al. 2011 is also reduced further as it considered the Italian healthcare perspective, which differs substantially from the UK system.

The analyses suggest that docetaxel may be a cost-effective addition to cisplatin and fluorouracil in patients with advanced head and neck cancer. However, the use of a general head and neck cancer population rather than a hypopharyngeal cancer population limits applicability. Further disease site specific evidence is required to conclusively demonstrate cost-effectiveness.

References

4. Liberato NL, Rognoni C, Rubrichi S, Quaglini S, Marchetti M, Gorlia T, Licitra L, Vermorken JB. Adding docetaxel to cisplatin and fluorouracil in patients with unresectable head and neck cancer: a cost-utility analysis. Annals of Oncology 2012; 23(7): 1825-1832.

5. Parthan A, Posner MR, Brammer C, Beltran P, Jansen JP. Cost utility of docetaxel as induction chemotherapy followed by chemoradiation in locally advanced squamous cell carcinoma of the head and neck. Head Neck 31 (10):1255-1262, 2009.

Full evidence table

The full details of the studies included in the evidence review are presented in the evidence table below.

Table 4.22. Full evidence table showing the included evidence on the most effective treatment for newly diagnosed T3 and T4 squamous cell carcinoma of the larynx

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Liberato et al **Year:** 2011 **Country:** Italy	**Type of analysis:** Cost-effectiveness analysis using QALYs as effectiveness measure i.e. cost-utility analysis. **Model structure:** Markov state transition model **Cycle length:** 1 week **Time horizon:** 5 years (60 months) **Perspective:** Italy regional (Lombardia) health care system **Source of base-line data:** Transition probabilities were obtained from the TAX 323 and 324 clinical trial reports. Further probabilities were obtained from medical literature or from expert opinion. Transition between first line treatment and response states were derived from the two trials. **Source of effectiveness data:**	**Base case (population):** Hypothetical cohort of patients using TPF compared to PF as induction chemotherapy in a patient with locally advanced SCCHN **Sample size:** Not stated. **Age:** Not reported. **Gender:** Not reported. **Subgroup analysis:** No subgroup analyses were performed.	Docetaxel plus cisplatin and fluorouracil (TPF) was compared against cisplatin and fluorouracil alone (PF)	**Effectiveness (QALYs):** PF (TAX 323) TPF (TAX 323) PF (TAX 324) TPF (TAX 324 **Total costs:** PF (TAX 323) TPF (TAX 323) PF (TAX 324) TPF (TAX 324 **ICER (cost per QALY):** TAX 323 TAX 324 **Uncertainty:** A one-way and probabilistic sensitivity analyses was conducted. The increase of time horizon up to lifetime increased the number of quality adjusted life years and reduced the overall ICERs further. No parameters	1.07 1.40 1.84 2.25 €7904 €11753 €11888 €14618 €11822 €6757 Increase in ICER above €20000 occurs if price of docetaxel rises above €563 in the TAX 323 protocol	**Funding:** Not reported. **Comments** No conflicts of interest were reported.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	The key effectiveness data informing the model is that described above (TAX trials). These figures were not well reported in the paper. The authors report that average mortality and progression rates were estimated from the trials using the OS and progression free survival curves. **Source of utility data:** Utility data for the model was derived from the literature and adjusted if on the basis of expert opinion they changed over time. From an input table in the report it there are 17 utility values included in the model. **Source of cost data:** Costs were estimated in Italy from the Lombardia health system point of view. Data on costs were obtained form 2010 DRG reimbursement rates and official charges. The model also included costs for the most server adverse events which included febrile neutropenia; infection from chemotherapy, esophagitis, dysphagia, and odynophagia for radiotherapy and chemoradiotherapy. **Currency unit:** Euros (€) **Cost year:**			Following PSA the results showed: TAX 323 TAX 324	 69% probability of cost-effectiveness at €50,000 99% probability of cost-effectiveness at €50,000	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	2010. **Discounting:** Costs and Outcomes were discounted at 3.5%					
Study 2						
Author: Parthan et al **Year:** 2009 **Country:** UK	**Type of analysis:** Cost-effectiveness analysis using QALYs as effectiveness measure i.e. cost-utility analysis. **Model structure:** Markov state transition model **Cycle length:** 3 week **Time horizon:** Lifetime **Perspective:** UK NHS perspective **Source of base-line data:** The 3 week probabilities of transition between health states for the TPF and PF arm of the model for the different steps of treatment were obtained form an additional analysis of the TAX 324 trial. **Source of effectiveness data:** The key effectiveness data informing the model is that described above (TAX 324	**Base case (population):** **Sample size:** Not stated. **Age:** Not reported. **Gender:** Not reported. **Subgroup analysis:** No subgroup analyses were performed.	Docetaxel plus cisplatin and fluorouracil (TPF) was compared against cisplatin and fluorouracil alone (PF) as induction chemotherapy for SCCHN.	**Effectiveness (QALYs):** PF TPF **Total costs:** PF TPF **ICER (cost per QALY):** TPF vs. PF **Uncertainty:** No One-way sensitivity analysis was conducted. However a probabilistic sensitivity analysis was undertaken. At a willingness to pay threshold of £20,000 per QALY, the results suggest a 96.4% probability of being cost effective.	2.04 4.12 £28,718 £32,440 £1782	**Funding:** None stated. **Comments** No conflicts of interest were declared.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	trial). These figures were not reported in the paper. **Source of utility data:** The authors state that no direct quality of life data was found in the literature relating to SCCHN patients. The authors used TAX 323 data which used the QLQ-C30 which is a cancer disease specific instrument. The authors then used a cross walking algorithm to convert QLQ-C30 scores into EQ-5D utility scores using a trial of patients with liver metastases that had the responsiveness of the 2 measures found to be comparable. **Source of cost data:** Unit costs for the model were derived from a NHS tariff and PSSRU 2006 prices. **Currency unit:** UK pound sterling (£) **Cost year:** 2006 **Discounting:** Costs and Outcomes were discounted at 3.5%					

1

Palliation of breathing difficulties

Clinical question: What are the most effective palliative treatments for people with incurable upper aerodigestive tract cancer experiencing breathing difficulties?

Background

Respiratory complications are a significant cause of mortality and morbidity in patients with locally advanced and/or metastatic CUADT. Patients can experience distressing symptoms including stridor and dyspnoea as a result of upper airway obstruction. Strategies to reduce these symptoms can be challenging and will often require a combination of surgical and non-surgical interventions and palliative care.

Tumour debulking, stenting or tracheostomy may be of benefit. The type of intervention depends on disease site and extent. There may be consequences which impact upon quality of life and place of care.

Chemotherapy and radiotherapy have significant side-effects which may make these therapies inappropriate or unacceptable to someone with advanced disease. Palliative care includes symptom control through the use of other drugs and planning end of life.

Evidence statements

The review identified no evidence that met the inclusion criteria of the review.

Evidence search details and references

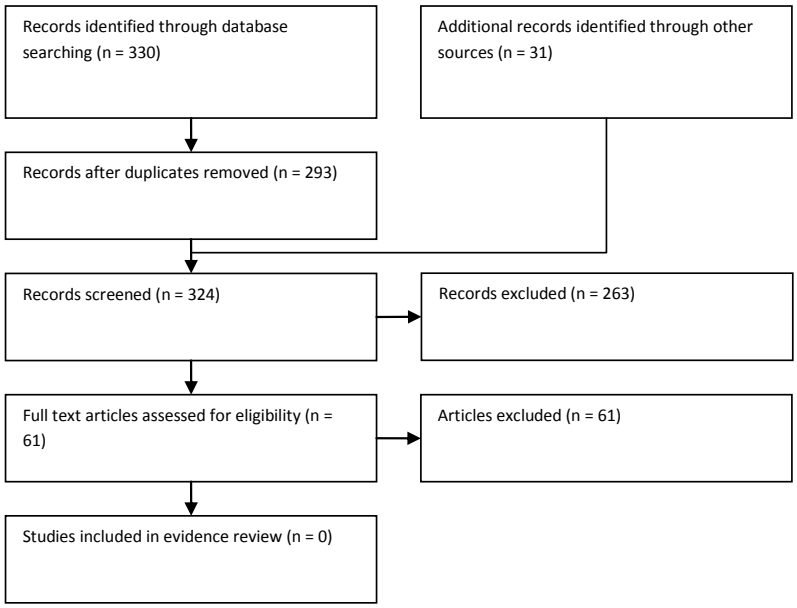
Review question in PICO format

Population	Intervention	Comparison	Outcomes
Adults with incurable upper aerodigestive tract cancer with: • dyspnoea • stridor	• Tracheostomy • De-bulking surgery • Radiotherapy • Chemoradiotherapy • Chemotherapy • Other systemic therapies • Best supportive care	Each other	• Symptom control • Treatment-related morbidity • Quality of life • Length of stay • Survival • Burden of care

Additional review protocol details (refer to Section 10 for full review protocol)

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.
Search strategies	None specified
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, and dose of any palliative treatment will be important considerations for the review.

Figure 4.5. Study flow diagram



Excluded studies

Allal, A. S., Nicoucar, K., Mach, N., and Dulguerov, P. Quality of life in patients with oropharynx carcinomas: assessment after accelerated radiotherapy with or without chemotherapy versus radical surgery and postoperative radiotherapy. Head Neck 2003. 25(10): 833-839.
Reason for exclusion: Population not relevant to PICO.

Arnold, D. J., Goodwin, W. J., Weed, D. T., and Civantos, F. J. Treatment of recurrent and advanced stage squamous cell carcinoma of the head and neck. Seminars in Radiation Oncology 2004. 14(2): 190-195.
Reason for exclusion: Editorial/narrative review.

Bausewein, C., Booth, S., Gysels, M., Kuhnbach, R., and Higginson, I. J. Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial. BMC Palliat Care 2010. 9: 22.
Reason for exclusion: Interventions/population not relevant to PICO.

Beamis, J. F. Interventional pulmonology techniques for treating malignant large airway obstruction: an update. Current Opinion in Pulmonary Medicine 2005. 11(4): 292-295.
Reason for exclusion: Population not relevant to PICO.

Bradley, P. J. Treatment of the patient with upper airway obstruction caused by cancer of the larynx. [Review] [25 refs]. Otolaryngology - Head & Neck Surgery 1999. 120(5): 737-741.
Reason for exclusion: Population not relevant to PICO.

Brennan, C. W. and Mazanec, P. Dyspnea Management Across the Palliative Care Continuum. Journal of Hospice & Palliative Nursing 2011. 13(3): 130-139.
Reason for exclusion: Editorial/narrative review.

Chan, J. Y., To, V. S., Wong, S. T., and Wei, W. I. Quality of dying in head and neck cancer patients: the role of surgical palliation. Eur Arch Otorhinolaryngol 2013. 270(2): 681-688.
Reason for exclusion: Insufficient outcome data reported.

Chan, T. and Devaiah, A. K. Tracheostomy in palliative care. Otolaryngol Clin North Am 2009. 42(1): 133-41, x.
Reason for exclusion: Population not relevant to PICO.

Claros, P. V. Lymphangioma of the larynx as a cause of progressive dyspnea. Anales otorrinolaringologicos ibero-americanos 1986. 13(4): 379-386.
Reason for exclusion: Non English publication.

Clemens, K. E. and Klaschik, E. Symptomatic therapy of dyspnea with strong opioids and its effect on ventilation in palliative care patients. Journal of Pain and Symptom Management 2007. 33(4): 473-481.
Reason for exclusion: Population not relevant to PICO.

Clemens, K. E. and Klaschik, E. Treatment of dyspnoea in patients receiving palliative care: nasal delivery of oxygen compared with opioid adminstration. Deutsche Medizinische Wochenschrift 2007. 132(38): 1939-1943.
Reason for exclusion: Non English publication.

Clemens, K. E., Quednau, I., and Klaschik, E. Use of oxygen and opioids in the palliation of dyspnoea in hypoxic and non-hypoxic palliative care patients: a prospective study. Supportive Care in Cancer 2009. 17(4): 367-377.
Reason for exclusion: Population not relevant to PICO.

Clough, A. and Clarke, P. Adenoid cystic carcinoma of the trachea: a long-term problem. ANZ Journal of Surgery 2006. 76(8): 751-753.
Reason for exclusion: Population not relevant to PICO.

Coulson, A. S., Rossiter, S. J., and Guernsey, J. M. Progressive tracheal obstruction. Journal of Thoracic & Cardiovascular Surgery 1974. 67(5): 733-743.
Reason for exclusion: Population not relevant to PICO.

Dawes, P. J., Agrawal, R. K., Williams, S., and Dawes, P. J. Tracheostomy and radiotherapy in the management of laryngeal carcinoma causing airway obstruction. Clinical Oncology (Royal College of Radiologists) 1997. 9(2): 115-118.
Reason for exclusion: Non comparative study.

Delap, T. G. and Dilkes, M. G. The use of CO2 laser for airway maintenance in obstructive supraglottic carcinoma. Journal of the Royal College of Surgeons of Edinburgh 1998. 43(2): 129-129.
Reason for exclusion: Comment on study.

Dhillon, N., Kopetz, S., Pei, B. L., Fabbro, E. D., Zhang, T., and Bruera, E. Clinical findings of a palliative care consultation team at a comprehensive cancer center. Journal of Palliative Medicine 2008. 11(2): 191-197.
Reason for exclusion: No relevant outcome data reported.

Elsayem, A. and Bruera, E. High-dose corticosteroids for the management of dyspnea in patients with tumor obstruction of the upper airway. Supportive Care in Cancer 2007. 15(12): 1437-1439.
Reason for exclusion: Population not relevant to PICO.

Ethunandan, M., Rennie, A., Hoffman, G., Morey, P. J., and Brennan, P. A. Quality of dying in head and neck cancer patients: a retrospective analysis of potential indicators of care. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005. 100(2): 147-152.
Reason for exclusion: Outcomes not relevant to PICO.

Farquhar, M. C., Prevost, A., McCrone, P., Brafman-Price, B., Bentley, A., Higginson, I. J., Todd, C., and Booth, S. Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial. BMC Medicine 2014. 12(1): 194.
Reason for exclusion: Population not relevant to PICO.

Forbes, K. Palliative care in patients with cancer of the head and neck. Clin Otolaryngol Allied Sci 1997. 22(2): 117-122.
Reason for exclusion: Comparison not relevant to PICO.

Fury, M. G. and Pfister, D. G. Current recommendations for systemic therapy of recurrent and/or metastatic head and neck squamous cell cancer. J Natl Compr Canc Netw 2011. 9(6): 681-689.
Reason for exclusion: Editorial/narrative review.

Galbraith, S., Fagan, P., Perkins, P., Lynch, A., and Booth, S. Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. J Pain Symptom Manage 2010. 39(5): 831-838.

Reason for exclusion: Population not relevant to PICO.

Han, C. C., Prasetyo, D., and Wright, G. M. Endobronchial palliation using Nd : YAG laser is associated with improved survival when combined with multimodal adjuvant treatments. Journal of Thoracic Oncology 2007. 2(1): 59-64.
Reason for exclusion: Population not relevant to PICO.

Higginson, I. J., Bausewein, C., Reilly, C. C., Gao, W., Gysels, M., Dzingina, M., McCrone, P., Booth, S., Jolley, C. J., and Moxham, J. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. Lancet Respiratory Medicine 2014. 2(12): 979-987.
Reason for exclusion: Population not relevant to PICO.

Hodson, D. I., Bruera, E., Eapen, L., Groome, P., Keane, T., Larsson, S., and Pearcey, R. The role of palliative radiotherapy in advanced head and neck cancer. Canadian Journal of Oncology 1996. 6(Suppl 1): 54-60.
Reason for exclusion: Review. References checked for relevance.

Isaacs, J. H., Jr. and Schnitman, J. R. Outcome of treatment of 160 patients with squamous cell carcinoma of the neck staged N3a. Head Neck 1990. 12(6): 483-487.
Reason for exclusion: Outcomes not relevant to PICO.

Jennings, A. L., Davies, A. N., Higgins, J. P., and Broadley, K. Opioids for the palliation of breathlessness in terminal illness. Cochrane Database Syst Rev 2001. (4): CD002066.
Reason for exclusion: Systematic review. Inclusion criteria not relevant to PICO. References within checked for relevance.

Jensen, N. F. B. The difficult airway in head and neck tumor surgery. Anesthesiology Clinics of North America 1993. 11(3): 475-507.
Reason for exclusion: Editorial/narrative review.

Jerjes, W., Upile, T., Akram, S., and Hopper, C. The surgical palliation of advanced head and neck cancer using photodynamic therapy. Clin Oncol (R Coll Radiol) 2010. 22(9): 785-791.
Reason for exclusion: Non comparative study; no outcome data reported.

Johnstone, R. E. and Brooks, S. M. Upper airway obstruction after extubation. JAMA 1971. 218(1): 92-93.
Reason for exclusion: Individual case report.

Kejner, A. E., Castellanos, P. F., Rosenthal, E. L., and Hawn, M. T. All-cause mortality after tracheostomy at a tertiary care hospital over a 10-month period. Otolaryngol Head Neck Surg 2012. 146(6): 918-922.
Reason for exclusion: Study design not relevant; unclear if population is relevant to PICO.

Kim, J. H., Shin, J. H., Song, H. Y., Ohm, J. Y., Lee, J. M., Lee, D. H., and Kim, S. W. Palliative treatment of inoperable malignant tracheobronchial obstruction: temporary stenting combined with radiation therapy and/or chemotherapy. AJR Am J Roentgenol 2009. 193(1): W38-W42.
Reason for exclusion: Population not relevant to PICO.

Koscielny S.Beleites. Modern possibilities of palliative surgical therapies in incurable head and neck tumors. Onkologe 2003. 9(2): 165-168.
Reason for exclusion: Non English publication.

Kowalski, L. P. and Carvalho, A. L. Natural history of untreated head and neck cancer. Eur J Cancer 2000. 36(8): 1032-1037.
Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Non English publication.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: No relevant outcome data reported.

Ledeboer, Q. C., van der Velden, L. A., de Boer, M. F., Feenstra, L., and Pruyn, J. F. Palliative care for head and neck cancer patients in general practice. Acta Otolaryngol 2006. 126(9): 975-980.
Reason for exclusion: Study design not relevant.

Lin, Y. L., Lin, I. C., and Liou, J. C. Symptom patterns of patients with head and neck cancer in a palliative care unit. J Palliat Med 2011. 14(5): 556-559.
Reason for exclusion: Comparison not relevant to PICO.

Lin, Z. M., Chen, P. R., Chou, A. S., and Hsu, L. P. Tracheal incision for elective tracheotomy in oral cavity cancer. Oral Oncology 2007. 43(1): 15-19.
Reason for exclusion: Population not relevant to PICO.

Lovel, T. Palliative care and head and neck cancer. British Journal of Oral and Maxillofacial Surgery 2000. 38(4): 253-254.
Reason for exclusion: Editorial/narrative review.

Navigante, A. H., Cerchietti, L. C., Castro, M. A., Lutteral, M. A., and Cabalar, M. E. Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. J Pain Symptom Manage 2006. 31(1): 38-47.
Reason for exclusion: Population not relevant to PICO.

Offerman, M. P., Pruyn, J. F., de Boer, M. F., Ledeboer, Q. C., van Busschbach, J. J., Baatenburg de Jong, R. J., and van der Velden, L. A. Experience of palliative care for patients with head and neck cancer through the eyes of next of kin: impact of an Expert Center. Head Neck 2014. 36(10): 1459-1466.
Reason for exclusion: Outcomes not relevant to PICO; study design not relevant.

Paleri, V., Stafford, F. W., and Sammut, M. S. Laser debulking in malignant upper airway obstruction. Head & Neck 2005. 27(4): 296-301.
Reason for exclusion: Non comparative study; population not relevant to PICO.

Paleri, V., Stafford, F. W., and Sammut, M. S. Laser debulking in malignant upper airway obstruction. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck 2005. 27(4): 296-301.
Reason for exclusion: Duplicate record.

Philip, J., Gold, M., Milner, A., Di, Iulio J., Miller, B., and Spruyt, O. A randomized, double-blind, crossover trial of the effect of oxygen on dyspnea in patients with advanced cancer. J Pain Symptom Manage 2006. 32(6): 541-550.
Reason for exclusion: Population not relevant to PICO.

Price, K. A. and Cohen, E. E. Current treatment options for metastatic head and neck cancer. Curr Treat Options Oncol 2012. 13(1): 35-46.
Reason for exclusion: Editorial/narrative review.

Price, K. A. R. Symptoms and terminal course of patients who died of head and neck cancer. Journal of Palliative Medicine 2009. 12(2): 117-118.
Reason for exclusion: Outcomes not relevant to PICO.

Roland, N. J. and Bradley, P. J. The role of surgery in the palliation of head and neck cancer. Current Opinion in Otolaryngology and Head and Neck Surgery 2014. 22(2): 101-108.
Reason for exclusion: Editorial/narrative review.

Sciubba, J. J. End of life considerations in the head and neck cancer patient. Oral Oncol 2009. 45(4-5): 431-434.
Reason for exclusion: Editorial/narrative review.

Sesterhenn, A. M., Folz, B. J., Bieker, M., Teymoortash, A., and Werner, J. A. End-of-life care for terminal head and neck cancer patients. Cancer Nurs 2008. 31(2): E40-E46.
Reason for exclusion: No relevant outcome data reported.

Shedd, D. P., Carl, A., and Shedd, C. Problems of terminal head and neck cancer patients. Head Neck Surg 1980. 2(6): 476-482.
Reason for exclusion: No relevant outcome data reported.

Shuman, A. G., Yang, Y., Taylor, J. M., and Prince, M. E. End-of-life care among head and neck cancer patients. Otolaryngol Head Neck Surg 2011. 144(5): 733-739.
Reason for exclusion: Study design not relevant.

Simon, S. T., Higginson, I. J., Booth, S., Harding, R., and Bausewein, C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database Syst Rev 2010. (1): CD007354.
Reason for exclusion: Systematic review. Inclusion criteria not relevant to PICO. References within checked for relevance.

Talmi, Y. P., Bercovici, M., Waller, A., Horowitz, Z., Adunski, A., and Kronenberg, J. Home and inpatient hospice care of terminal head and neck cancer patients. J Palliat Care 1997. 13(1): 9-14.
Reason for exclusion: Outcomes not relevant to PICO.

Talmi, Y. P., Roth, Y., Waller, A., Chesnin, V., Adunski, A., Lander, M. I., and Kronenberg, J. Care of the terminal head and neck cancer patient in the hospice setting. Laryngoscope 1995. 105(3 Pt 1): 315-318.
Reason for exclusion: Outcomes not relevant to PICO.

Timon, C. and Reilly, K. Head and neck mucosal squamous cell carcinoma: results of palliative management. J Laryngol Otol 2006. 120(5): 389-392.
Reason for exclusion: Population not relevant to PICO.

Truong, A. Late tracheostomy tube decannulation by progression of a laryngeal tumour: An approach for airway control. Canadian Journal of Anesthesia 2011. 58(8): 771-772.
Reason for exclusion: Individual case report.

Viola, R., Kiteley, C., Lloyd, N. S., Mackay, J. A., Wilson, J., Wong, R. K., and Supportive Care Guidelines Group of the Cancer Care Ontario Program in Evidence-Based Care. The management of dyspnea in cancer patients: a systematic review. Supportive Care in Cancer 2008. 16(4): 329-337.
Reason for exclusion: Systematic review. No relevant outcome data included. References checked for relevance.

Weissberg, J. B., Pillsbury, H., Sasaki, C. T., Son, Y. H., and Fischer, J. J. High fractional dose irradiation of advanced head and neck cancer. Implications for combined radiotherapy and surgery 30. Arch Otolaryngol 1983. 109(2): 98-102.
Reason for exclusion: Population not relevant to PICO.

5. HPV-related disease

HPV testing

Clinical question: What is the most effective test to identify an HPV-positive tumour in people with cancer of the upper aerodigestive tract?

Background

An increasing proportion of oropharyngeal squamous cell cancers are associated with HPV infection. Although there are clinical and histological pointers to which of these tumours are HPV-positive, confirmation requires specific tests. Accurate diagnosis is important because counselling and prognosis differs between people with HPV-positive and HPV-negative tumours.

Immunohistochemical staining for p16 can be used as a surrogate test but more accurate identification of HPV-positive tumours requires additional tests. These include DNA in situ hybridisation (ISH), RNA ISH, and polymerase chain reaction (PCR). The tests differ in the tissue sample required, specificity, sensitivity, overall accuracy, availability, expertise required, cost and time to issuing the report. Uncertainty exists over which of the specific tests, or combination of tests, is the most appropriate.

Evidence summary

Two studies were identified that were relevant to the review. Both investigated the effectiveness of a range of tests to detect human papillomavirus (HPV) in upper aerodigestive tract tumours. There were no major issues with study quality, although risks of bias could arise from the exclusion of some patients from the results without adequate explanation (both studies) and not detailing the basis on which patients were included in the study (one study). Furthermore, one study provided very limited information on patient characteristics, meaning it is unclear whether all patients were applicable to the population of interest.

One study (Schache 2011, Schache 2013) investigated the performance of four individual tests and four combinations of tests for detecting HPV in 108 tumours of the oropharynx. p16 immunohistochemistry (p16 IHC), high-risk HPV in-situ hybridisation (HR-HPV ISH), DNA quantitative PCR (qPCR) and RNAscope had reported sensitivities of 0.94 (95% confidence interval (CI) 0.81, 0.99), 0.89 (95% CI 0.73, 0.97), 0.97 (95% CI 0.85, 1.0), and 0.97 (95% CI 0.84, 1.00), and specificities of 0.82 (95% CI 0.70, 0.91), 0.89 (95% CI 0.78, 0.95), 0.87 (95% CI 0.77, 0.94) and 0.93 (95% CI 0.82, 0.99), respectively. Combined p16 IHC/HR HPV ISH, combined p16 IHC/DNA qPCR, combined p16 IHC/RNA qPCR and combined DNA qPCR/RNA qPCR had reported sensitivities of 0.89 (95%CI 0.73, 0.97), 0.97 (95%CI 0.84, 1.00), 0.93 (95%CI 0.78, 0.99) and 0.94 (95%CI 0.80, 0.99) and specificities of 0.90 (95%CI 0.80, 0.96), 0.95 (95%CI 0.85, 0.99), 1.0 (95%CI 0.93, 1.00) and 1.0 (95%CI 0.94, 1.00), respectively. However, the detail of how test combinations were performed and interpreted was not reported.

One study (Smeets 2007) evaluated the effectiveness of four tests for detecting HPV in oral cavity or oropharyngeal tumours. HR-HPV ISH, p16 IHC, DNA PCR and mRNA PCR had reported sensitivities of

0.83 [95%CI 0.52, 0.98], 0.92 [95%CI 0.62, 1.00], 0.92 [95%CI 0.62, 1.00], and 0.92 [95%CI 0.62, 1.00], and specificities of 1.00 [95%CI 0.90, 1.00], 0.82 [95%CI 0.65, 0.93], 0.86 [95%CI 0.70, 0.95], and 0.97 [95%CI 0.85, 1.00], respectively.

Study characteristics and quality

Both studies were conducted in Europe (one in the United Kingdom) and published within the last ten years, although one study (Smeets 2007) did not report the time period over which patients were tested. One study (Schache 2011, Schache 2013) tested oropharyngeal tumours only; the second study tested oral cavity (62.5%) and oropharyngeal (37.5%) tumours.

In both studies, the diagnostic accuracy of a range of tests was reported, allowing for direct comparison of test performance in the same studied population. However, the size of the studied populations was small (less than 100 patients in each study) and both studies excluded some patients from their results without adequate explanation, which may lead to overly optimistic estimates of test performance. It is not clear to what extent the results of each study can be compared; one study (Smeets 2007) reported very limited information on the characteristics of the patients included in the trial. Additionally, each trial applied a different threshold for what constituted a positive reference standard test result. This means that the two trials may have used different definitions for what constitutes a HPV-positive and HPV-negative tumour.

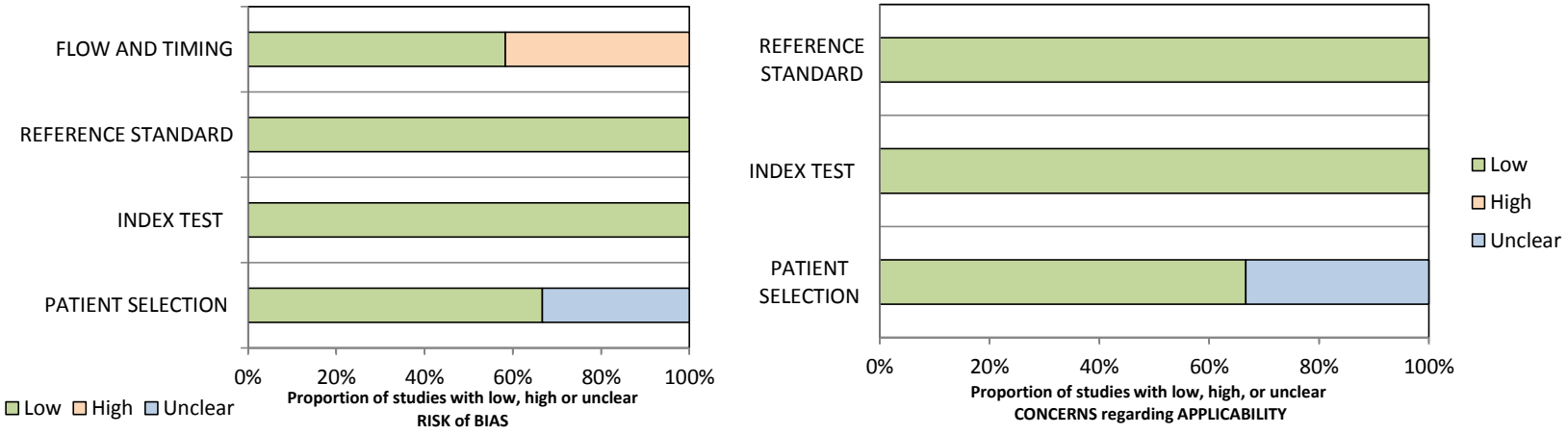
One study (Schache 2011) included the effectiveness of combinations of tests in addition to individual tests, but the methods used to assess combinations of tests are not clearly reported. For example, it is not clear whether the authors simply combined results of individual tests, or whether tests were re-run. It is also unclear how discordant results (i.e. one test in the combination reporting a positive result and one reporting a negative) were resolved. Furthermore, two test combinations utilise RNA qPCR, which was used as the reference standard against which test accuracy was assessed. It is not clear how RNA qPCR used in this way differs from the reference standard.

Table 5.1. Characteristics of included studies

Study ID	Study period	Patient characteristics	Number of patients	Studied test(s) (sample type)	Reference standard*
Schache 2011	1988–2009	Oropharyngeal SCC	97	p16 IHC (FFPE)	HPV16 E6 RNA quantitative PCR
			97	HR HPV ISH (FFPE)	
			97	Combined p16/HR HPV ISH (FFPE/fresh frozen, respectively)	
			98	DNA qPCR (fresh frozen)	
			88	Combined p16 IHC/DNA qPCR (FFPE/fresh frozen respectively)	
			84	Combined p16 IHC/RNA qPCR (FFPE/fresh frozen respectively)	
			93	Combined DNA qPCR/RNA qPCR (fresh frozen)	
Schache 2013	1988–2009	Oropharyngeal SCC	78	RNAscope (FFPE microarray)	
Smeets 2007	NR	Oral cavity or oropharyngeal SCC	45	P16 IHC (FFPE)	Analysis of viral load by measurement of HPV16 DNA copy numbers per cell, using real time PCR.
			47	GP5+/6+ DNA PCR (fresh frozen)	
			47	E6 mRNA PCR (FFPE)	
			47	HPV16/18 FISH (FFPE)	

* the reference standard was carried out using fresh frozen tissue in all cases.
Abbreviations: FFPE: formalin fixed paraffin-embedded tissue; FISH: fluorescence in-situ hybridisation; IHC: immunohistochemistry; ISH: in-site hybridisation; NR: not reported; qPCR: quantitative polymerase chain reaction; SCC: squamous cell carcinoma.

Figure 5.1. Summary of study quality (risks of bias and concerns regarding applicability). Each test, or combination of tests, was assessed individually, resulting in a total of 12 assessments (7 tests from Schache 2011, 1 test from Schache 2013, and 5 tests from Smeets 2007).



Outcomes

Table 5.2. Summary of the diagnostic accuracy of all tests.

Study	Test	Total number of patients	HPV prevalence, %*	Sensitivity (95% CI)	Specificity (95% CI)
Schache 2011	p16 IHC	97	35.7	0.94 [0.81, 0.99]	0.82 [0.70, 0.91]
	HR HPV ISH	97	35.7	0.89 [0.73, 0.97]	0.89 [0.78, 0.95]
	Combined p16/HR HPV ISH	97	35.7	0.89 [0.73, 0.97]	0.90 [0.80, 0.96]
	DNA qPCR	98	35.7	0.97 [0.85, 1.00]	0.87 [0.77, 0.94]
	Combined p16 IHC/DNA qPCR	88	35.7	0.97 [0.84, 1.00]	0.95 [0.85, 0.99]
	Combined p16 IHC/RNA qPCR	84	35.7	0.93 [0.78, 0.99]	1.00 [0.93, 1.00]
	Combined DNA qPCR/RNA qPCR	93	35.7	0.94 [0.80, 0.99]	1.00 [0.94, 1.00]
Schache 2013	RNAscope	78	35.7	0.97 [0.84, 1.00]	0.93 [0.82, 0.99]
Smeets 2007	HPV16/18 FISH	45	25.5	0.83 [0.52, 0.98]	1.00 [0.90, 1.00]
	P16 IHC	47	25.5	0.92 [0.62, 1.00]	0.82 [0.65, 0.93]
	GP5+/6+ DNA PCR	47	25.5	0.92 [0.62, 1.00]	0.86 [0.70, 0.95]
	E6 mRNA PCR	47	25.5	0.92 [0.62, 1.00]	0.97 [0.85, 1.00]

*Prevalence calculated from the proportion of samples testing positive with the reference standard (HPV16 E6 RNA quantitative PCR for Schache 2011 and Schache 2013; analysis of viral load by measurement of HPV16 DNA copy numbers per cell, using real time PCR for Smeets 2007)

Abbreviations: FISH: fluorescence in-situ hybridisation; IHC: immunohistochemistry; ISH: in-site hybridisation; NR: not reported; qPCR: quantitative polymerase chain reaction; SCC: squamous cell carcinoma.

Table 5.3. Estimates of the true positive, true negative, false positive and false negative rates of all tests, based on an assumed HPV prevalence of 35% in the tested population.

Study	Test	True positives, %	False positives, %	False negatives, %	True negatives, %
Schache 2011	p16 IHC	29	0	6	65
	HR HPV ISH	31	7	4	58
	Combined p16/HR HPV ISH	31	6	4	59
	DNA qPCR	34	8	1	57
	Combined p16 IHC/DNA qPCR	34	3	1	62
	Combined p16 IHC/RNA qPCR	33	0	2	65
	Combined DNA qPCR/RNA qPCR	33	0	2	65
Schache 2013	RNAscope	34	5	1	60
Smeets 2007	HPV16/18 FISH	29	0	6	65
	P16 IHC	32	12	3	53
	GP5+/6+ DNA PCR	32	9	3	56
	E6 mRNA PCR	32	2	3	66

Abbreviations: FISH: fluorescence in-situ hybridisation; IHC: immunohistochemistry; ISH: in-site hybridisation; NR: not reported; qPCR: quantitative polymerase chain reaction; SCC: squamous cell carcinoma.

Evidence tables for all included studies

Study, country

Schache, 2011 and 2013
United Kingdom (Liverpool Head and Neck Oncology Service)

Study type, study period

Retrospective cohort study.
1988 to 2009.

Number of patients

108 relevant cases identified; results available for between 78 and 97 patients, depending on the index test.

Patient characteristics

Inclusion criteria: all cases of oropharyngeal squamous cell carcinoma for which tissue bank records were available.

Gender	n (%)
Male	83 (77)
Female	25 (23)

Tumour site	n (%)
Tonsil	59 (55)
Soft palate	18 (17)
Base of tongue	20 (18)
Oropharynx; site not further specified	11 (10)

Mean age at diagnosis: 58.5 years.

Index tests

- P16 immunohistochemistry. Samples (FFPE) were scored as positive if there was strong and diffuse nuclear and cytoplasmic staining present in >70% of the malignant cells.
- High risk HPV in-situ hybridisation. Samples (FFPE) were scored as positive if there was any blue reaction product that co-localised with the nuclei of malignant cells.
- HPV E6 DNA quantitative PCR. Samples (fresh frozen tissue) were scored as positive if they had ≥1 E6 gene copy per diploid genome. Experiments were performed in duplicate, and only deemed positive if both runs met the threshold for positivity.
- RNAscope (RNA in-situ hybridisation of high-risk HPV).

Reference standard

HPV16 E6 RNA quantitative PCR. Carried out on fresh frozen sample tissue. The threshold for scoring a sample as HPV-positivewas not reported, but it is assumed that the same threshold as for HPV E6 DNA qPCR was used, i.e. samples with ≥1 E6 gene copy per diploid genome scored as positive.

Results

One hundred fresh frozen tissue samples and 97 formalin-fixed paraffin-embedded tissue blocks were available for analysis; tests results deemed not evaluable were excluded for each test.

Index test	N	True positives	False positives	False negatives	True negatives	Sensitivity (95% CI)	Specificity (95% CI)
p16 IHC	97	33	11	2	51	0.94 [0.81, 0.99]	0.82 [0.70, 0.91]
HR HPV ISH	97	31	7	4	55	0.89 [0.73, 0.97]	0.89 [0.78, 0.95]
Combined p16 IHC/HR HPV ISH	97	31	6	4	56	0.89 [0.73, 0.97]	0.90 [0.80, 0.96]
DNA qPCR	98	34	8	1	55	0.97 [0.85, 1.00]	0.87 [0.77, 0.94]
Combined p16 IHC/DNA qPCR	88	31	3	1	53	0.97 [0.84, 1.00]	0.95 [0.85, 0.99]
Combined p16 IHC/RNA qPCR	84	28	0	2	54	0.93 [0.78, 0.99]	1.00 [0.93, 1.00]
Combined DNA qPCR/RNA qPCR	93	31	0	2	60	0.94 [0.80, 0.99]	1.00 [0.94, 1.00]
RNAscope	78	32	3	1	42	0.97 [0.84, 1.00]	0.93 [0.82, 0.99]

Source of funding

Partially funded by Wellcome Trust; access to and cost associated with RNAscope testing was provided by Advanced Cell Diagnostics, Inc.

Comments on study quality

Risks of bias: The number of patients for whom test results were available (and therefore the number of tests used to calculate sensitivity and specificity) varies from one test to another. The reasons for this are not clearly explained by the study authors. It is unclear how results have been calculated for combinations of tests; for example whether the results of individual tests have simply been combined, or whether samples were retested; and how discordant results from the two tests used in combination were dealt with. As some test combinations use the reference standard as one test, it not clear how results are distinguished from the reference standard.
Concerns regarding applicability: no major concerns.

Additional comments

Study, country

Smeets, 2007
Netherlands, single centre.

Study type, study period

Retrospective cohort study.
Study period not reported.

Number of patients

48; results evaluable for a maximum of 47 patients.

Patient characteristics

Tumour site	n (%)
Oral cavity	30 (62.5)
Oropharynx	18 (37.5)

Index tests

- High-risk HPV fluorescence in-situ hybridisation. Staining intensity (rated as 0 to 3) and punctate and/or diffuse signals throughout the nucleus were evaluated. The threshold for positivity was not stated, but was assumed to be any staining intensity rating greater than 0.
- P16 immunohistochemistry. Any staining intensity greater than that of a background negative control (mouse IgG) was considered positive.
- Detection of high-risk HPV DNA by GP5+/GP6+ DNA PCR.
- Detection of HPV16 E6 mRNA by reverse transcription PCR. PCR products were detected using an enzyme immunoassay (EIA); samples were scored as positive when the EIA signal was greater than 3 times the average of the EIA signals of 4 negative controls

All index tests were performed on formalin-fixed paraffin-embedded samples.

Reference standard

Analysis of viral load by measurement of HPV16 DNA copy numbers per cell, using real time PCR. Tumours with >0.5 HPV16 DNA copies per cell were scored as positive.

The reference standard test was performed on fresh frozen tissue samples.

Results

Index test	N	True positives	False positives	False negatives	True negatives	Sensitivity (95% CI)	Specificity (95% CI)
HR HPV ISH	47	10	0	2	35	0.83 [0.52, 0.98]	1.00 [0.90, 1.00]
p16 IHC	45	11	6	1	27	0.92 [0.62, 1.00]	0.82 [0.65, 0.93]
GP5+/GP6+ DNA PCR	47	11	5	1	30	0.92 [0.62, 1.00]	0.86 [0.70, 0.95]
E6 mRNA qPCR	47	11	1	1	34	0.92 [0.62, 1.00]	0.97 [0.85, 1.00]

Source of funding

Not reported.

Comments on study quality

Risks of bias: It is unclear on what basis patients were included for testing. The period of time over which testing was conducted was not reported. Concerns regarding applicability: Limited information on patient characteristics was reported (tumour site only)

Additional comments

1

Evidence search details and references

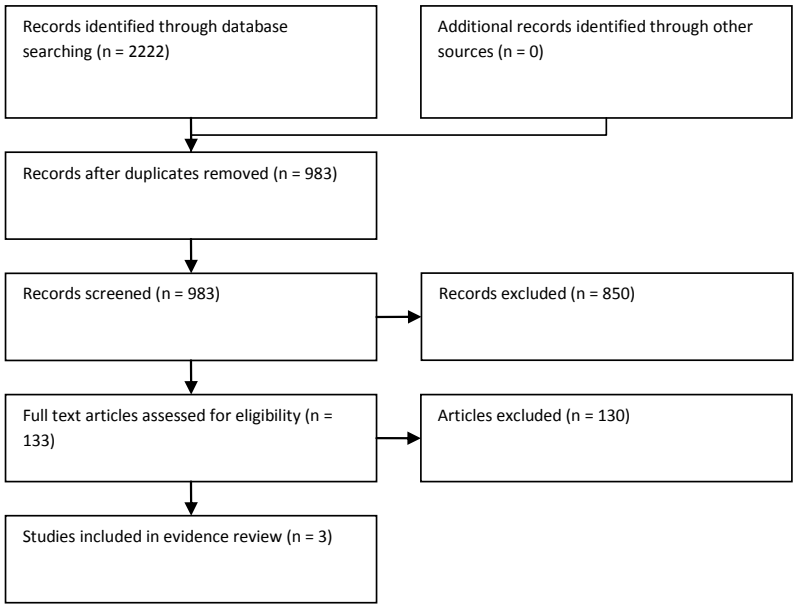
Review question in PICO format

Population	Intervention (Index Test)	Comparator (Reference Standard)	Outcomes
Adults diagnosed with cancer of the upper aerodigestive tract in whom HPV testing is indicated	• Immunohistochemistry (p16 IHC) • Quantitative polymerase chain reaction (qPCR) for viral E6 RNA (RNA qPCR) and DNA (DNA qPCR) • In situ hybridisation for high-risk HPV (HR HPV ISH) • Gene expression profiling • RNA in situ hybridisation test (RNAscope) • Combinations of the above	Real time DNA and RNA analysis using quantitative PCR on fresh tumour tissue	• Sensitivity • Specificity

Additional review protocol details (refer to Section 10 for full review protocol)

Type of review	Diagnostic test
Language	English only
Study design	Studies of diagnostic test accuracy
Status	Published data only
Other criteria for inclusion / exclusion of studies	Inclusion criteria: sufficient data reported to calculate the total number of true positives, true negative, false positives, and false negatives for the studied test(s). Exclusion criteria: reference standard is unclear or undefined.
Search strategies	Search from 2000 onwards
Review strategies	The evidence table for studies of diagnostic accuracy will be used (NICE Guidelines Manual Appendix J) to extract and present data from individual studies. Sensitivity and specificity data will be pooled when appropriate. Other outcomes will be presented as risk ratios or hazard ratios. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Different types of tumour tissue preparation (formalin fixed versus fresh frozen) for individual tests will also be compared, where this evidence is available.

Figure 5.2. Study flow diagram



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De-intensification of treatment

Clinical question: Is there a role for de-intensification of treatment in patients with HPV-positive upper aerodigestive tract tumours?

Background

Retrospective data analyses have suggested that people with HPV-positive oropharyngeal cancers (particularly those who have never smoked) have excellent cure rates with standard therapeutic approaches whether these are based around radiotherapy or surgery.

Radiation with chemotherapy has been a standard treatment option for oropharyngeal cancer for many years and predates the recognition of HPV-positive disease. Curative surgery can involve transoral or open techniques and is often followed by post-operative radiotherapy with or without chemotherapy.

These treatments have significant acute and long term morbidity with late effects varying from dysphagia to an increased risk of stroke. Now that the majority of HPV-positive patients can expect to remain disease free after treatment there is interest in reducing the intensity of initial therapy to improve long term quality of life without compromising cure rates.

Evidence statements

A systematic review of de-escalation treatment protocols for human papilloma virus (HPV) associated oropharyngeal squamous cell carcinoma (Masterson 2013, Masterson 2014) did not identify any published randomized trials. This review, however, identified nine ongoing trials due to complete data collection before 2021.

Accelerated fractionation radiotherapy versus standard fractionation radiotherapy

Overall mortality

Very low quality evidence from one observational study (Attner 2012) including 126 patients with HPV16 DNA-positiveand P16-positivetonsillar cancer suggests uncertainty over whether accelerated or standard fractionated radiotherapy is the more effective in terms of overall mortality (HR = 0.62, 95% CI 0.30, 1.41; HR <1 favours accelerated fractionation). Four-year overall survival was 84% with accelerated fractionation and 71% with conventional fractionation.

Disease recurrence

Low quality evidence about locoregional recurrence comes from a subgroup analysis of 179 patients with P16-positive larynx, pharynx, or oral cavity squamous cell carcinoma, who were part of a larger randomized trial (DAHANCA 6&7; Lassen 2011). The evidence suggests that locoregional recurrence is less likely with accelerated than with conventionally fractionated radiotherapy, (HR = 0.58, 95% CI 0.35, 0.99; HR <1 favours accelerated fractionation). Five-year locoregional recurrence free survival was 76% with accelerated radiotherapy and 60% with conventional radiotherapy.

Very low quality evidence from one observational study (Attner 2012) including 126 patients with HPV16 DNA-positiveand P16-positivetonsillar cancer suggests uncertainty over whether accelerated

or standard fractionated radiotherapy is the more effective in terms of disease recurrence (HR = 0.74, 95% CI 0.30, 1.75; HR <1 favours accelerated fractionation). Four-year recurrence-free survival was 85% with accelerated fractionation and 79% with conventional fractionation.

Treatment-related morbidity

Low quality evidence about late complications from a subgroup analysis of 179 patients with P16-positivelarynx, pharynx or oral cavity squamous cell carcinoma, who were part of a larger randomized trial (DAHANCA 6&7; Lassen 2011), suggests a similar rate of late radiation-induced morbidity for accelerated and conventional radiotherapy: 23% for accelerated radiotherapy versus 26% for conventional fractionation at 5 years after treatment (difference not statistically significant).

Radiotherapy versus chemoradiotherapy

Overall mortality

Very low quality evidence from an observational study (Attner et al, 2012) including 113 patients with HPV16 DNA-positiveand P16-positivetonsillar cancer, suggests uncertainty over whether radiotherapy or chemoradiotherapy is the more effective in terms of overall mortality (HR = 1.20; 95% CI 0.50, 2.90; HR < 1 favours radiotherapy). Four year overall survival was 71% with conventionally fractionated radiotherapy compared with 84% for chemoradiotherapy.

Disease recurrence

Very low quality evidence from three observational studies (Attner et al, 2012; Haughey et al, 2012 and O'Sullivan et al 2013) suggests uncertainty over whether chemoradiotherapy is more effective than radiotherapy in terms of disease recurrence. The hazard ratio for recurrence ranged from 1.08 to 2.40 (where HR >1 favours chemoradiotherapy). Although recurrence rates were lower with chemoradiotherapy than with radiotherapy, this difference was not statistically significant due to the low event rates in these studies.

Very low quality evidence from observational studies (Attner et al, 2012; Haughey et al, 2012 and O'Sullivan et al 2013) suggests uncertainty over whether chemoradiotherapy is more effective than radiotherapy in terms of metastasis. In Attner et al (2012) the hazard ratio for distant metastasis was 2.98 (95% CI 0.38, 23.46; HR <1 favours radiotherapy). Four-year metastasis-free survival was 89% with radiotherapy and 97% with chemoradiotherapy.

O'Sullivan et al (2013) performed subgroup comparisons of distant control with CRT versus RT according to T and N category in patients with low risk (T1–3; N0–2c) HPV-positive oropharyngeal tumours. Rates of distant metastasis did not differ significantly between chemoradiotherapy and radiotherapy when patients were grouped by T category (T1, T2 and T3) or for patients with N0–2a disease. Patients with N2b or N2c disease, however, had better distant control at 3 years with chemoradiotherapy than with radiotherapy alone. For patients with N2b disease, 3-year distant control rates were 98% with CRT and 89% with RT; for those with N2c the rates were 92% with CRT and 73% with RT.

Patient choice

Low quality evidence about patient choice came from a cross sectional study (Brotherson et al, 2013) which surveyed patients with oropharyngeal squamous cell carcinoma about treatment de-escalation. This evidence suggests that, given equivalent survival rates, patients are more likely to

choose radiotherapy than chemoradiotherapy, with 91% choosing radiotherapy in this scenario. If chemoradiotherapy had a 5% absolute survival benefit over radiotherapy, however, 69% of patients would choose chemoradiotherapy.

Low dose versus standard dose radiotherapy plus EGFR inhibitor (following chemotherapy)

Overall mortality

Low quality evidence about overall mortality comes from a phase II trial of 77 patients with stage III or IV HPV-positiveoropharyngeal carcinoma (Cmelak et al, 2014), which used a reduced dose (54 Gy) of intensity modulated radiotherapy (IMRT) plus cetuximab in patients with complete clinical response to induction chemotherapy. This evidence reports 2-year overall survival rates of 95% (90% CI 87%, 98%) with reduced dose IMRT. Patients without complete clinical response to induction chemotherapy had standard dose IMRT (70 Gy) plus cetuximab, with 2 year overall survival rates of 87% (90% CI 63% to 96%).

Disease progression

Low quality evidence from the Cmelak et al (2014) phase II trial suggests 23-month progression free survival rates of 84% (90% CI 74% to 90%) with reduced dose IMRT (54 Gy) plus cetuximab compared with 64% (90% CI 39% to 81%) for those receiving standard dose IMRT (70 Gy) plus cetuximab.

Low dose versus standard dose adjuvant chemotherapy (following surgery)

Overall mortality

Very low quality evidence from one observational study of 54 patients with locally advanced HPV and P16-positivehead and neck cancer (Geiger et al, 2014) suggests uncertainty over whether lower dose chemotherapy is as effective as standard dose chemotherapy following surgery in terms of overall mortality (HR 1.61, 95% CI 0.32, 7.97; HR <1 favours lower dose chemotherapy). Three-year overall survival was 86% with lower dose chemotherapy compared with 91% for standard dose chemotherapy.

Disease recurrence or mortality

Very low quality evidence from one observational study of 54 patients with locally advanced HPV and P16-positivehead and neck cancer (Geiger et al, 2014) suggests uncertainty over whether lower dose chemotherapy is as effective as standard dose chemotherapy following surgery in terms of disease recurrence or death (HR 1.05, 95% CI 0.30, 3.75; HR <1 favours lower dose chemotherapy). Three-year recurrence free survival was 82% with lower dose chemotherapy compared with 84% for standard dose in this study.

Radiotherapy plus EGFR inhibitor versus chemoradiotherapy

Overall mortality

Very low quality evidence about overall mortality comes from an observational study of patients with HPV16-positive (n = 17) or P16-positive (n = 18) stage III or IV head and neck squamous cell carcinoma (Pajares et al, 2013) comparing radiotherapy plus EGFR inhibitor to chemoradiotherapy. This evidence suggests better overall survival with RT plus EGFR inhibitor than with chemoradiotherapy. For patients with HPV16-positive tumours, HR = 0.22 (95% CI 0.05, 0.90); for patients with P16-positive tumours HR = 0.18 (95% CI 0.04, 0.88) (HR <1 favours RT plus EGFR

inhibitor). For patients with HPV16-positive tumours, two-year overall survival was 83% with RT plus EGFR inhibitor compared with 33% for chemoradiotherapy. For patients with P16-positive tumours, two-year overall survival was 88% with RT plus EGFR inhibitor compared with 60% for chemoradiotherapy.

Disease free survival

Very low quality evidence from an observational study (Pajares et al, 2013), suggests better disease free survival with RT plus EGFR inhibitor than with chemoradiotherapy. For patients with HPV16-positive tumours, HR = 0.19 (95% CI 0.47, 0.80), for patients with P16-positive tumours HR = 0.20 (95% CI 0.01, 2.40) (HR <1 favours RT plus EGFR inhibitor). For patients with HPV16-positive tumours, two-year disease free survival was 50% with RT plus EGFR inhibitor compared with 17% for chemoradiotherapy. For patients with P16-positive tumours, two-year disease free survival was 75% with RT plus EGFR inhibitor compared with 47% for chemoradiotherapy.

Chemotherapy plus EGFR inhibitor versus chemotherapy alone

Overall mortality

Low quality evidence about overall mortality comes from a subgroup analysis of patients with HP16-positive (N = 24) or P16-positive (N = 41) recurrent or metastatic head and neck squamous cell carcinoma in a randomised trial (EXTREME; Vermorken et al, 2014) which compared chemotherapy plus EGFR inhibitor to chemotherapy alone. This evidence suggests uncertainty over the effect of adding EGFR inhibitor to chemotherapy on overall survival. For patients with HPV16-positive tumours, HR = 0.72 (95% CI 0.28, 1.83), for patients with P16-positive tumours HR = 0.63 (95% CI 0.30, 1.34) (HR < 1 favours chemotherapy plus EGFR inhibitor). For patients with HPV16-positive tumours, median overall survival was 13.2 months with chemotherapy plus EGFR inhibitor compared with 7.1 months for chemotherapy alone. For patients with P16-positive tumours, median overall survival was 12.6 months with chemotherapy plus EGFR inhibitor compared with 9.6 months for chemotherapy alone.

Disease progression

Low quality evidence, from a subgroup analysis of a randomised trial (Vermorken et al, 2014), suggests uncertainty over the effect of adding EGFR inhibitor to chemotherapy on disease progression. For patients with HPV16-positive tumours, HR = 0.48 (95% CI 0.19, 1.21), for patients with P16-positive tumours HR = 0.73 (95% CI 0.36, 1.47) (HR < 1 favours chemotherapy plus EGFR inhibitor). For patients with HPV16-positive tumours, median progression free survival was 4.8 months with chemotherapy plus EGFR inhibitor compared with 4.3 months for chemotherapy alone. For patients with P16-positive tumours, median progression free survival was 12.6 months with chemotherapy plus EGFR inhibitor compared with 9.6 months for chemotherapy alone.

Treatment related morbidity

Low quality evidence about serious adverse events comes from a subgroup analysis of the EXTREME trial (Vermorken et al, 2014). This evidence suggests uncertainty over the effect of adding EGFR inhibitor to chemotherapy on serious adverse events. Serious adverse events occurred at similar rates in both treatment groups: around 37% for patients with HPV16-positive tumours and around 55% for patients with P16-positive tumours.

Study characteristics

Table 5.4. Characteristics of included studies

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	N	INTERVENTION	COMPARISON	OUTCOMES MEASURED
Attner 2012	Observational	Patients with both HPV16+ and P16+ tonsillar carcinoma (mostly stage III to IV)	153	Accelerated radiotherapy, conventional radiotherapy	Radiotherapy plus chemotherapy	Overall survival, disease free survival and metastasis free survival
Brotherston 2012	Cross sectional survey	Patients with oropharyngeal cancer (post chemoradiotherapy)	51	Radiotherapy	Radiotherapy plus chemotherapy	Treatment preference
Cmelak 2014	Phase II non-randomised trial	Patients with locally advanced resectable HPV-positive oropharyngeal cancer	77	Low dose IMRT plus cetuximab (following induction chemotherapy)	Standard dose IMRT plus cetuximab (following induction chemotherapy)	Progression free survival, overall survival.
Geiger 2014	Observational	Patients with HPV-positive and P16-positive locally advanced head and neck squamous cell carcinoma treated with surgery	54	Lower dose adjuvant chemotherapy (weekly cisplatin)	Standard adjuvant chemotherapy (high dose cisplatin)	Overall survival, recurrence free survival
Haughey 2012	Observational	Patients with HPV-positive oropharyngeal cancer	171	TLM without radiotherapy	TLM with chemotherapy and radiotherapy	Disease specific survival, disease free survival and recurrence
Lassen 2011	RCT	Patients with P16-positive squamous cell carcinoma of the larynx, pharynx or oral cavity.	179	Accelerated radiotherapy (6 fractions per week)	Conventional radiotherapy (5 fractions per week)	Locoregional control, late complications
Masterson 2013, Masterson 2014	Systematic review of RCTs	Patients with HPV-positive oropharyngeal cancer	0	De-escalation of treatment with radiotherapy, chemotherapy or immunotherapy.	Standard chemoradiotherapy	Overall survival, Treatment related morbidity and side effects.
O'Sullivan 2013	Observational	Patients with HPV-positive oropharyngeal cancer	286	Radiotherapy	Radiotherapy plus chemotherapy	Disease control (local, regional and distant failure)
Pajares 2013	Observational	Patients with HPV related head and neck cancer	18	RT plus EGFR inhibitor (cetuximab, panitumumab or gefitinib)	RT plus chemotherapy (cisplatin)	Overall survival, recurrence, complete response
Vermorken 2014	RCT	Patients with recurrent or metastatic HPV-positive head and neck squamous cell carcinoma	24	Chemotherapy	Chemotherapy plus cetuximab	Progression free survival, overall survival, response rate, adverse events
Abbreviations: RCT: randomised controlled trial; SCC: squamous cell carcinoma; TLM: transoral laser microsurgery						

GRADE evidence tables

Table 5.5. GRADE evidence profile: accelerated radiotherapy versus standard radiotherapy for HPV-positive upper airways cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated RT	Standard RT	Relative (95% CI)	Absolute	
Death from any cause[1] (follow-up median 4.1 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	8/40 (20%)	27/86 (31.4%)	HR 0.62 (0.30, 1.41)	4 year overall survival 84% for accelerated versus 71% for conventional RT.	⊕OOO VERY LOW
Late complications[3] (follow-up 5 years)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	?/86 (?%)[5]	?/68 (?%)[5]	Not reported	5 year late complication rate: 23% for accelerated RT versus 26% for conventional	⊕⊕OO LOW
Locoregional recurrence[3] (follow-up 5 years)											
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[2]	none	24/95 (25.3%)	32/84 (38.1%)	HR 0.58 (0.35, 0.99)	5 year late locoregional recurrence free survival rate: 76% for accelerated RT versus 60% for conventional RT.	⊕⊕OO LOW
Disease recurrence[1] (follow-up median 4.1 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	7/40 (17.5%)	18/86 (20.9%)	HR 0.74 (0.30, 1.75)	4 year disease free survival 85% for accelerated versus 79% for conventional RT.	⊕OOO VERY LOW

[1] Attner (2012) [2] Low event rate [3] Lassen (2011) [5] Number of events not reported [6] Subgroup analysis of a larger trial - unclear whether this was a planned or post-hoc analysis.

Table 5.6. GRADE evidence profile: radiotherapy versus chemo-radiotherapy for HPV-positive upper airways cancer.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	Chemo-radiotherapy	Relative (95% CI)	Absolute	
Death from any cause[1] (follow-up median 4.1 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	27/86 (31.4%)	4/27 (14.8%)	HR 1.20 (0.50, 2.90)	4 year overall survival 71% for conventional RT versus 84% for chemoradiotherapy	⊕OOO VERY LOW
Disease recurrence (follow-up median 3.9 to 4.1 years)											
3	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50/309 (16.2%)	21/232 (9.1%)	HR ranged from 1.08 to 2.40 (0.70, 8.14)	4 year disease free survival 79% for conventional RT versus 91% for chemoradiotherapy (Attner et al 2012)	⊕OOO VERY LOW
Metastasis (follow-up median 3.9 to 4.1 years)											
3	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	26/309 (8.4%)	13/232 (5.6%)	HR 2.98 (0.38, 23.46)	4 year metastasis free survival 89% for conventional RT versus 97% for chemoradiotherapy (Attner et al 2012)	⊕OOO VERY LOW
Patient choice (if survival were equivalent)[3]											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/51 (90.2%)	5/51 (9.8%)	Not applicable	For every 100 patients 90 would choose RT and 10 ChemoRT, if overall survival was equivalent	⊕⊕OO LOW

[2] Low number of events [3] Brotherson (2013)

Table 5.7. GRADE evidence profile: low dose radiotherapy plus EGFR inhibitor versus standard dose radiotherapy plus EGFR inhibitor after chemotherapy for HPV-positive upper airways cancer.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose radiotherapy plus cetuximab (post chemo)	Standard dose radiotherapy plus cetuximab (post chemo)	Relative (95% CI)	Absolute	
Death from any cause[1] (follow-up 2 years)											
1	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	?/62 [4]	?/15 [4]	Not reported	2 year overall survival was 95% for low dose RT versus 87% for standard dose	⊕OOO VERY LOW
Disease progression[1] (follow-up 2 years)											
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	?/62 [4]	?/15 [4]	Not reported	2 year progression free survival was 85% for low dose RT versus 64% for standard dose	⊕OOO VERY LOW

[1] Cmelak (2014)
[2] Only patients with complete clinical response to induction chemotherapy could receive reduced dose IMRT.
[3] Low number of events
[4] Event rates not reported

Table 5.8. GRADE evidence profile: lower dose adjuvant chemotherapy versus standard dose adjuvant chemotherapy after surgery for HPV-positive upper airways cancer.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose adjuvant chemotherapy (post surgery)	Standard dose adjuvant chemotherapy (post surgery)	Relative (95% CI)	Absolute	
Death from any cause (median follow up 5 years)[1]											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	3/22 (13.6%)	3/32 (9.4%)	HR 1.61 (0.32, 7.97)	3 year overall survival 86% for low dose versus 91% for standard dose	⊕OOO VERY LOW
Disease recurrence or death (median follow up 5 years)[1]											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	4/22 (18.2%)	6/32 (18.8%)	HR 1.06 (0.30, 3.75)	3 year recurrence free survival 82% for low dose versus 84% for standard dose	⊕OOO VERY LOW

[1] Geiger (2014)
[2] Low event rate

Table 5.9. GRADE evidence profile: radiotherapy plus EGFR inhibitor versus radiotherapy plus chemotherapy for HPV16-positive upper airways cancer.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy plus EGFR inhibitor	Radiotherapy plus Chemotherapy	Relative (95% CI)	Absolute	
Death from any cause[1] (follow-up 2 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	?/11 [3]	?/6 [3]	HR = 0.22 (0.05, 0.90)	2 year overall survival 83% for RT+EGFR inhibitor versus 33% for RT+Chemo	⊕OOO VERY LOW
Disease recurrence or death from any cause[1] (follow-up 2 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	?/11 [3]	?/6 [3]	HR = 0.19 (0.47, 0.80)	2 year disease free survival 50% for RT+EGFR inhibitor versus 17% for RT+Chemo	

[1] Pajares (2013)
[2] Low event rate
[3] Event rate not reported

Table 5.10. GRADE evidence profile: radiotherapy plus EGFR inhibitor versus radiotherapy plus chemotherapy for P16-positive upper airways cancer.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy plus EGFR inhibitor	Radiotherapy plus Chemotherapy	Relative (95% CI)	Absolute	
Death from any cause[1] (follow-up 2 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	none	2/8 (25%)	7/10 (70%)	HR 0.18 (0.04, 0.88)	2 year overall survival 88% for RT+EGFR inhibitor versus 60% for RT+Chemo	⊕OOO VERY LOW
Disease recurrence or death from any cause (follow-up 2 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	1/8 (12.5%)	4/10 (40%)	HR 0.2 (0.01, 2.4)	2 year disease free survival 75% for RT+EGFR inhibitor versus 47% for RT+Chemo	⊕OOO VERY LOW

[1] Pajares (2013)

[2] Low event rate

Table 5.11. GRADE evidence profile: chemotherapy plus EGFR inhibitor versus chemotherapy for HPV16-positive upper airways tumours

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy plus EGFR inhibitor	Chemotherapy	Relative (95% CI)	Absolute	
Death from any cause[1] (follow-up 2.25 years)											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	8/11 (72.7%)	10/13 (76.9%)	HR 0.72 (0.28, 1.83)	Median overall survival 13.2 months for chemo plus EGFR inhibitor versus 7.1 months for chemo alone	⊕⊕OO LOW
Disease progression[1] (follow-up 2.25 years)											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	10/11 (90.9%)	11/13 (84.6%)	HR 0.48 (0.19, 1.21)	Median progression free survival 4.8 months for chemo plus EGFR inhibitor versus 4.3 months for chemo alone	⊕⊕OO LOW
Serious adverse events[1]											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	4/11 (36.4%)	5/13 (38.5%)	RR 0.95 (0.33, 2.68)	19 fewer per 1000 (from 258 fewer to 646 more)	⊕⊕OO LOW

[1] Vermorken (2014)
[2] Subgroup analysis of larger trial - unclear whether this was a pre-planned analysis
[3] Low event rate

Table 5.12. GRADE evidence profile: chemotherapy plus EGFR inhibitor versus chemotherapy for P16-positive upper airways tumours

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy plus EGFR inhibitor	Chemotherapy	Relative (95% CI)	Absolute	
Death from any cause[1]											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	10/18 (55.6%)	17/23 (73.9%)	HR 0.63 (0.30, 1.34)	Median overall survival 12.6 months for chemo plus EGFR inhibitor versus 9.6months for chemo alone	⊕⊕OO LOW
Disease progression[1] **(follow-up 2.25 years)**											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	15/18 (83.3%)	17/23 (73.9%)	HR 0.73 (0.36, 1.47)	Median progression free survival 5.6 months for chemo plus EGFR inhibitor versus 3.6 months for chemo alone	⊕⊕OO LOW
Serious adverse events[1]											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	10/18 (55.6%)	12/22 (54.5%)	RR 1.04 (0.30, 3.64)	22 more per 1000 (from 382 fewer to 1000 more)	⊕⊕OO LOW

[1] Vermorken (2014)
[2] Subgroup analysis of larger randomised trial - unclear if pre-planned analysis
[3] Low event rate

Evidence tables for all included studies

Study, country
Masterson 2013, 2014. UK
Study type, study period
Systematic review of RCTs published 1926-2012
Number of patients
0. No published RCTs were identified.
Patient characteristics
Patients with carcinoma of the oropharynx. Cancers were primary squamous cell carcinoma arising from the oropharyngeal mucosa, diagnosed to be HPV16-positiveby PCR or DNA/RNA in situ hybridization and displaying p16 activity using IHC.
Intervention
De-escalation treatment (use of a less toxic treatment than standard)
Comparison
Standard treatment
Length of follow-up
Not specified
Outcome measures and effect size
Nine ongoing trials of de-escalation in HPV associated head and neck cancer identified:

Trial name	Patients	Intervention	Comparison	Data collection complete
Cohen 2010	Locally advanced stage III or IV head and neck SCC	Everolimus escalating dose	Placebo	2016
De-ESCALaTE 2012	Stage III-IVa oropharyngeal carcinoma	Cetuximab plus RT	Cisplatin plus RT	2015
ECOG 1308	Stage III-IV oropharyngeal carcinoma	Low dose IMRT plus cetuximab	High dose IMRT plus cetuximab	2014
Quarterback 2012	Stage III-IV oropharyngeal, nasopharyngeal or unknown primary SCC	Following induction chemotherapy reduced dose radiotherapy.	Following induction chemotherapy standard dose radiotherapy.	2019
RTOG	Oropharyngeal carcinoma	Cetuximab plus RT	Cisplatin plus RT	2020
TROG-12.01	Locally advanced oropharyngeal carcinoma	Cetuximab plus RT	Cisplatin plus RT	2019
ADEPT	Surgically treated oropharyngeal carcinoma, stage III-IV	RT after surgery	RT plus cisplatin after surgery	2017
ECOG 3311	Surgically treated oropharyngeal carcinoma, stage III-IV; intermediate risk patients	50 Gy IMRT	60 Gy IMRT	2016
PATHOS	Surgically treated oropharyngeal carcinoma, stage III-IV; intermediate or high risk patients	Intermediate risk patients: 50 Gy IMRT. High risk patients: 60 Gy IMRT	Intermediate risk patients: 60 Gy IMRT. High risk patients: 60 Gy IMRT plus cisplatin	2019

Source of funding
No conflicts of interest were declared
Risks of bias
Not applicable.
Additional comments

Study, country
Cmelak 2014. USA
Study type, study period
Non randomized phase II trial – a smaller trial designed to see if de-intensified treatment is safe and effective enough to be tested in a full scale trial. 2010 - 2014
Number of patients
90 enrolled, 77 analyzed
Patient characteristics
HPV-positive (p16 on IHC or HPV-16 on FISH) patients with resectable III/Iva,b oropharyngeal squamous cell carcinoma
Intervention
All patients had induction chemotherapy (3 cycles of: cisplatin IV on day 1, paclitaxel IV and cetuximab IV on days 1, 8 and 15). Complete clinical responders then received lower dose IMRT (54Gy) + cetuximab: IMRT 5 days per week for 5 weeks (27 fractions) and cetuximab IV once weekly for 6 weeks.
Comparison
Patients with partial response to induction chemotherapy received standard dose IMRT (69Gy) + cetuximab: IMRT 5 days per week for 6

weeks (33 fractions) and cetuximab IV once weekly for 7 weeks.

Length of follow-up

24 months

Outcome measures and effect size

Treatment group	23 month progression free survival (90% C.I.)	24 month overall survival (90% C.I.)
Lower dose treatment (n = 62)	84% (74%, 90%)	95% (87%, 98%)
Standard dose treatment (n = 15)	64% (39%, 81%)	87% (63%, 96%)

Treatment described as well tolerated: 96% of patients all 3 cycles of induction chemotherapy, 71% had complete clinical response to induction chemotherapy.

Source of funding

Sponsors and collaborators: Eastern Cooperative Oncology Group, National Cancer Institute

Risks of bias

Non randomized trial, low number of events, treatment selected on the basis of response to induction therapy (cannot compare outcomes between lower and standard dose treatment).

Additional comments

Abstract only

1

Study, country

Attner, 2012; Sweden

Study type, study period

Observational study, retrospective. 2000-2007

Number of patients

153

Patient characteristics

Patients with tonsillar squamous cell carcinoma, treated with curative intent, with HPV-DNA-positive and P-16-positive tumours.
Patients in the different treatment groups were similar, except for stage – those in the chemoradiotherapy group had significantly higher stage than those in the other groups.

Intervention

Conventional radiotherapy (N = 86)

Comparison

Accelerated radiotherapy (N = 40)
Chemo-radiotherapy (N = 27)

Length of follow-up

Outcome measures and effect size

	Accelerated RT	Conventional RT	HR (95% C.I.)*	P
Time to death from any cause	8/40	27/86	0.62 (0.30, 1.41)	0.250
Time to recurrence	7/40	18/86	0.74 (0.30, 1.75)	0.489

*Multivariate analysis incorporating age, sex and tumour stage. HR < 1 favours accelerated RT.

	Conventional RT	Chemoradiotherapy	HR (95% C.I.)*	P
Time to death from any cause	27/86	4/27	1.20 (0.50, 2.90)	0.672
Time to recurrence	13/86	3/27	2.40 (0.70, 8.14)	0.155
Time to metastasis	8/86	1/27	2.98 (0.38, 23.46)	0.300

*Multivariate analysis incorporating age, sex and tumour stage. HR < 1 favours conventional RT.

Source of funding

The Swedish Cancer Foundation, The Stockholm Cancer Society, Swedish Research Council, The Laryngeal Foundation, Henning and Isa Perssons Foundation, Stockholm City Council, The Karolinska Institutet and The ACTA Otolaryngologica foundation.

Risks of bias

Non randomized retrospective study, treatment groups were unbalanced in terms of baseline characteristics (especially tumour stage), low number of patients and events.

Additional comments

2

Study, country

Lassen, 2011. Denmark

Study type, study period

RCT. 1992-1999

Number of patients

179

Patient characteristics

Conventional RT group (N = 84)

P16-positive patients, median age 61 years (range 41 to 83 years), 74% male, primary site larynx (42%) oropharynx (42%) pharynx-other (10%) oral cavity (6%), T1-2 (69%), T3-4 (31%), N0 (54%), N1-3 (46%), stage I-II (39%), stage III-IV (61%).

Accelerated RT group (N = 95)

P16-positive patients, median age 60 years (range 21 to 87 years), 76% male, primary site larynx (37%) oropharynx (51%) pharynx-other (3%) oral cavity (9%), T1-2 (68%), T3-4 (32%), N0 (56%), N1-3 (44%), stage I-II (40%), stage III-IV (60%).

Intervention

Accelerated radiotherapy; 6 fractions per week, 2Gy per fraction with a minimum tumour dose of 66 to 68 Gy

Comparison

Conventionally fractionated radiotherapy; 5 fractions per week, 2Gy per fraction with a minimum tumour dose of 66 to 68 Gy

Length of follow-up

At least 5 years or until death

Outcome measures and effect size

	Accelerated RT	Conventional RT	HR (95% CI)	P
Locoregional failure	24/95	32/84	HR = 0.58 (0.35, 0.99)	P = 0.05
Absolute locoregional failure rate at 5 years	24%	40%	-	-
Late complications	?/86	?/68	NR	P = 0.70
Absolute late complication rate at 5 years	23%	26%	-	-

Source of funding

Danish Cancer Society, Danish Council for Strategic Research, Danish Ministry of Health, CIRRO-The Lundbeck Foundation Centre for Interventional Research in Radiation Oncology, The Danish Cancer Research Foundation and The Faculty of Health, Aarhus University

Risks of bias

Unclear allocation concealment, relatively low event rate, subgroup analysis of a randomized trial (unclear whether this was a planned analysis and whether the trial was powered for this analysis)

Additional comments

1

Study, country

Brotherston 2013. Canada

Study type, study period

Cross sectional survey. 2011

Number of patients

51

Patient characteristics

Patients with oropharyngeal cancer who had received chemoradiotherapy, 88% male, median age 58 years, primary cancer site: base of tongue (43%) tonsil (55%) unknown (2%), 51% HPV-positive,

Intervention

Radiotherapy

Comparison

Chemo-radiotherapy

Length of follow-up

Not applicable

2

Outcome measures and effect size
Patients were asked how much hypothetical survival benefit they would be prepared to trade off when choosing between radiotherapy (RT) and chemoradiotherapy (CRT). When survival rates were first presented as identical, 90% of patients (46/51) would choose RT over CRT. However few patients would tolerate significantly reduced survival to receive RT alone: 63% (35/51) chose CRT if the difference in survival rate was 5%. 5 patients chose CRT over RT even in the scenario where survival was the same, despite additional counselling that there was no survival benefit with CRT – these patients said that maximal treatment gave them peace of mind. Patients were asked which treatment they found most disruptive in their own personal experience and wished to avoid most, 81% (41 out of 51) would choose to avoid chemotherapy. Participants considered the following factors when selecting between treatments in the trade off task: 55% (28/51) considered survival rate, 47% (24/51) physician's advice and 10% (5/51) their own research or knowledge. 10% (5/51) offered family as a factor in treatment decision making and 4% (2/51) considered the impact on work as an important factor.
Source of funding
Ontario Institute of cancer Research
Risks of bias
Observational study,
Additional comments

1

Study, country
Geiger 2014. USA
Study type, study period
Observational study, retrospective. 2004-2010
Number of patients
54
Patient characteristics
Patients with HPV associated locally advanced (stage III or IV) hand and neck squamous cell carcinoma treated with curative intent surgery followed by adjuvant chemotherapy.
Intervention
Weekly cisplatin group (N = 22). Following surgery weekly cisplatin (25-30 mg/m^2 weekly) plus radiotherapy 6000 cGy in 30 fractions using IMRT.
Comparison
High dose cisplatin group (N = 32). Following surgery weekly cisplatin (100 mg/m^2 IV every 21 days for 3 cycles) plus radiotherapy 6000 cGy in 30 fractions using IMRT.
Length of follow-up
Median follow up was 5 years.
Outcome measures and effect size

	Weekly cisplatin	**High dose cisplatin**	**HR (95%CI)***	**P**
Death from any cause	3/22	3/32	1.61 (0.32, 7.97)	0.56
3 year overall survival	86%	91%	-	-
Recurrence or death	4/22	6/32	1.06 (0.30, 3.75)	0.93
3 year rate of recurrence free survival	82%	84%	-	-

*HR not reported but calculated using the event rates and log-rank test results.

Source of funding
National Center for Advancing Translational Sciences
Risks of bias
Non randomized study, low event rate, baseline characteristics not reported separately for HPV-positive patients so it is unclear whether the treatment groups were comparable – although a multivariate model was used for analysis (using age, gender, smoking history, open versus transoral surgery, HPV status and prior alcohol abuse).
Additional comments

2

Study, country

Pajares, 2013. Spain

Study type, study period

Observational, 200-2011

Number of patients

22 HPV positive; 18 P16 positive

Patient characteristics

Patients with locally advanced (stage III-IV, non metastatic) head and neck squamous cell carcinoma. 17 were positive for high risk HPV (HPV16, 18, 51 and 58), 3 for low risk HPV (HPV5 and 6) and 2 for unknown subtypes. 18 patients had P16-positive tumours

Intervention

Radiotherapy plus EGFR inhibitor. EGFR inhibitor was typically cetuximab but some received panitumumab or gefitinib (proportion not reported for the HPV/P16-positive subgroups). Radiotherapy was 3DCRT median dose 72 Gy (range 57-78 Gy). Some patients received accelerated fractionation but this proportion is not reported by HPV or P16-positive subgroups.

Comparison

Radiotherapy plus chemotherapy. Chemotherapy was three weekly cisplatin doses of 100 mg/m2 or weekly cisplatin at 40,g/m2. Radiotherapy was 3DCRT median dose 72 Gy (range 57-78 Gy). Some patients received accelerated fractionation but this proportion is not reported by HPV or P16-positive subgroups.

Length of follow-up

Median 35 months

Outcome measures and effect size

For **HPV16-positive** patients

	RT+EGFR	RT+chemotherapy	HR (95%CI)	P
Time to death from any cause	?/11	?/6	0.22 (0.05, 0.90)	0.02
2 year overall survival	83%	33%	-	-
Time to recurrence	?/11	?/6	0.19 (0.47, 0.80)	0.01
2 year disease free survival	50%	17%	-	-

For **P16-positive** tumours

	RT+EGFR	RT+chemotherapy	HR (95%CI)	P
Time to death from any cause	2/8	7/10	0.18 (0.04, 0.88)	0.01
2 year overall survival	88%	60%	-	-
Time to recurrence	1/8	4/10	0.2 (0.01, 2.4)	0.30
2 year disease free survival	75%	47%	0.17 (0.03, 0.80)	0.01
Complete response rate	8/8	8/10	OR = 2 (1.6, 3.2)	0.40

Source of funding

Andalusian Cancer Society

Risks of bias

Observational study, very small sample sizes and event rates, unclear whether patient characteristics were balanced between treatment groups.

Additional comments

1

Study, country

Vermorken, 2014. International

Study type, study period

RCT. 2004-2007

Number of patients

41 P16 positive, 24 HPV positive

Patient characteristics

Patients with stage III or IV recurrent and or metastatic head and neck squamous cell carcinoma.

Intervention

Chemotherapy (5FU and carboplatin or cisplatin) plus cetuximab

Comparison

Chemotherapy (5FU and carboplatin or cisplatin)

Length of follow-up

Median not reported, survival outcomes reported over 27 months

Outcome measures and effect size

For **HPV16-positive** patients

	Chemotherapy + cetuximab	Chemotherapy	HR (95%CI)	P
Time to death from any cause	8/11	10/13	0.72 (0.28, 1.83)	0.486
Median overall survival	13.2 months	7.1 months	-	-
Time to disease progression	10/11	11/13	0.48 (0.19, 1.21)	0.110
Median progression free survival	4.8 months	4.3 months	-	-
Any serious adverse event	4/11	5/13		
Any grade III/IV adverse event	11/11	11/13		
Any fatal adverse event	2/11	3/13		

For **P16-positive** tumours

	Chemotherapy + cetuximab	Chemotherapy	HR (95%CI)	P
Death from any cause	10/18	17/23	0.63 (0.30, 1.34)	0.224
Median overall survival	12.6 months	9.6 months	-	-
Time to disease progression	15/18	17/23	0.73 (0.36, 1.47)	0.376
Median progression free survival	5.6 months	3.6 months	-	-
Any serious adverse event	10/18	12/22		
Any grade 3 or 4 adverse event	16/18	17/22		
Any fatal adverse event	3/18	4/22		

Source of funding

Merck KGaA

Risks of bias

Retrospective subgroup analysis of a randomized trial, very small sample size and event rate

Additional comments

1

Study, country

Haughey, 2012.
USA

Study type, study period

Retrospective observational study. 1996-2010

Number of patients

171

Patient characteristics

P16-positive oropharyngeal cancer treated surgically with TLM (N = 6 no neck dissection, N = 133 ipsilateral neck dissection, N = 32 bilateral neck dissection).
Clinical T stage: 36% cT1, 31% cT2, 19% cT3 and 14% cT4
Pathological T stage: 41% pT1, 34% pT2, 26% pT3 and 9% pT4

Intervention

Transoral laser microsurgery with adjuvant therapy (N = 142; N = 73 RT alone, N = 69 CRT)

Comparison

Transoral laser microsurgery without adjuvant therapy (N = 29)

Length of follow-up

Minimum of 12 months follow up in survivors.

Outcome measures and effect size

	TLM with adjuvant therapy (RT or CRT) (N = 142)	TLM without adjuvant therapy (N = 29)	
Disease specific survival	96.4% at 5 years	90% at 5 years	HR = 0.36 [95% CI 0.07, 1.88], P = 0.227
Disease free survival-	90.3% at 5 years	71.2% at 5 years	HR = 0.57 [95% CI 0.19, 1.74], P = 0.327
Recurrence	10/142 (7%)	2/29 (7%)	

In multivariate analysis adjuvant therapy was not a significant predictor of disease free survival if T stage was included in the model.
If T stage was excluded from the multivariate model, adjuvant therapy was associated with an 8-fold decrease in the risk of recurrence or death: HR = 0.21 (95% CI 0.06, 0.71), P = 0.012.

	TLM with CRT (N = 69)	TLM with RT (N = 73)	
Disease specific survival	N.R.	N.R.	HR = 1.89 [0.32, 11.41], P = 0.484
Disease free survival	N.R.	N.R.	HR = 0.93 [0.32, 2.69], P = 0.888
Recurrence	4/69	6/73	P >0.05
Local recurrence	0/69	1/73	
Regional recurrence	1/69	3/73	
Distant recurrence	3/69	2/73	

Source of funding

The authors reported no financial relationships or other conflicts of interest

Risks of bias

Non-randomised study. Large number of variables included in prognostic model. Groups unbalanced in size (N = 29 for no adjuvant therapy versus N = 142 for adjuvant therapy).

Additional comments

1

Study, country

O'Sullivan, 2013.
Canada

Study type, study period

Retrospective observational study. 2001-2009

Number of patients

286

Patient characteristics

Patients with oropharyngeal carcinoma, HPV (p16+) positive, low risk: N0-N2c and T1-T3.

Intervention

Radiotherapy alone (N = 150)

Comparison

Chemoradiotherapy (N = 136)

Length of follow-up

Median 3.9 years

Outcome measures and effect size

	RT (N = 150)	CRT (N = 136)	
Local failure	8/150 (5%)	3/136 (2%)	
Regional failure	7/150 (5%)	2/136 (1%)	
Distant failure	16/150 (11%)	9/136 (7%)	
Distant control at 3 years (T1) N = 73	95%	88%	P = 0.29
Distant control at 3 years (T2) N = 126	92%	97%	P = 0.09
Distant control at 3 years (T3) N = 87	85%	94%	P = 0.28
Distant control at 3 years (N0-N2a) N = 107	97%	88%	P = 0.07
Distant control at 3 years (N2b) N = 112	89%	98%	P = 0.03
Distant control at 3 years (N2c) N = 67	73%	92%	P = 0.02

Source of funding

The authors reported no financial relationships or other conflicts of interest

Risks of bias

High risk of bias. Non-randomised study. Multiple comparisons – without correction of significance level. Details of surgery not reported. Univariate analysis of distant control at 3 years.

Additional comments

Study also included high risk patients (N3 or T4) but RT versus CRT comparison was not reported in the high risk group.

2

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Intervention	Comparison	Outcomes
Adults diagnosed with HPV-positive cancer of the upper aerodigestive tract Subgroups: • site • stage	• Radiotherapy (altered fractionation) • Chemotherapy (induction/neo-adjuvant and concomitant) • Other systemic therapies (e.g. lapatinib, EGFR antagonists) • Surgery (trans oral or open) • Combinations of above	Standard dose chemoradiotherapy	• Overall survival • Event free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Health related quality of life

3

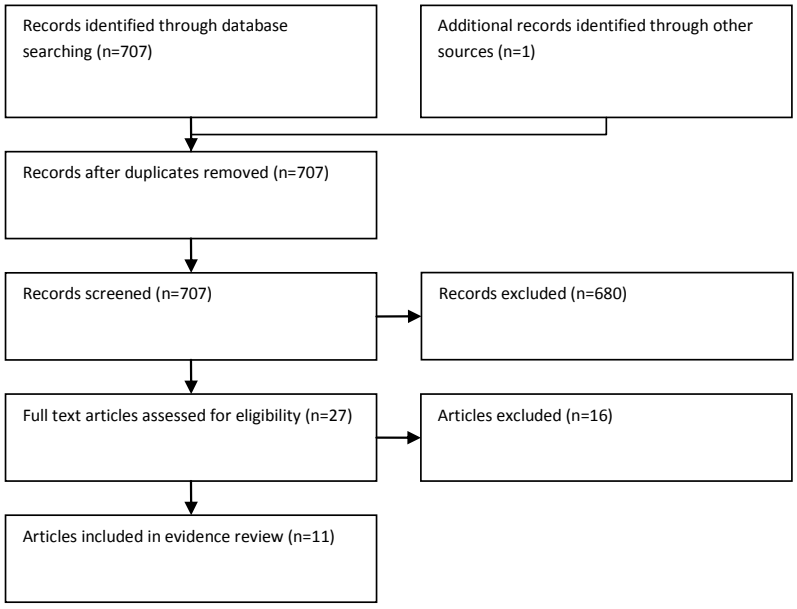
4 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.
Search strategies	Searches will be conducted from 2000 onwards
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.

5

Ten studies, with results from 11 articles, were included – a Cochrane review (Masterson et al, 2013; Masterson et al, 2014), two subgroup analyses of randomised trials (Lassen et al, 2011; Vermorken et al, 2014), a cross sectional patient survey (Brotherson et al, 2012), a phase II trial (published as an abstract only;Cmelak et al, 2014) and five observational studies (Attner et al, 2012; Geiger et al, 2014; Haughey et al, 2012; O'Sullivan et al, 2013 and Pajares et al, 2013). Nine ongoing randomised trials were identified in the Masterson (2014) systematic review.

Figure 5.3. Study flow diagram



Included studies

Attner, P., Nasman, A., Du, J., Hammarstedt, L., Ramqvist, T., Lindholm, J. et al. (2012). Survival in patients with human papillomavirus positive tonsillar cancer in relation to treatment.[Erratum appears in Int J Cancer. 2012 Nov 1;131(9):E1183]. International Journal of Cancer, 131, 1124-1130.

Brotherston, D. C., Poon, I., Le, T., Leung, M., Kiss, A., Ringash, J. et al. (2013). Patient preferences for oropharyngeal cancer treatment de-escalation. Head & Neck, 35, 151-159.

Cmelak A., Li S., Marur S., et al. E1308: Reduced-dose IMRT in human papilloma virus (HPV)-associated resectable oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC) (abstract LBA 6006). 2014 American Society of Clinical Oncology meeting.

Geiger, J. L., Lazim, A. F., Walsh, F. J., Foote, R. L., Moore, E. J., Okuno, S. H. et al. (2014). Adjuvant chemoradiation therapy with high-dose versus weekly cisplatin for resected, locally-advanced HPV/p16-positive and negative head and neck squamous cell carcinoma. Oral Oncology, 50, 311-318.

Haughey, B. H. & Sinha, P. (2012). Prognostic factors and survival unique to surgically treated p16+ oropharyngeal cancer. Laryngoscope, 122, S13-S33.

Lassen, P., Eriksen, J. G., Krogdahl, A., Therkildsen, M. H., Ulhoi, B. P., Overgaard, M. et al. (2011). The influence of HPV-associated p16-expression on accelerated fractionated radiotherapy in head and neck cancer: evaluation of the randomised DAHANCA 6&7 trial. Radiotherapy & Oncology, 100, 49-55.

O'Sullivan, B., Huang, S. H., Siu, L. L., Waldron, J., Zhao, H., Perez-Ordonez, B. et al. (2013). Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. Journal of Clinical Oncology, 31, 543-550.

Masterson, L., Moualed, D., Masood, A., Dwivedi, R. C., Benson, R., Sterling, J. C. et al. (2014). De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cochrane Database of Systematic Reviews, 2, CD010271.

Masterson L, Masterson L, Moualed D, Liu ZW, Howard J. De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma: a systematic review and meta-analysis of current clinical trials. European Journal of Cancer 2014; 50(15):2636-2648.

Pajares, B., Trigo, J. M., Toledo, M. D., Alvarez, M., Gonzalez-Hermoso, C., Rueda, A. et al. (2013). Differential outcome of concurrent radiotherapy plus epidermal growth factor receptor inhibitors versus radiotherapy plus cisplatin in patients with human papillomavirus-related head and neck cancer. BMC Cancer, 13, 26.

Vermorken, J. B., Psyrri, A., Mesia, R., Peyrade, F., Beier, F., de, B. B. et al. (2014). Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial. Annals of Oncology, 25, 801-807.

Excluded studies

Ang, K. K., Harris, J., Wheeler, R., Weber, R., Rosenthal, D. I., Nguyen-Tân, P. F. et al. (2012). Human papillomavirus and survival of patients with oropharyngeal cancer. The New England journal of medicine, 363, 24-35. **Does not compare treatments for HPV+ patients**

Dobrosotskaya, I. Y., Bellile, E., Spector, M. E., Kumar, B., Feng, F., Eisbruch, A. et al. (2014). Weekly chemotherapy with radiation versus high-dose cisplatin with radiation as organ preservation for patients with HPV-positive and HPV-negative locally advanced squamous cell carcinoma of the oropharynx. Head and Neck, 36, 617-623. **Does not compare treatments for HPV+ patients**

George, M. (2014). Should patients with HPV-positive or negative tumors be treated differently? Current Oncology Reports, 16, 384. **Expert review**

Junor, E., Kerr, G., Oniscu, A., Campbell, S., Kouzeli, I., Gourley, C. et al. (2012). Benefit of chemotherapy as part of treatment for HPV DNA-positive but p16-negative squamous cell carcinoma of the oropharynx. British Journal of Cancer, 106, 358-365. **Does not compare treatments for HPV+ patients**

Lanning, R. M., Beattie, B., Humm, J., Zanzonico, P., Rao, S., Romesser, P. et al. (2014). Preliminary results of a prospective trial of IMRT dose de-escalation to gross nodal disease in human papillomavirus (HPV)-positive oropharyngeal carcinoma (OPC) based on assessment of tumor

hypoxia using 18f-fmiso pet imaging. International Journal of Radiation Oncology Biology Physics, 88, 474. **Abstract only, non comparative study.**

Lindel, K., Beer, K. T., Laissue, J., Greiner, R. H., & Aebersold, D. M. (2001). Human papillomavirus positive squamous cell carcinoma of the oropharynx - A radiosensitive subgroup of head and neck carcinoma. Cancer, 92, 805-813. **Does not compare treatments for HPV+ patients**

O'Sullivan, B. (2012). HPV positive vs. HPV negative oropharyngeal carcinoma: Deescalating vs. intensified treatment. Radiotherapy and Oncology, 103, S234-S235. **Expert review**

Michiels, S., Le, M. A., Buyse, M., Burzykowski, T., Maillard, E., Bogaerts, J. et al. (2009). Surrogate endpoints for overall survival in locally advanced head and neck cancer: meta-analyses of individual patient data. Lancet Oncology, 10, 341-350. **Does not compare treatments for HPV+ patients**

Patel, S. C., Hackman, T., Hayes, D. N., & Chera, B. S. (2012). De-intensification of treatment for human papilloma virus associated oropharyngeal squamous cell carcinoma: A discussion of current approaches. Practical Radiation Oncology, 2, 282-287. **Expert review**

Peres, J. (2010). HPV-positive oropharyngeal cancer: data may justify new approach.[Erratum appears in J Natl Cancer Inst. 2010 Nov 17;102(22):1697]. Journal of the National Cancer Institute, 102, 1456-1459. **Awaiting full text copy of this paper**

Petrelli, F., Sarti, E., & Barni, S. (2014). Predictive value of human papillomavirus in oropharyngeal carcinoma treated with radiotherapy: An updated systematic review and meta-analysis of 30 trials. Head & Neck, 36, 750-759. **Does not compare treatments for HPV+ patients**

Petrelli F, Petrelli F, Coinu A, Riboldi V, Borgonovo K, Ghilardi M et al. Concomitant platinum-based chemotherapy or cetuximab with radiotherapy for locally advanced head and neck cancer: a systematic review and meta-analysis of published studies. *Oral Oncology* 2014; 50(11):1041-1048. **Systematic review. Eligibility criteria not relevant to this evidence review**.

Psychogios, G., Alexiou, C., Agaimy, A., Brunner, K., Koch, M., Mantsopoulos, K. et al. (2014). Epidemiology and survival of HPV-related tonsillar carcinoma. Cancer Medicine, 3, 652-659. . **Does not compare treatments for HPV+ patients**

Quon, H. & Richmon, J. D. (2012). Treatment deintensification strategies for HPV-associated head and neck carcinomas. [Review]. Otolaryngologic Clinics of North America, 45, 845-861. **Expert review**

Rietbergen, M. M., Brakenhoff, R. H., Bloemena, E., Witte, B. I., Snijders, P. J. F., Heideman, D. A. M. et al. (2013). Human papillomavirus detection and comorbidity: Critical issues in selection of patients with oropharyngeal cancer for treatment De-escalation trials. Annals of Oncology, 24, 2740-2745. **Does not compare treatments for HPV+ patients**

Quon, H. & Forastiere, A. A. (2013). Controversies in treatment deintensification of human papillomavirus-associated oropharyngeal carcinomas: should we, how should we, and for whom? Journal of Clinical Oncology, 31, 520-522. **Expert review**

6. Less common upper aerodigestive tract cancers

Carcinoma of the nasopharynx

Clinical question: What is the most effective curative treatment for carcinoma of the nasopharynx?

Background

Carcinoma of the nasopharynx is rare and accounts for approximately 2-3% of all head and neck cancers diagnosed in the UK. It is distinct from other head and neck squamous carcinomas in terms of natural history and response to treatment.

Treatment of carcinoma of the nasopharynx is primarily non-surgical. Various combinations of radiotherapy and chemotherapy are used. The benefits of adding chemotherapy to radiotherapy for advanced disease are well established but there is a lack of consensus regarding the applicability of this approach for early stage disease.

Surgery may be used for recurrent disease.

Evidence statements

Concomitant chemotherapy (+/- adjuvant chemotherapy) versus radiotherapy alone

Overall survival, locoregional recurrence and distant metastasis

Evidence comparing concomitant platinum based chemotherapy (with or without adjuvant chemotherapy) to radiotherapy alone came from a network meta-analysis of 8 randomised trials (Chen et al, 2014) in 2144 patients with stage II to IV (typically WHO type 2 or 3) nasopharyngeal cancer. Moderate quality evidence suggests concomitant chemotherapy (CCRT) is more effective than radiotherapy alone in terms of overall survival (HR 0.69; 95% CI 0.48, 0.92; where HR < 1 favours CCRT) and distant metastasis (HR 0.76; 95% CI 0.56, 0.97; where HR < 1 favours CCRT). There was uncertainty about whether CCRT was more effective than radiotherapy alone in terms of locoregional recurrence (HR 0.80; 95% CI 0.51, 1.12; where HR < 1 favours CCRT).

Moderate quality evidence suggests concomitant chemotherapy plus adjuvant chemotherapy (CCRT+AC) is more effective than radiotherapy alone in terms of overall survival (HR 0.59; 95% CI 0.48, 0.71; where HR < 1 favours CCRT+AC), locoregional recurrence (HR 0.56; 95% CI 0.36, 0.81; where HR < 1 favours CCRT+AC) and distant metastasis (HR 0.64; 95% CI 0.50, 0.81; where HR < 1 favours CCRT+AC).

Treatment related mortality

Moderate quality evidence from a meta-analysis of 13 randomised trials (Zhang et al, 2012), suggests treatment related mortality is more likely with cisplatin based chemoradiotherapy than with radiotherapy alone. The rates of treatment related mortality were 1.9% versus 0.3% for chemoradiotherapy versus radiotherapy alone (RR = 3.11; 95% CI 1.60, 6.05; where RR > 1 favours RT alone).

In subgroup analyses by timing of chemotherapy, treatment related mortality was more likely with sequential chemotherapy (neoadjuvant or adjuvant therapy) than with radiotherapy alone (RR 4.24; 95% CI 1.76, 10.23; RR > 1 favours RT alone). There was uncertainty about whether treatment related mortality was more likely with concomitant chemotherapy than RT alone (RR 1.85; 95% CI 0.64, 5.33; RR > 1 favours RT alone).

Adverse events

Low quality evidence from a meta-analysis of 13 randomised trials including 2829 patients with nasopharyngeal cancer (Zhang et al, 2013) suggests that severe adverse events (WHO grade 3 or 4) are more likely with cisplatin based chemoradiotherapy than with radiotherapy alone. The rates of anaemia, leucopoenia, thrombocytopenia, mucositis and nausea/vomiting were significantly higher in patients treated with chemoradiotherapy than in those receiving radiotherapy alone.

Stage II patients

A single randomised trial in 230 patients with stage II nasopharyngeal cancer (Chen et al, 2011) provides moderate quality evidence, that CCRT is more effective than RT alone in terms of overall survival, locoregional recurrence and distant metastasis. Grade 3 to 4 toxicity, however, was more likely with CCRT than with RT, with rates of 64% versus 40% respectively (P<0.001, favours RT).

WHO type 1 patients

Low quality evidence comparing CCRT with RT in 55 patients with WHO type 1 disease comes from an individual patient meta-analysis of 8 randomised trials (Baujat et al, 2009). In patients with WHO type 1 disease CCRT was more effective than RT alone (HR 0.30; 95% CI 0.15, 0.59; HR <1 favours CCRT).

Adding neoadjuvant or adjuvant chemotherapy to concomitant chemoradiotherapy

Moderate quality evidence, from a network meta-analysis of 8 trials (Chen et al, 2014) including 2144 patients suggests uncertainty over whether adding adjuvant chemotherapy to concomitant chemotherapy improves outcomes in terms of overall survival (HR 0.86; 95% CI 0.60, 1.16; where HR < 1 favours CCRT+AC), locoregional recurrence (HR 0.72; 95% CI 0.43, 1.15; where HR < 1 favours CCRT+AC) or distant metastasis (HR 0.86; 95% CI 0.62, 1.16; where HR < 1 favours CCRT+AC).

Moderate quality evidence from a network meta-analysis of 25 trials (Yan, 2015) including 5576 patients suggests uncertainty about the benefit of adding neoadjuvant chemotherapy (NACT) to concomitant chemoradiotherapy in terms of overall survival (HR 1.03; 95% CI 0.69, 1.47; where HR < 1 favours NACT+CCRT). The estimates of 3-year overall survival from this analysis were 61% for CCRT+AC, 59% for NACT+CCRT and 60% for CCRT.

Neoadjuvant chemotherapy versus no neoadjuvant chemotherapy

Evidence about the effectiveness of neoadjuvant chemotherapy (NACT) came from a meta-analysis of 6 randomised trials in 1418 patients with nasopharyngeal carcinoma (OuYang et al, 2013). Moderate quality evidence suggested that the addition of NACT improved overall survival (HR 0.82; 95% CI 0.69, 0.98; HR <1 favours NACT) and reduced risk of distant metastasis (HR 0.69; 95% CI 0.56, 0.84; HR <1 favours NACT), with uncertain effect on locoregional recurrence (HR 0.90; 95% CI 0.66, 0.98; HR <1 favours NACT).

Low quality evidence from a meta-analysis of 4 randomised trials including 751 patients (Zhang et al, 2012), suggests treatment related mortality is more likely with cisplatin based neoadjuvant sequential chemoradiotherapy than with radiotherapy alone. The rates of treatment related mortality were 2.9% versus 1.2% for neoadjuvant + concomitant chemotherapy and radiotherapy respectively (RR = 4.20; 95% CI 1.52, 6.05; where RR > 1 favours RT alone).

IMRT versus conventional/conformal radiotherapy

Evidence comparing IMRT to conventional comes from a systematic review of 3 randomised trials (Kam et al, 2007; Peng et al, 2012 and Pow et al, 2006) including 717 patients with stage I to III nasopharyngeal cancer (Marta et al, 2014) . Moderate quality evidence from 2 randomised trials (Kam et al 2007; suggests that xerostomia (grade 2 to 4) at 6 to 12 months post RT is less likely with IMRT than with conventional RT (HR 0.75; 95% CI 0.64, 0.87; HR < 1 favours IMRT). The rates of xerostomia were 28% with IMRT versus 59% with conventional RT.

From one trial (Peng et al, 2012; N = 616) there is moderate quality evidence that IMRT improves overall survival when compared with 2D-RT (HR 0.56; 95% CI 0.39, 0.80; HR < 1 favours IMRT) but uncertainty about whether IMRT improves local control (HR 0.91; 95% CI 0.78, 1.06; HR < 1 favours IMRT) when compared with conventional RT.

Low quality evidence from one randomised trial (Pow et al 2006; N = 46) suggests Global health scores showed continuous improvement in quality of life after both IMRT and CRT but at 12 months after RT, SF-36 subscale scores for role-physical, bodily pain and physical function are significantly better with IMRT.

Study characteristics

Table 6.1. Characteristics of included primary randomised trials

Study	Stage (system)	WHO histology	% WHO 2 or 3	Intervention	Comparison
Al-Sarraf 1998 (T-0099)	III-IV (AJCC)	1-3	76%	CCRT+AC	RT
Chan 1995 (PWH-88)	III-IV (Ho)	3	100%	IC+RT+AC	RT
Chan 2002 (PWHQEH-94)	II-IV (AJCC)	1-3	99%	CCRT	RT
Chi 2002 (TCOG-94)	IV (AJCC)	1-3	99%	RT+AC	RT
Chua 1998 (AOCOA)	II-IV (AJCC)	2-3	100%	IC+RT	RT
Chen 2008	III-IV (AJCC)	2-3	100%	CCRT+AC	RT
Chen 2011	II (Chinese)	2-3	100%	CCRT	RT
Chen 2012	III-IV (AJCC)	2-3	100%	CCRT+AC	CCRT
Cvitkovic 1996 (VUMCA-89)	III-IV (AJCC)	1-3	97%	IC+RT	RT
Kam 2007	I-II (AJCC)	2-3	100%	IMRT	2D-CRT
Fountzillas 2012	IIB-IVB (AJCC)	1-3	91%	IC+CCRT	RT
Hareyama 2002 (Japan-91)	I-IV, M0 (AJCC)	1-3	96%	IC+RT	RT
Hui 2009	III-IVB (UICC)	NR	NR	IC+CCRT	RT
Kwong 2004 (QMH-95)	II-IV (AJCC)	1-3	99%	CCRT+AC	CCRT, RT
Lee 2005 (NPC-9901)	III-IV (AJCC)	2	100%	CCRT+AC	RT
Lee 2006 (NPC-9902)	III-IV (AJCC)	2	100%	CCRT+AC	RT
Ma 2001	III-IV (Chinese)	1-3	97%	IC+RT	RT
Peng 2012	I-IV (AJCC)	1-2	97%	IMRT	2D-CRT
Pow 2006	II (AJCC)	NR	NR	IMRT	2D-CRT
Rossi 1988	I-IV, M0 (AJCC)	1-3	70%	RT+AC	RT
Wee 2005	II-IV (AJCC)	2-3	100%	CCRT+AC	RT
Zhang 2005	III-IV (AJCC)	2-3	100%	CCRT	RT

Abbreviations: AC, adjuvant radiotherapy; CCRT, concomitant chemoradiotherapy; 2D-CRT, two dimensional conventional radiotherapy; IC, induction (neoadjuvant) chemotherapy; IMRT, intensity modulated radiotherapy; RT, radiotherapy; NR, not reported

Table 6.2. Trials included in the systematic reviews

		Systematic reviews						
Trial	**Comparison**	**Chen 2014**	**Zhang 2010**	**OuYang 2013**	**Zhang 2012**	**Baujat 2009**	**Marta 2014**	**Blanchard 2015**
Chan 2002 (PWHQEH-94)	CCRT vs. RT	✔	✔		✔	✔		✔
Chen 2011	CCRT vs. RT				✔			✔
Zhang 2005	CCRT vs. RT	✔	✔					
Chen 2012	CCRT+AC vs. CCRT	✔		✔				✔
Kwong 2004 (QMH-95)	CCRT+AC vs. CCRT vs. RT	✔	✔	✔	✔	✔		✔
Al-Sarraf 1998 (INT-0099)	CCRT+AC vs. RT	✔			✔	✔		✔
Chen 2008	CCRT+AC vs. RT	✔	✔		✔			✔
Lee 2005 (NPC-9901)	CCRT+AC vs. RT	✔	✔		✔			✔
Lee 2006 (NPC-9902)	CCRT+AC vs. RT	✔	✔		✔			✔
Wee 2005	CCRT+AC vs. RT	✔	✔		✔			✔
Fountzillas 2012 (HeCOG)	IC+CCRT vs. CCRT			✔				✔
Hui 2009 (NPC-008)	IC+CCRT vsCC RT			✔				✔
Chua 1998 (AOCOA)	IC+RT vs. RT			✔	✔	✔		✔
Cvitkovic 1996 (VUMCA-89)	IC+RT vs. RT			✔	✔	✔		✔
Hareyama 2002 (Japan-91)	IC+RT vs. RT			✔	✔	✔		✔
Ma 2001	IC+RT vs. RT			✔				✔
Chan 1995 (PWH-88)	IC+RT+AC vs. RT			✔	✔	✔		
Chi 2002 (TCOG-94)	RT+AC vs. RT			✔	✔	✔		✔
Rossi 1988	RT+AC vs. RT			✔				
Kam 2007	IMRT vs. 2D-RT						✔	
Peng 2012	IMRT vs. 2D-RT						✔	
Pow 2006	IMRT vs. 2D-RT						✔	

Abbreviations: AC, adjuvant radiotherapy; CCRT, concomitant chemoradiotherapy; IC, induction (neoadjuvant) chemotherapy; IMRT, intensity modulated radiotherapy; RT, radiotherapy

GRADE evidence tables

Table 6.3. GRADE evidence profile: concomitant platinum based chemotherapy (with or without adjuvant chemotherapy) and radiotherapy.

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	**Hazard ratio (95%CI)**	**Quality of evidence**	**Hazard ratio (95%CI)**	**Quality of evidence**	**Hazard ratio (95%CI)**	**Quality of evidence**
Overall mortality (Chen et al, 2014)						
CCRT+AC *v* CCRT	0.77 (0.46, 1.29)	moderate[1,2]	NR	-	0.86 (0.60, 1.16)	moderate[1,2]
CCRT+AC *v* RT	0.64 (0.53, 0.76)	moderate[1]	NR	-	0.59 (0.48, 0.71)	moderate[1]
CCRT *v* RT	0.66 (0.46, 1.29)	moderate[1]	NR	-	0.69 (0.48, 0.92)	moderate[1]
Locoregional recurrence (Chen et al, 2014)						
CCRT+AC *v* CCRT	0.50 (0.21–1.17)	moderate[1,2]	NR	-	0.72 (0.43, 1.15)	moderate[1,2]
CCRT+AC *v* RT	0.59 (0.40, 0.89)	moderate[1]	NR	-	0.56 (0.36, 0.81)	moderate[1]
CCRT *v* RT	0.72 (0.47, 1.10)	moderate[1]	NR	-	0.80 (0.51, 1.12)	moderate[1]
Distant metastases (Chen et al, 2014)						
CCRT+AC *v* CCRT	0.71 (0.46, 1.10)	moderate[1,2]	NR	-	0.86 (0.62, 1.16)	moderate[1,2]
CCRT+AC *v* RT	0.67 (0.52, 0.87)	moderate[1]	NR	-	0.64 (0.50, 0.81)	moderate[1]
CCRT *v* RT	0.68 (0.50, 0.95)	moderate[1]	NR	-	0.76 (0.56, 0.97)	moderate[1]
Treatment related mortality (Zhang et al, 2012)						
CCRT+AC *v* CCRT	NR	-	NR	-	NR	-
CCRT+AC *v* RT	RR 4.35 (0.75, 25.6)	low[3]	NR	-	NR	-
CCRT *v* RT	RR 1.85 (0.64, 5.33)	low[3]	NR	-	NR	-

Abbreviations: AC, adjuvant chemotherapy; CCRT, concomitant chemoradiotherapy; CI, confidence interval; NR, not reported; RT, radiotherapy

[1] Allocation concealment was inadequate in all trials; [2] imprecise effect estimate: confidence interval crosses both no effect and appreciable benefit or harm; [3] very low number of events.

Table 6.4. GRADE profile: neoadjuvant chemotherapy versus no neoadjuvant chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant chemo plus RT	RT	Relative (95% CI)	Absolute	
Treatment related mortality (Zhang, 2012)											
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	16/358 (4.5%)	3/393 (0.76%)	RR 4.20 (1.52, 11.63)	24 more per 1000 (from 4 more to 81 more)	⊕⊕⊕O LOW
Overall survival (event is death from any cause) (OuYang, 2013)											
6	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	214/712 (30.1%)	243/706 (34.4%)	HR 0.82 (0.62, 0.98)	-	⊕⊕⊕O MODERATE
Locoregional recurrence (OuYang, 2013)											
6	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	146/712 (20.5%)	176/700 (25.1%)	HR 0.90 (0.66, 1.22)	-	⊕⊕⊕O MODERATE
Distant metastasis (OuYang, 2013)											
6	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	131/712 (18.4%)	189/706 (26.8%)	RR 0.69 (0.56, 0.84)	-	⊕⊕⊕O MODERATE

[1] Very low number of events

[2] Various regimens used - 4/6 used no concomitant chemotherapy.

Table 6.5. GRADE profile: IMRT versus conventional/conformal radiotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IMRT	2D-RT	Relative (95% CI)	Absolute	
Xerostomia (follow-up 6-12 months) (Marta, 2014)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	95/334 (28.4%)	199/338 (58.9%)	HR 0.75 (0.64, 0.87)	-	⊕⊕⊕O MODERATE
Local recurrence (Peng, 2012)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/306 (9.5%)	50/310 (16.1%)	HR 0.91 (0.78, 1.06)	5-year local control rate 90.5% with IMRT vs. 83.8% with 2D-RT	⊕⊕⊕O MODERATE
Overall survival (event is death from any cause) (Peng, 2012)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62/306 (20.3%)	101/310 (32.6%)	HR 0.56 (0.39, 0.80)	5-year overall survival 76.9% with IMRT vs. 67.1% with 2D-RT	⊕⊕⊕O MODERATE
Quality of life, 6-12 months post RT (Pow, 2006)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	21	continuous improvement in quality of life after both IMRT and CRT but at 12 months after RT, SF-36 subscale scores for role-physical, bodily pain and physical function were significantly better with IMRT.		⊕⊕OO LOW

[1] Studies were at unclear risk of bias using the Cochrane risk of bias criteria.

[2] Very low number of patients

Evidence tables for all included studies

Study, country

Chen, Y. P., Wang, Z. X., Chen, L., Liu, X., Tang, L. L., Mao, Y. P. et al. (2015). A Bayesian network meta-analysis comparing concurrent chemoradiotherapy followed by adjuvant chemotherapy, concurrent chemoradiotherapy alone and radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. Annals of Oncology, 26, 205-211.

Study type, study period

Systematic review and network meta-analysis

Number of patients

8 RCTs including 2144 patients

Patient characteristics

Locoregionally advanced nasopharyngeal cancer, typically stage III to IV (

Intervention

CCRT+AC (platinum based chemotherapy)
CCRT, (platinum based chemotherapy)

Comparison

RT

Length of follow-up

Median ranged from 32 to 114 months

Outcome measures and effect size

	Direct evidence	Network meta-analysis
Comparison	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**
Overall mortality		
CCRT+AC *v* CCRT (1 trial, N = 508)	0.77 (0.46, 1.29)	0.86 (0.60, 1.16)
CCRT+AC *v* RT (2 trials, N = 465)	0.64 (0.53, 0.76)	0.59 (0.48, 0.71)
CCRT *v* RT (5 trials, N = 1171)	0.66 (0.46, 1.29)	0.69 (0.48, 0.92)
Locoregional recurrence		
CCRT+AC *v* CCRT (1 trial, N = 508)	0.50 (0.21, 1.17)	0.72 (0.43, 1.15)
CCRT+AC *v* RT (2 trials, N = 465)	0.59 (0.40, 0.89)	0.56 (0.36, 0.81)
CCRT *v* RT (5 trials, N = 1171)	0.72 (0.47, 1.10)	0.80 (0.51, 1.12)
Distant metastases		
CCRT+AC *v* CCRT (1 trial, N = 508)	0.71 (0.46, 1.10)	0.86 (0.62, 1.16)
CCRT+AC *v* RT (2 trials, N = 465)	0.67 (0.52, 0.87)	0.64 (0.50, 0.81)
CCRT *v* RT (5 trials, N = 1171)	0.68 (0.50, 0.95)	0.76 (0.56, 0.97)

Grade III or higher toxicity

In the initial phases severe adverse events occurred more often following CCRT than with RT alone.
In the adjuvant chemotherapy study (Chen, 2012) the commonest severe adverse events were neutropaenia 14.1%, nausea 13.4%, leukopaenia 13.3% and mucositis 12.0%.

Source of funding

Not reported

Risks of bias

	Adequate randomization	Estimation of sample size	Adequate allocation concealment	Intention to treat analysis	Description of loss to follow	Description of dropout	Jadad score *
Al-sarraf 1998	N	Y	N	Y	Y	Y	2
Wee 2005	Y	Y	N	Y	Y	Y	3
Lee 2005	Y	N	N	Y	Y	Y	3
Lee 2006	Y	Y	N	Y	Y	Y	3
Chen 2008	Y	Y	N	Y	Y	Y	3
Chan 2002		Y	N	Y	N	Y	3
Zhang 2005	N	Y	N	N	N	Y	2
Chen 2012	y	y	N	y	y	y	3

*Higher score indicates lower risk of bias

Additional comments

1

Study, country

Zhang, A. M., Fan, Y., Wang, X.-X., Xie, Q.-C., Sun, J.-G., Chen, Z.-T. et al. (2012). Increased treatment-related mortality with additional cisplatin-based chemotherapy in patients with nasopharyngeal carcinoma treated with standard radiotherapy. Radiotherapy & Oncology, 104, 279-285.

Study type, study period

Systematic review and meta-analysis. RCTs published before 2012.

Number of patients

13 RCTs (2829 patients)

Patient characteristics

Histologically confirmed nasopharyngeal carcinoma

Intervention

Chemoradiotherapy (concurrent 8 trials, induction 4 trials, adjuvant 2 trials)

Comparison

Radiotherapy

Length of follow-up

Not reported

Outcome measures and effect size

	Chemoradiotherapy	Radiotherapy	RR (95% CI)
Treatment-related mortality (13 trials)	28/1459	5/1370	3.11 (1.60, 6.05)
Treatment-related mortality (concurrent chemo. 8 trials)	9/670	1/900	1.85 (0.64, 5.33)
Treatment-related mortality (induction chemo. 4 trials)	16/358	3/393	4.20 (1.52, 11.63)
Treatment-related mortality (adjuvant chemo. 2 trials)	6/131	1/132	4.35 (0.75, 25.26)
Anaemia*	40/569	1/558	20.11 (4.96, 81.57)
Leukopaenia*	194/950	9/940	38.44 (15.98, 92.50)
Thrombocytopaenia*	21/950	1/940	5.31 (1.97, 14.33)
Mucositis*	389/942	306/968	1.29 (1.15, 1.45)
Skin reaction*	92/1020	90/1037	1.04 (0.80, 1.37)
Stomatitis*	139/565	86/558	1.69 (0.98, 2.90)
Nausea/vomiting*	109/950	5/940	12.85 (4.53, 36.44)
Diarrhea *	0/182	0/166	0.91 (0.10, 8.66)
Renal impairment*	5/470	0/456	4.06 (0.69, 23.78)

*WHO grade 3 - 4

Source of funding
National Natural Science Foundation of China and the Natural science Foundation Project of CQCSTC.
Risks of bias
Adequate allocation concealment in 7/13 trials, no trial was blinded, all trials described withdrawals and drop-outs. Follow-up was completed in all trials. Jadad score ranged from 5 to 8 (8 regarded as high quality, 5-6 low quality). Sensitivity analysis by study quality (high and low) yielded similar results.
Additional comments

1

Study, country
Zhang, L., Zhao, C., Ghimire, B., Hong, M.-H., Liu, Q., Zhang, Y. et al. (2010). The role of concurrent chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma among endemic population: a meta-analysis of the phase III randomized trials. BMC Cancer, 10, 558.
Study type, study period
Systematic review and meta analysis of RCTs published before 2010 (exact search date not reported)
Number of patients
7 trials (1608 patients)
Patient characteristics
Patients with nasopharyngeal carcinoma, from areas where NPC is endemic (Southern China and Southeast Asia)
Intervention
Concurrent chemotherapy (with or without adjuvant chemotherapy)
Comparison
Radiotherapy alone
Length of follow-up
Outcomes summarized at 2, 3 and 5 years of follow-up.
Outcome measures and effect size

	CCRT	RT	RR (95% CI)
Overall survival – 2 years (event is death from any cause)	95/725	149/718	0.63 (0.50, 0.80) favours CCRT
Overall survival – 3 years (event is death from any cause)	123/677	152/615	0.76 (0.61, 0.93) favours CCRT
Overall survival – 5 years (event is death from any cause)	142/508	191/504	0.74 (0.62, 0.89) favours CCRT
Failure of locoregional control – 3 years	68/677	85/615	0.67 (0.49, 0.91) favours CCRT
Distant metastases – 3 years	123/677	161/615	0.71 (0.58, 0.88) favours CCRT

Source of funding
Not reported
Risks of bias
Not reported (risk of bias information available from other reviews of these trials)
Additional comments
RR inappropriate for analysis of overall survival/mortality

2

Study, country
Baujat, B. & Audry, H. (2009). Chemotherapy as an adjunct to radiotherapy in locally advanced nasopharyngeal carcinoma. Cochrane Database of Systematic Reviews.
Study type, study period
Systematic review and individual patient meta-analysis of RCTs published before 2009
Number of patients
8 RCTs including 1753 patients.
Patient characteristics
Patients with untreated non-metastatic nasopharyngeal carcinoma (WHO type 1,2 or 3). WHO type 1 4%, WHO type 2 18%, WHO type 3 78%. T1 46%, T2 27%, T3-4, 27%. N0 10%, N1-2 65%, N3 25%. 75% were male.
Intervention
Chemotherapy plus radiotherapy.
Comparison
Radiotherapy alone
Length of follow-up
Median follow-up was 5 years or more in 6/8 trials

3

Outcome measures and effect size

	Chemo+RT	RT	HR (95% CI)
All trials (n = 8)			
Overall survival (event is death from any cause)	990	985	0.82 (0.71, 0.95) favours chemo
Overall survival (WHO type 1)	29	26	0.30 (0.15, 0.59) favours chemo
Overall survival (WHO type 2 or 3)	958	959	0.85 (0.73, 0.98) favours chemo
Event free survival (event is death or tumour failure)	990	985	0.76 (0.67, 0.86) favours chemo
Event free survival (WHO type 1)	29	26	0.18 (0.09, 0.36) favours chemo
Event free survival (WHO type 2 or 3)	958	959	0.78 (0.69, 0.89) favours chemo
Locoregional failure	990	985	0.76 (0.63, 0.91) favours chemo
Distant metastasis	990	985	0.72 (0.59, 0.87) favours chemo
Induction +/- adjuvant chemo (n = 4)			
Overall survival (event is death from any cause)	415	415	0.99 (0.80, 1.21)
Event free survival (event is death or tumour failure)	415	415	0.82 (0.68, 0.97) favours chemo
Locoregional failure	415	415	0.76 (0.60, 0.97) favours chemo
Distant metastasis	415	415	0.65 (0.49, 0.86) favours chemo
Concomitant +/- adjuvant chemo (n = 3)			
Overall survival (event is death from any cause)	384	381	0.60 (0.48, 0.76) favours chemo
Event free survival (event is death or tumour failure)	384	381	0.63 (0.51, 0.78) favours chemo
Locoregional failure	287	285	0.81 (0.55, 1.18)
Distant metastasis	287	285	0.69 (0.49, 0.97) favours chemo
Adjuvant chemo (n = 3)			
Overall survival (event is death from any cause)	191	189	0.97 (0.18, 1.38)
Event free survival (event is death or tumour failure)	191	189	0.90 (0.67, 1.20)
Locoregional failure	191	189	0.71 (0.48, 1.04)
Distant metastasis	191	189	1.11 (0.66, 1.85)

Source of funding

Aventis, Sanofi and Schering-Plough supported the review financially.

Risks of bias

Allocation concealment was judged adequate in all the trials. Very few data were missing. No other aspects of risk of bias were reported.

Additional comments

Possible unit of analysis issue with Kwong (2004) – treatment arms included more than once in analysis. However sensitivity analysis excluding Kwong (2004) gives similar results.

1

Study, country

OuYang, P. Y. & Xie, C. (2013). Significant efficacies of neoadjuvant and adjuvant chemotherapy for nasopharyngeal carcinoma by meta-analysis of published literature-based randomized, controlled trials. Annals of Oncology, 24, 2136-2146.

Study type, study period

Systematic review and meta-analysis, (search date not reported)

Number of patients

11 trials (6 neoadjuvant chemo, 5 adjuvant chemotherapy)

Patient characteristics

Patients with nasopharyngeal carcinoma, typically stage III-IV

Intervention

Adjuvant chemotherapy versus no adjuvant chemotherapy
Neoadjuvant chemotherapy versus no neoadjuvant chemotherapy

Comparison

See above

Length of follow-up

Median follow up ranged from 29 to 62 months.

2

Outcome measures and effect size

Neoadjuvant chemotherapy (NACT, n = 6 trials)	NACT	No NACT	HR (95% CI)
Overall survival at 3 years (event is death from any cause)	214/712	243/706	0.82 (0.69, 0.98) favours NACT
Locoregional recurrence	146/712	176/706	0.90 (0.66, 1.22)
Distant metastasis	131/712	189/706	0.69 (0.56, 0.84) favours NACT
Severe adverse events during NACT:			**Incidence (%; 95%CI)**
Anaemia	10/?	-	2.3% (1.3, 4.3%)
Leucopoenia	12/?	-	3.3% (1.9, 5.6%)
Thrombocytopenia	6/?	-	2.0% (0.4, 9.6%)
Nausea/vomiting	172/?	-	19.7% (9.6, 36.2%)
Neutropaenia	42/?	-	35.5% (3.3, 90.0 %)
Neutropaenic fever	19/?	-	5.9% (3.8, 9.1%)
Fatigue	3/?	-	3.7% (1.2, 10.9%)
Hair loss	81/?	-	42.4% (15.1, 75.4%)
Renal toxicity	15/?	-	9.3% (5.7, 14.8%)
Toxic death	2/?	-	0.8% (0.2, 3.6%)

Adjuvant chemotherapy (AC, n = 5 trials)	AC	No AC	HR (95% CI)
Overall survival at 3 years (event is death from any cause)	143/589	127/598	1.04 (0.79, 1.37)
Locoregional recurrence	61/589	87/598	0.71 (0.53, 0.96) favours AC
Distant metastasis	106/589	120/598	0.93 (0.65, 1.33)
Severe adverse events during AC:			**Incidence (%) and (95%CI)**
Anaemia	14/?	-	4.1% (0.6, 22.3%)
Leucopoenia	102/?	-	32.7% (11.0, 65.6%)
Thrombocytopenia	12/?	-	3.5% (2.0, 6.0%)
Nausea/vomiting	56/?	-	12.9% (6.3, 24.4%)
Neutropaenia	21/?	-	2.5% (0.3, 19.2 %)
Mucositis	43/?	-	3.0% (0.2, 36.7%)
Neurotoxicity	2/?	-	0.9% (0.3, 2.7%)
Toxic death	5/?	-	1.5% (0.2, 10.8%)

Source of funding

Authors reported receiving no external funding for this meta-analysis

Risks of bias

NACT trials Jadad Scores (higher is better): 2 (Ma), 3 or more (Chua, Cvitcovics, Fountzilas, Hareyama and Hui)
AC trials: 2 (Kwong, Rossi), 3 or more (Chan, Chen, Chi)

Additional comments

1

Study, country

Chen, Q. Y. & Wen, Y.-F. (2011). Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. Journal of the National Cancer Institute, 103, 1761-1770.

Study type, study period

RCT, 2003-2007

Number of patients

230 patients

Patient characteristics

Patients with stage II (Chinese 1992 system – T1-2N1M0 or T2N0M0) untreated nasopharyngeal carcinoma, WHO type 2 or 3, age 18-70 years (median 43 years), adequate haematologic, renal and hepatic function, ECOG performance status 0-1

Intervention

Concurrent chemotherapy with radiotherapy. 30 mg/m^2 cisplatin over 2 hours on a weekly basis during RT. Radiotherapy was 2D, given 5 times a week at 2Gy/day. The nasopharynx and upper neck were irradiated in one volume for the first 40 Gy, and then smaller separate fields were used. Total dose to the tumour was 68-70 Gy. The neck lymph nodes received a total dose of 60-62 Gy (if positive) or 50 Gy (if negative).

Comparison

Radiotherapy alone (as described above)

Length of follow-up

Median follow-up was 5 years

2

Outcome measures and effect size

	CCRT	RT	
Complete response (at 3 months)	115/116	110/114	No sig. Difference P = 0.35
Death from any cause	6/116	19/114	HR 0.30 (0.12 – 0.76) favours CCRT
Disease progression (local or distant)	13/116	28/114	HR 0.45 (0.13 – 0.88) favours CCRT
Locoregional recurrence	8/116	12/114	HR 0.61 (0.25 – 1.51)
Distant metastasis	5/116	17/114	HR 0.27 (0.10 – 0.74) favours CCRT
Grade 3-4 toxicity	74/116	46/114	Favours RT, P = 0.001
Toxic death	0/116	0/114	No difference
Grade 3 haematologic toxicity	15/116	0/114	Favours RT, P<0.001
Grade 3 nausea/vomiting	10/113	0/114	Favours RT, P = 0.001
Grade 3-4 mucositis	53/116	37/114	Favours RT, P = 0.04

Source of funding

National Natural Sciences Foundation of China, Sci-Tech Project Foundations of Guangdong Province and Guangzhou City, Guangdong Provincial Medical Research Foundation, Dun Yat-sen University Clinical Research 5010 program and the Fundamental Research Funds for the Central Universities

Risks of bias

Adequate allocation concealment and randomisation. Blinding unclear (unlikely),baseline characteristics balanced, follow up complete, ITT analysis

Additional comments

1

Study, country

Marta, G. N. (2014). Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiotherapy & Oncology, 110, 9-15.

Study type, study period

Systematic review and meta-analysis (included trials published 2006, 2007 and 2012)

Number of patients

3 trials (N = 717 patients)

Patient characteristics

Nasopharyngeal cancer, stage I/II (2 trials), stage I-III(1 trial)

Intervention

IMRT

Comparison

Conventional RT (2D or 3D)

Length of follow-up

Outcome measures and effect size

	IMRT	2D/3D RT	
Xerostomia (grade 2-4) at 6-12 months (Kam 2007, Peng 2012)	95/334	199/338	HR = 0.75 (0.64 – 0.87) – favours IMRT
Mean salivary flow rate at 12 months (mL/min, Pow 2007)	0.27 (SD 0.17)	0.05 (0.05)	Favours IMRT (P<0.05)
Locoregional control (Peng, 2012)	277/306	260/310	HR = 1.10 (0.94 – 1.29)
Overall survival (Peng, 2012)	244/306	208/310	HR = 1.15 (0.98 – 1.35)

Quality of life (Pow, 2007; N = 46) Global health scores showed continuous improvement in QOL after both IMRT and CRT but at 12 months SF-36 subscale scores for role-physical, bodily pain and physical function were significantly better with IMRT.

Source of funding

Not reported

Risks of bias

Studies were classified as at unclear risk of bias using Cochrane bias assessment tool.

Additional comments

Study, country

Blanchard P, Lee A, Marguet S, Leclercq J, Ng WT, Ma J et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. Lancet Oncology 2015; 16(6):645-655.

Study type, study period

Systematic review and meta-analysis of randomised trials

Number of patients

19 trials (4806 patients)

Patient characteristics

Nasopharyngeal cancer (non metastatic)

Intervention

Treatment strategy with one chemotherapy timing (i,e, RT plus concomitant chemotherapy, RT plus induction chemotherapy or RT plus adjuvant chemo)

Comparison

The same treatment strategy with chemotherapy at another timing or no chemotherapy (RT alone).

Length of follow-up

Individual patient data analysis over 12 years.

Outcome measures and effect size

Overall survival

	N trials (N patients)	HR (95%CI)	Abs difference at 5 yrs (95% CI)*
Induction chemotherapy vs. control	6 (1039)	0.96 (0.80, 1.16)	+2.5% (-4.2, 9.2%)
Adjuvant chemotherapy vs. control	4 (888)	0.87 (0.68, 1.12)	+3.3% (-3.8, 10.4%)
Concomitant chemotherapy vs. control	6(1834)	0.80 (0.70, 0.93)	+5.3% (0.8, 9.8%)
Concomitant + adjuvant chemotherapy vs. control	6 (1267)	0.65 (0.56, 0.76)	+12.4% (7.0, 17.8%)
Any chemotherapy vs. control	19 (5028)	0.79 (0.73, 0.86)	

*from individual patient meta-analysis

Progression free survival

	N trials (N patients)	HR (95%CI)	Abs difference at 5 yrs (95% CI)*
Induction chemotherapy plus RT vs. RT alone	6 (1039)	0.81 (0.69, 0.95)	+7.7% (1.3, 14.1%)
Adjuvant chemotherapy plus RT vs. RT alone	4 (888)	0.80 (0.64, 1.00)	+6.1% (-0.6, 12.8%)
Concomitant chemotherapy and RT vs. RT alone	6(1834)	0.81 (0.71, 0.92)	+6.6% (1.9, 11.3%)
Concomitant + adjuvant chemotherapy and RT vs. RT alone	6 (1267)	0.62 (0.53, 0.72)	+12.4% (6.8, 18.0%)
Any chemotherapy plus RT versus RT alone	22 (5028)	0.75 (0.69, 0.81)	

*from individual patient meta-analysis

Acute toxicity

	N trials (N patients)	Incidence with chemotherapy	Incidence with control	OR (95% CI)
Anaemia	15(4059)	4.3%	1.5%	2,95 (2.11, 4.12)
Neutropenia	15 (4028)	25.7%	4.9%	6.71 (5.53, 8.14)
Mucositis	14 (3870)	40.6%	31.2%	1.51 (1.31, 1.73)
Cutaneous	13 (3828)	12.7%	11.0%	1.18 (0.97, 1.44)
Nausea/vomiting	13 (3585)	12.2%	5.3%	2.49 (1.97, 3.13)
Thrombocytopenia	14 (3737)	3.0%	1.5%	2.06 (1.39, 3.06)
Kidney failure	12 (3542)	0.2%	0.1%	1.94 (0.91, 4.14)
Neurotoxicity	11 (2998)	0.2%	0.1%	1.65 (0.73, 3.75)
Hearing loss	11 (3037)	2.9%	1.3%	2.28 (1.46, 3.55)
Weight loss	9 (2350)	14.4%	8.2%	1.88 (1.44, 2.45)
Febrile neutropenia	8 (1995)	3.0%	2.3%	1.30 (0.79, 2.16)

Late toxicity

	N trials (N patients)	Incidence with chemotherapy	Incidence with control	OR (95% CI)
Bone necrosis	10(2404)	0.5%	0.4%	1.17 (0.51, 2.66)
Visual deficit	9 (2324)	1.7%	1.3%	1.28 (0.69, 2.38)
CNS damage	9 (2298)	0.7%	0.5%	1.25 (0.57, 2.74)
Temporal lobe necrosis	9 (2266)	1.9%	2.1%	0.91 (0.52, 1.60)
Xerostomia	9 (2030)	5.1%	3.6%	1.45 (0.95, 2.21)
Cranial nerve palsy	9 (2013)	11.4%	8.7%	1.35 (1.00, 1.82)
Hearing deficit	9 (2009)	20.9%	15.1%	1.49 (1.18, 1.87)
Cutaneous fibrosis	7 (1643)	2.6%	2.1%	1.25 (0.67, 2.32)
Trismus	7 (1686)	1.5%	1.2%	1.26 (0.62, 2.60)

Source of funding

French Ministry of Health, Ligue Nationale Contre Le Cancer and Sanof-Aventis
Risks of bias
Study quality was assessed and no major bias identified – *however the supplementary appendix describing the quality of the trials was not available at the time of appraisal.*
Additional comments
Comprehensive systematic review – but studies already included in OuYang (2013) and Chen (2014) reviews – which also used network meta-analysis

1

Study, country
Yan M, Kumachev A, Siu LL, Chan KK. Chemoradiotherapy regimens for locoregionally advanced nasopharyngeal carcinoma: A Bayesian network meta-analysis. Eur J Cancer 2015;epub ahead of print.
Study type, study period
Systematic review and meta-analysis
Number of patients
25 trials including 5576 patients
Patient characteristics
Patients with locoregionally advanced nasopharyngeal cancer
Intervention
Concomitant chemoradiotherapy (CRT)
Comparison
Radiotherapy (RT), neoadjuvant followed by concomitant chemotherapy (N-CCRT), adjuvant plus concomitant chemotherapy (CCRT+AC), RT followed by adjuvant chemotherapy (RT-A), neoadjuvant followed by RT (N-RT) or neoadjuvant followed by RT followed adjuvant chemotherapy (N-RT-AC)
Length of follow-up
Not reported
Outcome measures and effect size

	Direct evidence	Network meta-analysis
Comparison	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**
Overall mortality		
CCRT+AC *v* CCRT	0.77 (0.46, 1.29)	0.98 (0.71, 1.29)
N-CCRT *v* CCRT	0.88 (0.57, 1.36)	1.03 (0.69, 1.47)
CCRT+AC *v* N-CCRT	0.92 (0.29, 2.97)	0.96 (0.64, 1.48)
CCRT+AC *v* RT	0.66 (0.54, 0.81)	0.66 (0.52, 0.83)
CCRT *v* RT	0.60 (0.48, 0.76)	0.67 (0.52, 0.88)
N-CCRT v RT	-	0.69 (0.47, 0.98)

Regimen	Probability of being the best regimen	Estimated 3yr OS rate
CCRT+AC	28%	61%
N-CCRT	25%	59%
CCRT	24%	60%
N-RT-AC	21%	57%

All regimens that included concomitant chemoradiotherapy performed significantly better than RT alone – however there was uncertainty about the benefit of adding adjuvant or neoadjuvant chemotherapy to concomitant chemoradiotherapy.

Source of funding
No funding received for this study
Risks of bias
Not assessed
Additional comments
NMA used Bayesian network meta-analysis using MCMC in WinBUGS

2

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Intervention	Comparison	Outcomes
Adults diagnosed with newly diagnosed non-metastatic carcinoma of the nasopharynx Subgroups: • EBV status (type 3 WHO pathology) • early stage (stage 1 and 2a) • advanced stage (stage 2b, 3 and 4)	• Radiotherapy (altered fractionation, brachytherapy) • Chemotherapy (induction/neo-adjuvant and concomitant) • Other systemic therapies (e.g. lapatinib, EGFR antagonists) • Combinations of above) • Surgery	Each other	• Overall survival • Disease free survival • Progression free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Organ preservation rates • Health related quality of life

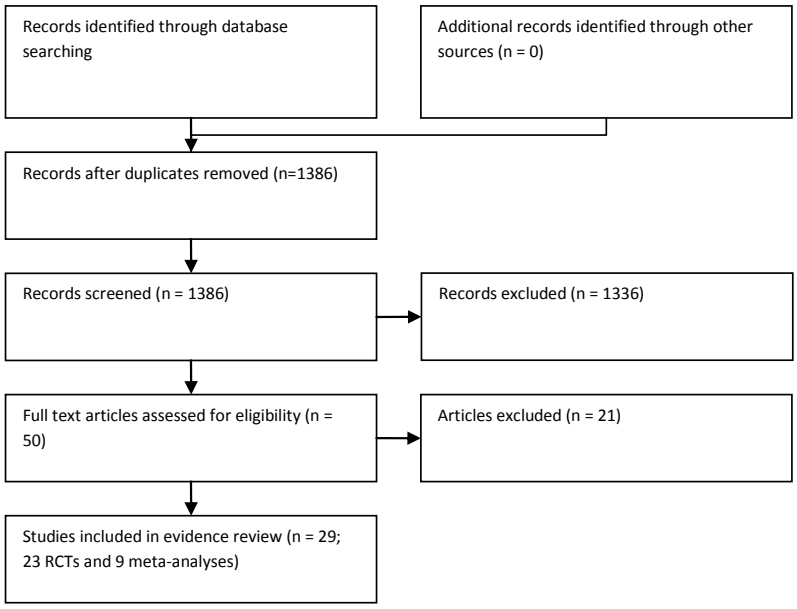
3

1 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour site of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10; At least 75% of the included patients meet the population defined in the PICO.
Search strategies	Search from 1994 onwards.
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.

2

Figure 6.1. Study flow diagram



Included studies: meta analyses

Baujat, B. & Audry, H. (2009). Chemotherapy as an adjunct to radiotherapy in locally advanced nasopharyngeal carcinoma. Cochrane Database of Systematic Reviews.

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Liang, Z. G., Zhu, X. D., Tan, A. H., Jiang, Y. M., Qu, S., Su, F. et al. (2013). Induction Chemotherapy Followed by Concurrent with or without Adjuvant Chemotherapy for Locoregionally Advanced Nasopharyngeal Carcinoma: Meta-analysis of 1,096 Patients from 11 Randomized Controlled Trials. Asian Pacific Journal of Cancer Prevention, 14, 515-521.

Marta, G. N. (2014). Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiotherapy & Oncology, 110, 9-15.

OuYang, P. Y. & Xie, C. (2013). Significant efficacies of neoadjuvant and adjuvant chemotherapy for nasopharyngeal carcinoma by meta-analysis of published literature-based randomized, controlled trials. Annals of Oncology, 24, 2136-2146.

Yan M, Kumachev A, Siu LL, Chan KK. Chemoradiotherapy regimens for locoregionally advanced nasopharyngeal carcinoma: A Bayesian network meta-analysis. Eur J Cancer 2015;epub ahead of print.

Zhang, A. M., Fan, Y., Wang, X.-X., Xie, Q.-C., Sun, J.-G., Chen, Z.-T. et al. (2012). Increased treatment-related mortality with additional cisplatin-based chemotherapy in patients with nasopharyngeal carcinoma treated with standard radiotherapy. Radiotherapy & Oncology, 104, 279-285.

Zhang, L., Zhao, C., Ghimire, B., Hong, M.-H., Liu, Q., Zhang, Y. et al. (2010). The role of concurrent chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma among endemic population: a meta-analysis of the phase III randomized trials. BMC Cancer, 10, 558.

Included studies: primary trials

Al-Sarraf, M. & LeBlanc, M. (1998). Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. Journal of Clinical Oncology, 16, 1310-1317.

Chan, A. T. & Teo, P. M. L. (2002). Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. Journal of Clinical Oncology, 20, 2038-2044.

Chan, A. T. C. (1995). A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics, 33, 569-577.

Chen, L., Hu, C.-S., Chen, X.-Z., Hu, G.-Q., Cheng, Z.-B., Sun, Y. et al. (2012). Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. Lancet Oncology, 13, 163-171.

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Chen, Y., Liu, M.-Z., Liang, S.-B., Zong, J.-F., Mao, Y.-P., Tang, L.-L. et al. (2008). Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china. International Journal of Radiation Oncology, Biology, Physics, 71, 1356-1364.

Chi, K. H., Chang, Y. C., Guo, W. Y., Leung, M. J., Shiau, C. Y., Chen, S. Y. et al. (2002). A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. International.Journal of Radiation.Oncology, Biology., Physics., 52, 1238-1244.

Chua, D. T., Sham, J. S., Choy, D., Lorvidhaya, V., Sumitsawan, Y., Thongprasert, S. et al. (1998). Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of

patients with locoregionally advanced nasopharyngeal carcinoma. Asian-Oceanian Clinical Oncology Association Nasopharynx Cancer Study Group. Cancer, 83, 2270-2283.

Cvitkovic, E., Eschwege, F., Rahal, M., -Dosen, Mersic, Z., Krajina, Z. et al. (1996). Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. Radiotherapy alone in stage IV (less than or equalN2, M0) undifferentiated nasopharyngeal carcinoma: A positive effect on progression-free survival. International.Journal of Radiation.Oncology Biology.Physics., 35, 463-469.

Fountzilas, G., Ciuleanu, E., & Bobos (2012). Induction chemotherapy followed by concomitant radiotherapy and weekly cisplatin versus the same concomitant chemoradiotherapy in patients with nasopharyngeal carcinoma: a randomized phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation. Annals of Oncology, 23, 427-435.

Hareyama, M., Sakata, K., Shirato, H., Nishioka, T., Nishio, M., Suzuki, K. et al. (2002). A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. Cancer, 94, 2217-2223.

Hui, E. P., Ma, B. B., Leung, S. F., King, A. D., Mo, F., Kam, M. K. et al. (2009). Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. Journal of Clinical.Oncology, 27, 242-249.

Kam, M. K., Leung, S. F., Zee, B., Chau, R. M., Suen, J. J., Mo, F. et al. (2007). Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. Journal of Clinical.Oncology, 25, 4873-4879.

Kwong, D. L., Sham, J. S., Au, G. K., Chua, D. T., Kwong, P. W., Cheng, A. C. et al. (2004). Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. Journal of Clinical.Oncology, 22, 2643-2653.

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Peng, G., Wang, T., Yang, K.-Y., Zhang, S., Zhang, T., Li, Q. et al. (2012). A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiotherapy & Oncology, 104, 286-293.

Pow, E. H. N. (2012). Can intensity-modulated radiotherapy preserve oral health-related quality of life of nasopharyngeal carcinoma patients? International Journal of Radiation Oncology Biology Physics, 83, e213-e221.

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Tan T, Lim WT, Fong KW, Cheah SL, Soong YL, Ang MK et al. Concurrent Chemo-Radiation With or Without Induction Gemcitabine, Carboplatin, and Paclitaxel: A Randomized, Phase 2/3 Trial in Locally Advanced Nasopharyngeal Carcinoma. International Journal of Radiation Oncology Biology Physics 2015; 91(5):952-960.

Wee, J., Tan, E. H., Tai, B. C., Wong, H. B., Leong, S. S., Tan, T. et al. (2005). Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. Journal of Clinical Oncology, 23, 6730-6738.

Zhang, L., Zhao, C., Peng, P.-J., Lu, L.-X., Huang, P.-Y., Han, F. et al. (2005). Phase III study comparing standard radiotherapy with or without weekly oxaliplatin in treatment of locoregionally advanced nasopharyngeal carcinoma: preliminary results. Journal of Clinical Oncology, 23, 8461-8468.

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Baujat, B., Audry, H., Bourhis, J., & Chan, A. (2006). Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. [Review] [28 refs]. International Journal of Radiation Oncology, Biology, Physics, 64, 47-56. **(outdated systematic review)**

Baujat, B., Bourhis, J., Blanchard, P., Overgaard, J., Ang, K. K., Saunders, M. et al. (2010). Hyperfractionated or accelerated radiotherapy for head and neck cancer. Cochrane.Database.of Systematic.Reviews.. **(excludes patients with nasopharynx cancer)**

Bourhis, J., Le Maitre, A., Baujat, B., Audry, H., Pignon, J.-P., Meta-Analysis of Chemotherapy in Head, N. C. C. G. et al. (2007). Individual patients' data meta-analyses in head and neck cancer. [Review] [29 refs]. Current Opinion in Oncology, 19, 188-194. **(expert review)**

Cao CN, Luo JW, Gao L, Yi JL, Huang XD, Wang K et al. Concurrent Chemotherapy for T4 Classification Nasopharyngeal Carcinoma in the Era of Intensity-Modulated Radiotherapy. Plos One 2015; 10(3). **(not RCT)**

Cao CN, Luo JW, Gao L, Yi JL, Huang XD, Wang K et al. Update report of T4 classification nasopharyngeal carcinoma after intensity-modulated radiotherapy: An analysis of survival and treatment toxicities. Oral Oncol 2015; 51(2):190-194. **(not RCT)**

Chua, D. T. & Ma, J. (2005). Long-term survival after cisplatin-based induction chemotherapy and radiotherapy for nasopharyngeal carcinoma: a pooled data analysis of two phase III trials. Journal of Clinical Oncology, 23, 1118-1124. (**Trials included in other meta-analysis)**

Du CR, Ying HM, Kong FF, Zhai RP, Hu CS. Concurrent chemoradiotherapy was associated with a higher severe late toxicity rate in nasopharyngeal carcinoma patients compared with radiotherapy alone: a meta-analysis based on randomized controlled trials. Radiation Oncology 2015; 10(1):70. **(review questions is covered by Zhang et al review, with a greater number of included trials)**

Huncharek, M. & Kupelnick, B. (2002). Combined chemoradiation versus radiation therapy alone in locally advanced nasopharyngeal carcinoma: results of a meta-analysis of 1,528 patients from six randomized trials. American Journal of Clinical Oncology, 25, 219-223. **(outdated systematic review)**

Kam, M. K., Leung, S. F., Zee, B., Chau, R. M., Suen, J. J., Mo, F. et al. (2007). Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. Journal of Clinical.Oncology, 25, 4873-4879. **(RCT compares IMRT with 2DRT)**

Kong F, Kong F, Cai B, Lin S, Zhang J, Wang Y et al. Assessment of radiotherapy combined with adjuvant chemotherapy in the treatment of patients with advanced nasopharyngeal carcinoma: a prospective study. Journal of B 2015; U.On.. 20(1):206-211. **(M stage unknown)**

Langendijk, J. A. (2004). The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 22, 4604-4612. **(outdated systematic review)**

Lee AWM, Ngan RKC, Tung SY, Cheng A, Kwong DLW, Lu TX et al. Preliminary Results of Trial NPC-0501 Evaluating the Therapeutic Gain by Changing From Concurrent-Adjuvant to Induction-Concurrent Chemoradiotherapy, Changing From Fluorouracil to Capecitabine, and Changing From Conventional to Accelerated Radiotherapy Fractionation in Patients With Locoregionally Advanced Nasopharyngeal Carcinoma. Cancer 2015; 121(8):1328-1338. **(preliminary results from a relevant trial – but cannot integrate this into existing meta-analysis; HRs not reported for accelerated versus conventional fractionation).**

Li MY. Glycididazole sodium combined with radiochemotherapy for locally advanced nasopharyngeal carcinoma. Asian Pacific Journal of Cancer Prevention: Apjcp 2014; 15(6):2641-2646. **(M stage unknown)**

Liang, Z. G., Zhu, X. D., Zhou, Z. R., Qu, S., Du, Y. Q., & Jiang, Y. M. (2012). Comparison of concurrent chemoradiotherapy followed by adjuvant chemotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a meta-analysis of 793 patients from 5 randomized controlled trials (Provisional abstract). Asian Pacific.Journal of Cancer Prevention., 13, 5747-5752. **(includes phase II studies, review is superceeded by Chen 2014)**

Ramaekers, B. L. T. (2011). Systematic review and meta-analysis of radiotherapy in various head and neck cancers: Comparing photons, carbon-ions and protons. Cancer Treatment Reviews, 37, 185-201. **(compares IMRT and protons)**

Song Y, Wang W, Tao G, Zhou X. Survival benefit of induction chemotherapy in treatment for locally advanced nasopharyngeal carcinoma - A time-to-event meta-analysis. Oral Oncol 2015; **(Relevant systematic review – but there is overlap with the Yan 2015 systematic review which also includes network meta-analysis for more robust conclusions)**

Yang SP, Lin SM, Fu Q, Cai BZ, Kong F, Huang G et al. The Effect of Adjuvant Chemotherapy on Survival in Patients with Residual Nasopharyngeal Carcinoma after Undergoing Concurrent Chemoradiotherapy. Plos One 2015; 10(3). **Not RCT,**

Zackrisson, B., Mercke, C., Strander, H., Wennerberg, J., & Cavallin-Stahl, E. (2003). A systematic overview of radiation therapy effects in head and neck cancer. [Review] [43 refs]. Acta Oncologica, 42, 443-461. **(outdated systematic review – contains relevant RCTs – CT: Al-Sarraf 1998, VUMCA, 1996, Chua 1998; RT, Teo 2000)**

Zeng Q, Xiang YQ, Wu PH, Lv X, Qian CN, Guo X. A Matched Cohort Study of Standard Chemo-Radiotherapy versus Radiotherapy Alone in Elderly Nasopharyngeal Carcinoma Patients. Plos One 2015; 10(3). **Not RCT.**

Zhang L, Shan GP, Li P, Cheng PJ. The role of concurrent chemotherapy to intensity-modulated radiotherapy (IMRT) after neoadjuvant docetaxel and cisplatin treatment in locoregionally advanced nasopharyngeal carcinoma. Med Oncol 2015; 32(3). **Not RCT**

Zhong, J. H., Liu, R. L., Chen, J., Hu, X. G., Wang, L. Q., & Wang, Y. (2009). Efficacy and adverse effects of gemcitabine plus cisplatin regimen and fluorouracil plus cisplatin regimen in treatment of advanced nasopharyngeal carcinoma: a meta-analysis (Provisional abstract). Academic.Journal of Second Military.Medical.University., 30, 926-931. **Abstract only – Chinese language**

Carcinoma of the paranasal sinuses

Clinical question: What is the optimal role and timing (in relation to other treatments) of surgery in the management of paranasal sinus carcinoma?

Background

The management of patients with carcinoma of the paranasal sinuses is challenging. Surgery and reconstruction is the current standard of care but results in significant morbidity particularly, for example, if the orbital contents are removed.

Adjuvant radiotherapy is usually used after surgery to improve local control rates but the optimal sequencing of treatment in borderline resectable disease is unclear.

There is also uncertainty about the role of chemotherapy in the treatment of carcinoma of the paranasal sinuses.

Evidence statements

Surgery with radiotherapy versus surgery alone

Very low quality evidence from a meta-analysis of 16 observational studies (Amit 2013, 356 patients) suggests that the addition of radiotherapy or chemoradiotherapy to surgery does not improve overall survival in patients treated for adenoid cystic carcinoma of the nasal cavity or paranasal sinuses. Five-year overall survival was estimated to be 63% for patients receiving radiotherapy or chemoradiotherapy in addition to surgery, and 74% in patients receiving surgery alone. Similarly, very low quality evidence from a meta-analysis of non-comparative case series (Husain 2013; 39 studies, 57 patients) suggests that the addition of radiotherapy to surgery results in similar overall survival in patients treated for sinonasal adenoid cystic carcinoma. In the surgery only group, 63.2% of patients were alive at last reported follow-up compared with 68.4% of patients treated with both surgery and radiotherapy.

Four observational trials (very low quality evidence) also studied the effect of adding radiotherapy to surgery (407 patients in total). Inclusion criteria for each trial varied in terms of tumour site and/or histology, and so the results could not be pooled. None of these trials demonstrated a significant benefit from the addition of radiotherapy to surgery in terms of overall survival, disease-free survival, or disease control.

Type of surgery

Very low quality evidence from one observational study (Resto 2008, 70 patients) suggests that in patients with sinonasal malignancies, overall survival and disease-free survival are higher in patients treated with complete surgical tumour resection than in patients treated with partial resection (5-year overall survival 90% and 53%, and 5-year disease-free survival 90% and 49% for complete and partial resection, respectively). Rates of local control and regional metastasis-free survival were similar regardless of the type of surgery patients received.

Very low quality evidence from one observational study (Liu 2013, 61 patients) suggests that in patients with advanced maxillary sinus cancer, quality of life after surgery is improved by treatment with conservative maxillectomy compared with radical maxillectomy (measured up to 18 months after surgery). Overall survival at 2, 3 and 5 years was similar in patients treated with radical or conservative maxillectomy.

Very low quality evidence from one observational study (Vergez 2012, 48 patients) suggests that treatment with endoscopic surgery or lateral rhinotomy has similar outcomes in sinonasal adenocarcinoma patients. There was no significant difference in rates of overall survival, disease recurrence, or metastasis between treatment groups.

Chemotherapy

Very low quality evidence from one observational study (Kreppel 2012, 53 patients) suggests that in surgically-treated patients with squamous cell carcinoma of the maxillary sinus receiving neoadjuvant radiochemotherapy, cisplatin treatment results in higher rates of complete response, overall survival and locoregional control than carboplatin treatment.

Very low quality evidence from one observational study (Isobe 2005, 124 patients) suggests that in patients treated with surgery and radiotherapy, treatment with the combination of neoadjuvant chemotherapy and concurrent chemoradiotherapy improves local control, disease-free survival and overall survival compared to the use of either treatment in isolation.

Type of radiotherapy

Two observational studies (very low quality evidence) suggest that in patients with paranasal sinus carcinoma, some outcomes may be improved by treatment with postoperative intensity-modulated radiotherapy (IMRT) instead of conventional radiotherapy. In one study (Dirix 2010, 81 patients) rates of local control, disease-free survival, and overall survival were higher 2 years after treatment with IMRT than with conventional radiotherapy. The incidence of treatment related morbidities was also lower in IMRT-treated patients. A second study (Duthoy 2005, 58 patients), conducted in ethmoid adenocarcinoma patients only, did not find any significant effect of the type of radiotherapy on overall survival or local control.

Study characteristics and quality

Two meta-analyses and nine individual trials were identified as relevant to the review. The characteristics of each study are summarised in Table 6.6.

The two meta-analyses included non-comparative data from small case series (rated as very low quality evidence). In the meta-analysis by Husain, average length of follow up was longer for patients treated with surgery and radiotherapy. This may have introduced bias into the results reported for overall mortality, as there was more time for this event to be detected in one group than the other.

Both meta-analyses only included patients with adenoid cystic carcinoma. The wider relevance of these results to carcinoma of the paranasal sinuses in general is not clear.

Many of the observational studies accrued patients over long periods (greater than 10 years), presumably due to the rarity of the disease, necessitating long accrual periods. Nevertheless, trials were relatively small (median 70 patients per trial for 11 observational studies, range 48–156 patients). All studies were retrospective with the exception of one trial (Vergez 2012), which

recruited patients for one intervention prospectively but compared them with a historical control group.

Five trials were assessed as having a high risk of bias, and all trials were assessed as 'bias unknown or unclear' for at least one category. No trial was randomised, and few trials reported sufficient detail to allow assessment of whether treatment groups were comparable. In some cases, treatment groups had notably different baseline characteristics, or the differences in the care they received were not limited to the studied intervention.

1 **Table 6.6. Characteristics of included studies**

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	NUMBER OF PATIENTS	INTERVENTION	COMPARISON	OUTCOMES MEASURED	NARRATIVE SUMMARY OF OUTCOMES
Agger 2009	Observational study	SCC of the nasal vestibule.	50 eligible for review (total study population = 174)	Surgery + radiotherapy	Surgery alone	5 year overall survival; 5-year disease free survival; 5-year locoregional control	No difference between groups for any measured outcome
Amit 2013	SRMA	Adenoid cystic carcinoma of the nasal cavity or paranasal sinuses	356 eligible for review (total study population = 440)	Surgery + radiotherapy/chemoradiotherapy	Surgery alone	5 year overall survival	No difference between groups for any measured outcome
Blanch 2004	Observational study	Any sinonasal malignancy	91	Surgery + radiotherapy	Surgery alone	Overall survival	No difference between groups for any measured outcome
Choussy 2010	Observational study	Nasoethmoidal adenocarcinoma	110	Surgery + radiotherapy	Surgery alone	Overall survival; incidence of recurrence; postoperative complications	No difference between groups for any measured outcome

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	NUMBER OF PATIENTS	INTERVENTION	COMPARISON	OUTCOMES MEASURED	NARRATIVE SUMMARY OF OUTCOMES
Dirix 2010	Observational study	Cancer of the paranasal sinuses or nasal cavity	81	Postoperative IMRT	Postoperative CRT	2-year local control; 2-year disease free survival; 2-year overall survival; 2-year distant control	2-year disease free survival significantly improved in patients treated with IMRT. Incidence of adverse events significantly lower in patients treated with IMRT, with the exception of dysphagia (no significant difference between groups). 2-year local control and 2-year overall survival favour IMRT, but results did not reach statistical significance.
Dulguerov 2001	Observational study	Carcinoma of the nasal cavity or paranasal sinuses	156 eligible for review (total study population = 220)	Surgery + radiotherapy	Surgery alone	Locoregional control; carcinoma-specific survival (both measured at two, five and ten years)	All outcomes numerically favour surgery + radiotherapy (no statistical analysis performed)
Duthoy 2005	Observational study	Ethmoid adenocarcinoma	58	Postoperative IMRT	Postoperative CRT	Overall survival; local control (both measured at two and four years)	No difference in any measured outcome
Husain 2013	SRMA	Sinonasal adenoid cystic carcinoma	57	Surgery + radiotherapy	Surgery alone	Overall survival	No difference in any measured outcome

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	NUMBER OF PATIENTS	INTERVENTION	COMPARISON	OUTCOMES MEASURED	NARRATIVE SUMMARY OF OUTCOMES
Isobe 2005	Observational study	Maxillary sinus carcinoma	124	Neoadjuvant + concurrent chemotherapy	Neoadjuvant chemotherapy alone; concurrent chemotherapy alone	Overall survival; disease-free survival; local control	Outcomes numerically favour neoadjuvant + concurrent chemotherapy over each treatment alone, but no statistical analysis performed.
Kreppel 2012	Observational study	Maxillary sinus squamous cell carcinoma	53	1. 40 Gy radiotherapy. 2. Chemotherapy with carboplatin	1. 50 Gy radiotherapy. 2. Chemotherapy with cisplatin	5-year overall survival; 5-year locoregional control; incidence of complete response	Outcomes favour higher dose RT and treatment with cisplatin. Significant difference between groups only for complete response to chemotherapy (favours cisplatin)
Liu 2013	Observational study	Primary advanced maxillary sinus malignancy	61	Conservative maxillectomy	Radical maxillectomy	2-year, 3-year and 5-year overall survival; HRQOL 6 months, 12 months and 18 months after treatment	Similar overall survival at all measured time points. Patients treated with conservative surgery had significantly better HRQOL 12 and 18 months after their surgery.
Resto 2008	Observational study	Sinonasal malignancies with skull base involvement	70 eligible for review (total study population = 102)	Complete tumour resection	Partial tumour resection	Local control; disease-free survival; overall survival; metastasis-free survival (all measured at 5 years)	5-year overall survival and 5-year disease-free survival and 5-year metastasis free survival improved in complete resection group. Rates of local control, regional metastasis and distant treatment failures were all similar between groups.

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	NUMBER OF PATIENTS	INTERVENTION	COMPARISON	OUTCOMES MEASURED	NARRATIVE SUMMARY OF OUTCOMES
Vergez 2012	Observational study	Sinonasal adenocarcinoma	48	Endoscopic surgery	Lateral rhinotomy	Overall survival; disease free survival; local recurrence; incidence of metastasis; overall mortality; disease-related mortality; posoperative complications	No significant difference between groups for any outcome.
Abbreviations: HRQOL: health-related quality of life; IMRT: intensity-modulated radiotherapy; SCC: squamous cell carcinoma; SRMA: systematic review and meta-analysis.							

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GRADE evidence tables

Table 6.7. GRADE evidence profile: surgery + radiotherapy versus surgery alone in SCC of the nasal vestibule

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + radiotherapy (SRT)	Surgery alone (S)	Absolute	
5-year overall survival										
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	22	17	SRT: 53 ± 13% S: 57 ± 17%	⊕OOO VERY LOW
5-year disease-specific survival										
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	22	17	SRT: 91 ± 6% S: 96 ± 4%	⊕OOO VERY LOW
5-year locoregional control										
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	22	17	SRT: 87 ± 7% S: 94 ± 6%	⊕OOO VERY LOW

[1] Agger 2013

[2] Postoperative RT was administered selectively to surgically-treated patients with involved or unclear margins. Length of follow up is not clear. Comparative results are only reported for a subset of patients (T1); reasons for this are not explained by the authors.

[3] Small study population.

Table 6.8. GRADE evidence profile: surgery + radiotherapy/chemoradiotherapy versus surgery alone in adenoid cystic carcinoma of the nasal cavity or paranasal sinuses

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + radiotherapy/chemoradiotherapy	Surgery alone	Absolute	
5-year overall survival										
15[1]	observational studies	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	282	77	Surgery + RT/ChRT group = 63%; surgery only group = 74%	⊕OOO VERY LOW

[1] Amit 2013
[2] Not all included studies directly compared the two interventions.
[3] Analysis based on small (median 22 patients) studies.

Table 6.9. GRADE evidence profile: surgery + radiotherapy versus surgery alone for treatment of sinonasal malignancies

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + radiotherapy	Surgery alone	Absolute	
5-year overall survival										
1[1]	observational studies	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	40	55	Surgery + RT group = 26%; surgery only group = 41%	⊕OOO VERY LOW

[1] Blanch 2004
[2] Unclear how patients were assigned to treatment, and whether baseline characteristics of the different treatment groups were similar.
[3] 22% of included patients had tumor histology catergorised as "nonepithelial forms'.
[4] Small study population.

Table 6.10. GRADE evidence profile: surgery + radiotherapy versus surgery alone for treatment of nasoethmoidal adenocarcinoma

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + radiotherapy	Surgery alone	Relative (95% CI)	Absolute	
Incidence of disease recurrence (follow-up length not reported)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	31/55 (56.4%)	28/55 (50.9%)	RR 1.11 (0.78, 1.57)	56 more per 1000 (from 112 fewer to 290 more)	⊕OOO VERY LOW

[1] Choussy 2010
[2] Length of follow up is not reported.
[3] Small population size.

Table 6.11. GRADE evidence profile: surgery + radiotherapy versus surgery alone for treatment of carcinoma of the nasal cavity or paranasal sinuses

Quality assessment							No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + radiotherapy	Surgery alone	Absolute			
Carcinoma-specific actuarial survival (follow-up median 72 months)												
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	113	44		**SRT (n = 113)**	**S (n = 44)**	⊕OOO VERY LOW
									2 years, %	82 ± 6	84 ± 6	
									5 years, %	66 ± 5	79 ± 6	
									10 years, %	60 ± 5	76 ± 6	
Locoregional control (follow-up median 72 months)												
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	113	44		**SRT (n = 113)**	**S (n = 44)**	⊕OOO VERY LOW
									2 years, %	70 ± 4	74 ± 7	
									5 years, %	63 ± 4	70 ± 7	
									10 years, %	57 ± 8	70 ± 7	

[1] Dulguerov 2001

[2] The study authors noted that patients treated with surgery and radiation had less favourable prognosis; significant differences in histology, tumour location and stage between treatment groups.

[3] Small study population

Table 6.12. GRADE evidence profile: surgery + radiotherapy versus surgery alone be used for treatment of sinonasal adenoid cystic carcinoma

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + radiotherapy	Surgery alone	Absolute	
Number of deaths at last follow up (median follow up 50.1 months for surgery only; 61.5 months for surgery combined with radiotherapy)										
39[1]	observational studies	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	38	19	Surgery only group: 12/19 (63.2%) Surgery combined with radiotherapy: 26/38 (68.4%)	⊕OOO VERY LOW

[1] Husain 2013
[2] Included studies did not directly compare the two interventions.
[3] The majority of included studies were small case series or individual case reports (study size range: 1-22 patients).

Table 6.13. GRADE evidence profile: postoperative IMRT versus postoperative CRT for cancer of the paranasal sinuses or nasal cavity

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative IMRT	Postoperative CRT	Relative (95% CI)	Absolute	
2-year local control											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	40	41	-	IMRT = 76%; CRT = 67%	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative IMRT	Postoperative CRT	Relative (95% CI)	Absolute	
2-year overall survival											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	40	41	-	IMRT = 89%; CRT = 73%	⊕OOO VERY LOW
2-year disease free survival											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	40	41	-	IMRT = 72%; CRT = 60%	⊕OOO VERY LOW
Disease control											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	40	41	-	IMRT = 89%; CRT = 89%	⊕OOO VERY LOW
Incidence of mucositis											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	25/40 (62.5%)	40/41 (97.6%)	RR 0.64 (0.50, 0.82)	351 fewer per 1000 (from 176 fewer to 488 fewer)	⊕OOO VERY LOW
Incidence of dysphagia											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	9/40 (22.5%)	14/41 (34.1%)	RR 0.66 (0.32, 1.35)	116 fewer per 1000 (from 232 fewer to 120 more)	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative IMRT	Postoperative CRT	Relative (95% CI)	Absolute	
Incidence of xerostomia											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	15/40 (37.5%)	37/41 (90.2%)	RR 0.42 (0.28, 0.63)	523 fewer per 1000 (from 334 fewer to 650 fewer)	⊕OOO VERY LOW
Incidence of pain											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	18/40 (45%)	34/41 (82.9%)	RR 0.54 (0.37, 0.79)	381 fewer per 1000 (from 174 fewer to 522 fewer)	⊕OOO VERY LOW
Incidence of smell disturbance											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	18/40 (45%)	36/41 (87.8%)	RR 0.51 (0.36, 0.74)	430 fewer per 1000 (from 228 fewer to 562 fewer)	⊕OOO VERY LOW
Incidence of taste disturbance											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	29/40 (72.5%)	38/41 (92.7%)	RR 0.78 (0.63, 0.96)	204 fewer per 1000 (from 37 fewer to 343 fewer)	⊕OOO VERY LOW
Incidence of fatigue											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	20/40 (50%)	32/41 (78%)	RR 0.64 (0.45, 0.91)	281 fewer per 1000 (from 70 fewer to 429 fewer)	⊕OOO VERY LOW

[1] Dirix 2010

[2] Historical control group used. Imbalances in the background care received by the two different treatment groups.

[3] Small study population.

Table 6.14. GRADE evidence profile: postoperative IMRT versus postoperative CRT for ethmoid adenocarcinoma

Quality assessment							No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative IMRT	Postoperative CRT	Absolute			
Overall survival												
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	28	30		**IMRT group**	**Conventional RT group**	⊕OOO VERY LOW
									2 years, %	65	83	
									4 years, %	58	66	
Local control												
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	28	30		**IMRT group**	**Conventional RT group**	⊕OOO VERY LOW
									2 years, %	69	70	
									4 years, %	63	63	

[1] Duthoy 2005

[2] Historical control group used. Limited data on patient characteristics or care given in addition to the intervention.

[3] Small population size.

Table 6.15. GRADE evidence profile: neoadjuvant + concurrent chemotherapy versus neoadjuvant chemotherapy alone for treatment of maxillary sinus carcinoma

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant + concurrent chemotherapy (NA + CRT)	Neoadjuvant chemotherapy alone (NA)	Absolute	
5-year overall survival										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	47	39	NA + CRT = 66.7% NA = 54.2%	⊕OOO VERY LOW
5-year disease free survival										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none			NA + CRT = 62.5% NA = 50.0%	⊕OOO VERY LOW
5-year local control										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none			NA + CRT = 87.5% NA = 65.6%	⊕OOO VERY LOW

[1] Isobe 2005

[2] Treatment in addition to the intervention varied substantially between patients. Differences specific to treatment groups are not reported.

[3] Small population size

Table 6.16. GRADE evidence profile: neoadjuvant + concurrent chemotherapy versus concurrent chemotherapy alone be used for treatment of maxillary sinus carcinoma

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant + concurrent chemotherapy	Concurrent chemotherapy alone	Absolute	
5-year overall survival										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	NA + CRT = 66.7% CRT = 54.2%	⊕OOO VERY LOW
5-year disease free survival										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	NA + CRT = 62.5% CRT = 44.4%	⊕OOO VERY LOW
5-year local control										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	NA + CRT = 87.5% CRT = 68.8%	⊕OOO VERY LOW

[1] Isobe 2005

[2] Treatment in addition to the intervention varied substantially between patients. Differences specific to treatment groups are not reported.

[3] Small population size.

Table 6.17. GRADE evidence profile: 40 Gy radiotherapy versus 50 Gy radiotherapy for maxillary sinus squamous cell carcinoma

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	40 Gy radiotherapy	50 Gy radiotherapy	Absolute	
5-year overall survival										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	18	35	40 Gy = 41.7%; 50 Gy = 31.3%	⊕OOO VERY LOW
5-year locoregional control										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	18	35	40 Gy = 58.9%; 50 Gy = 57.8%	⊕OOO VERY LOW

[1] Kreppel 2012

[2] Unclear how patients were assigned to treatment, and whether baseline characteristics of the different treatment groups were similar

[3] Small population size.

Table 6.18. GRADE evidence profile: carboplatin versus cisplatin for maxillary sinus squamous cell carcinoma

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carboplatin	Cisplatin	Absolute	
5-year overall survival										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	20	33	Carboplatin = 31.7%; Cisplatin = 37.2%	⊕OOO VERY LOW
5-year locoregional control										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	20	33	Carboplatin = 49.4%; Cisplatin = 63.9%	⊕OOO VERY LOW
Complete response rate										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	1/20 (5%)	10/33 (30.3%)	303 fewer per 1000	⊕OOO VERY LOW

[1] Kreppel 2012
[2] Unclear how patients were assigned to treatment, and whether baseline characteristics of the different treatment groups were similar.
[3] Small population size.

Table 6.19. GRADE evidence profile: conservative maxillectomy versus radical maxillectomy be used for primary advanced maxillary sinus malignancy

Quality assessment							No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radical maxillectomy	Conservative maxillectomy	Absolute			
Overall survival												
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	27	34		**Radical maxillectomy group (n = 27)**	**Conservative maxillectomy group (n = 34)**	⊕OOO VERY LOW
									Overall survival, %			
									2 years	67.65	66.67	
									3 years	58.11	53.68	
									5 years	44.97	42.95	
Health related quality of life (assessed with: University of Washington QOL scale, higher score indicates better QOL)												
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	27	34		**Radical maxillectomy group (n = 27)**	**Conservative maxillectomy group (n = 34)**	⊕OOO VERY LOW
									Composite score at baseline (pre-surgery)	837 ± 103	831 ± 86	
									Composite score at 6 months	658 ± 103	746 ± 104	
									Composite score at 12 months	655 ± 101	763 ± 88	
									Composite score at 18 months*	637 ± 130	759 ± 97	

[1] Liu 2013

[2] Unclear how patients were assigned to treatment. Limited baseline characteristics reported

[3] Small population size.

Table 6.20. GRADE evidence profile: complete tumour resection versus partial tumour resection or sinonasal malignancies with skull base involvement

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Complete tumour resection	Partial tumour resection	Absolute	
5 year local control (follow-up median 3.5 years)										
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	Complete resection = 95%; Partial resection = 82%	⊕OOO VERY LOW
5 year disease free survival (follow-up median 3.5 years)										
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	Complete resection = 90%; Partial resection = 49%	⊕OOO VERY LOW
5 year overall survival (follow-up median 3.5 years)										
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	Complete resection = 90%; Partial resection = 53%	⊕OOO VERY LOW
5 year regional metastasis free survival (follow-up median 3.5 years)										
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	Complete resection = 87%; Partial resection = 88%	⊕OOO VERY LOW
5 year distant metastasis free survival (follow-up median 3.5 years)										
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	Complete resection = 95%; Partial resection = 69%	⊕OOO VERY LOW

[1] Resto 2008.
[2] Higher radiotherapy dose delivered to the partial resection group.
[3] Small population size.

Table 6.21. GRADE evidence profile: endoscopic surgery versus lateral rhinotomy sinonasal adenocarcinoma

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopic surgery	Lateral rhinotomy	Relative (95% CI)	Absolute	
Number of deaths, any cause (follow up: Endoscopic surgery group: mean 38 months; lateral rhinotomy group: mean 89 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	6/24 (25%)	10/24 (41.7%)	RR 0.60 (0.26, 1.39)	167 fewer per 1000 (from 308 fewer to 163 more)	⊕OOO VERY LOW
Number of deaths, disease related (follow up: Endoscopic surgery group: mean 38 months; lateral rhinotomy group: mean 89 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	2/24 (8.3%)	4/24 (16.7%)	RR 0.50 (0.10, 2.48)	83 fewer per 1000 (from 150 fewer to 247 more)	⊕OOO VERY LOW
Incidence of local recurrence (follow up: Endoscopic surgery group: mean 38 months; lateral rhinotomy group: mean 89 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	3/24 (12.5%)	9/24 (37.5%)	RR 0.33 (0.10, 1.08)	251 fewer per 1000 (from 338 fewer to 30 more)	⊕OOO VERY LOW
Incidence of distant metastasis (follow up: Endoscopic surgery group: mean 38 months; lateral rhinotomy group: mean 89 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	2/24 (8.3%)	1/24 (4.2%)	RR 2.0 (0.19, 20.6)	42 more per 1000 (from 34 fewer to 817 more)	⊕OOO VERY LOW
3 year local control rate											
1[1]	observational studies	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	24	24	-	Endoscopic surgery = 87.5%; lateral rhinotomy = 75%	⊕OOO VERY LOW

[1] Vergez 2012

[2] Longer follow up for comparison group, giving more time in which to detect death or disease recurrence. Unclear how patients were assigned to treatment. Limited detail of care received in addition to the intervention. Some patients received radiotherapy and some did not; unclear if the proportions were split evenly between treatment groups.

[3] Small population size.

[4] Unclear how patients were assigned to treatment. Limited detail of care received in addition to the intervention. Some patients received radiotherapy and some did not; unclear if the proportions were split evenly between treatment groups.

Evidence tables for all included studies

Study, country

Agger 2009.
Denmark, five centres.

Study type, study period

Observational study, retrospective.
1993 to 2002.

Number of patients

39 eligible for review (total study population = 174)

Patient characteristics

Inclusion criteria: patients with SCC of the nasal vestibule. Patients of any stage were recruited, but relevant results are only reported for T1 patients.

Median age 69 years (range 36 to 94 years).

Gender	n (%)
Male	97 (56)
Female	77 (44)

T classification, UICC/Wang	T1 (Wang)	T2 (Wang)	T3 (Wang)	Total
T1 (UICC)	102	6	1	109
T2 (UICC)	6	22	2	30
T3 (UICC)	-	1	3	4
T4 (UICC)	1	18	12	31
Total	109	47	18	174

Staging of cases was classified according to both the Wang and UICC (2002) systems.

Intervention

Surgery (n = 17). The majority of patients were treated with excision of the tumour and skin transplant; some patients were treated with a local flap or free flap.

Comparison

Surgery followed by radiotherapy (no further details reported). n = 22.

Length of follow-up

Unclear. The authors state that patients were followed up until 5 years after last treatment, but it is not clear if 5 years of follow up data was available for all patients.

Outcome measures and effect size

Outcomes for surgically-treated T1 patients only:

	Surgery	Surgery + radiotherapy
5-year overall survival, % ± SE	57 ± 17	53 ± 13
5-year disease-specific survival, % ± SE	96 ± 4	91 ± 6
5-year locoregional control, % ± SE	94 ± 6	87 ± 7

Source of funding

Not reported.

Risks of bias

Selection bias: high risk. Postoperative RT was administered selectively to surgically-treated patients with involved or unclear margins.
Performance bias: unclear/unknown risk. The study was conducted across a number of centres; unclear if care (other than the intervention) was similar across different patients/centres.
Attrition bias: high risk. Length of follow up is not clear. Comparative results are only reported for a subset of patients (T1); reasons for this are not explained by the authors.
Detection bias: unclear/unknown risk. No definition of outcomes reported.

Additional comments

Other patients in the study population were treated with primary radiotherapy (n = 120) or palliative/no treatment (n = 4). Only surgically treated patients are eligible for the review, but comparative data on surgically treated patients is only reported for the subgroup of patients staged as T1 (Wang classification). Information on baseline characteristics specific to this subgroup of patients is not reported.

Study

Amit 2013.

Study type, study period

Systematic review and meta-analysis.
Studies included from 1975 to 2012.

Trial characteristics

Inclusion criteria:
Randomised controlled trials, prospective and retrospective cohort studies, case-control study designs, case reports and case series.
Histopathologic diagnosis of adenoid cystic carcinoma involving the paranasal sinuses or the orbit.
Minimum of 6 months of follow up (except in cases of death before 6 months)
Outcome data on survival and/or recurrence reported.

The authors also included their own previously unpublished results on the treatment of 99 patients with adenoid cystic carcinoma of the paranasal sinuses.

Number of trials/patients included

15 published trials (421 patients) plus data from the study authors' cohort of 99 patients. Of these, 356 patient had been surgically treated and had comparative outcome data available.

Intervention

Surgery followed by radiotherapy or chemoradiotherapy (n = 282).

Comparison

Surgery alone (n = 77)

Patient characteristics

Median age: 50 years (range 38 to 55 years).
Median follow up: 60 months (range 32 to 100 months)

Involved site	n (%)
Maxillary sinus	286 (54.7)
Nasal cavity	57 (10.9)
Nasopharynx	29 (5.5)
Ethmoid sinus	22 (4.2)
Sphenoid sinus	16 (3)
Not specified	110 (21)

T stage	n (%)
T1 or T2	81 (15.6)
T3 or T4	288 (55.4)
Not specified	151 (29.0)

Outcome measures and effect size

5-year overall survival: surgery + RT/ChRT group = 63%; surgery only group = 74%. No significant difference between groups (p = 0.58).

Source of funding

Government grants.

Additional comments

1

Study, country

Blanch 2004
Spain, single centre.

Study type, study period

Observational study (retrospective).
1974 to 1995.

Number of patients

125 patients included; data available for 91.

Patient characteristics

Inclusion criteria: any sinonasal tumour.

Primary site	n (%)
Maxillary sinus	58 (46.4)
Ethmoid sinus	34 (27.2)
Nasal fossa	15 (12)
Nasal septum	14 (11.2)
Frontal sinus	4 (3.2)

Histological type	n (%)
Squamous cell carcinoma	56 (44.8)
Adenocarcinoma	15 (12.0)
Undifferentiated carcinoma	10 (8.0)
Other epithelial forms	16 (12.8)
Nonepithelial forms	28 (22.4)

Tumour stage	n (%)
1	64 (51.2)
2	36 (28.8)
3	25 (20.0)

N stage	n (%)
0	114 (91.2)
1 to 3	11 (8.8)

Tumours were staged according to the University of California system (Parsons, 1988)

Intervention

Surgery plus radiotherapy (n = 40)

Comparison

Surgery alone (n = 55)

Length of follow-up

Mean 44 months (range 9.6 to 180 months).

2

Outcome measures and effect size
5-year overall survival: surgery + RT group = 26%; surgery only group = 41%. No significant difference between groups (p value not reported)
Source of funding
Not reported.
Risks of bias
Selection bias: Unclear/unknown risk. Unclear how patients were assigned to treatment, and whether baseline characteristics of the different treatment groups were similar. Performance bias: Unclear/unknown risk. No detail of care given in addition to the intervention. Attrition bias: Low risk Detection bias: Low risk
Additional comments
No details reported of the type of surgery or radiotherapy patients received.

1

Study, country
Choussy 2010. France (11 centres)
Study type, study period
Observational study (retrospective). January 1976 to December 2001.
Number of patients
110
Patient characteristics
Inclusion criteria: patients presenting with adenocarcinoma of the ethmoid bone. A total of 418 potentially eligible patients were identified, of which 55 received surgery alone and the remainder received combined treatment (surgery and radiotherapy). A cross-matched population analysis was performed to select 55 patients receiving combined treatment who had similar characteristics to the surgery-only group.
Intervention
Surgery and radiotherapy (n = 55). Type of surgery not reported. Radiotherapy was external in all patients with no intensity-modulated radiotherapy or conformal radiation therapy. Once daily fractionation scheme was used with a median dose of 61 Gy (range 50 to 70 Gy) in 30 fractions.
Comparison
Surgery only (n = 55; transfacial in 42 patients; transcranial only in 3 patients; combined transcranial and transfacial in 8 patients; endoscopic in 2 patients).
Length of follow-up
Not reported.
Outcome measures and effect size
5-year overall survival: 61% for both treatment groups. No statistically significant difference between groups for any outcome.
Source of funding
Not reported.
Risks of bias
Selection bias: Unclear/unknown risk. Attempts have been made to ensure the characteristics of the treatment groups were similar, but it is unclear what characteristics were taken into account, and only limited details of baseline characteristics are reported. Performance bias: Unclear/unknown risk. No detail of care given in addition to the intervention. Attrition bias: Unclear/unknown risk. Length of follow up is not reported. Detection bias: Low risk.

	n (%)	
	Surgery + RT (n =55)	**Surgery only (n =55)**
Male	49 (89)	49 (89)
Female	6 (11)	6 (11)
Brain or dura involvement	7 (13)	7 (13)
Stage T4 tumour	16 (29)	16 (29)
Mean age, yrs	63.3	63.1
History of wood particle exposure	47 (85)	43 (78)

	n (%)	
	Surgery + RT (n = 55)	**Surgery only (n = 55)**
Incidence of disease recurrence	31 (56)	28 (51)
Local	29 (52.7)	24 (43.6)
Regional	1 (1.8)	2 (3.6)
Distant	1 (1.8)	2 (3.6)

Additional comments

1

Study, country
Dirix 2010. Belgium, single centre.
Study type, study period
Observational study (retrospective). January 2003 to December 2008 (comparison group are historical controls from 1992 to 2002).
Number of patients
81.
Patient characteristics
Inclusion criteria: patients with malignancies of the nasal cavity or paranasal sinuses, treated with surgery and postoperative radiotherapy.

	IMRT group (n = 40)	**3D-RT group (n = 41)**
Mean age, years (range)	63 (37-84)	61 (37-85)
Gender, n (%)		
Male	34 (85)	34 (82.9)
Female	6 (15)	7 (17.1)
Tumour site		
Ethmoid sinus	33 (82.5)	30 (73.2)
Nasal cavity	6 (15)	2 (4.9)
Maxillary sinus	1 (2.5)	7 (17.1)
Sphenoid sinus	0	1 (2.4)
Frontal sinus	0	1 (2.4)
Histology		
Adenocarcinoma	31 (77.5)	25 (61.0)
Neuroendocrine carcinoma	4 (10)	0
Esthesioneuroblastoma	2 (5)	0
Squamous cell carcinoma	2 (5)	9 (22)
Undifferentiated carcinoma	1 (2.5)	5 (12.2)
Adenoid cystic carcinoma	0	2 (4.8)
T classification		
T2	9 (22.5)	10 (24.4)
T3	19 (47.5)	23 (56.1)
T4a	7 (17.5)	5 (12.2)
T4b	5 (12.5)	3 (7.3)
Type of surgery		
External	2 (5)	12 (29.3)
Endoscopic	38 (95)	29 (70.7)

Intervention
Postoperative IMRT (n = 40). Total dose was 60 Gy in 30 daily fractions (5 fractions per week). Patients with positive surgical margins (n = 19) received an additional 6 Gy.
Comparison
Historical controls, treated with postoperative 3D radiotherapy (without intensity modulation), doses as for intervention (n = 41).
Length of follow-up
IMRT group: median follow up 30 months (range 4 to 74 months). 3D-RT group: median 67 months.
Outcome measures and effect size

	IMRT (n = 40)	**3DRT (n = 41)**	
2-year local control, %	76	67	p = 0.06
2-year disease free survival, %	72	60	p = 0.02
2-year overall survival, %	89	73	p = 0.07
Disease control, %	89	89	p = 0.68
Incidence of adverse events (any grade), n (%)			
Mucositis	25 (62.5)	40 (97.6)	p = 0.0004
Dysphagia	9 (22.5)	14 (34.1)	p = 0.25
Xerostomia	15 (37.5)	37 (90.2)	p < 0.0001
Pain (headache)	18 (45)	34 (82.9)	p = 0.001
Disturbance to sense of smell	18 (45)	36 (87.8)	p = 0.0003
Disturbance to taste	29 (72.5)	38 (92.7)	p = 0.02
Fatigue	20 (50)	32 (78)	p = 0.01

Source of funding
Public body grants.
Risks of bias
Selection bias: Unclear/unknown risk. Historical control group used. Performance bias: High risk. Significantly more patients in the IMRT group were treated with endoscopic rather than external surgery Attrition bias: Low risk Detection bias: Low risk
Additional comments

1

Study, country
Dulguerov 2001 United States (one centre) and Switzerland (one centre)
Study type, study period
Observational study (retrospective). January 1975 to December 1994.
Number of patients
156 eligible for review (total study population = 220)
Patient characteristics
Inclusion criteria: • Patients receiving primary treatment for carcinoma of the nasal cavity and paranasal sinuses Exclusion criteria: • Benign tumours • Palate or skin primary tumours with secondary invasion of the sinuses and nose • Nasal vestibule primary tumours

	S+RT (n = 113)	**S (n = 44)**
Primary site	**n (%)**	**n (%)**
Maxillary sinus	59 (52.2)	17 (38.6)
Ethmoid sinus	25 (22.1)	1 (2.3)
Nasal cavity	29 (25.7)	25 (56.8)
Sinus, not otherwise specified	0 (0)	1
Histological type	**n (%)**	**n (%)**
Squamous cell carcinoma	56 (49.6)	32 (72.7)
Glandular carcinoma	22 (19.5)	8 (18.2)
Adenocarcinoma	18 (15.9)	4 (9.1)
Undifferentiated carcinoma	17 (15.0)	0 (0)
Tumour stage	**n (%)**	
T1	9 (8.0)	13 (29.5)
T2	34 (30.1)	11 (25.0)
T3	26 (23.0)	10 (22.7)
T4	44 (38.9)	10 (22.7)

Intervention
Surgery with radiotherapy (n = 113). Radiotherapy was administered with daily doses of 1.8 to 2.0 Gy, 5 days per week for a total dose of 60 to 65 Gy.
Comparison
Surgery alone (n = 44).
Length of follow-up
Median 72 months.
Outcome measures and effect size

	SRT (n =113)	**S (n = 44)**
Carcinoma-specific actuarial survival		
2 years, %	82 ± 6	84 ± 6
5 years, %	66 ± 5	79 ± 6
10 years, %	60 ± 5	76 ± 6
Actuarial locoregional control		
2 years, %	70 ± 4	74 ± 7
5 years, %	63 ± 4	70 ± 7
10 years, %	57 ± 8	70 ± 7

2

Source of funding
Not reported
Risks of bias
Selection bias: High risk. The study authors noted that patients treated with surgery and radiation had less favourable prognosis; significant differences in histology, tumour location and stage between treatment groups. Performance bias: Unclear/unknown risk. No detail of care given in addition to the intervention. Attrition bias: Low risk. Detection bias: Low risk.
Additional comments

1

Study, country
Duthoy 2005. Belgium, single centre.
Study type, study period
Observational study (retrospective). 1998 to 2003 for the intervention group (historic control cohort treated between 1985 and 1998).
Number of patients
58
Patient characteristics
Inclusion criteria: adenocarcinoma of the ethmoid sinus. Median age at diagnosis (IMRT group): 62 years (range 30 to 78 years). **T stage, n (%)** / **IMRT group** / **Conventional RT group** **T1** 0 (0) 2 (6.7) **T2** 13 (46.4) 8 (26.7) **T3** 4 (14.3) 9 (30.0) **T4** 11 (39.3) 11 (36.7)
Intervention
Postoperative IMRT (n = 28). Prescribed dose 60 to 70 Gy.
Comparison
Postoperative conventional or 3D conformal radiotherapy (n = 30, 19 with conventional radiotherapy, 11 with 3D conformal radiotherapy). Median dose was 66 Gy (range 54 to 66 Gy) delivered in 2 Gy fractions.
Length of follow-up
Median 31 months (range 9 to 67 months) for the intervention group; median 83 months for the comparison group.
Outcome measures and effect size
IMRT group (n = 28) / **Conventional RT group (n = 30)** **Overall survival, %** **2 years** 65 83 **4 years** 58 66 **Local control, %** **2 years** 69 70 **4 years** 63 63 No significant difference between groups for any outcomes.
Source of funding
Government grants.
Risks of bias
Selection bias: Unclear/unknown risk. Historical control group used. Limited data on patient characteristics reported. Performance bias: Unclear/unknown risk. No detail of care given in addition to the intervention. Attrition bias: Low risk. Detection bias: Low risk.
Additional comments

2

Study
Husain 2013.
Study type, study period
Systematic review and meta-analysis. Studies included from 1960 to 2012.

3

Trial characteristics

Inclusion criteria:
All English studies of sinonasal adenoid cystic carcinoma reporting either aggregate or individual patient data.

Comparative evidence is reported only for the individual patient data. Aggregate patient data was non-comparative and therefore not relevant to this review.

Number of trials/patients included

39 trials (88 patients) with individual patient data. Of these, 57 patients had been surgically treated and had comparative outcome data available.

Intervention

Surgery combined with radiotherapy (n = 38).

Comparison

Surgery alone (n = 19)

Patient characteristics

Mean age: 56 years (range 22 to 78 years).
Mean follow up: 51 months (range 1 to 198 months).

Gender	n (%)
Male	56 (64)
Female	44 (34)

Involved site	n (%)
Maxillary sinus (antrum)	54 (61.3)
Nasal cavity (+ septum)	11 (12.5)
Ethmoid sinus	5 (5.7)
Nasopharynx	4 (4.5)
Multiple sites	3 (3.4)
Paranasal sinus	3 (3.4)
Sphenoid sinus	3 (3.4)
Frontal sinus	2 (2.3)
Anterior skull base (ethmoid)	2 (2.3)
Orbit	1 (1.1)

Outcome measures and effect size

Number of patients alive at last reported follow up:
Surgery only group: 12/19 (63.2%)
Surgery combined with radiotherapy: 26/38 (68.4%)
Difference between treatment groups not significant.

Source of funding

Not reported

Additional comments

Average length of follow up for the two treatment groups: surgery only 50.1 months; surgery combined with radiotherapy 61.5 months.

1

Study, country

Isobe 2005.
Japan, single centre.

Study type, study period

Observational study (retrospective).
1983 to 2002.

Number of patients

124

Patient characteristics

Inclusion criteria: patients with maxillary sinus carcinoma receiving radiotherapy with curative intent.
Exclusion criteria: recurrent cancer; histology other than squamous cell carcinoma; distant metastases at presentation; previous or concurrent history of other malignancies.

Age (mean ± standard deviation) = 60.8 ± 11.2 years.

Gender	n (%)
Male	96 (77.4)
Female	28 (22.6)

Histological grade	n (%)
Well differentiated	36 (29.0)
Moderately differentiated	37 (29.8)
Poorly or undifferentiated	25 (20.2)
Not known	26 (21.0)

T stage	n (%)
T1	0 (0)
T2	9 (7.3)
T3	53 (42.7)
T4	62 (50.0)

N stage	n (%)
N0	103 (83.1)
N1	8 (6.4)
N2	13 (10.5)
N3	0 (0)

Intervention

Neoadjuvant chemotherapy (NA) (n = 39).

2

Comparison (1)

Concurrent chemoradiotherapy (CRT) (n = 38).

Comparison (2)

Both neoadjuvant chemotherapy and concurrent chemoradiotherapy (n = 47).

Length of follow-up

Median 46.4 months (range 1.6 to 19.6 years).

Outcome measures and effect size

	NA (n = 39)	CRT (n = 38)	NA + CRT (n = 47)
5-year overall survival, %	54.2	54.2	66.7
5-year disease free survival, %	50.0	44.4	62.5
5-year local control, %	65.6	68.8	87.5

Figures estimated from Kaplan-Meier survival curves.

Source of funding

Not reported.

Risks of bias

Selection bias: Unclear/unknown risk. Unclear how patients were assigned to treatment, and whether baseline characteristics of the different treatment groups were similar.
Performance bias: Unclear/unknown risk. Treatment in addition to the intervention varied substantially between patients. Differences specific to treatment groups are not reported.
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

1

Study, country

Kreppel 2012.
Germany, single centre.

Study type, study period

Observational study (retrospective).
1980 to 2006

Number of patients

53

Patient characteristics

Inclusion criteria: treatment naïve patients with biopsy-proven primary squamous cell carcinoma of the maxillary sinus, treated with curative intent.
All patients received concomitant neoadjuvant radiochemotherapy followed by radical surgery.

Median age: 58 years (range 18 to 78 years)

Gender	n (%)
Male	41 (77.4)
Female	12 (22.6)

UICC stage	n (%)
II	2 (3.8)
III	10 (18.9)
IVa	36 (67.9)
IVb	5 (9.4)

T stage	n (%)
T2	3 (5.7)
T3	11 (20.8)
T4a	34 (64.1)
T4b	5 (9.4)

N stage	n (%)
N0	28 (52.8)
N1	6 (11.3)
N2	19 (35.8)

Intervention (1)

Radiotherapy dose = 40 Gy (n = 18)

Comparison (1)

Radiotherapy dose = 50 Gy (n = 35)

Intervention (2)

Chemotherapy with carboplatin (n = 20)

Comparison (2)

Chemotherapy with cisplatin (n = 33)

Length of follow-up

Median 79 months.

2

Outcome measures and effect size

	5-year overall survival, %	5-year locoregional control, %	Complete response rate, n (%)
Radiotherapy			
40 Gy	41.7	58.9	-
50 Gy	31.3	57.8	-
Chemotherapy			
Carboplatin	31.7	49.4	1 (5)*
Cisplatin	37.2	63.9	10 (30.3)*

*indicates significant (p <0.05) difference between treatment groups.

Source of funding

Risks of bias

Selection bias: Unclear/unknown risk. Unclear how patients were assigned to treatment, and whether baseline characteristics of the different treatment groups were similar.
Performance bias: Low risk.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

Study, country

Liu 2013.
China, single centre.

Study type, study period

Observational study (retrospective).
2004 to 2006.

Number of patients

61

Patient characteristics

Inclusion criteria: patients with previously untreated primary advanced maxillary sinus malignancy, treated with radical or conservative maxillectomy.
Exclusion criteria: recurrent or synchronous malignancies; patients unable to complete the proposed quality of life questionnaires.

	Radical maxillectomy group (n = 27)	Conservative maxillectomy group (n = 34)
Median age, yrs (range)	50 (32–75)	51 (21–74)
Gender, n (%)		
Male	19 (70.4)	25 (73.5)
Female	8 (29.6)	9 (26.5)
Histological type, n (%)		
Squamous cell carcinoma	18 (66.7)	24 (70.6)
Adenocarcinoma	3 (11.1)	3 (8.8)
Adenoid cystic carcinoma	1 (3.7)	2 (5.9)
Sarcoma	3 (11.1)	2 (5.9)
Other (not specified)	2 (7.4)	3 (8.8)
Clinical stage, n (%)		
Stage III	12 (44.4)	16 (47.1)
Stage IV	15 (55.6)	18 (52.9)

Intervention

Radical maxillectomy (n = 27).

Comparison

Conservative maxillectomy (n = 34).

Length of follow-up

Average 37.9 months (range 4 to 72 months).

2

Outcome measures and effect size

	Radical maxillectomy group (n = 27)	Conservative maxillectomy group (n = 34)
Overall survival, %		
2 years	67.65	66.67
3 years	58.11	53.68
5 years	44.97	42.95
Quality of life (assessed by University of Washington QOL scale, higher score indicates better QOL)		
Composite score at baseline (pre-surgery)	837 ± 103	831 ± 86
Composite score at 6 months	658 ± 103	746 ± 104
Composite score at 12 months	655 ± 101	763 ± 88
Composite score at 18 months*	637 ± 130	759 ± 97

*significant difference between groups (p <0.01).

Source of funding

Not reported. The authors declared that they have no conflicts of interest.

Risks of bias

Selection bias: Unclear/unknown risk. Unclear how patients were assigned to treatment. Limited baseline characteristics reported.
Performance bias: Low risk
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

1

Study, country

Resto 2008.
United States, single centre.

Study type, study period

Observational study, retrospective.
1991 to 2002.

Number of patients

70 eligible for review (total study population = 102, patients not treated with tumour resection are excluded from this review).

Patient characteristics

Inclusion criteria: Sinonasal malignancies with skull base involvement, treated with curative intent.

Median age (all recruited patients): 50 years (range 15 to 82 years).

	Complete resection	Partial resection
Tumour histology		
Squamous cell carcinoma, n (%)	7 (35)	18 (36)
Carcinoma with neuroendocrine features, n (%)	8 (40)	9 (18)
Adenoid cystic carcinoma, n (%)	1 (5)	10 (20)
Soft tissue sarcoma, n (%)	4 (20)	7 (14)
Adenocarcinoma, n (%)	0 (0)	6 (12)
Median radiation dose, Gy (range)	67.6 (59.4–79.4)	75.6 (59.4–79.4)

Intervention

Complete tumour resection (n = 20). Total extirpation of tumour with negative pathologic margins documented.

Comparison

Partial tumour resection (n = 50). Total gross tumour removal with positive pathologic margins, or near-total tumour removal.

Length of follow-up

Median 3.6 years (range 0.11 to 13 years)

Outcome measures and effect size

	Complete resection	Partial resection
5 year local control, %	95	82
5 year disease free survival, %	90	49
5 year overall survival, %	90	53
5 year regional metastasis free survival, %	87	88
5 year distant metastasis free survival, %	95	69
Number of treatment failures due to distant metastasis, n (%)	2/20 (10)	14/50 (28)

Source of funding

Government grant.

Risks of bias

Selection bias: Unclear/unknown risk. Unclear how patients were assigned to treatment, and whether baseline characteristics of the different treatment groups were similar.
Performance bias: High risk. Higher radiotherapy dose delivered to the partial resection group.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

Study, country

Vergez 2012.
France, single centre.

Study type, study period

Observational study. Intervention group prospectively recruited (1999 to 2009) and compared with a retrospectively identified control group (treated between 1993 and 2007).

Number of patients

48

Patient characteristics

Inclusion criteria: all patients presenting with sinonasal adenocarcinoma who underwent endoscopic resection or transfacial rhinotomy

Postoperative radiotherapy was delivered to 43 out of 48 patients.

	Endoscopic surgery (n = 24)	Lateral rhinotomy (n = 24)
Average age, yrs (range)	67 (44–83)	66 (48–90)
Gender		
Male	22 (92)	24 (100)
Female	2 (8)	0 (0)
T stage		
T1–T2	11 (46)	12 (50)
T3–T4	13 (54)	12 (50)

Intervention

Endoscopic surgery (n = 24)

Comparison

Lateral rhinotomy (n = 24)

Length of follow-up

Endoscopic surgery group: mean 38 months; lateral rhinotomy group: mean 89 months.

Outcome measures and effect size

	Endoscopic surgery (n = 24)	Lateral rhinotomy (n = 24)
Overall mortality, n (%)	6	10
Disease-related mortality, n (%)	2	4
Incidence of local recurrence, n (%)	3	9
Incidence of distant metastasis, n (%)	2	1
3-year local control, %	87.5	75

No significant difference between groups for any outcome.

Source of funding

Not reported. Authors disclosed no conflicts of interest.

Risks of bias

Selection bias: Unclear/unknown risk. Unclear how patients were assigned to treatment; time periods for recruitment of the two groups overlap, and so presumably this is not purely based on time of treatment. Limited baseline characteristics reported, although those that were reported were similar between groups.
Performance bias: Unclear/unknown risk. Limited detail of care received in addition to the intervention. Some patients received radiotherapy and some did not; unclear if the proportions were split evenly between treatment groups.
Attrition bias: High risk. Longer follow up for comparison group, giving more time in which to detect death or disease recurrence.
Detection bias: Low risk.

Additional comments

2

1 Evidence search details and references

2 ***Review question in PICO format***

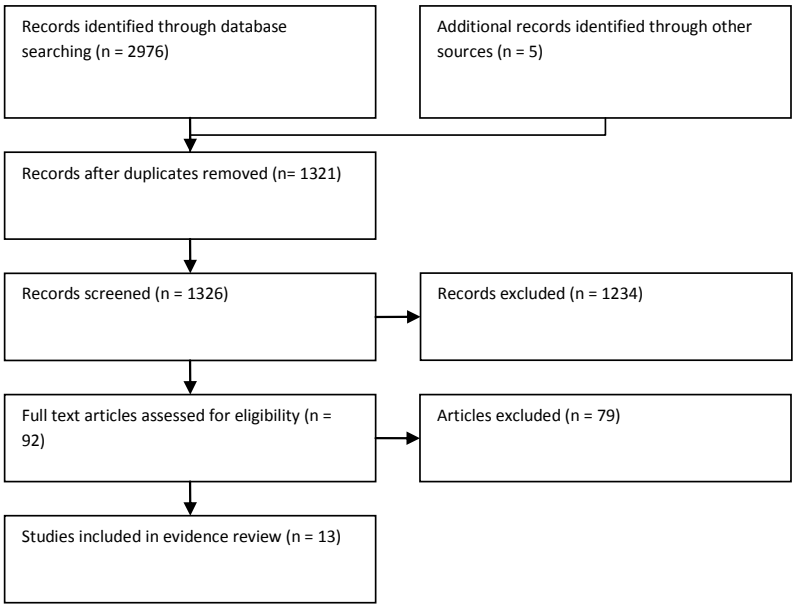
Population	Intervention	Comparison	Outcomes
Adults diagnosed with new carcinoma of the paranasal sinuses in whom surgery is indicated. Subgroups: • stage • histology	• Radiotherapy (altered fractionation, bracytherapy) • Surgery (+/- obturator; +/- reconstruction; endoscopic or open surgery) (including timing of surgery) • Chemotherapy (induction/neo-adjuvant and concomitant) • Other systemic therapies (e.g. lapatinib, EGFR antagonists) • Combinations of above	Each other	• Overall survival • Disease free survival • Progression free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Eye/organ preservation rates • Health related quality of life

3

Additional review protocol details (refer to Section 10 for full review protocol)

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Retrospective studies comparing interventions will be included where a minimum of 10 patients received each studied intervention. Prospective studies of any population size will be included. For studies where only some of the population meets the definition in the PICO, studies will be included only if subgroup analysis of the relevant patients alone is possible, or the proportion of patients relevant to the PICO is <75%. Studies of patients with secondary tumours in the nose/paranasal sinuses will be excluded. Studies focussing on curative treatment only will be included; studies of patients receiving palliative care will be excluded. Melanoma and olfactory neuroblastoma will be excluded (see notes in the review strategy on included histopathologies). Inverting papilloma will also be excluded as this is a precancerous condition.
Search strategies	Limit search to 1994 onwards. According to the GC, this is the date of publication for the earliest evidence on this topic.
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing of surgery as an intervention will be an important consideration for this review. The timing, dose, duration, and sequence of other interventions will be considered where relevant evidence is available. The histopathology of nasal sinus tumours will be considered. Evidence is expected to focus on the treatment of squamous cell carcinoma, but tumours of other carcinoma histopathologies (adenoid cystic carcinoma, sinonasal undifferentiated carcinoma, adenocarcinoma) will be included in the review, and subgroup analyses carried out by histopathology if possible.

Figure 6.2. Study flow diagram



Included studies

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Amit, M., Binenbaum, Y., Sharma, K., Naomi, R., Ilana, R., Abib, A., Miles, B., Yang, X., Lei, D., Kristine, B., Christian, G., Thomas, M., Klaus-Dietrich, W., Fliss, D., Eckardt, A. M., Chiara, C., Sesenna, E., Frank, P., Patel, S., and Gil, Z. Adenoid cystic carcinoma of the nasal cavity and paranasal sinuses: a meta-analysis. Journal of Neurological Surgery, Part B, Skull Base 2013. 74(3): 118-125

Blanch, J. L., Ruiz, A. M., Alos, L., Traserra-Coderch, J., and Bernal-Sprekelsen, M. Treatment of 125 sinonasal tumors: prognostic factors, outcome, and follow-up. Otolaryngology - Head & Neck Surgery 2004. 131(6): 973-976

Choussy, O., Ferron, C., Vedrine, P. O., Toussaint, B., Lietin, B., Marandas, P., Babin, E., De, Raucourt D., Reyt, E., Cosmidis, A., Makeieff, M., and Dehesdin, D. Role of radiotherapy in the treatment of nasoethmoidal adenocarcinoma. Archives of Otolaryngology -- Head & Neck Surgery 2010. 136(2): 143-146

Dirix, P., Vanstraelen, B., Jorissen, M., Vander, Poorten, V, and Nuyts, S. Intensity-modulated radiotherapy for sinonasal cancer: improved outcome compared to conventional radiotherapy. International Journal of Radiation Oncology, Biology, Physics 2010. 78(4): 998-1004

Dulguerov, P., Jacobsen, M. S., Allal, A. S., Lehmann, W., and Calcaterra, T. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. Cancer 2001. 92(12): 3012-3029

Duthoy, W., Boterberg, T., Claus, F., Ost, P., Vakaet, L., Bral, S., Duprez, F., Van, Landuyt M., and Vermeersch, H. Postoperative intensity-modulated radiotherapy in sinonasal carcinoma: clinical results in 39 patients. [Review] [22 refs]. Cancer 2005. 104(1): 71-82

Husain, Q., Kanumuri, V. V., Svider, P. F., Radvansky, B. M., Boghani, Z., Liu, J. K., and Eloy, J. A. Sinonasal adenoid cystic carcinoma: systematic review of survival and treatment strategies. Otolaryngology - Head and Neck Surgery 2013. 148(1): 29-39

Isobe, K., Uno, T., Hanazawa, T., Kawakami, H., Yamamoto, S., Suzuki, H., Iida, Y., and Ueno, N. Preoperative chemotherapy and radiation therapy for squamous cell carcinoma of the maxillary sinus. Japanese Journal of Clinical Oncology 2005. 35(11): 633-638

Kreppel, M. Neoadjuvant chemoradiation in squamous cell carcinoma of the maxillary sinus: A 26-year experience. Chemotherapy Research and Practice 2012. 2012 , 2012. Article Number: 413589

Liu, L. T., Liu, D., Guo, Q. Y., and Shen, B. Quality of Life in Advanced Maxillary Sinus Cancer After Radical Versus Conservative Maxillectomy. Journal of Craniofacial Surgery 2013. 24(4): 1368-1372

Resto, V. A., Chan, A. W., Deschler, D. G., and Lin, D. T. Extent of surgery in the management of locally advanced sinonasal malignancies. Head Neck 2008. 30(2): 222-229.
Note: This study is included in the systematic review by Amit et al, but only adenoid cystic carcinoma patients are included, and data is not presented for all outcomes.

Vergez, S., Martin-Dupont, N., Lepage, B., De, Bonnecaze G., Decotte, A., and Serrano, E. Endoscopic vs transfacial resection of sinonasal adenocarcinomas. Otolaryngology - Head & Neck Surgery 2012. 146(5): 848-853

Excluded studies

Al-Jhani, A. S., Al-Rajhi, N. M., El-Sebaie, M. M., Nooh, N. S., Mahasen, Z. Z., Al-Amro, A. S., and Otieschan, A. T. Maxillary sinus carcinoma. Natural history and outcome. Saudi Medical Journal 2004. 25(7): 929-933.
Reason for exclusion: Comparison not relevant to PICO (one intervention arm included less than 10 patients).

Al-Mamgani, A., van, Rooij P., Mehilal, R., Tans, L., and Levendag, P. C. Combined-modality treatment improved outcome in sinonasal undifferentiated carcinoma: single-institutional experience of 21 patients and review of the literature. European Archives of Oto-Rhino-Laryngology 2013. 270(1): 293-299.
Reason for exclusion: Comparison not relevant to PICO (one intervention arm included less than 10 patients).

Albu, S., St, Florian, I, Szabo, I., Baciut, G., Baciut, M., Mitre, I., Albu, S., St Florian, I., Szabo, I., Baciut, G., Baciut, M., and Mitre, I. Craniofacial resection for malignant tumors of the paranasal sinuses. Chirurgia (Bucuresti) 2011. 106(2): 219-225.
Reason for exclusion: Comparison not relevant to PICO.

Allen, M. W., Schwartz, D. L., Rana, V., Adapala, P., Morrison, W. H., Hanna, E. Y., Weber, R. S., Garden, A. S., and Ang, K. K. Long-term radiotherapy outcomes for nasal cavity and septal cancers. International Journal of Radiation Oncology, Biology, Physics 2008. 71(2): 401-406.
Reason for exclusion: Comparison not relevant to PICO. One intervention arm included less than 10 patients.

Almeyda, R., Capper, J., Almeyda, R., and Capper, J. Is surgical debridement and topical 5 fluorouracil the optimum treatment for woodworkers' adenocarcinoma of the ethmoid sinuses? A case-controlled study of a 20-year experience. Clinical Otolaryngology 2008. 33(5): 435-441.
Reason for exclusion: Comparison not relevant to PICO. Two treatment groups studied, but each group included a range of different interventions. Not all patients treated surgically.

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Reason for exclusion: Minor correction to published study.

Arnold, A., Ziglinas, P., Ochs, K., Alter, N., Geretschlager, A., Ladrach, K., Zbaren, P., and Caversaccio, M. Therapy options and long-term results of sinonasal malignancies. Oral Oncology 2012. 48(10): 1031-1037.
Reason for exclusion: Population not relevant to PICO.

Bhattacharyya, N. Cancer of the nasal cavity: survival and factors influencing prognosis. Archives of Otolaryngology -- Head & Neck Surgery 2002. 128(9): 1079-1083.
Reason for exclusion: Insufficient outcome data reported.

Blanco, A. I., Chao, K. S., Ozyigit, G., Adli, M., Thorstad, W. L., Simpson, J. R., Spector, G. J., Haughey, B., and Perez, C. A. Carcinoma of paranasal sinuses: long-term outcomes with radiotherapy. International Journal of Radiation Oncology, Biology, Physics 2004. 59(1): 51-58.
Reason for exclusion: Comparison not relevant to PICO. Not all patients were treated with surgery.

Bozec, A., Poissonnet, G., Chamorey, E., Casanova, C., Vallicioni, J., Demard, F., Mahdyoun, P., Peyrade, F., Follana, P., Bensadoun, R. J., Benezery, K., Thariat, J., Marcy, P. Y., Sudaka, A., and Dassonville, O. Free-flap head and neck reconstruction and quality of life: a 2-year prospective study. Laryngoscope 2008. 118(5): 874-880.
Reason for exclusion: Population not relevant to PICO.

Bristol, I. J., Ahamad, A., Garden, A. S., Morrison, W. H., Hanna, E. Y., Papadimitrakopoulou, V. A., Rosenthal, D. I., and Ang, K. K. Postoperative radiotherapy for maxillary sinus cancer: long-term outcomes and toxicities of treatment. International Journal of Radiation Oncology, Biology, Physics 2007. 68(3): 719-730.
Reason for exclusion: Comparison not relevant to PICO.

Carrau, R. L., Segas, J., Nuss, D. W., Snyderman, C. H., Janecka, I. P., Myers, E. N., D'Amico, F., and Johnson, J. T. Squamous cell carcinoma of the sinonasal tract invading the orbit. Laryngoscope 1999. 109(2 Pt 1): 230-235.
Reason for exclusion: Comparison not relevant to PICO.

Carrillo, J. F., Guemes, A., Ramirez-Ortega, M. C., and Onate-Ocana, L. F. Prognostic factors in maxillary sinus and nasal cavity carcinoma. European Journal of Surgical Oncology 2005. 31(10): 1206-1212.

Reason for exclusion: Comparison not relevant to PICO. Not all patients treated with surgery.

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Reason for exclusion: Comparison not relevant to PICO.

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Reason for exclusion: Population not relevant to PICO.

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Reason for exclusion: Comparison not relevant to PICO.

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Reason for exclusion: Systematic review - outcomes not relevant to PICO.

Unknown primary of presumed upper aerodigestive tract origin

Clinical question: What is the most effective treatment for unknown primary of presumed upper airways tract origin (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)?

Background

Unknown primary is a relatively rare presentation accounting for approximately 2% of all CUADT cases. The reported incidence of these tumours has declined in recent years with improved diagnostic and imaging techniques. The majority of patients present with unilateral lymph node metastases. Optimal management of this patient group is unknown and variations in practice exist.

In addition, there is a lack of consensus about the radiotherapy target volumes that should be treated. The most common controversy is whether to include potential primary sites as well as the involved neck in the radiotherapy target volume. Doing so significantly increases the morbidity of treatment. Ipsilateral neck irradiation alone may make further radiotherapy difficult to deliver if a primary tumour is subsequently detected.

Evidence statements

There is uncertainty about the most effective treatment for adults presenting with metastatic neck disease and clinically occult primary presumed to be of upper aerodigestive tract origin, due to a lack of well designed comparative studies. Very low quality evidence about the following treatment outcomes comes from case series in which treatment allocation is likely to have been biased by performance status, fitness and prognosis.

Overall survival

One observational study (Demiroz et al., 2014) reported overall survival at 4 years post-treatment as 85.6% for radiotherapy alone and 85.3% for neck dissection plus radiotherapy. Eight studies reported overall survival at 5 years after treatment (Grau et al., 2000; Sivars et al., 2014; Madani, Vakaet, Bonte, Boterberg, & De, 2008; Davidson, Spiro, Patel, Patel, & Shah, 1994; Strojan, 1998; Mistry, Qureshi, Talole, & Deshmukh, 2008; Park et al., 2012; Chen et al., 2011); this was 65% for neck dissection alone, 37% for radiotherapy alone, 25%-80% for neck dissection plus radiotherapy and 44%-71% neck dissection plus chemoradiotherapy (see table 1). HPV positivity was associated with better overall survival (Sivars et al., 2014; Park et al., 2012).

Disease specific survival

Disease specific survival at 5 years after treatment was 76% - 80% for neck dissection alone, 45% for radiotherapy alone, and 49%-66% for neck dissection plus radiotherapy (Grau et al., 2000; Davidson et al., 1994; Wang, Goepfert, Barber, & Wolf, 1990; Strojan, 1998).

Recurrence free survival

Recurrence free survival at 5 years after treatment was 61%-72% for neck dissection plus radiotherapy and 65%-85% neck dissection plus chemoradiotherapy (Madani et al., 2008; Reddy & Marks, 1997; Park et al., 2012).

Local control

Local control in the neck at 5 years after treatment was 58% for neck dissection alone, 50% for radiotherapy alone, 57%-86% for neck dissection plus radiotherapy and 80% neck dissection plus chemoradiotherapy (Grau et al., 2000; Davidson et al., 1994; Iganej et al., 2002; Chen et al., 2011).

Detection of primary

From one retrospective study including 69 patients treated with either neck dissection, neck dissection with post-operative radiotherapy or neck dissection with adjuvant radiotherapy (Guntinas-Lichius et al., 2006), primary tumour was detected in 33% of patients and in a second retrospective study (Park et al., 2012), primary tumour was detected in 38% of patients [very low quality evidence].

Feeding tube requirement

Feeding tube was required at 6 months after surgery plus chemoradiotherapy in 11% of those receiving IMRT versus 42% of those treated with conventional radiotherapy (Chen et al., 2011).

Mucositis

Grade 3 or more mucositis following radiotherapy occurred in 12% to 59% of patients following conventional radiotherapy versus 28% to 50% following IMRT (Chen et al., 2011; Strojan, 1998; Madani et al., 2008).

Xerostomia

Grade 3 or more xerostomia following radiotherapy occurred in 21% - 58% of patients following conventional radiotherapy versus 11% to 12% following IMRT (Chen et al., 2011; Strojan, 1998; Madani et al., 2008; Reddy & Marks, 1997).

Neck fibrosis

Late neck fibrosis following radiotherapy occurred in 19% to 39% of patients (Strojan, 1998; Reddy & Marks, 1997; Iganej et al., 2002).

Study characteristics and quality

The evidence base consisted a large number of single arm (non-comparative), retrospective case series, all of which were judged to be very low quality as assessed by GRADE and NICE checklists. All studies were single-centre studies with highly selected populations. None of the included studies were conducted in the UK, and for this reason there is a risk of bias associated with the included studies in relation to the applicability of the evidence.

All included studies had very small sample sizes. In some studies it was unclear whether the unknown primary was considered to be from the upper airways tract. Due to the relative rarity of unknown primary cancer some of the series included patients from as far back as the 1960s and the applicability of these historical cohorts to the present day population is questionable.

There was a high degree of heterogeneity across all the studies. For example, patients in studies reporting the effectiveness of radiotherapy typically had varying degrees of surgery (biopsy, local excision or neck dissection) and may also have had chemotherapy. Therefore, it was difficult to compare effectiveness between studies. Some studies noted that choice of treatment was related to the prognosis: patients treated with excisional biopsy alone may have been too unwell to receive agressive therapy, those treated with RT alone may have had inoperable disease, and those treated

with surgery plus RT plus chemotherapy may have had high risk disease. Despite the number of studies available to inform this topic, no meta-analysis could be performed due to the degree of heterogeneity.

Given these considerations therefore, the evidence presented should be considered with caution.

Table 6.22. Characteristics of included studies

Study	Study type/setting	N	Intervention	Comparison	Follow-up	Outcomes
Chen A et al (2011)	Retrospective case series Single Centre (USA) January 2001 to March 2009	51	Neck dissection + conventional RT ± chemotherapy	Neck dissection + IMRT ± chemotherapy	Median follow-up was 29 months for the whole cohort (range, 6-84 months) Median follow-up for patients treated with chemotherapy was 32 months (6-84 months) Median follow-up for patients treated with IMRT was 25 months (range, 6-51 months)	Overall survival Disease free survival Locoregional control Toxicity
Compton A et al (2011)	Retrospective case series Single institute	25	Surgery + postop RT + chemotherapy N = 22 had neck dissection, N = 3 excisional biopsy, N = 22 had chemotherapy	None	Median follow-up 33.8 months (1-93 months)	Overall survival Disease free survival
Davidson B et al (1994)	Retrospective case series Single institute Operative records – 1977-1983 Service database – 1984-1990	73	Surgery and postop RT (>81% of cases) N = 65 had neck dissection, N = 6 had excisional biopsy.	None	Survival outcomes reported to 70 months	Overall survival Disease free survival Disease control

Study	Study type/setting	N	Intervention	Comparison	Follow-up	Outcomes
Demiroz et al (2015)	Retrospective case series study Single centre (USA) 1994 to 2009	41	Neck dissection + radiation therapy	Definitive radiation therapy	Median 73 months (range 18 to 126 months) for the neck dissection + radiation therapy group; median 39 months (range 11 to 98 months) for the definitive radiation therapy group	Overall survival Progression-free survival Locoregional recurrence-free survival Emergence of primary site
Erkal H et al (2001)	Retrospective case series study Single centre (USA) 1964-1997	126	Radiotherapy + neck dissection (N = 50) Also compares outcomes for preop versus postop RT.	RT alone (N = 50)	All patients followed-up for at least 2 years (113 patients had follow-up for at least 5 years)	Overall survival Cause specific survival Disease control Complications
Frank S et al (2010)	Retrospective case series Single centre (USA) 1998-2005	52	Intensity modulated radiotherapy (IMRT) ± neck dissection ± chemotherapy	None	Median follow up for the whole cohort was 3.7 years (range 1-7.6)	Disease control Overall survival Disease free survival Complications
Guntinas-Lichius O et al (2006)	Retrospective case series Single centre (USA) March 1987-April 2002	46	Surgery ± post-operative radiotherapy ±chemoradiotherapy	None	Follow-up time for patients with unknown primary ranged from 0.4-169.8 months (mean 33.83 months) Observation time for patients alive without disease at last follow-up ranged from 0.9-120.4 months (mean 38.57 months)	Detection of primary Survival Disease free survival

Study	Study type/setting	N	Intervention	Comparison	Follow-up	Outcomes
Grau (2000)	Retrospective observational study (national) Denmark	277	Neck dissection alone (N = 23)	RT alone (N = 213) RT plus surgery (N = 26)	At least 5 years follow up	Overall survival, disease specific survival, neck control
Ignajej (2002)	Retrospective case file review. USA	106	Excisional biopsy + RT (N = 15), Neck dissection alone (N = 29), Neck dissection + RT (N = 26), RT alone (N = 26)	None	At least 5 years. Median 82 months in survivors	Neck control, mucosal control, distant failure, adverse events
Klem et al (2008)	Retrospective case series Single centre February 2001 to July 2005	21	IMRT ± concurrent chemotherapy ± neck dissection N = 13 patients underwent initial neck dissection, N = 3 excisional biopsy, N = 14 had chemotherapy	None	Median follow-up was 20.1 months (range 5-21) for all patients and 23.8 months for living patients.	Relapse free survival Disease free survival Overall survival Toxicity and compications
Lu H et al (2009)	Retrospective case series Single centre (USA) February 2000 to November 2006	18.	IMRT ± neck dissection ± chemotherapy N = 8 had neck dissection, N = 3 excisional biopsy, N = 6 chemotherapy	None	Median follow-up for all patients was 25.5 months (range 3.3-86.3) and for living patients was 35.5 months (range, 6.5-86.3 months)	Overall survival Recurrence free survival Adverse events
Madani I et al (2008)	Retrospective case series Single centre (Belgium) February 2003 to September 2006	23	IMRT + neck dissection Overall 19 patients had neck dissection	Conventional radiotherapy + neck dissection	IMRT: Median follow-up of patients alive at last follow-up was 17 months (range, 2-39 months) Controls Median follow-up was 37 months (range 4-100 months)	Relpase Overall survival Disease free survival Toxicity

Study	Study type/setting	N	Intervention	Comparison	Follow-up	Outcomes
Mistry (2008)	Retrospective observational study. India	89	Neck dissection ± radiotherapy N = 9 patients did not complete RT and had dose <40Gy	Neck dissection alone (N = 10 patients refused RT)	Not reported	Overall survival (OS) disease specific survival (DSS) regional (ipsilateral & contralateral neck) control and mucosal control
Oen A et al (1995)	Retrospective case series Single centre (Netherlands) 1978-1988	66	Surgery ± radiotherapy ± chemotherapy	none	Mean follow-up as 3.4 years and no patients were lost during follow-up Minimum follow up until death was 3 weeks	Overall Survival
Park G et al (2012)	Retrospective case series Single centre (Korea) 1997-2009	58	93% had neck dissection, 86% had chemoradiotherapy	none	Median follow up = 49 months (range 5-132 months)	Identification of primary site HPV status Overall survival Disease free survival
Reddy (1997)	Retrospective observational study USA 1974-1989	46	Bilateral neck and mucosal RT (N = 36). 20/36 had neck dissection	Ipsilateral neck RT (N = 16)	Survival outcomes reported at 5 years follow up.	Overall survival, disease free survival, acute complications and late complications.
Sher A et al (2011)	Retrospective case series Single centre (USA) August 2004 to March 2009	24	IMRT ± chemotherapy ± surgery N = 3 had neck dissection, N = 8 local excision	none	Median follow-up for surviving patients from the end of radiotherapy was 2.1 years (IQR, 1.6-3.3)	Overall survival Progression free survival Toxicity

Study	Study type/setting	N	Intervention	Comparison	Follow-up	Outcomes
Sivar L et al (2014)	Retrospective case series Single institute (Sweden) 2000-2007	50	Neck dissection plus RT HPV DNA Analysis	none	Miinimum follow up was 60 months	HPV status Overall survival Disease free survival
Strojan (1998)	Retrospective observational study Slovenia	56	Surgery + postop RT. N = 48 had neck dissection	None	The median follow-up time was 8.6 years (range: 1.6 to 17.8 years) and 79% of patients were followed for a minimum of 5 years	Overall survival, disease specific survival, neck control, mucosal control, distant failure, adverse events.
Van der Planken H et al (1997)	Retrospective case series Single institute (Netherlands) June 1974-October 1991	44	Surgery ±radiotherapy or RT alone	none	Follow-up for patients still alive ranged from 2 years to 18.8 years (median 7.3)	Local control Overall survival Toxicity Subsequent primaries
Wallace A et al (2011)	Retrospective case series Multicentre (2 centres, USA) Centre 1: November 1964-April 2005 Centre 2: October 1990-September 2006	179	Radiotherapy ± neck dissection	None	Median follow-up was 4.2 years (range 0.2-25.64 years) Median follow-up for survivors was 6.8 years (range 1.1-23.4 years)	Time to recurrence Local (mucosal) control Neck control Distant metastases free survival Cause specific survival Overall survival Complications

Study	Study type/setting	N	Intervention	Comparison	Follow-up	Outcomes
Wang (1990)	Retrospective case series. USA 1953-1988	328	Surgery alone 36%, surgery + preoperative RT 7%, surgery + postop RT 19%, RT alone 36% and other treatment 2%	None	Median follow up was 3.9 years (range <1 year to 28 years)	Overall survival

1

2

GRADE evidence tables

Table 6.23. GRADE evidence profile: neck dissection alone versus radiotherapy (RT) alone for unknown primary metastatic cancer of presumed head and neck origin

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neck dissection alone	RT alone	Relative (95% CI)	Absolute	
Overall survival (at 5 years post-treatment)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	23	213	-	65% with neck dissection vs. 37% with RT alone	VERY LOW
Disease specific survival (at 5 years post-treatment)											
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	141	213	-	76% to 86% with neck dissection vs. 45% with RT alone	LOW
Muocsitis (grade 3 or 4)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	11/26 (42.3%)	-	-	VERY LOW
Late neck fibrosis (grade 3 or 4)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	7/29 (24.1%)	-	-	VERY LOW

[1] Small sample size

Table 6.24. GRADE evidence profile: neck dissection plus RT versus neck dissection, chemotherapy and RT for unknown primary metastatic cancer of presumed head and neck origin

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neck dissection plus RT	Neck dissection, chemotherapy and RT	Relative (95% CI)	Absolute	
Overall survival (at 5 years post treatment)											
8	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	317	109	-	28% to 80% with neck dissection + RT vs. 44% to 71% with neck dissection + RT + Chemo.	VERY LOW
Disease specific survival (at 5 years post-treatment)											
4	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	483	-	-	49% to 66% with neck dissection + RT	VERY LOW
Recurrence free survival (at 5 years post-treatment)											
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	69	59	-	61% to 72% with neck dissection + RT vs. 65% to 85% with neck dissection + RT + Chemo	VERY LOW
Muocsitis (grade 3 or 4)											
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	51	-	48% to 59% with neck dissection + RT vs. 12% to 28% with neck dissection + RT + Chemo	VERY LOW
Xerostomia (grade 3 or 4)											
4	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	125	51	-	12% to 63% with neck dissection + RT vs. 11% to 58% with neck dissection + RT + chemo -	VERY LOW

Oesophageal strictures (grade 3 or 4)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	8/51 (16%)	-	-	VERY LOW
Oesophagitis (grade 3 or 4)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	24/51 (47%)	-	-	VERY LOW
Late neck fibrosis (grade 3 or 4)											
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	128	-	19% to 39% with neck dissection + RT	VERY LOW

[1] Studies were non-comparative - effectiveness estimates come from single group case series

Table 6.25. Outcomes by treatment group

Outcome	Neck dissection alone	RT alone	Neck dissection plus RT	Neck dissection plus Chemotherapy plus RT
Overall survival at 2 years post op.	NR	93.3% (Demiroz 2015)	90.7% (Demiroz 2015)	NR
Overall survival at 4 years post op.	NR	85.6% (Demiroz 2015)	85.3% (Demiroz 2015)	NR
Overall survival at 5 years post op.	65% (Grau-2000)	37% (Grau-2000)	28% (Grau-2000) 36% (HPV- Sivars, 2014) 44% (CRT, Madani 2008) 45% (Davidson-1994) 52% (Strojan 1998) 55% (Mistry-2008) 80% (HPV+ Sivars, 2014)	44% (HPV- Park 2012) 65% (CRT, Chen 2011) 71% (HPV+ Park 2012)
Disease specific survival at 5 years post op.	76% (Grau-2000) 86% (Wang-1990)	45% (Grau-2000)	49% (Grau-2000) 60% (Davidson-1994) 63% (Wang-1990) 66% (Strojan 1998)	NR
Progression-free survival at 4 years post op.	NR	75.0% (Demiroz 2015)	76.1% (Demiroz 2015)	NR
Recurrence free survival at 5 years post op	NR	NR	61% (Reddy-1997) 72% (CRT, Madani 2008)	65% (HPV- Park 2012) 85% (HPV+ Park 2012)
Local control in the neck at 5 years post op.	58% (Grau-2000)	50% (Grau-2000)	57% (Davidson-1994,ECE) 62% (Grau-2000) 80% (Iganej-2002) 86% (Davidson-1994, no ECE)	80% (CRT, Chen 2011)
Death due to treatment toxicity	NR	NR	<1% (Iganej-2002)	NR

Outcome	Neck dissection alone	RT alone	Neck dissection plus RT	Neck dissection plus Chemotherapy plus RT
Feeding tube required	NR	NR	NR	11% (IMRT, at 6 months, Chen 2011) 42% (CRT, at 6mths, Chen 2011)
Mucositis*	NR	43% (Iganej-2002)	48% (Strojan 1998) 50% (IMRT, Madani 2008) 59% (CRT, Madani 2008)	12% (CRT, Chen 2011) 28% (IMRT, Chen 2011)
Xerostomia*	NR	NR	12% (IMRT, Madani 2008) 21% (Reddy-1997) 53% (CRT, Madani 2008) 63% (persistent xerostomia, Strojan 1998)	11% (IMRT, Chen 2011) 58% (CRT, Chen 2011)
Oesophageal stricture*	NR	NR	NR	15% (IMRT, Chen 2011) 17% (CRT, Chen 2011)
Oesophagitis*	NR	NR	NR	47% (Chen 2011)
Late neck fibrosis*	NR	27% (Iganej-2002)	19% (Reddy-1997) 27% (Iganej-2002) 39% (Strojan 1998)	NR

*Grade 3 or 4 toxicity unless otherwise stated

Abbreviations: CRT, conventional radiotherapy; HPV, human papillomavirus; IMRT, intensity modulated radiotherapy; NR, not reported; RT, radiotherapy.

Evidence tables for all included studies

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow-up	Outcomes
Chen A et al (2011)	Retrospective case series Single Centre (USA) January 2001 to March 2009	To compare differences in dosimetric, clinical and quality of life endpoints among a cohort of patients treated by intensity modulate radiotherapy and conventional radiotherapy for head and neck cancer of unknown primary origin.	N = 51 patients with histologically proven squamous cell carcinoma of unknown primary origin involving cervical lymph nodes	Radiotherapy Surgery Chemotherapy Combination treatment	None	Median follow-up was 29 months for the whole cohort (range, 6-84 months) Median follow-up for patients treated with chemotherapy was 32 months (6-84 months) Median follow-up for patients treated with IMRT was 25 months (range, 6-51 months)	Mean dose to the contralateral parotid gland was 24.7Gy (range 21.8-28.9Gy) for patients treated with IMRT compared with 51.4Gy (range, 48.5-56.9Gy) for those treated by chemoradiotherapy (p<0.001). There was also a statistically significant in the volume receiving 30Gy or greater (V30) when comparing chemoradiotherapy with IMRT (95.8% versus 39.3%, p<0.001). The D50 of the contralateral parotid gland was 25.3Gy (20.3-28.7) for patients treated with IMRT and 48.9Gy (range 40.5-52.8) for patients treated with chemoradiotherapy. (p<0.001). Patients treated with IMRT had lower doses to auditory structures compared with patients treated with CRT. There was a significant difference in the maximum dose to ipsilateral inner and middle ears between patients treated with CRT versus IMRT: Inner ear 53.8Gy versus 45.1Gy (p = 0.01) Middle Ear: 50.0Gy versus 44.4Gy, p = 0.01 The maximum dose to the contralateral inner ear was 51Gy for CRT and 47.4GY for IMRT (p = 0.33) The maximum dose to the contralateral middle ear was 48.3Gy for CRT and 46.5Gy for IMRT (p = 0.1) Maximum doses to the spinal cord, brain stem and temporal lobe were greater for patients treated by CRT compared with IMRT. IMRT was associated with significantly higher maximum doses to the oral cavity (p = 0.01) and to the mandible (p = 0.04) compared with CRT. *Disease Control* 2 year estimate of overall survival: whole cohort = 86% IMRT = 87% CRT = 86% 6 patients (2 IMRT & 4 CRT) experienced disease progression or recurrence of locoregional disease. 2 year estimate of local-regional control was 89%. Local regional control for IMRT was 92% and for CRT was 87% (p =

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow-up	Outcomes
							0.44). Median time to local-regional relapse was 12 months (range, 6-28 months). 8 patients developed distant metastasis at a median time of 16 months (range, 4-21 months) 2 year estimated disease free survival was 84% for the whole cohort. *Toxicity* Mucositis was the most commonly reported grade 3 toxicity and was significantly higher in patients treated with IMRT (IMRT = 28% versus CRT = 12% p = 0.01). Other grade 3 toxicities included: Severe oesophigitis (n = 24) Moist desquamation (n = 12) Laryngeal oedema with hoarseness (n = 11) Otitis media (n = 3) No grade V toxicities were observed. Incidence of late grade 3+ toxicity was 63% among patients treated with CRT and 29% among patients treated with IMRT (p<0.001). The most commonly reported grade 3 toxicity was related to dysphagia (CRT = 42% versus IMRT = 17% reporting grade 3 oesophageal toxicity, p<0.001). With respect to xerostomia, 58% of patients treated by CRT and 11% of patients treated with IMRT reported complete dryness of mouth at any point in the late setting (p<0.001). 62% of patients treated with CRT and 11% of patients treated with IMRT were G-tube dependent at 6 months (p<0.001). The corresponding figures at 1 year were 33% and 0% (p<0.001).
Compton A et al (2011)	Retrospective Case Series Single Institute	To determine human papillomavirus incidence in unknown primary squamous cell carcinomas of the head and	N = 25 <u>*Inclusion*</u> Patients who underwent neck dissection or cervical lymph node biopsy prior to radiation and had	HPV + (25%, n = 7)	HPC – (75%, n = 18)	Median follow-up 33.8 months (1-93 months)	HPV status was not significantly associated with gender, race, nodal stage or alcohol or tobacco use. After a median follow-up of 17 months the 5 year overall survival was 51.3% and 5 year disease free survival was 55.4%/ *HPV+ versus HPV-* 5 year overall survival was 66.7% versus 48.5% (p = 0.35) 5 year disease free survival was 66.7% versus 48.5% (p = 0.54)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow-up	Outcomes
		neck and investigate if HPC status influenced survival	adequate tissue for testing All patients received curative intent postoperative radiotherapy ± chemotherapy to include Waldeyer's ring				
Davidson B et al (1994)	Retrospective Case Series Single Institute Operative records – 1977-1983 Service database – 1984-1990	To assess whether increasing use of adjunctive radiotherapy has an impact on survival, disease control and incidence of subsequent primary tumours.	N = 73 Mean age = 60 years (27-82) 71% were Stage N2 or N3 22% had a history or previous malignancy				Overall Survival Disease Free survival 89% (n = 65) patients underwent surgical resection (n = 59 comprehensive neck dissections) 83% of resected patients underwent radiotherapy (pre-operatively in 5 patients). Pathologic N stage was higher clinical stage in 22/65 (34%) of surgically treated patients. Extracapsular spread was observed in 42/73 (58%) of patients including 7/21 with clinical N1 disease and 35/52 staged N2 or N3. Neck dissection was performed in 19 patients who had no detectable clinical disease after excisional biopsy of a solitary neck mass, 37% of whom had additional positive nodes in the surgical specimen. Primary tumours were subsequently detected in 12% between 2 and 77 months after neck treatment. Primary tumours became manifest in 36% of patients who did not receive radiotherapy compared with 9% of patients treated with surgery and radiotherapy (p = 0.038). Control of the treated neck was achieved in 74% of patients. Actuarial control of disease of the neck was related to clinical N status and, at 5 years was 82% for N1, 70% for N2 and 58% for N3 disease. N1 versus N3, p = 0.051 Neck control was 86% at 5 years in patients with extracapsular spread (p = 0.032) and multivariate analysis of neck control found ECS to be the only significant predictor of neck failure.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow-up	Outcomes
							In addition to the 19 patients whose cancer recurred in the treated neck, 14 patients developed a primary lesion, disease in the contralateral side of the neck or distant metastases despite control of the treated neck. Control of disease in these 33 patients was poor. Of the 54 patients whose neck disease was controlled; 17% developed distant metastases. Of the 47 patients who remained disease free in the head and neck, 6 had distal metastases. Cumulative survival at 5 years was 45% Disease specific survival was 60% Cumulative survival was significantly lower forN3 disease than for N1 (p = 0.011). Multivariate analysis showed that complete resection of neck disease was correlated with both overall and disease free survival.
Demiroz et al (2015)	Retrospective Case Series Study Single centre (USA) 1994 to 2009	To assess whether the addition of neck dissection offers any additional benefit to radiotherapy in patients with squamous cell carcinoma of unknown primary of the head and neck.	Inclusion criteria: patients with biopsy-confirmed squamous cell carcinoma limited to the cervical lymph nodes without an identifable primary tumour. N = 41 Median age 53 years (range 38 to 72 years)	Neck dissection + radiation therapy	Definitive radiation therapy	Median 73 months (range 18 to 126 months) for the neck dissection + radiation therapy group; median 39 months (range 11 to 98 months) for the definitive radiation therapy group	2-year overall survival: ND+RT: 90.7% RT: 93.3% 4-year overall survival: ND+RT: 85.3% RT: 85.6% No significant difference in overall survival between groups (p = 0.64) 4-year progression-free survival: ND+RT: 67.9% RT: 70.1%% 4-year locoregional recurrence-free survival: ND+RT: 76.1% RT: 75.0%% A primary mucosal tumour emerged in two patients; one in each treatment group. One patient in each treatment group experienced ipsilateral neck recurrence.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow-up	Outcomes
Erkal H et al (2001)	Retrospective Case Series Study Single Centre (USA) 1964-1997	To assess the treatment of patients with squamous cell carcinoma metastatic to cervival lymph nodes from an unknown head and neck site with radiotherapy alone or in combination with neck dissection	N = 126 with previously untreated squamous cell carcinoma to cervical lymph nodes from an unknown head and neck site. *Exclusions* Patients treated with palliative intent	Radiotherapy±Neck Dissection	Each Other	All patients followed-up for at least 2 years (113 patients had follow-up for at least 5 years)	56 patients were treated with radiotherapy alone 20 patients were treated with unilateral neck dissection followed by radiotherapy 45 patients were treated with radiotherapy followed by planned unilateral neck dissection 5 patients treated with radiotherapy followd by planned bilateral neck dissection. Radiotherapy doses: Range, 47.3Gy-86Gy (median, 65 Gy) at 1.5-2.5Gy per fraction (median, 1.8Gy) for patients treated with once daily fractionation. Range, 60-76.8Gy (median, 69.6Gy) at 1.2Gy per fraction for 3 patients treated with twice daily fractionation. Overall treatment time ranged from 31-78 days (median, 62 days) for patients treated with continuous course radiotherapy and from 46-73 days (median, 62 days) for patients treated with planned split course radiotherapy. 10% of patients developed squamous cell carcinoma in head and neck mucosal sites at 0.5-10.9 yeas (median, 1.8 years) after initial treatment. Overall rate of mucosal recurrence at 5 years was 13%. Histologic differentiation significantly affected the rate of developing carcinomas in head and neck sites. Rates of nodal control by N stage after initial treatment were: N1 = 100% N2A = 100% N2B = 81% N2C = 880% N3 = 46% Overall rate of neck disease control was 78% at 5 years. Nodal size (p = 0.02), N stage (p = 0.0001) and planned Neck Dissection (p = 0.003) significantly affected the rate of nodal control. 15% of patients developed distant metastasis at 0.2-5.1 years (median, 0.9 years). 5 year rate of distant metastases was 14%

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow-up	Outcomes
							Rates of distant metastases by N stage: N1 = 0% N2A = 7% N2B = 14% N2C = 14% N3 = 26% Extracapsular extension (p = 0.001) and radiotherapy dose for metastatic cervical lymph nodes (p = 0.06) significantly affected the rate of distant metastases. Absolute survival rates by N stage after treatment: N1 = 62% N2A = 64% N2B = 45% N2C = 38% N3 = 32% 5 year overall survival rate was 47% Extracapsular extension (p = 0.006), Nstage (p = 0.0001), radiotherapy dose for head & neck sites (p = 0.02) and planned neck dissection significanlty affected the rate of absolute survival. Cause specific survival rates after treatment: N1 = 100% N2A = 88% N2B = 75% N2C = 46% N3 = 39% Overall 5 year cause specific survival rate was 67%. Extracapsular extention (p = 0.006), nodal size (p = 0.0001), N stage (p = 0.09), overall treatment time (p = 0.07) and planned neck dissection (p = 0.009) significantly affected the rate of cause specific survival. For the 20 patients treated with neck dissection followed by radiotherapy, no patients reported had severe post operative complications For the 50 patients treated with radiotherapy and planned bneck dissection, 8 patients had severe postoperative complications. Of all the patients treated with radiotherapy, 6 patients had severe late complications.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow-up	Outcomes
Frank S et al (2010)	Retrospective case series Single centre (USA) 1998-2005	To review the outcomes and patterns of failurefor head and neck cancer from unknown primary in patients treated with intensity modulated radiotherapy (IMRT)	N = 52 patients Median age = 56 years Tumour histological type was confirmed by fine needle aspiration in 26 patients, excisional node biopsy in 14 patients and neck dissection in 12 patients.	Intensity modulated radiotherapy (IMRT) 13 patients underwent neck dissection before IMRT 13 patients underwent selective neck dissection following IMRT 14 patients had received systemic therapy	None	Median follow up for the whole cohort was 3.7 years (range 1-7.6)	*Primary mucosal and regional control* The 5 year actuarial rate of primary mucosal control was 98.1% The 5 year actuarial rate of regional control was 94.2%. All recurrences occurred within 2 years after treatment. *Distant Control* 5 year actuarial rate of distant metastasis was 8.3% and all distant metastases developed within 2 years of treatment. Median time to death after the appearance of distant metastases was 4 months (range, 2-15). *Overall survival and disease free survival* 5 year actuarial disease free survival rate was 88% for the entire cohort 5 year overall survival rate for the whole cohort was 81% *Complications* There were no Grade 4 complications Grade 3 oesophageal toxicity occurred in 2 patients. Grade II complications were hypothyroidism in 1 patient and xerostomia in 3 patients Xerostomia was the most common grade I complications (6 patients).
Grau 2000	Retrospective observational study **Country:** Denmark	.	277 patients. Nodal stage was N1, N2 and N3 in 17%, 48% and 34% of cases respectively. **Inclusion criteria:** Metastatic squamous cell or undifferentiated carcinoma in cervical lymph nodes from an unknown primary tumour, seen between 1975 and 1995 at any of five institutions, entered into a common database. **Exclusion criteria:**	Surgery alone (radical neck dissection, N = 23),	RT alone (N = 213) or RT plus surgery (either radical neck dissection or lymph node excision, N = 26). RT to neck only: median dose 59 Gy (range 28 to 93 Gy). RT to neck and mucosa: median dose 66 Gy (range 20 to 70 Gy). 2 Gy per fraction and 5 fractions per week.	At least 5 years.	5 year overall survival: 65% vs. 37% vs. 28% (surgery alone vs. RT alone vs. surgery plus RT; P = 0.04) 5 year disease specific survival: 76% vs. 45% vs. 49% (surgery alone vs. RT alone vs. surgery plus RT; P = 0.0025) 5 year neck control: 58% vs. 50% vs. 49% (surgery alone vs. RT alone vs. surgery plus RT; P>0.05) The "surgery only" group contained a greater proportion of N1 patients (39%) than the other treatment groups (<20%). 15 patients with isolated supraclavicular lymph node metastases were included

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow-up	Outcomes
			None reported.				
Guntinas-Lichius O et al (2006)	Retrospective Case Series Single Centre (USA) March 1987-April 2002	To analyse the outcome of neck dissection alone, neck dissection combined with post-operative radiotherapy or neck dissection and adjuvant radiotherapy in patients with head and neck cancer of unknown primary.	N = 69 patients N = 46 patients with carcinoma of unknown primary following a complete diagnostic work-up.	Neck dissection Neck dissection + post-ooperative radiotherapy Neck dissection+ adjuvant radiotherapy	Each Other	Follow-up time for patients with unknown primary ranged from 0.4-169.8 months (mean 33.83 months) Observation time for patients alive without disease at last follow-up ranged from 0.9-120.4 months (mean 38.57 months)	Primary tumour was detected in 33% (n = 23) patients. During follow-up a primary tumour was detected in 3 patients giving a primary emergence rate of 7%. Priamries were detected between 5.8-51.9 months (mean, 23.57 months). Survival time after the detection of primary site ranged from 51.57 to 70.50 months (mean 58.49 months). 9% of patients (4/46) developed a tumour recurrence during follow-up time – 2 regional relapses, 1 regional relapse with distant metastasis and 1 distant metastasis. Survival time with relapse ranged between 1 and 25 months (mean 16.9 months). Mean disease free time was 133.16 months (95% CI 117.47, 148.84) 5 year disease free rate was 90% 41% of patients with unknown primary died. Mean survival time was 88.85 months (95% CI, 60.37, 117.33 months). 5 year overall survival rate = 52% 10 year overall survival rate = 43% *Univariate Analaysis* • 5 year survival rates: • 88% fron non-smokers compared with 32% for smokers (p = 0.0212) • 77% for no/moderate alcohol consumption compared with none of the patients with heavy alcohol consumption surviving to 5 years (p<0.0001) • 55% for M0 patients compared with 0% for M1 patients (p = 0.0009). • 57% for patients with unknown primary who underwent bilateral tonsillectomy compared with 42% for patients without tonsilectomy (p = 0.0218). • 53% for patients receiving treatment with postoperative radiotherapy compared with 44% for patients with treatment without radiotherapy (p = 0.0506).

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow-up	Outcomes
Iganej 2002	Retrospective observational study **Country:** United States of America	This study describes a comparative, retrospective case file review of 106 patients treated for cervical lymph node metastases between January 1969 and December 1994 by one American medical group.	N = 106 including 82 males. Median age: 58 years (mean: 57.3 years). 93% of patients had a smoking history. Nodal staging was: N1 = 14, N2a = 27, N2b = 39, N2c = 2, N3 = 24. **Inclusion criteria:** Patients presenting with ipsilateral (n = 104) or bilateral adenopathy with a diagnosis of cancer of unknown primary. **Exclusion criteria:** Patients with distant metastases at time of diagnosis, primary site discovered during work-up, non-squamous histology, inadequate documentation, requirement for palliation only or comorbidity.	This group received various treatment regimens: Excisional biopsy only (n = 12),	Excisional biopsy then RT (n = 15), Radical neck dissection (n = 29), RT alone (n = 24), Radical neck dissection then RT (n = 26) Patients treated with excisional biopsy alone had generally refused further treatment or were too unwell to receive aggressive therapy and patients receiving RT alone usually had inoperable disease. The median dose of RT was 66Gy (range: 48 to 70Gy) for those patients who had no further treatment and 60Gy (range: 50 to 70Gy) for those who had received prior surgery. Treatment areas	Two patients were lost to follow-up after 36 and 40 months but neither had signs of disease. Minimum follow-up for the remainder of patients was 5 years or until patients had died. Median follow-up for surviving patients was 82 months and for all patients, 56 months.	**Overall survival:** 5 year OS rate: 53% (no 95% CI given) **Disease-specific survival:** 5 year DSS rate: no data given but, from graph, appears to be 64% Prognostic factors: Neck stage at presentation (N1 or N2a vs. N2b) (P = 0.0009) and the presence or absence of ECE (P = 0.017). The appearance of a primary tumour did not significantly affect either outcome. **Neck control:** Neck control in all patients: 66% Neck control in patients receiving any single treatment regimen only: 59% Neck control in patients receiving combined treatment: 80% (P = 0.02) Prognostic factors: No statistically significant prognostic factors were identified. Tumour control above the clavicle was better for patients having received a combined treatment modality than for those on any single therapy but the difference was non-significant once the sub-group of patients treated with RT only were removed from the analysis. The volume of RT was not a prognostic factor of local control. **Mucosal control:** Primary tumours were detected in 19 patients: tonsil (n = 6) base of tongue (n = 4) pyriform sinus (n = 4) supraglottis (n = 3) and nasopharynx (n = 2). All lesions were ipsilateral to initial presentation. Patients who received RT (including 39 patients who did not have radical neck dissection) had a significantly lower rate of primary lesion appearance (9%) compared with patients who did not receive RT as a component of their therapy (32%) (P = 0.006). **Distant failure:** Distant metastases were identified in 10 patients after a median time after treatment of 4 months. The most common sites of metastasis were in the lung, followed by bone. All but one patient had initially presented with nodal stage N2b. **Adverse events:** All patients who had been irradiated experienced varying degrees of acute mucositis (43% grade 3/4 by RTOG criteria) and xerostomia (61% grade 1/2 by RTOG criteria). More patients having receiving combined therapy (radical neck dissection then

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					encompassed the nasopharynx, oropharynx, larynx and hypopharynx.		RT) experienced severe late neck fibrosis (27%) compared with patients having received a single treatment modality (4%) (P<0.05).
Klem et al (2008)	Retrospective case series Single Centre Febraury 2001 to July 2005	To assess the use of IMRT for head and neck cancer of unknown primary site assessing the preliminary treatment outcomes associated with IMRT and examining the dosimetric paramaters of tumour and normal structures using IMRT and evaluate the toxicity of IMRT alone and IMRT with concurrent chemotherapy	N = 21 patients undergoing IMRT for head and neck cancer of unknown primary Median age = 57 years (range 39-80) Pretreatment evaluation included complete history and physical examination, direct flexible fibreoptic endoscopic examination, complete blood count, liver function tests, chest x-ray, pathology review and CT and/or MRI of the head and neck	IMRT ± concurrent chemotherapy N = 16 patients underwent initial surgery	None	All patients were evaluated at least once a week during RT and returned for follow-up visits every 1-2 months for the first 6 months, every 3 months for the next 6-12 months , every 4-6 months through 3 years and annually thereafter. Median follow-up was 20.1 months (range 5-21) for all patients and 23.8 months for living patients.	*Dosimetric Analysis* In 9 patients (43%), both parotids met the constraint of a mean parotid dose of <26Gy In 6 patients (33%) one parotid gland met the constrait of a mean parotid dose of <26Gy In 5 patients (24%) both parotids received >26Gy with every attempt made to limit the parotid dose as much as possible. 2 patients had persistent disease following treatment 1 patient had late regional failure 2 patients were diagnosed with metastatic disease during follow-up, both within 6 months of initial diagnosis. 2 year estimate of relapse free survival was 85% 2 year estimate of locoregiona progression free survival was 90% 2 year estimate of distant metastases free survival was 90% 2 year estimate of overall survival was 85% *Acute and chronic toxicity* No patient require a treatment break due to toxicities. 5 patients required hospitalisation during IMRT and 2 required hospitalisation within 2 weeks of completing IMRT. The most common acute toxicites were mucositis, skin toxicity, fatigue, xerostomia and nausea. There were no reported Grade 4 toxicities 10 patients experienced at least one Grade 3 toxicity including: Haematological toxicities (10%) Acute skin toxicity (5%) Mucositis (14%) Dehydration (10%) Renal toxicity (5%) Pulmonary toxicity (5%) Infection (5%) Pain (5%) Gastrointestinal toxicity (5%)

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							1 patient experienced grade I chronic tinnitus, 5 patients developed grade I/II hearing loss and 5 patients developed grade I chronic neuropathy. Of the 11 patients with chronic toxicities, 9 patients had received concurrent chemotherapy. All patients experienced grade I or II xerostomia during treatment which improved with time from radiotherapy. 62% of patients (13/21) required a PEG tube before or during treatment. 3 patients were treated with IMRT alone and 10 were treated with chemoradiotherapy. By 1 month after RT treatment, 11 patients remaind PEG dependent and by last follow-up only 1 patients remained PEG dependent. Median period from PEG placement to removal was 5.6 months (range 2.3-14.5)
Lu H et al (2009)	Retrospective Case Series Single Centre (USA) February 2000 to November 2006	To evaluate the efficacy and feasibility of irradiation with intesity modulate radiotherapy (IMRT) in patients with head and neck cancer of unknown primary	N = 18 patients diagnosed with head and neck carcinoma of unknown primary and treated with curative intent. Median age was 55 years (range, 37-89 years) 16 patients had squamous cell carcinoma and 2 patients had undifferentiated carcinoma suspicious for lymphoepithelioma.	Intensity Modulated radiotherapy N = 12 patients had initial surgery before radiation 1 patients had neck dissection following treatment 5 patients had no surgery N = 6 patients received concurrent chemotherapy during IMRT, 2 after neck dissection, 1 after excisional biopsy and 3 with no initial neck surgery.	None	Patients were followed up 1 month post radiation and every 6-8 weeks thereafter in the first year and every 2-3 months in the second year. Median follow-up for all patients was 25.5 months (range 3.3-86.3) and for living patients was 35.5 months (range, 6.5-86.3 months)	6 patients had definitive IMRT 4 patients received IMRT after excisional biopsy 3 received IMRT after full neck dissection. 5 patients died, 2 of distant meatstases, 1 lung cancer and 2 intercurrent diseases. Estimated 2 year overall survival was 74.2% Estimated 2 year regional recurrence free survival was 88.5% Estimated distant metastasses free survival was 88.2% Grade 3 mucositis and grade II dermatitis were the most severe toxicities. No patient experienced complications that interrupted treatment.
Madani I et al (2008)	Retrospective Case Series	To comapre the effectiveness of intensity	N = 25 patients (23 with squamous cell carcinoma)	Intensity modulated radiotherapy	Conventional radiotherapy	Patients were examined clinically at least once a week during treatment.	*Treatment Outcomes* IMRT was stopped in 3 patients

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	Single Centre (Belgium) February 2003 to September 2006	modulated radiotherapy and conventional radiotherapy in the treatment of cervical lymph node metastases from unknown primary cancer	 Median age was 61 years (47-85) 16 patients had extracapsular extension N = 18 historical controls (Feb 2003 to October 2003) Median age was 58 (38-75) 10 patients had extracapsular extension	(IMRT)		After treatment patients were seen by radiation oncologists and head and neck surgeons at month 1 and 3 and 6 month intervals thereafter. IMRT: Median follow-up of patients alive at last follow-up was 17 months (range, 2-39 months) Controls Median follow-up was 37 months (range 4-100 months)	All patients in the historical control group completed radiotherapy (2 patients needed a treatment break) In IMRT there was no emergence of primary during treatment. Median time to relapse was 7.5 months and relapse was predominantly distant. In the historical controls, the primery tumour emerged in 2/18 patients at 32 months and 66 months of follow-up respectively. There was no statistically significant difference in the rate of distant relapse in the rate of distant relapse comparing the IMRT group to the controls (p = 0.42). Median time to detection of distant relapse was 7.5 months in the IMRT group and 17 months in the control group. 2 year overall survival rate was 74.8% in the IMRT group and 61.1% in the control group (p = 0.97). Distant disease free probability in survivors was 76.3% in the IMRT group and 68.4% in the control group (p = 0.99). *Acute and Late Toxicity* No patient experienced Grade 4 acute toxicity 11 patients in the IMRT group and 10 patients in the control group experienced Grade 3 mucositis. Incidence and severity of dysphagia was significantly higher in the historical control group (p<0.003). There were no significant differences between the groups for radiation dermatitis, , loss of body weight, or requirement for PEG. In relation to late toxicity, conventional radiotherapy affected the salivary glands and skin signifcantly more than did IMRT (p = 0.003 for both). Late dysphagia was significantly greater in the historical control group (p = 0.01) There were no significant differences betweenthe two groups for laryngeal hoarseness. Dose volume toxicity relationships were investigted in the IMRT

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							group only. V27, a dose volume constraint for the parotid was met in 12/19 cases (10 unilateral). The highest AUC predictive value was for V27 (0.86) whereas the lowest was for V15 (0.72).
Mistry 2008	Retrospective observational study **Country:** India.	This study describes a retrospective case file review of 89 patients treated for cervical lymph node metastases between 1989 and 1994 by one Indian hospital. Data were	N = 89 including 78 males. Median age: 55 years (range: 28 to 84 years). Levels of nodal metastases were: I = 9, II = 67, III = 46, IV = 12, V = 1. Nodal staging was: N1 = 10, N2a = 25, N2b = 20, N2c = 31, Nx = 3 **Inclusion criteria:** Patients with metastatic squamous cell carcinoma from an occult primary site. **Exclusion criteria:** Patients who had received palliative RT because of advanced or comorbid disease. Those with histology other than squamous cell carcinoma or those with metastatic disease at presentation	All patients underwent neck dissection and were advised to have a course of RT which 10 patients refused and 9 patients failed to complete. Therefore, for these patients the dose of RT ranged between 0Gy to 40Gy. The remaining patients received >40Gy.	Overall survival (OS) disease specific survival (DSS) regional (ipsilateral & contralateral neck) control and mucosal control.	At the time of last review, 51 patients were alive. Ten patients had died from disease recurrence, 10 died from a primary lesion and 9 from metastatic disease. In 8 patients, cause of death was unknown.	**Overall survival:** 5 year OS rate for all patients: 55% (no 95% CI given) 8 year OS rate for all patients: 51% (no 95% CI given) Median OS: 98 months Prognostic factors: extra nodal spread and neck stage at presentation were not significant predictors of survival. Postoperative RT, prior open biopsy of the neck or involvement of nodes at multiple nodes similarly had no impact on survival. **Neck control and/or distant metastases:** 29/89 patients experienced disease relapse, 19 with disease in the neck, 9 patients with distant metastases and 1 patient with both. Of those who had received RT>40Gy, 15/60 patients experienced neck relapse compared with 4/19 patients who had received <40Gy but the difference between these groups was not significant. **Mucosal control:** A primary lesion was detected in 13 patients of which, 11 had received RT >40Gy. Mean time to detection was 24 months. Primary lesions were located in: oropharynx (n = 6) pyriform sinus (n = 2) larynx (n = 2) lung (n = 2) or oral cavity (n = 1). All but 3 of these patients died of their disease.
Oen A et al (1995)	Retrospective Case Series Single Centre (The Netherlands) 1978-1988	To assess the value of surgery and/or radiation for the treatment of cervical metastsis from	N = 66 with cervical metastases from unknown primary Mean Age: 64 years (range 15-89 years)	Surgery and/or radiotherapy	Each Other	Mean follow-up qas 3.4 years and no patients were lost during follow-up Minimum follow up until death was 3 weeks	3 year overall survival was 44% 5 year overall survival was 31% 3 year overall survival, corrected for intercurrent death, was 58% 5 year overall survival, corrected for intercurrent death was 50% 3 year overall survival for patients with squamous cell carcinoma

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		unknown primary	*Exclusions* History of previous malignancy apart from basal cell carcinoma of the skin Patients with solitary supraclavicular nodes unless present in combination with other cervical metastases				was 62% 5 year overall survival for patients with squamous cell carcinoma was 58% N and M status and involvement of supraclavicular nodes were significantly correlated with intercurent death corrected survival. Patients with involvement of supraclavicular nodes had a significantly worse prognosis when compared with those who did not (5 year survival = 20% versus 60%). Intercurrent death corrected survival decreased significantly with increasing N category (p = 0.02): 5 year survival for N1 = 76% 5 year survival for N2 = 48% 5 year survival for N3 = 34% M1 patients had worse 5 year survival compared with M0 (0% versus 58%). On multivariate analysis only the presence of supraclavicular metastases and M category were independently related to survival and significant differences were no longer present among nodal categories.
Park G et al (2012)	Retrospective Case Series Single Centre (Korea) 1997-2009	To investigate whether HPV and p16 expression in metastatic cervivcal lymph nodes can help identfy ooropharyngeal primaries and predict survival outcomes	N = 58 patients with CUP of squamous cell carcinoma Median Age = 59 years (range, 39-79) *Exclusions* • History of previous treatments • Different pathological diagnoses • Inadequate clinical or pathological data • Lack of sufficient			Median follow up = 49 months (range 5-132 months)	Primary site was identified in 22/58 patients and were widely resected with tumour free margins. Radical or modified neck dissection was performed in 54 patients and 50 patients received postoperative chemoradiotherapy. 2 patients received radiotherapy alone and 2 underwent concurrent chemoradiotherpay without neck dissection procedures. 31 patients were positive for HPV 29 patients were positive for p16 18 patients were positive for p53 Result of HPV *in situ* hybridisation were well matched with those of p16 staining in 48 patients (82.8%, kappa = 0.655, p<0.001). HPV ISH and p16 IHC showed a reverse correlation with p53 staining: 74.1%, kappa = 0.495, p<0.001 70.7%, kappa = 0.414, p = 0.001

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			specimen to generate a tissue microarray				Comparing the resutls of biomarkers in the 20 patients with oropharyngeal primaries with those in the other 38 patients with other site or unknown primaries, the sensitivity of HPV for localisation of oropharyngeal primaries was 90%, specificity was 65.8% negative predictive value was 92.6% and the positive predictive value was 58.1%. Accuracy was 74.1% the sensitivity of p16 for localisation of oropharyngeal primaries was 80%, specificity was 65.8%, negative predictive value was 86.2% and the positive predictive value was 55.2%. Accuracy was 70.7%. p53 was not considered to be useful in determining primary tumour location. Multivariate analysis showed that location of the largest metastatic lymph nodes at presentation (OR = 10.873, 95% CI 1.187, 99.556, p = 0.035) and HPV (OR = 11.396, 95% CI 2.130, 60.957, p = 0.004) were independent predictors of primary tumours in the oropharynx. 65.5% were still alive after median follow-up of 49 months. 4 year overall survival was 67.3%% 4 year disease free survival was 70.8% p16 was a significant predictor of disease free survival (HR = 0.286, 95% CI, 0.092, 0.887; p = 0.03) Extracapsular spread was a significant predictor of overall survival (HR3.924, 95% CI, 1.387, 11.097; p = 0.01) P53 staining was a significant predictor of overall survival (HR = 3.154, 95% CI = 1.288, 8.103; p = 0.017).
Reddy 1997	Retrospective observational study **Country:** USA		**Inclusion criteria:** Patients with metastatic SCC to the cervical lymph nodes of unknown primary treated with RT between 1974 and 1989 at a single institution. **Exclusion criteria:** supraclavicular	Bilateral neck and mucosa RT (N = 36), 20 of these patients had lymph node dissection	Ipsiplateral neck RT (N = 16) with an electron beam: The dose to the ipsilateral neck ranged from 60 to 76 Gy; the dose to the contralateral neck was 46 to		5 year overall survival, for all patients, was 40% 5 year disease free survival, for all patients, was 51% 5 year disease free survival, for patients who received lymph node dissection plus RT, was 61%. **Acute complications:** All patients in the bilateral RT group had mucositis and dry desquamation of the skin. 56% of patients in the unilateral RT group had ipsilateral mucositis and moist desquamation of the skin.

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			metastases only, incurable disease, death during treatment from non-cancer causes, non SCC histology		50 Gy.		**Late complications:** Severe xerostomia 31% in the bilateral RT group, none in the unilateral group. Severe neck fibrosis 19% in the bilateral RT group, 3% in the unilateral group.
Sher A et al (2011)	Retrospective case series Single Centre (USA) August 2004 to March 2009	To compare IMRT and concurrent chemotherapy regimens for the treatment of head and neck cancer of unknown primary	N = 24 patients with head and neck cancer of unknown primary treated with IMRT Median age at first diagnosis was 54 years (IQR, 48-65) HPV 16 status was tested in 15 patients and was postive in 7 (29% of total cohort/47% of tested patients)	IMRT±concurrent chemotherapy	None	Patients were followed up by a multimodality treatment team every 4-6 weeks in the first year and every 2 months in the 2nd year and less frequently in subsequent years. Median follow-up for surviving patients from the end of radiotherapy was 2.1 years (IQR, 1.6-3.3)	Before radiotherapy, 13 patients underwent biopsy only, 8 underwen local excision and 3 underwent modified radical neck dissection. Median involved nodal dose of IMRT was 70Gy (IQR 64-70) Median whole mucosal dose was 60Gy (range 54.25-64) Median contralateral parotid mean dose was 27.2Gy (IQR, 25.4-28.9) 7 patients were treated with induction chemotherapy Actuarial 1 and 2 year overall survival rate were both 92%. Median survival had not been reached at time of last follow-up Actuarial 1 and 2 year progression free survival rates were 92% Median progression free survival had not been reached 2 year locoregional progression free survival was 100% 2 year metastasis free survival was 96% *Acute and late toxicity* 75% of patients developed at least grade 3 mucositis 29% of patients experienced grade 3 or 4 dermatitis 21 patients had a gastronomy tube place with 95% having it removed at a median 6 months post treatment completion. 6 patients developed grade II xerostomia and 12 patients developed grade I xerostomia 11 patients (46%) developed oesophageal stricture requiring dilations which were performed a median of 3.6 months after treatment completion. No relationship was found between prescribed mucosal dose and the likelihood of stricture.
Sivar L et al (2014)	Retropsective Case Series	To examine for the presence of	N = 50 patients with a primary initial	HPV DNA Analysis	N/A	Miinimum follow up was 60 months	HPV DNA was detected in 40% of metastases p16 overexpression was observed in 42% of metastases

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	Single Institute (Sweden) 2000-2007	HPV DNA in lymph node metastases and investigate whether the presence of HPV DNA is correlated to 5 year overall and disease free survival	diagnosis of CUP in the head and neck region, who have been treated with intent to cure and with available formalin fixed paraffin embedded material.				18/21 (86%) of samples exhibited both p16 overexpression and HPV DNA. There were no signficant differences between HPV DNA+ patients and HPV DNA- patients. 28% of samples showed 90-100% p53 expression 12% showed 10-60% p53 expression 12% showed <10% p53 expression 48% showed no p53 expression. There was a correlation between smoking history and p53 over expression (p = 0.021). 5 year overall survival for the whole cohort was 54% 5 year overall survival was significantly higher in the HPV DNA+ metastases groups compared with the HPV DNA- group (80% versus 36.7%, log rank p = 0.004) HR = 0.236, 95% CI: 0.080, 0.696, p = 0.009 (univariate analysis) 5 year overall survival for HPV DNA+ **and** p16+ was 77.8% compared with 40.6% for patients with HPV DNA **or** p16 negative metastases (p = 0.017). 5 year disease free surival for patients with HPV DNA+ metastases was 85% compared with 63.3% for patients with HPV DNA- metastases (p = 0.053). 5 year overall survival was 76.2% in patients with p16-positive metastases compared with 37.9% in p16 negative patients (p = 0.007). 5 year disease free survival in patients with p16+ metastases was 85.7% compared with 62.1% in the p16 negative group (p = 0.032). 5 year overall survival rate was 69.4% in patients with absent or intermediary-low (0-60%) p53 expression as compared with 14.3% in the group with high (≥90%) p53 expression (p<0.001). HR = 6.561, 95% CI 2.789, 15.436, p<0.001 (univariate analysis) 5 year disease free survival was 83.3% in patients with absent or intermediary-low (0-60%) p53 expression as compared with 42.9% in the group with high (≥90%) p53 expression (p<0.001). Patients with HPV DNA+ metastases had a better 5 year overall

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							survival when tumours had absent/intermediary-low p53 expression when compared with high p53 expression (88.2% versus 33.3%, p = 0.01). Patients with HPV DNA- metastases had better 5 year overall survival when tumours had absent/intermediary-low p53 expression when compared with high p53 expression (52.6% versus 9.1%, p<0.001). Multivariate analysis including HPV DNA, p53-expression, gender, age and smoking habits: HPV DNA+ status conferred a survival benefit: HR = 0.29, 95% CI 0.092, 0.913, p = 0.034). P53 overexpression was correlated with survival independently of HPV status: HR = 6.909, 95% CI 2.354, 20.273, p<0.001) Mean age correlated to 5 year overall survival (p = 0.036) Patients with no smoking history had a 5 year overall survival rate of 63.6% compared with 50% for smokers (p = 0.277) Patients with less advanced nodal spread had a 5 year overall survival rate of 85.7% for N1 disease, 61.3% for N2 disease, and 60% for N3 disesae (p = 0.263). Gender did not correlate to the 5 year overall survival rate (p = 0.886).
Strojan 1998	Retrospective observational study **Country:** Slovenia	This study describes a retrospective case file review of 56 patients treated for cervical lymph node metastases with surgery and post-operative RT between 1975 and 1994 at one Slovenian university oncology institute. .	N = 56 including 50 males. Median age: 56 years (range: 33 to 81 years). Levels of nodal metastases were: I = 14, II = 39, III = 19, IV = 8, V = 9. Nodal staging was: N1 = 6, N2 = 37 and N3 = 13. **Inclusion criteria:** Patients with metastatic squamous cell carcinoma of cervical lymph nodes from an unknown primary	All patients underwent surgery and post-operative RT. Neck dissection was performed in 48 patients and extended to neighbouring structures (parotid gland, mandible and external carotid artery) in 6 patients. The surgery was classified as: · Radical neck dissection (n = 29) · Modified radical neck dissection	None	**Follow-up:** The median follow-up time was 8.6 years (range: 1.6 to 17.8 years) and 79% of patients were followed for a minimum of 5 years.	**Overall survival:** 5 year OS rate for all patients: 52% (95%CI: 38, 65%) 10 year OS rate for all patients: 22% (95%CI: 5, 38%) **Disease-specific survival:** 5 year DSS rate for all patients: 66% (95%CI: 52, 79%) 10 year DSS rate for all patients: 52% (95%CI: 31, 72%) Prognostic factors: extracapsular spread (ECS, +ve vs. -ve) and the extent of the irradiation field (unilateral neck vs. neck and potential primary tumour sites) were significant predictors of a poorer 5 year DSS (P = 0.01 and P = 0.04 respectively). **Neck control:** Neck failure occurred in 10 patients, 9 of whom failed a median of 4 months after treatment (38 months for 1 patient). All but one of the patients experienced failure in the RT field, at the site of pre-existent nodal disease (n = 7) and/or outside of it (n = 2). Prognostic factors: neck failure was correlated significantly with the extent of the RT field (P = 0.03) since when the neck alone received RT the failure rate was 50% compared with RT of potential primary sites (12%).

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			tumour. **Exclusion criteria:** None stated.	only (n = 7) · Selective neck dissection (n = 6) · Extended neck dissection (n = 6) These procedures were assessed to have been complete in 45 cases but, in 11 patients, residual tumour was detected in histological samples. Post-operative RT was given to 48 patients at a dose of 18 to 62Gy (median 50Gy) in 1.8 to 2Gy daily fractions applied five times weekly, although 6 patients received a lower dose of <50Gy. Five patients refused treatment and 1 patient died before receiving RT. The field of treatment depended on the level of nodal involvement and patient lifestyle i.e. history of smoking and/or drinking.			**Mucosal control:** A primary lesion was detected in 5 patients after a median interval of 21 months (range: 16 to 98 months). None of the primary tumours occurred below the clavicles: oropharynx (n = 2) maxillary sinus (n = 1) nasopharynx (n = 1) larynx (n = 1). After further surgical or RT treatment, these patients survived between 29 and 108 months. One patient died of unrelated causes, 3 died of disease and 1 patient had no evidence of disease at last follow-up. **Distant failure:** Recurrence at distant sites was experienced by 6 patients within a median time after treatment of 7 months (range: 2 to 39 months). Metastases occurred in: liver (n = 3) bone (n = 2) lung (n = 3) and other lymph nodes (n = 1). All patients had ECS and were of stages N2 (n = 4) or N3 (n = 2). There Prognostic factors: there were no prognostic factors for this outcome. **Adverse events:** Thirty-three patients, all of whom had received radical, or extended radical, neck dissection experienced surgical morbidity to some extent, including pain and reduced mobility. In patients irradiated by a large field technique, 27 patients reported mucositis (grade III in 23 patients and grade 4 in 4 patients) and 3 patients had grade 3 dermatitis. Late adverse effects included xerostomia (n = 35) subcutaneous and/or muscular fibrosis (n = 22) and trismus (n = 2).
Van der Planken H et al (1997)	Retrospective Case Series Single Institute (the Netherlands) June 1974-	To establish an optimal treatment policy and look for prognostic parameters for patients with	N = 44 patients with cervical lymph node metastasis of unknown primary N = 33 patients recceived treatment	Radiotherapy Alone Surgery + radiotherapy	Each other	Follow-up for patients still alive ranged from 2 years to 18.8 years (median 7.3)	*Diagnostic Work up* Oral and ENT exam X ray of the thorax Endoscopy under general anaesthetic Later years, CT and/or NMR-scan of the head and neck have been added

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	October 1991	cervical lymph node metastases of unknown primary	with curative intent Only patients with carcinoma confined to one or more lymph nodes in the neck and who received radiotherapy alone or postoperatively were included *Exclusion* History of another malignancy apart from cervical carcinoam in situ.				66% of patients treated with curative intent had a neck dissection and postoperative radiotherapy. *Local Control* 5 year locoregional disease free survival for the whole cohort was 63% and for patients treated with curative intent it was 83%. All 11 patients treated with palliative intent died with 2.9 years (median survival of 7.5 months) *Survival and Toxicity* No significant difference in overall survival was observed for patients treated with radical radiotherapy alone or after excisional biopsies compared to neck dissection and radiotherapy. Side effects generally consisted of xerostomia though one case of severe hearing loss was observed. *Subsequent primary cancers* 5 patients developed subsequent primary cancers of which 4 were in the head and neck region. The cumulative incidence of subsequent primaries was 21% after 5 years
Wallace A et al (2011)	Retrospective Case Series Multicentre (2 centres – USA) Centre 1: November 1964-April 2005 Centre 2: October 1990-September 2006	To present experience treating patients with squamous cell carcinoma from an unknown head and neck primary site and determine whether a policy change excluding	N = 179 patients Median age = 61 years (range 26->89years)	Radiotherapy alone or with surgery Median mucosal dose was 5670cGy (range, 2400-7440 cGy) 168 patients treated with once daily radiotherpay 11 patients treated with twice daily fractionation 13 patients received adjuvant chemotherapy Planned neck dissection was performed in 109		Median follow-up was 4.2 years (range 0.2-25.64 years) Median follow-up for survivors was 6.8 years (range 1.1-23.4 years)	*Time to Recurrence* 32% (n = 58) developed recurrent cancer, (76% within 2 years and 94% within 5 years) *Local (mucosal) control* 5 year rate of local control was 92% For patients (n = 28) treated with mucosal portals limited to the nasopharynx and oropharynx the 5 year rate of local control was 100%. *Neck Control* 5 year rates of neck control were: Overall = 81% N1 = 94% N2a = 98% N2b = 86% N2c = 86% N3 = 57% 5 year neck control rates:

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				patients (before radiotherapy in 44 patients and after radiotherapy in 65 patients).			Pre-radiotherapy neck dissection = 93% Post radiotherapy neck dissection = 82% No neck dissection = 73% Multivariate analysis showed that patients with N1 and N2 tumours did better than those with higher N stages (p<0.0001) Patients with neck dissection had better neck control than those who did not (p = 0.0029). *Distant Metastases free survival* 5 year rate of distant metastases free survival: Overall = 86% N1 = 100% N2a = 91% N2b = 87% N2c = 100% N3 = 74% N stage was a significant predictor of distant metastases free survival (p = 0.0031) with patients with N1 or N2 stage doing better. *Cause specific survival* 5 year rates of cause specific survival: Overall = 73% N1 = 94% N2a = 88% N2b = 82% N2c = 71% N3 = 48% Patients with N1 and N2 tumours fared better than did those with higher Nstage (p<0.0001) Patients with neck dissection had better neck control than those who did not (p = 0.0029). *Overall Survival* 5 year rates of overall survival: Overall = 52% N1 = 50% N2a = 70% N2b = 59% N2c = 45% N3 = 34%

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow-up	Outcomes
							Paients with N1-N2 tumours had significantly better overall survival than patients with higher N stages (p = 0.0031). *Complications* 7% (n = 11) of patients developed severe complications including 2 patients who developed acut toxicity requiring hospitalisation. Late complications included permanent gastrostomy, permanent gastrostomy and tracheotomy, temporary tracheotomy and mandibular osteoradionecrosis.
Wang 1990	Retrospective case series **Country:** USA	Probably differences in baseline characteristics The surgery only group contained fewer patients with N3 disease and more patients with NX disease than the other treatment groups.	N = 328. Mean age 60.5 years. **Inclusion criteria:** Patients listed at a single institution between 1953 and 1988, with metastatic SCC to the neck and unknown primary tumour. **Exclusion criteria:** Treatments elsewhere, lack of pathological confirmation, lack of follow up or primary tumour found.	Surgery alone 36%, surgery + preoperative RT 7%, surgery + postop RT 19%, RT alone 36% and other treatment 2%	5 yr overall survival.	Median follow up was 3.9 years (range <1 year to 28 years)	See tables 1 and 2

1

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Intervention	Comparison	Outcomes

Adults presenting with metastatic neck disease (squamous cell carcinoma) and clinically occult primary presumed to be of upper aerodigestive tract origin
 	
Subgroups:
• HPV status
• tests performed
	• Primary site:
	  • active surveillance
	  • radiotherapy (total mucosal radiation or sub site limited)
	• Neck:
	  • surgery (neck dissection)
	  • radiotherapy
	  • chemotherapy
	  • other systemic therapies
	  • combinations of the above
	• Radical surgical clearance plus chemoradiotherapy
	• Radiotherapy
	• Chemoradiotherapy
		Each other	• Overall survival
			• Disease free survival
			• Progression free survival
			• Tumour recurrence in the neck
			• Emergence of primary site
			• Treatment related mortality
			• Organ preservation rates
			• Treatment related morbidity
			• Health related quality of life

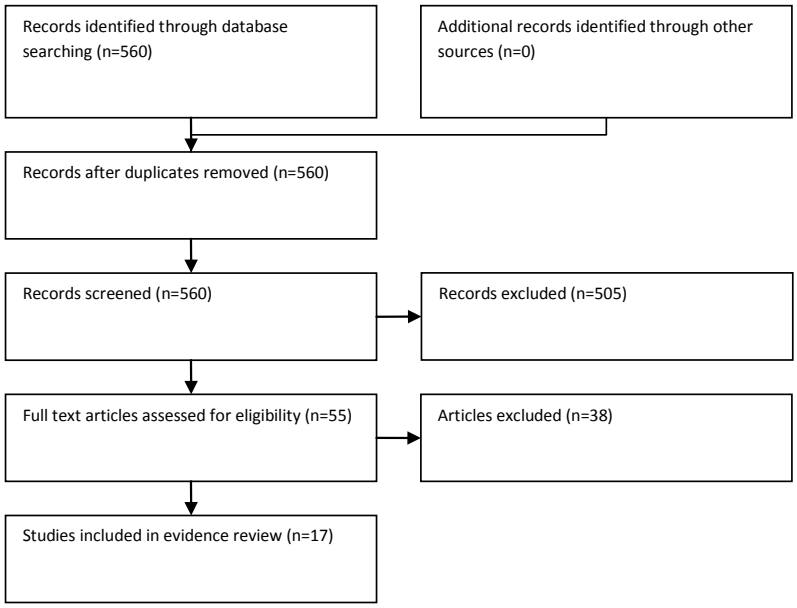
3

1 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour type of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour type, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10; At least 75% of the included patients meet the population defined in the PICO.
Search strategies	Search from 1994 onwards.
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.

2

Figure 6.3. Study flow diagram



Included studies

Chen, A. M., Li, B. Q., Farwell, D. G., Marsano, J., Vijayakumar, S., & Purdy, J. A. (2011). Improved dosimetric and clinical outcomes with intensity-modulated radiotherapy for head-and-neck cancer of unknown primary origin. International Journal of Radiation Oncology, Biology, Physics, 79, 756-762.

Compton, A. M., Moore-Medlin, T., Herman-Ferdinandez, L., Clark, C., Caldito, G. C., Wang, X. I., Thomas, J., Abreo, F. W., and Nathan CO. Human papillomavirus in metastatic lymph nodes from unknown primary head and neck squamous cell carcinoma. Otolaryngology - Head & Neck Surgery 145[1], 51-57. 2011.

Davidson, B. J., Spiro, R. H., Patel, S., Patel, K., and Shah, J. P. Cervical metastases of occult origin: the impact of combined modality therapy. American Journal of Surgery 168[5], 395-399. 1994.

Demiroz C, Vainshtein JM, Koukourakis GV, Gutfeld O, Prince ME, Bradford CR et al. Head and neck squamous cell carcinoma of unknown primary: Neck dissection and radiotherapy or definitive radiotherapy. *Head* and Neck-Journal for the Sciences and Specialties of the Head and Neck 2014; 36(11):1589-1595.

Erkal, H.S et al Squamous Cell Carcinoma Metastatic to Cervical Lymph Nodes from an Unknown Head and Neck Mucosal Site Treated with Radiation Therapy Alone or in Combination with Neck Dissection International Journal Radiation Oncology 50[1], 55-63. 2001

Grau C, Johansen LV, Jakobsen J, Geertsen P, Andersen E, Jensen BB. Cervical lymph node metastases from unknown primary tumours. Results from a national survey by the Danish Society for Head and Neck Oncology. Radiotherapy and Oncology 2000;55(2):121-9.

Guntinas-Lichius, O., Peter, Klussmann J., Dinh, S., Dinh, M., Schmidt, M., Semrau, R., and Mueller, R. P. Diagnostic work-up and outcome of cervical metastases from an unknown primary. Acta Oto-Laryngologica 126[5], 536-544. 2006.

Iganej S, Kagan R, Anderson P, Rao A, Tome M, Wang R, et al. Metastatic squamous cell carcinoma of the neck from an unknown primary: management options and patterns of relapse. Head and Neck 2002;24(3):236-46.

Mistry R, Qureshi S, Talole S, Deshmukh S. Cervical lymph node metastases of squamous cell carcinoma from an unknown primary: Outcomes and patterns of failure. Indian Journal of Cancer 2008;45(2):54-8.

Oen, A. L. Cervical metastasis from the unknown primary tumor. European Archives of Oto-Rhino-Laryngology 252[4], 222-228. 1995.
Ref Type: Journal

Park, G. C., Lee, M., Roh, J. L., Yu, M. S., Choi, S. H., Nam, S. Y., Kim, S. Y., and Cho, K. J. Human papillomavirus and p16 detection in cervical lymph node metastases from an unknown primary tumor. Oral Oncology 48[12], 1250-1256. 2012.

Reddy SP, Marks JE. Metastatic carcinoma in the cervical lymph nodes from an unknown primary site: results of bilateral neck plus mucosal irradiation vs. ipsilateral neck irradiation. International Journal of Radiation Oncology, Biology, Physics 1997;37(4):797-802.

Sivars, L., Nasman, A., Tertipis, N., Vlastos, A., Ramqvist, T., Dalianis, T., Munck-Wikland, E., and Nordemar, S. Human papillomavirus and p53 expression in cancer of unknown primary in the head and neck region in relation to clinical outcome. Cancer Medicine 3[2], 376-384. 2014.

Strojan P, Anicin A. Combined surgery and postoperative radiotherapy for cervical lymph node metastases from an unknown primary tumour. Radiotherapy and Oncology 1998;49(1):33-40.

van der Planken, H. J., Tiwari, R. M., and Karim, A. B. Treatment of cervical lymph node metastasis from an unknown primary tumor, with a review of the literature. Strahlentherapie und Onkologie 173[3], 163-169. 1997.

Wallace, A., Richards, G. M., Harari, P. M., Kirwan, J. M., Morris, C. G., Katakam, H., and Mendenhall, W. M. Head and neck squamous cell carcinoma from an unknown primary site. American Journal of Otolaryngology 32[4], 286-290. 2011.

Wang RC, Goepfert H, Barber AE, Wolf P. Unknown primary squamous cell carcinoma metastatic to the neck. Archives of Otolaryngology -- Head & Neck Surgery 1990;116(12):1388-93.

Excluded studies

Baykara, M. Efficacy and safety of concomitant chemoradiotherapy with cisplatin and docetaxel inpatients with locally advanced squamous cell head and neck cancers. Asian Pacific Journal of Cancer Prevention 14[4], 2557-2561. 2013.

Reason: not unknown primary – study includes locally advanced head and neck cancer

Beitler, J. J. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. International Journal of Radiation Oncology Biology Physics 50[1], 55-63. 2001.
Reason: *not stated*

Beldi, D., Jereczek-Fossa, B. A., D'Onofrio, A., Gambaro, G., Fiore, M. R., Pia, F., Chiesa, F., Orecchia, R., and Krengli, M. Role of radiotherapy in the treatment of cervical lymph node metastases from an unknown primary site: retrospective analysis of 113 patients. International Journal of Radiation Oncology, Biology, Physics 69[4], 1051-1058. 15-11-2007.
Reason: Comparison not relevant to PICO

Daly, M. E., Lieskovsky, Y., Pawlicki, T., Yau, J., Pinto, H., Kaplan, M., Fee, W. E., Koong, A., Goffinet, D. R., Xing, L., and Le, Q. T. Evaluation of patterns of failure and subjective salivary function in patients treated with intensity modulated radiotherapy for head and neck squamous cell carcinoma. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck 29[3], 211-220. 2007.

Reason: includes locally advanced head and neck cancer

Delaney, G. Estimation of an optimal external beam radiotherapy utilization rate for head and neck carcinoma. Cancer 103[11], 2216-2227. 2005.
Reason: Not relevant to PICO

Delaney, G., Jacob, S., and Barton, M. Estimating the optimal radiotherapy utilization for carcinoma of the central nervous system, thyroid carcinoma, and carcinoma of unknown primary origin from evidence-based clinical guidelines. Cancer 106[2], 453-465. 15-1-2006.
Reason: Not relevant to PICO

Dragovic, A. F. Factors associated with distant metastasis in squamous cell carcinoma of the head and neck treated with definitive radiation therapy: the uab Experience. International Journal of Radiation Oncology Biology Physics Conference[var.pagings], 3. 2010.
Reason: Abstract

Dragovic, A. F. Complete response to definitive radiotherapy with concurrent systemic therapy for locally advanced head and neck cancer: Associated factors and impact on outcomes. American Journal of Clinical Oncology: Cancer Clinical Trials Conference[var.pagings], 2. 2011.
Reason: Abstaract

Erkal, H. S., Mendenhall, W. M., Amdur, R. J., Villaret, D. B., and Stringer, S. P. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head and neck mucosal site treated with radiation therapy with palliative intent. Radiotherapy & Oncology 59[3], 319-321. 2001.

Reason: palliative therapy

Fernandez, J. A., Suarez, C., Martinez, J. A., Llorente, J. L., Rodrigo, J. P., and Alvarez, J. C. Metastatic squamous cell carcinoma in cervical lymph nodes from an unknown primary tumour: prognostic factors. Clinical Otolaryngology & Allied Sciences 23[2], 158-163. 1998.
Reason: No treatment comparisons

Fury, M. G. A randomized phase II study of cetuximab (C) every 2 weeks at either 500 or 750 mg/m2 for patients (Pts) with recurrent or metastatic (R/M) head and neck squamous cell cancer (HNSCC). Journal of Clinical Oncology Conference[var.pagings], 15. 2011.
Reason: Abstract

Gensheimer, M. F. Safety of submandibular gland-sparing intensity modulated radiation therapy for head-and-neck cancer. International Journal of Radiation Oncology Biology Physics Conference[var.pagings], 2. 2013.
Reason: Abstract

Hu, K. Five-year outcomes of oropharynx (OPX) targeted radiation therapy (RT) for metastatic squamous cell carcinoma of unknown primary (MUP) in the head and neck. International Journal of Radiation Oncology Biology Physics Conference[var.pagings], 3. 2012.
Reason: Abstract

Jilani, O. K., Singh, P., Wernicke, A. G., Kutler, D. I., Kuhel, W., Christos, P., Nori, D., Sabbas, A., Chao, K. S. C., and Parashar, B. Radiation therapy is well tolerated and produces excellent control rates in elderly patients with locally advanced head and neck cancers. Journal of Geriatric Oncology 3[4], 337-343. 2012.

Reason: most included patients were not unknown primary

Karni, R. J., Rich, J. T., Sinha, P., and Haughey, B. H. Transoral laser microsurgery: a new approach for unknown primaries of the head and neck. Laryngoscope 121[6], 1194-1201. 2011.
Reason: Not relevant to PICO

Karakaya E., Yetmen. Is a routine neck dissection necessary following chemoradiation therapy for N2 head-and-neck squamous cell carcinoma? International Journal of Radiation Oncology Biology Physics Conference[var.pagings], 3. 2012.
Reason: Abstract

Karakaya E., Yetmen. Is a routine neck dissection required after chemoradiotherapy for N3 head and neck squamous cell carcinoma? Radiotherapy and Oncology Conference[var.pagings], S278-S279. 2012.
Reason: Abstract

Kutter, J., Ozsahin, M., Monnier, P., and Stupp, R. Combined modality treatment with full-dose chemotherapy and concomitant boost radiotherapy for advanced head and neck carcinoma. European Archives of Oto-Rhino-Laryngology 262[1], 1-7. 2005.

Reason: only 3 patients with CUP included in this study

Yao, M., Lu, M., Savvides, P. S., Rezaee, R., Zender, C. A., Lavertu, P., Buatti, J. M., and Machtay, M. Distant metastases in head-and-neck squamous cell carcinoma treated with intensity-modulated radiotherapy. International Journal of Radiation Oncology, Biology, Physics 83[2], 684-689. 1-6-2012.
Reason: Not relevant to PICO (Not CUP)

Kirke, D. N., Porceddu, S., Wallwork, B. D., Panizza, B., and Coman, W. B. Pathologic occult neck disease in patients with metastatic cutaneous squamous cell carcinoma to the parotid. Otolaryngology - Head & Neck Surgery 144[4], 549-551. 2011.
Reason: Outcomes not relevant to PICO

Lango, M. N. Impact of neck dissection on long-term feeding tube dependence in patients with head and neck cancer treated with primary radiation or chemoradiation. Head and Neck 32[3], 341-347. 2010.
Reason: Outcomes not relevant to PICO

Limaye, S. A. Concurrent chemoradiotherapy with weekly platinum for patients with unresectable/locally advanced SCCHN and comorbidities. Journal of Clinical Oncology Conference[var.pagings], 15. 2010.
Reason: Abstract

Liu, J. T. Prognostic value of radiographic extracapsular extension in locally advanced head and neck squamous cell cancers. Journal of Clinical Oncology Conference[var.pagings], 15. 2014.
Reason: Abstract

Mourad, W. F. Long-term outcome of seropositive HIV patients with head and neck squamous cell carcinoma treated with radiation therapy and chemotherapy. Anticancer Research 33[12], 5511-5516. 2013.

Reason: only includes 4 patients with CUP

Mukhija, V. Selective neck dissection following adjuvant therapy for advanced head and neck cancer. Head and Neck 31[2], 183-188. 2009.

Reason: only includes 4 patients with CUP

Oozeer NB. Voice and swallowing outcome following radiotherapy for head and neck squamous carcinoma of unknown primary. *Otolaryngology - Head and Neck Surgery (United States)* 2014; Conference(var.pagings):1.
Reason: insufficient outcome data reported. Conference abstract only

Sanchíz, F., Millá, A., Torner, J., Bonet, F., Artola, N., Carreño, L., Moya, L. M., Riera, D., Ripol, S., and Cirera, L. Single fraction per day versus two fractions per day versus radiochemotherapy in the treatment of head and neck cancer. International Journal of Radiation Oncology, Biology, Physics 19[6], 1347-1350. 1990.
Reason: Population not relevant

Santa Maria, P. L. Neck dissection for squamous cell carcinoma of the head and neck. Otolaryngology - Head and Neck Surgery 136[4 SUPPL.], S41-S45. 2007.
Reason: Population not relevant to PICO (Not CUP)

Speel, E.-J. Diagnostic and prognostic value of oncogenic human papillomavirus in patients with carcinoma of unknown primary of the neck. Cancer Research Conference[var.pagings], 8. 2011.
Reason: Abstract

Spencer, C. R. Reduction in radiation therapy volumes for patients with head and neck squamous cell carcinoma improves patient-reported quality of life. International Journal of Radiation Oncology Biology Physics Conference[var.pagings], 2. 2013.
Reason: Abstract

Spencer, C. R. Patterns of failure after IMRT in head and neck squamous cell carcinoma (hnscc). International Journal of Radiation Oncology Biology Physics Conference[var.pagings], 3-S428. 2010.
Reason: Abstract

Straetmans J, Vent J, Lacko M, Speel EJ, Huebbers C, Semrau R et al. Management of neck metastases of unknown primary origin united in two European centers. *Eur Arch Otorhinolaryngol* 2015; 272(1):195-205.
Reason: intervention/comparison not relevant to PICO

Unger, K. R. Hpv-positive status predicts for improved outcomes in head and neck squamous cell carcinoma after concurrent cetuximab and radiation therapy. International Journal of Radiation Oncology Biology Physics Conference[var.pagings], 3. 2010.
Reason: Abstract

Weiss, D. Prevalence and impact on clinicopathological characteristics of human papillomavirus-16 DNA in cervical lymph node metastases of head and neck squamous cell carcinoma. Head and Neck 33[6], 856-862. 2011.
Reason: Population not relevant to PICO (not CUP)

Wirth, L. J., Allen, A. M., Posner, M. R., Haddad, R. I., Li, Y., Clark, J. R., Busse, P. M., Chan, A. W., Goguen, L. A., Norris, C. M., Annino, D. J., and Tishler, R. B. Phase I dose-finding study of paclitaxel with panitumumab, carboplatin and intensity-modulated radiotherapy in patients with locally advanced squamous cell cancer of the head and neck. Annals of Oncology 21[2], 342-347. 2010.
Reason: Population not relevant to PICO (Not CUP)

Yao, M. Distant metastasis in head and neck cancer after intensity modulated radiotherapy. International Journal of Radiation Oncology Biology Physics Conference[var.pagings], 3. 2010.
Reason: Abstract

Yetmen, Oksuz D. C. Do we still need routine neck dissection after chemoradiotherapy/radiotherapy for n 2-3 head and neck scc? Radiotherapy and Oncology Conference[var.pagings], S314. 2010.
Reason: Abstract

Zhang, J. Correlating planned radiation dose to the cochlea with primary site and tumor stage in head-and-neck patients treated with intensity modulated radiation therapy. International Journal of Radiation Oncology Biology Physics Conference[var.pagings], 3-S530. 2012.
Reason: Abstract

Mucosal melanoma

Clinical question: What is the optimal locoregional treatment for newly diagnosed upper airways tract mucosal melanoma in the absence of systemic metastases?

Background

Mucosal melanoma represents a small but important subset of CUADT. There is no consensus on the optimal treatment for the primary tumour or for potential or established regional nodal disease. Currently surgery, radiotherapy, and chemotherapy either alone or in combination may be used. Each of these modalities has different consequences for the patient in terms of toxicity, functional outcomes and quality of life.

There are an increasing number of new treatments being trialled for cutaneous melanoma. It is not known if these would be effective for mucosal melanoma.

Evidence statements

Surgery and radiotherapy or chemotherapy versus surgery alone

Very low quality evidence from a systematic review of observational studies (Wushou 2015, five studies including 343 patients) suggests uncertainty over the effect of the addition of radiotherapy to surgical treatment on overall survival in people with mucosal melanoma of the upper aerodigestive tract (MM-UADT). Rates of overall survival after 3 years or 5 years of follow up were not significantly different between patients treated with surgery and radiotherapy compared with surgery alone (hazard ratios (HRs) 1.14 (95% CI 0.60, 1.61) and 1.34 (95% CI 0.97, 1.85) for 3- and 5-year overall survival; values <1 favour surgery + radiotherapy). Evidence from three further observational studies (Lund 2012, Meng 2015, Temam 2005) reported median overall survival as between 13 months shorter and 14 months longer for patients having radiotherapy in addition to surgery.

Very low quality evidence from a systematic review of observational studies (Wushou 2015, four studies including 262 patients) suggests that in people with MM-UADT, the incidence of local or locoregional recurrence is reduced by the addition of radiotherapy to surgery when compared with surgical treatment alone (odds ratio (OR) 0.36, 95% CI 0.22, 0.60; values <1 favour surgery + radiotherapy). However, there is uncertainty over the effect of radiotherapy after surgery on the incidence of distant metastasis (Meleti 2008, Owens 2003, Temam 2005 151 patients in total, very low quality evidence, RR 0.98, 95% CI 0.74, 1.29) or distant recurrence (Nakashima 2008, Freedman 1973, 58 patients in total, very low quality evidence, RR 0.46, 95% CI 0.14, 1.47).

One additional observational trial (Meng 2015, 69 patients, very low quality evidence) compared surgery alone to surgery plus radiotherapy, or surgery plus radiotherapy and chemotherapy. The results suggest uncertainty about which combination of treatments offers the most benefit: 5-year overall survival was greatest for patients receiving surgery and radiotherapy (55% compared to 32% for either surgery alone or surgery plus radiotherapy and chemotherapy), but median overall survival was longest for patients receiving all three treatments (42 months compared to 18 months for surgery alone and 32 months for surgery plus radiotherapy).

Primary surgery versus primary radiotherapy

Very low quality evidence (Freedman 1973, Gal 2011, Tanaka 2004, 216 patients) suggests uncertainty over the probability of 5-year overall survival in people with MM-UADT following treatment with primary surgery or primary radiotherapy. The absolute difference in 5-year overall survival ranged from a 61.3 lower probability to a 19.9 greater probability of 5-year survival in patients treated with radiotherapy when compared with surgically-treated patients. There was also very low quality evidence suggesting uncertainty over the effect of these treatment options on rates of local disease control, locoregional recurrence or distant metastasis. No more than one study reported each of these outcomes.

Other treatment comparisons

Low quality evidence from one randomised trial (Lian 2013, 59 patients) suggests that adjuvant treatment with interferon prolongs overall survival (median 9.2 months longer) and relapse-free survival (median 10.8 months longer) when compared with adjuvant chemotherapy.

Very low quality evidence from one observation trial (Ahn 2010, 32 patients) suggests that adjuvant chemotherapy after primary treatment prolongs overall survival (median 27 months longer) and both local and distant relapse free survival (median 10 and 9 months longer repectively) in people with MM-CUADT.

Very low quality evidence from one observational trial (Kanetaka 2011, 13 patients) suggests uncertainty in the effect of high-dose interferon after primary treatment on rates of overall mortality in people with MM-UADT (RR 1.43, 95% CI 0.57, 3.61).

Very low quality evidence from one observational trial (Sun 2012, 21 patients) suggests that in people with MM-CUADT, the probability of 3- and 5-year overall survival is greater following treatment with surgery plus biotherapy when compared with surgery alone (45.1 % greater probability of 3-year survival; 45.9% greater probability of 5-year survival).

No evidence was identified on the effect of any intervention on treatment-related mortality, treatment-related morbidity or health-related quality of life in people with MM-UADT.

Study characteristics and quality

One systematic review and 17 individual studies were identified. The systematic review and eight individual studies compared surgery alone with surgery plus radiotherapy. Three studies compared surgery with radiotherapy (two trials had three arms: radiotherapy, surgery, and surgery plus radiotherapy. These two trials contribute data to each relevant comparison). A further seven trials studied six other treatment combinations (see Table 6.26 for details).

One trial was randomised (Lian 2013); the remainder were non-randomised retrospective studies, most of which were conducted in a single treatment centre. Many of these trials included low numbers of patients and included data collected over long periods (up to 36 years), presumably due to the rarity of MM-UADT. For all the included non-randomised trials, it is unclear if the groups of patients allocated to different interventions were comparable at baseline; three studies (Freedman 1973, Nakashima 2008, Temam 2005) reported imbalances between treatment groups for factors that may influence outcomes independently of treatment, such as disease stage and tumour site.

Most trials included patients with MM-UADT at any site in the head and neck; where these criteria were used most patients had tumours at oral or sinonasal sites. The randomised trial (Lian 2013) included patients with mucosal melanoma at any anatomical site; 31.2% (59/189) had MM-UADT and a subgroup analysis for these patients is the only data included from this study.

Two trials (Gal 2011, Shiga 2012) included some patients with distant metastases, or whose metastatic status is unknown. These trials have been included as the majority of patients did not have metastases, but results of these trials should be interpreted with their applicability to the population of interest in mind.

Table 6.26. Characteristics of included studies

STUDY ID	DESIGN	SITE	N	TREATMENT COMPARISON	FOLLOW UP
Wushou 2015	SRMA	Any head and neck	423 (8 studies)	Surgical treatment vs. surgery plus post-operative radiotherapy	Median 18 to 65 months, not reported for one study
Ahn 2010	RCS	Any head and neck	32	Adjuvant chemotherapy after primary treatment vs. no adjuvant chemotherapy after primary treatment	Median 22.1 months (range 4 months to 15.6 years)
Benlyazid 2010	RCS	Any head and neck	160	Surgery vs. surgery+RT	Median 65.2 months
Douglas 2010	RCS	Any head and neck	55	Surgery with or without RT vs. radical RT	Minimum 15 months
Freedman 1973	RCS	Nasal cavity or paranasal sinuses	56	Surgery vs. surgery+RT vs. primary RT	NR
Gal 2011	RCS	Nasal cavity, nasopharynx or paranasal sinuses	304	Surgery vs. surgery+RT vs. primary RT	NR
Kanetaka 2011	RCS	Any head and neck	13	Immunotherapy after primary treatment vs. primary treatment alone	Median 48 months (range 10-115 months)
Kingdom 1995	RCS	Nasal cavity or paranasal	13	Surgery alone vs. surgery +RT	Range 6-76 months

STUDY ID	DESIGN	SITE	N	TREATMENT COMPARISON	FOLLOW UP
Lian 2013	RCT	Any head and neck	59	After primary surgery: adjuvant interferon vs. adjuvant chemotherapy	Median 28.6 months (range 5.9-53.9 month)
Lund 2012	RCS	Sinonasal	109	Surgery vs. surgery+RT OR endoscopic vs. open surgery	Mean 37.5 months (range 2-360 months)
Meleti 2008	RCS	Any head and neck	38	Surgery vs. surgery+RT	Mean 27.8 months (range 2-80 months)
Meng 2015	RCS	Sinonasal	69	Surgery vs. RT OR surgery, RT and chemotherapy	Mean 34 months (range 1-144 months)
Nakashima 2008	RCS	Any head and neck	20	Surgery vs. surgery+RT	Median 38 months (range 7-160)
Owens 2003	RCS	Any head and neck	44	Surgery vs. surgery+RT	NR
Shiga 2012	RCS	Any head and neck	94	Surgery as primary treatment vs. RT as primary treatment	NR
Sun 2012	RCS	Oral	21	Surgery vs. surgery + biotherapy	NR
Tanaka 2004	RCS	Oral	30	Surgery vs. RT	NR
Temam 2005	RCS	Any head and neck	69	Surgery vs. surgery+RT	Median 3.8 years (range 8-384 months).

Abbreviations: NR: not reported; RCT: randomised controlled trial; RCS: retrospective cohort study; RT: radiotherapy; SRMA: systematic review and meta-analysis

GRADE evidence tables

Table 6.27. GRADE evidence profile: surgery alone versus surgery + radiotherapy for newly diagnosed upper aerodigestive tract mucosal melanoma in the absence of systemic metastases

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery alone	Surgery + RT		
3-year overall survival (median follow-up 38 months)										
5[19]	observational studies	serious[3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	157	186	HR = 1.14 (95% CI 0.60, 1.61) (values <1 favour surgery + RT)	⊕OOO VERY LOW
5-year overall survival (follow-up 2-160 months)										
5[19]	observational studies	serious[3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	157	186	HR = 1.34 (95% CI 0.97, 1.85) (values <1 favour surgery + RT)	⊕OOO VERY LOW
Median overall survival (follow-up 2-384 months)										
2[10,11]	observational studies	serious[12]	no serious inconsistency	no serious indirectness	serious[18]	none	94	74	Overall survival, months (Kaplan-Meier estimates) **STUDY** / **Surgery** / **SRT** / **Difference (SRT-surgery)** Lund (n = 115): 28 / 24 / -4 Temam (n = 69): 30 / 17 / -13	⊕OOO VERY LOW

Quality assessment							No of patients		Effect				Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery alone**	**Surgery + RT**					
5-year relapse free survival (follow-up not known)													
1[5]	observational studies	serious[3,4]	no serious inconsistency	no serious indirectness	serious[18]	none	82	78		5-yr RFS, % (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Surgery**	**SRT**	**Difference (SRT-surgery)**	
									Benlyazid (n = 160)	26.5	29.4	2.9	
Local recurrence (median follow-up 38 months)													
4[19]	observational studies	serious[3,4]	no serious inconsistency	no serious indirectness	serious[18]	none	133	129	OR = 0.36 (95% CI 0.22, 0.60) (values <1 favour surgery + RT)				⊕OOO VERY LOW
Incidence of distant metastasis (follow-up 2-384 months)													
3[8,9,11]	observational studies	serious[13]	no serious inconsistency	no serious indirectness	serious[15]	none	39/69 (56.5%)	48/82 (58.5%)	RR 0.98 (0.74, 1.29)	12 fewer per 1000 (from 152 fewer to 170 more)			⊕OOO VERY LOW

Quality assessment							No of patients		Effect				Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery alone**	**Surgery + RT**					
Time to local recurrence (follow-up 6-76 months)													
1[1]	observational studies	serious[3,4]	no serious inconsistency	no serious indirectness	serious[18]	none	6	7		Time to recurrence, months (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Surgery**	**SRT**	**Difference (SRT-surgery)**	
									Kingdom (n = 13)	8	25	17	
Time to locoregional recurrence (follow-up 7-160 months)													
1[2]	observational studies	serious[16]	no serious inconsistency	no serious indirectness	serious[18]	none	8	12		Time to recurrence, months (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Surgery**	**SRT**	**Difference (SRT-surgery)**	
									Nakashima (n = 20)	9	45	36	
Incidence of local failure (follow-up 2-80 months)													
1[8]	observational studies	serious[3,4]	no serious inconsistency	no serious indirectness	serious[18]	none	11/19 (57.9%)	5/19 (26.3%)	RR 2.2 (0.95, 5.12)	316 more per 1000 (from 13 fewer to 1000 more)			⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery alone**	**Surgery + RT**			
Incidence of distant recurrence (follow-up 7-160 months)											
2[2,6]	observational studies	serious[14]	no serious inconsistency	no serious indirectness	serious[18]	none	3/25 (12%)	9/33 (27.3%)	RR 0.46 (0.14, 1.47)	147 fewer per 1000 (from 235 fewer to 128 more)	⊕OOO VERY LOW
Time to distant recurrence (follow up not reported)											
1[2]	observational studies	serious[16]	no serious inconsistency	no serious indirectness	serious[18]	none	8	12	Time to recurrence, months (Kaplan-Meier estimates) **STUDY** / **Surgery** / **SRT** / **Difference (SRT-surgery)** Nakashima (n = 20) / 14.9 / 25.5 / 10.6		⊕OOO VERY LOW
Time to distant metastasis (follow-up not reported)											
1[9]	observational studies	serious[3,4]	no serious inconsistency	no serious indirectness	serious[18]	none	20	24	Time to recurrence, months (Kaplan-Meier estimates) **STUDY** / **Surgery** / **SRT** / **Difference (SRT-surgery)** Owens (n = 44) / 30.3 / 17.5 / -12.8		⊕OOO VERY LOW
Abbreviations: RFS:relapse-free survival; RT: radiotherapy; SRT: surgery with radiotherapy.											

[1] Kingdom 1995
[2] Nakashima 2008

[3] Criteria used to allocate patients to treatment not reported.
[4] Unclear if different treatment groups were comparable at baseline.
[5] Benlyazid 2010
[6] Freedman 1973
[7] Gal 2011
[8] Meleti 2008
[9] Owens 2003
[10] Lund 2012
[11] Temam 2005
[12] Alllocation to treatment based on clinician/patient preference in one study (Lund 2012); results may be biased towards treatment with surgery alone in one study (Temam 2005) as a higher proportion of patients in this group had early stage disease.
[13] Results may be biased towards treatment with surgery alone in one study (Temam 2005) as a higher proportion of patients in this group had early stage disease.
[14] Treatment groups were not comparable at baseline in terms of tumour stage for one study (Freedman 1973) and tumour site for a second study (Nakashima 2008).
[15] 95% confidence includes appreciable benefit, no effect and appreciable harm.
[16] Treatment groups were not comparable at baseline in terms of tumour stage.
[17] Results across studies range from appreciable benefit to appreciable harm.
[18] Overall number of measured events is low.
[19] Washou 2015

Table 6.28. GRADE evidence profile: surgery versus radiotherapy for newly diagnosed upper aerodigestive tract mucosal melanoma in the absence of systemic metastases

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	RT		
3-year overall survival										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	17	18	3-yr overall survival, % (Kaplan-Meier estimates) **STUDY** / **Surgery** / **RT** / **Difference (RT-surgery)** Freedman (n = 35) / 75 / 5.5 / -69.5	⊕OOO VERY LOW
5-year overall survival										
3[1,3,4]	observational studies	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	158	58	5-yr overall survival, % (Kaplan-Meier estimates) **STUDY** / **Surgery** / **RT** / **Difference (RT-surgery)** Freedman (n = 35) / 61.3 / 0 / -61.3 Gal (n = 151) / 20 / 9 / -11 Tanaka (n = 30) / 15.4 / 35.3 / 19.9	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	RT			
Primary lesion controlled after treatment (follow-up period not reported)											
1[4]	observational studies	serious[6]	no serious inconsistency	no serious indirectness	serious[8]	none	12/13 (92.3%)	9/17 (52.9%)	RR 0.16 (0.02, 1.15)	445 fewer per 1000 (from 519 fewer to 79 more)	⊕OOO VERY LOW
Incidence of tumour recurrence (follow-up period not reported)											
1[4]	observational studies	serious[6]	no serious inconsistency	no serious indirectness	serious[8]	none	2/13 (15.4%)	0/17 (0%)	RR 6.43 (0.33, 123.43)	Not estimable[7]	⊕OOO VERY LOW
Incidence of locoregional recurrence (follow-up period not reported)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	14/17 (82.4%)	13/18 (72.2%)	RR 1.14 (0.79, 1.64)	101 more per 1000 (from 152 fewer to 462 more)	⊕OOO VERY LOW
Incidence of distant metastasis (follow-up period not reported)											
1[4]	observational studies	serious[6]	no serious inconsistency	no serious indirectness	serious[8]	none	10/13 (76.9%)	11/17 (64.7%)	RR 1.19 (0.75, 1.88)	123 more per 1000 (from 162 fewer to 569 more)	⊕OOO VERY LOW
Incidence of distant recurrence (follow-up period not reported)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	1/17 (5.9%)	2/18 (11.1%)	RR 0.53 (0.05, 5.32)	52 fewer per 1000 (from 106 fewer to 480 more)	⊕OOO VERY LOW

[1] Freedman 1973

[2] Criteria used to decide treatment received by patients was not reported. Treatment groups were not comparable for tumour stage.

[3] Gal 2011
[4] Tanaka 2005
[5] Criteria used to decide treatment received by patients was not reported for one study. Treatment groups were not comparable for tumour stage for one study (Freedman).
[6] Criteria for allocation to treatment not reported.
[7] No events in the RT group means this cannot be calculated.
[8] Overall number of measured events is low.

Table 6.29. GRADE evidence profile: adjuvant chemotherapy after primary treatment versus no adjuvant chemotherapy after primary treatment for newly diagnosed upper aerodigestive tract mucosal melanoma in the absence of systemic metastases

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adjuvant chemotherapy after primary treatment**	**No adjuvant chemotherapy after primary treatment**		
3-year overall survival (follow-up 4-187 months)										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	16	16	3-yr overall survival, % (Kaplan-Meier estimates) **STUDY** / **Adjuvant chemo** / **No adjuvant chemo** / **Difference (no adj chemo-adj chemo)** Ahn (n = 32) / 59 / 10 / -49	⊕OOO VERY LOW

Quality assessment							No of patients		Effect				Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adjuvant chemotherapy after primary treatment**	**No adjuvant chemotherapy after primary treatment**					
Median overall survival (follow-up 4-187 months)													
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	16	16		Overall survival, months (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Adjuvant chemo**	**No adjuvant chemo**	**Difference (no adj chemo-adj chemo)**	
									Ahn (n = 32)	45	18	-27	
Median local relapse-free survival (follow-up 4-187 months)													
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	16	16		Local RFS, months (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Adjuvant chemo**	**No adjuvant chemo**	**Difference (no adj chemo-adj chemo)**	
									Ahn (n = 32)	23	13	-10	

Quality assessment							No of patients		Effect				Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adjuvant chemotherapy after primary treatment**	**No adjuvant chemotherapy after primary treatment**					
Median distant relapse-free survival (follow-up 4-187 months)													
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	16	16		Distant RFS, months (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Adjuvant chemo**	**No adjuvant chemo**	**Difference (no adj chemo-adj chemo)**	
									Ahn (n = 32)	26	17	-9	

[1] Ahn 2010

[2] Allocation to groups not reported; unclear if different treatment groups were comparable at baseline

[3] Overall number of measured events is low.

Table 6.30. GRADE evidence profile: surgery (with or without RT) versus radical RT for newly diagnosed upper aerodigestive tract mucosal melanoma in the absence of systemic metastases

Quality assessment							No of patients		Effect				Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery (with or without RT)	Radical RT					
5 year overall survival (follow-up minimum 15 months)													
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	25	30		Overall survival, % (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Surgery**	**Radical RT**	**Difference (RT-surgery)**	
									Douglas (n = 55)	46	13	-33	
5 year cancer specific survival (follow-up minimum 15 months)													
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	25	30		Cancer-specific survival, % (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Surgery**	**Radical RT**	**Difference (RT-surgery)**	
									Douglas (n = 55)	58	25	-33	

[1] Douglas 2010

[2] Criteria used to decide treatment received by patients was not reported; No detail on what care was given in addition to intervention/comparison. Long study period means this is likely to have varied over time.

[3] Overall number of measured events is low.

Table 6.31. GRADE evidence profile: immunotherapy after primary treatment versus primary treatment alone for newly diagnosed upper aerodigestive tract mucosal melanoma in the absence of systemic metastases

Quality assessment							No of patients		Effect				Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDI after primary treatment	Primary treatment alone					
5 year cause-specific survival (follow-up 10-115 months)													
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	7	6	Cause-specific survival, % (Kaplan-Meier estimates)				⊕OOO VERY LOW
									STUDY	**HDI**	**No HDI**	**Difference (no HDI-HDI)**	
									Kanetaka (n = 13)	33	66	33	
Overall mortality (follow-up 10-115 months)													
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	5/7 (71.4%)	3/6 (50%)	RR 1.43 (0.57, 3.61)		215 more per 1000 (from 215 fewer to 1000 more)		⊕OOO VERY LOW
Abbreviations: HDI: high dose interferon.													

[1] Kanetaka 2011
[2] Patients received different local treatment (surgery or radiotherapy); details of this according to treatment group not reported. Criteria for allocation to treatment not reported.
[3] 95% confidence interval encompasses significant beneft, significant effect and significant harm.
[4] Overall number of measured events is low.

Table 6.32. GRADE evidence profile: after primary surgery: adjuvant interferon versus adjuvant chemotherapy for newly diagnosed CUADT mucosal melanoma in the absence of systemic metastases

Quality assessment							No of patients		Effect				Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	After primary surgery: adjuvant interferon	Adjuvant chemotherapy					
Median overall survival (follow-up 6-54 months)													
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	29	30		Overall survival, months (Kaplan-Meier estimates)			⊕⊕OO LOW
									STUDY	**Interferon**	**Chemotherapy**	**Difference (chemo-interferon)**	
									Lian (n = 59)	49.6	40.4	-9.2	
Median relapse free survival (follow-up 6-54 months)													
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	29	30		RFS, months (Kaplan-Meier estimates)			⊕⊕OO LOW
									STUDY	**Interferon**	**Chemotherapy**	**Difference (chemo-interferon)**	
									Lian (n = 59)	19.6	8.8	-10.8	

[1] Lian 2013
[2] Methods of randomisation to treatment/concealment of randomisation sequence not reported
[3] Overall number of events measured is low

Table 6.33. GRADE evidence profile: surgery as primary treatment versus radiotherapy as primary treatment for newly diagnosed upper aerodigestive tract mucosal melanoma in the absence of systemic metastases

Quality assessment							No of patients		Effect				Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery as primary treatment	RT as primary treatment					
5-year overall survival (follow-up period not reported)													
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	27		Overall survival, % (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Surgery**	**RT**	**Difference (RT-surgery)**	
									Shiga (n = 83)	38.6	29.9	-8.7	

[1] Shiga 2012

[2] Allocation to groups not reported; unclear if different treatment groups were comparable at baseline

Table 6.34. GRADE evidence profile: surgery versus surgery + biotherapy for newly diagnosed upper aerodigestive tract mucosal melanoma in the absence of systemic metastases

Quality assessment							No of patients		Effect				Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery**	**Surgery + biotherapy**					
3-year overall survival (follow-up period not reported)													
1[1]	observational studies	serious[2,3,4]	no serious inconsistency	no serious indirectness	serious[5]	none	11	10		Overall survival, % (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Surgery**	**Surgery + biotherapy**	**Difference (biotherapy-no biotherapy)**	
									Sun (n = 21)	25	70.1	45.1	
5-year overall survival (follow-up period not reported)													
1[1]	observational studies	serious[2,3,4]	no serious inconsistency	no serious indirectness	serious[5]	none	11	10		Overall survival, % (Kaplan-Meier estimates)			⊕OOO VERY LOW
									STUDY	**Surgery**	**Surgery + biotherapy**	**Difference (biotherapy-no biotherapy)**	
									Sun (n = 21)	12.5	58.4	45.9	

[1] Sun 2012
[2] Allocation to groups not reported; unclear if different treatment groups were comparable at baseline
[3] No detail on what care was given in addition to intervention/comparison.
[4] Number of patients for whom outcome data is available (and for how long patients were followed up) is unclear
[5] Overall number of measured events is low.

1 Evidence tables for all included studies

2 *Systematic review*

Study

Wushou, 2015

Study type,search period

Systematic review of observational studies.
Last searches conducted 30 April 2014; no lower date limits used.

Eligibility criteria

Studies investigating treatment outcomes of head and neck mucosal melanoma, where treatment outcome was explored by comparing only surgical treatment and surgery plus post-operative radiotherapy (PORT).
Studies including less than 15 patients were excluded.

Number of patients/trials

423 patients from 8 studies (median sample size 53 patients)

Trial characteristics

Author, year	Country	Total patients	Surgery alone	Surgery + PORT	PORT dose, Gy	Median follow-up, months
Harrison, 1968	UK	18	5	13	NR	37.2
Yii, 2003	UK	56	18	38	NR	24
Owens, 2003	USA	44	20	24	30-60	NR
Martin, 2004	Australia	18	3	15	60	18.3
Temam, 2005	France	69	30	39	NR	45.6
Nakashima, 2008	Brazil	20	8	12	54	49
Meleti, 2008	Italy	38	19	19	30	27.8
Benlyazid	France	160	82	78	25-70	65.2

NR: not reported.

Intervention

Surgery alone.

Comparison

Surgery + PORT.

Outcome measures and effect size

3-year overall survival (5 studies): HR = 1.14 (95% CI 0.60, 1.61) (values <1 favour surgery + RT)
5-year overall survival (5 studies): HR = 1.34 (95% CI 0.97, 1.85) (values <1 favour surgery + RT)
Local recurrence (4 studies): OR = 0.36 (95% CI 0.22, 0.60) (values <1 favour surgery + RT)

Source of funding

Not reported; authors declared no conflicts of interest.

Additional comments

No study quality assessment reported. Limited detail reported of the methods used to pool outcomes/estimate effect sizes.

3

4 *Individual studies*

Study, country

Ahn, 2010.

Korea, single centre

Study type, study period

Retrospective cohort study.
July 1989 to March 2004.

Number of patients

32

Patient characteristics

Inclusion criteria:
Mucosal melanoma of the head and neck with no distant metastasis; head and neck confirmed as the site of the primary lesion.
Patients receiving curative treatment.

Gender	n (%)
Male	17 (53)
Female	15 (47)

Primary tumour origin	n (%)
Oral cavity	12 (37.5)
Sinonasal	20 (62.5)

Disease stage	n (%)
Stage I	23 (72)
Stage II	9 (28)

Patients were treated with curative surgery or radiation (no details given on number receiving each type of treatment).

Intervention

Adjuvant chemotherapy after primary treatment (n = 16). Regimen used: dacarbazine 250 mg/m^2 on days 1-5, carmustine 150 mg/m^2 or lomustine 175 mg/m^2 on day 1 of every other cycle, and vincristine 1.4 mg/m^2 on days 1 and 8. Cycles begun every three weeks for up to five cycles (median number of cycles received was three).

Comparison

No adjuvant chemotherapy after primary treatment (n = 16.

Length of follow-up

Median 22.1 months (range 4 months to 15.6 years)

Outcome measures and effect size

	Adjuvant chemotherapy	No adjuvant chemotherapy
Probability of 36 month overall survival*	0.59	0.1
Median overall survival, months*	45	18
Median local relapse-free survival, months*	23	13
Median distant relapse-free survival, months*	26	17

*figures estimated from Kaplan-Meier survival curves.

Source of funding

Not reported; authors declared no conflicts of interest.

Risks of bias

Selection bias: High risk. Allocation to groups not reported; unclear if different treatment groups were comparable at baseline
Performance bias: Unclear/unknown risk. Patients received different local treatment (surgery or radiotherapy); details of this according to treatment group not reported
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

1

Study, country

Benlyazid, 2010.
France, 13 institutions.

Study type, study period

Retrospective cohort study.
1980 to 2008.

Number of patients

160

Patient characteristics

Inclusion criteria: diagnosis of head and neck mucosal melanoma treated with surgery with or without postoperative radiotherapy
Exclusion criteria: treatment with radiotherapy alone; metastatic disease; disease of unknown stage.

	Surgery (n = 82)	Surgery+RT (n = 78)
Gender	**n (%)**	**n (%)**
Male	27 (32.9)	28 (35.9)
Female	55 (67.1)	50 (64.1)

	Surgery (n = 82)	Surgery+RT (n = 78)
Stage	**n (%)**	**n (%)**
1	80 (98.8)	73 (93.6)
2	1 (1.2)	5 (6.4)

	Surgery (n = 82)	Surgery+RT (n = 78)
Site	**n (%)**	**n (%)**
Sinonasal	73 (89.0)	72 (92.3)
Oral cavity	8 (9.8)	4 (5.1)
Other	1 (1.2)	2 (2.6)

	Surgery (n = 82)	Surgery+RT (n = 78)
TNM stage at diagnosis	**n (%)**	**n (%)**
T1/T2	40 (48.7)	33 (42.3)
T3/T4	13 (15.8)	21 (26.9)
Unknown	29 (35.4)	24 (30.7)

Median age was 67 years in both treatment groups.

Intervention

Surgery alone (n = 82)

Comparison

Surgery with postoperative radiotherapy (n = 78)

Length of follow-up

Median 62.5 months

2

Outcome measures and effect size

	Surgery (n = 82)	Surgery+RT (n = 78)	
5 year overall survival, %*	46.2	27.5	p = 0.31
5 year relapse-free survival, %*	26.5	29.4	P = 0.63
5 year probability of locoregional recurrence, %*	55.6	29.9	P < 0.01
5 year probability of distant metastasis, %*	17.9	40.7	p = 0.01

*estimated by the Kaplan-Meier method.

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Criteria used to decide treatment received by patients was not reported
Performance bias: Unclear/unknown risk. All patients received surgery; no detail on type of surgery performed. Likely to be differences in practice across the multiple institutions included in the study.
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

Recurrence outcomes also reported in systematic review by Washou et al (2015)

1

Study, country

Douglas, 2010.
United Kingdom, single centre.

Study type, study period

Retrospective cohort study.
1965 to 2001.

Number of patients

55.

Patient characteristics

Patients with mucosal melanoma treated with curative intent.

	RT (n = 30)	Surgery (n = 25)
Gender	**n (%)**	**n (%)**
Male	12 (40)	9 (36)
Female	18 (60)	16 (64)

	RT (n = 30)	Surgery (n = 25)
Neck node status	**n (%)**	**n (%)**
Positive	5 (17)	4 (16)
Negative	25 (83)	21 (84)

	RT (n = 30)	Surgery (n = 25)
Site	**n (%)**	**n (%)**
Sinonasal	22 (73)	11 (44)
Oral cavity	3 (10)	8 (32)
Other	5 (17)	6 (24)

Mean patient age: 63 years (63.5 years RT group; 62.5 years surgery group)

Intervention

Radical radiotherapy (n = 30)

Comparison

Surgery with or without postoperative radiotherapy (n = 25)

Length of follow-up

Minimum 15 months (no further details reported)

Outcome measures and effect size

	RT (n = 30)	Surgery (n = 25)	
5 year overall survival, %*	13	46	p = 0.021
5 year cancer-specific survival, %*	25	58	P = 0.20

*estimated by the Kaplan-Meier method.

Source of funding

Not reported; authors declared no conflicts of interest.

Risks of bias

Selection bias: High risk. Criteria used to decide treatment received by patients was not reported
Performance bias: Unclear/unknown risk. No detail on what care was given in addition to intervention/comparison. Long study period means this is likely to have varied over time.

Attrition bias: Unclear/unknown risk. Number of patients for whom outcome data is available (and for how long patients were followed up) is unclear
Detection bias: Unclear/unknown risk. Length of follow up unclear.

Additional comments

1

Study, country

Freedman, 1973.
United States, single centre.

Study type, study period

Retrospective cohort study.
Study period not reported.

Number of patients

56

Patient characteristics

Patients with malignant melanoma primary in the nasal cavity or paranasal sinuses.

Gender	n (%)
Male	33 (59)
Female	23 (41)

Age	n (%)
≤ 60 years	26 (46)
> 60 years	30 (54)

Primary site	n (%)
Nasal cavity	29 (52)
Sinus	18 (32)
Unknown	9 (16)

	Surgery + RT (n = 21)	RT (n = 18)	Surgery (n = 17)
Stage	**n (%)**	**n (%)**	**n (%)**
I	9 (16)	3 (5)	8 (14)
II	10 (18)	4 (7)	8 (14)
III	1 (2)	5 (9)	0
IV	0 (0)	4 (7)	0
Unknown	1 (2)	2 (4)	1 (2)

Intervention

Surgery in combination with radiotherapy (n = 21)

Comparison

Primary site radiotherapy (n = 18)

Comparison

Primary site surgery (n = 17)

Length of follow-up

Not reported.

Outcome measures and effect size

	Surgery + RT (n = 21)	RT (n = 18)	Surgery (n = 17)
3 year overall survival, %*	60.7	5.5	75
5 year overall survival, %*	34.2	0	61.3
Incidence of recurrence, n (%)			
Any recurrence	18 (85)	15 (83)	15 (88)
Locoregional	13 (62)	13 (72)	14 (82)
Distant	5 (24)	2 (11)	1 (6)

*estimated by the Kaplan-Meier method.

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Criteria used to decide treatment received by patients was not reported. Treatment groups were not comparable for tumour stage.
Performance bias: Unclear/unknown risk. No detail on what care was given in addition to intervention/comparison.
Attrition bias: Unclear/unknown risk. Number of patients for whom outcome data is available (and for how long patients were followed up) is unclear
Detection bias: Unclear/unknown risk. Length of follow up unclear.

Additional comments

2

3

Study, country

Gal. 2011.
United States, multiple centres.

Study type, study period

Retrospective cohort study.
2000 to 2007.

Number of patients

304

Patient characteristics

Patients with mucosal melanoma of the nasal cavity, nasopharynx or paranasal sinuses.

Gender	n (%)
Male	133 (43.8)
Female	171 (56.3)

Tumour site	n (%)
Nasal cavity	199 (65.5)
Sinonasal	105 (34.5)

Median age at diagnosis: 71.2 years.

Intervention

Surgery in combination with radiotherapy (n = 120)

Comparison

Treatment with radiotherapy alone (n = 23)

Comparison

Treatment with surgery alone (n = 128)

Length of follow-up

Not reported

Outcome measures and effect size

	Surgery + RT (n = 120)	RT (n = 23)	Surgery (n = 128)
5 year overall survival, %*	31	9	20

*figures estimated from Kaplan-Meier survival curves.

Source of funding

Not reported; authors declared no conflicts of interest.

Risks of bias

Selection bias: High risk. Allocation to groups not reported; unclear if different treatment groups were comparable at baseline
Performance bias: Unclear/unknown risk. No detail on what care was given in addition to intervention/comparison.
Attrition bias: Unclear/unknown risk. Number of patients for whom outcome data is available (and for how long patients were followed up) is unclear
Detection bias: Unclear/unknown risk. Length of follow up unclear

Additional comments

Not all patients are within the population of interest: approximately 25% of the study population had distant metastases or an unknown metastatic status.

1

Study, country

Kanetaka, 2011.
Japan, single centre

Study type, study period

Retrospective cohort study.
June 1992 to November 2010.

Number of patients

13

Patient characteristics

Patients with head and neck mucosal melanoma.

Gender	n (%)
Male	3 (23)
Female	10 (77)

Tumour site	n (%)
Nasal cavity	8 (62)
Sinonasal	5 (38)

Tumour stage	n (%)
Ia	5 (38)
Ib	6 (46)
II	1 (7)
III	1 (7)

Median age: 60.8 years (range 39-78 years).
Initial treatment consisted of primary surgery (with or without chemotherapy or radiotherapy) or primary radiotherapy.

Intervention

Primary treatment plus immunotherapy (n = 7) consisting of lymphokine activated killer cell therapy.

Comparison

Primary treatment alone (n = 6)

Length of follow-up

Median 48 months (range 10-115 months)

Outcome measures and effect size

	Primary treatment plus immunotherapy (n = 7)	Primary treatment alone (n = 6)
Overall mortality, n (%)	5 (71%)	3 (50%)
5 year cause specific survival, %*	33	66

*estimated by the Kaplan-Meier method.

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Allocation to groups not reported; unclear if different treatment groups were comparable at baseline.
Performance bias: Unclear/unknown risk. Patients received different local treatment (surgery or radiotherapy); details of this according to treatment group not reported.
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

1

Study, country

Kingdom, 1995.
United States, single centre.

Study type, study period

Retrospective cohort study.
1981 to 1993

Number of patients

13

Patient characteristics

Patients evaluated and treated for primary mucosal melanoma of the nasal cavity or paranasal sinuses, treated with surgical resection with or without adjuvant radiotherapy.

Average age at presentation: 68 years (range 56 to 85 years).

Intervention

Surgery followed by radiotherapy. Dose to the primary site ranged from 30 to 62 Gy (n = 7).

Comparison

Surgery alone (n = 6).

Length of follow-up

Range 6-76 months.

Outcome measures and effect size

	Surgery + RT (n = 7)	Surgery (n = 6)
3-year overall survival, %	80	0
Incidence of local recurrence, n (%)	5 (71)	6 (100)
Time to local recurrence, months	25	8

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Allocation to groups not reported; unclear if different treatment groups were comparable at baseline
Performance bias: Unclear/unknown risk. No detail on what care was given in addition to intervention/comparison.
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

2

3

Study, country

Lian, 2013.
China.

Study type, study period

Randomised controlled trial.

Number of patients

Full study population: 189. Subgroup of interest (actively treated CUADT mucosal melanoma patients): 59
January 2007 to July 2009.

Patient characteristics

Inclusion criteria:
Pathologically confirmed diagnosis of stage II or stage III mucosal melanoma.
Completely resected primary tumour.

Exclusion criteria
Distant metastatic disease.
Prior systemic adjuvant therapy or regional radiotherapy.

Intervention

Adjuvant high dose interferon-α2b (HDI): intravenous 15 x 10^6 U/m^2/day on days one to five each week for four weeks, then subcutaneous 9 x 10^6 U/m^2/day three times per week for 48 weeks. CUADT patients: 29 (total treatment group: 63)

Comparison

Adjuvantchemotherapy: 200 mg/m^2/day temozolomide on days one to five plus 75 mg/m^2 cisplatin divided over 3 days, repeated every three weeks for six cycles. CUADT patients: 30 (total treatment group: 63)

Length of follow-up

Median 28.6 months (range 5.9-53.9 month) for the full study population.

Outcome measures and effect size

	HDI (n = 29)	Chemotherapy (n = 30)	
Median overall survival	49.6	40.4	HR 0.37 (95% CI 0.14, 0.93)
Median relapse-free survival	19.6	8.8	HR 0.21 (95% CI 0.11, 0.39)

Source of funding

Not reported.

Risks of bias

Selection bias: Unclear/unknown risk. Method of randomisation allocation/concealment not reported
Performance bias: Low risk.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

Full study includes mucosal melanoma at sites other than the upper aerodigestive tract; results for the CUADT mucosal melanoma subgroup are presented above. An observation group was also included in the trial; no relevant results are available for this group.

1

Study, country

Lund, 2012.
United Kingdom, single centre.

Study type, study period

Retrospective cohort study.
1963 to 2010.

Number of patients

115.

Patient characteristics

Included patients had primary sinonasal melanoma and underwent surgery with curative intent. Surgery included open surgical approaches before 1996 and endoscopic resection thereafter.

Gender	n (%)
Female	64 (55.7)
Male	51 (44.3)

Site of disease origin	n (%)
Nasal cavity	90 (78.3)
Ethmoids (with or without nasal cavity involvement)	12 (10.5)
Maxilla	7 (6.1)
Could not be determined	6 (5.2)

Mean age: 65.9 years (range 15-91years)

2

Intervention (1)	**Intervention (2)**
Surgery alone (n = 64)	Endoscopic tumour resection (n = 31)
Comparison (1)	**Comparison (2)**
Surgery with radiotherapy (n = 35)	Open surgery (n = 78)
Length of follow-up	
Mean 37.5 months (range 2-360 months) in 109 patients were follow up was recorded. Six patients lost to follow up.	
Outcome measures and effect size	

	Surgery alone	**Surgery+RT**	**Endoscopic surgery (n = 31)**	**Open surgery (n = 78)**
Median overall survival, months (95% CI)	28 (7.4, 48.5)	24 (10.7, 37.3)	59 (23.9, 94.1)	18 (13.6, 22.6)
Median local control	21 (6.7, 35.2)	23 (18.3, 27.6)	50 (13.7, 86.2)	18 (13.5, 22.5)

Source of funding
Not reported; authors declared no conflicts of interest.
Risks of bias
Selection bias: High risk. Allocation influenced by patient preference or time of treatment. Performance bias: Unclear/unknown risk. No detail on what care was given in addition to intervention/comparison. Long study period means this is likely to have varied over time. Attrition bias: Unclear/unknown risk. Number of patients lost to follow up reported, but not the treatment these patients received. Detection bias: Low risk.
Additional comments

1

Study, country
Meleti, 2008. Italy (one centre) and Netherlands (one centre).
Study type, study period
Retrospective cohort study. 1976 to 2006.
Number of patients
38.
Patient characteristics
Inclusion criteria: Patients referred with head and neck mucosal melanoma who received surgery as primary treatment. Exclusion criteria: Neck lymph node metastasis from cutaneous melanoma or form an unknown primary. Patients with a metastasis to the head and neck from another region of the body.

Gender	**n (%)**
Male	16 (42)
Female	26 (58)

Site	**n (%)**
Sinonasal	25 (59.5)
Oral cavity	17 (40.5)

Mean age: 62.7 years (range 31-91 years)

Intervention
Surgical resection alone (n = 19)
Comparison
Surgical resection with postoperative radiotherapy (n = 19). Most frequently adopted scheme consisted of 600 cGy twice weekly for a total dose of 3000 cGy.
Length of follow-up
Mean 27.8 months (range 2-80 months)
Outcome measures and effect size

	Surgery (n = 19)	**Surgery+RT (n = 19)**	
Incidence of regional (neck) lymph node metastasis, n (%)	11 (58)	4 (21)	p = 0.044
Incidence of local failure, n (%)	11 (58)	5 (26)	p = 0.099
Incidence of distant metastasis, n (%)	10 (53)	9 (47)	p = 1.0
5 year survival, %*	35	0	p = 0.003

*figures estimated from Kaplan-Meier survival curves.

2

Source of funding
Not reported.
Risks of bias
Selection bias: High risk. Allocation to groups not reported; unclear if different treatment groups were comparable at baseline Performance bias: Unclear/unknown risk. No detail on what care was given in addition to intervention/comparison. Attrition bias: Low risk. Detection bias: Low risk.
Additional comments
Recurrence and survival outcomes also reported in systematic review by Washou et al (2015)

1

Study, country
Meng, 2015. China, single centre.
Study type, study period
Retrospective cohort study. 2000 to 2010.
Number of patients
69
Patient characteristics
Inclusion criteria: Patients with a histopathological and clinical diagnosis of sinonasal malignant melanoma who received surgery as primary treatment. Exclusion criteria: Metastases to the sinonasal region from other sites; and patients whose primary surgery was not conducted at the study centre. **Gender / n (%)**: Male 37 (54); Female 32 (46) **T stage / n (%)**: T3 37 (54); T4a 27 (39); T4b 5 (7) Mean age: 65.9 years (range 28-89 years). No cases had distant metastasis at presentation.
Intervention
Surgical treatment alone (n = 27)
Comparison
Surgery with postoperative radiotherapy (n = 24)
Comparison
Surgery with radiotherapy plus chemotherapy (n = 18)
Length of follow-up
Mean 34 months (range 1-144 months)
Outcome measures and effect size

	Surgery (n = 27)	Surgery+RT (n = 24)	Surgery + RT +chemo (n = 18)
Median overall survival, months	18	32	42
3-year overall survival, %	14.8	5.6	45.1
5-year overall survival, %	31.6	55	32.1
3-year local control rate, %	25.3	48.7	42.9
Median disease-free survival, months	11	16	16

Source of funding
Not reported.
Risks of bias
Selection bias: High risk. Allocation to groups not reported; unclear if different treatment groups were comparable at baseline Performance bias: Unclear/unknown risk. No detail on what care was given in addition to intervention/comparison. Attrition bias: Low risk. Detection bias: Low risk.
Additional comments

2

3

Study, country

Nakashima, 2008
Brazil

Study type, study period

Retrospective cohort study.
January 1983 to December 2003.

Number of patients

20.

Patient characteristics

Confirmed histological diagnosis of mucosal melanoma in the head and neck region, treated with curative intent.

	Surgery alone (n = 8)	Surgery + RT (n = 12)
Gender	**n (%)**	**n (%)**
Male	5 (62.5)	7 (58.3)
Female	3 (37.5)	3 (41.7)

	Surgery alone (n = 8)	Surgery + RT (n = 12)
Site	**n (%)**	**n (%)**
Sinonasal	2 (25.0)	8 (66.7)
Oral cavity	6 (75.0)	4 (33.3)

Average age at diagnosis: 62 years (range 17-90)

Intervention

Surgery (n = 8)

Comparison

Surgery followed by post-operative radiotherapy (n = 12). Mean dose 5,400 cGy (range 4,500-7,000) in 25 fractions (range 20-35); mean dose per fraction 216 cGy (range 180-250).

Length of follow-up

Median 38 months (range 7-160).

Outcome measures and effect size

	Surgery alone (n = 8)	Surgery + RT (n =12)
3-year overall survival, %	37.5	58
5-year overall survival, %	25	25
Incidence of locoregional recurrence, n (%)	4 (50)	4 (12)
Time to locoregional recurrence, months	9	45
Incidence of distant recurrence, n (%)	2 (25)	4 (12)
Time to distant recurrence, months	14.9	25.5

*figures estimated from Kaplan-Meier survival curves.

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Allocation to groups not reported. Tumour sites not comparable between treatment groups.
Performance bias: Unclear/unknown risk. No detail on type of surgery received.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

Recurrence and survival outcomes also reported in systematic review by Washou et al (2015)

1

Study, country

Owens, 2003.
United States (single centre).

Study type, study period

Retrospective cohort study.
1985 to 1998.

Number of patients

48. Data analysed for 44 patients (4 patients not treated surgically).

Patient characteristics

Patients with mucosal melanoma of the head and neck treated surgically.

Gender	n (%)
Male	39 (81.2)
Female	9 ()18.8

Site	n (%)
Oral cavity	37 (77.0)
Sinonasal	11 (23.0)

Average age: 55.5 years (range 3 months to 88 years).

Intervention

Surgery (n = 20)

2

Comparison

Surgery followed by postoperative radiotherapy (n = 24)

Length of follow-up

Not reported

Outcome measures and effect size

	Surgery (n = 20)	Surgery + RT (n = 24)
Incidence of locoregional recurrence, n (%)	9 (45)	4 (17)
Incidence of distant metastases, n (%)	10 (50)	11 (46)
Time to distant metastases, months	30.3	17.5
5-year overall survival, months*	45	39

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Allocation to groups not reported; unclear if different treatment groups were comparable at baseline
Performance bias: Unclear/unknown risk. No detail on what care was given in addition to intervention/comparison.
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

Recurrence and survival outcomes also reported in systematic review by Washou et al (2015)

1

Study, country

Shiga, 2012
Japan (multiple centres)

Study type, study period

Retrospective cohort study.
1998 to 2007.

Number of patients

94.

Patient characteristics

Patients with mucosal malignant melanoma of the head and neck, confirmed by histopathologic examination.
Average age 68.4 years (range 37-96 years).

Gender	n (%)
Male	46
Female	48

Tumour site	n (%)
Nasal cavity	54
Oral cavity	14
Ethmoid sinus	9
Maxillary sinus	8
Nasopharynx	3
Primary unknown	3
External ear	2
Mesopharynx	1

Intervention

Surgery as primary treatment (n = 56), either alone or with another treatment (usually chemotherapy or radiotherapy).

Comparison

Radiation therapy (n = 27) either alone or with chemotherapy.

Length of follow-up

Not reported.

2

Outcome measures and effect size

	Surgery (n = 56)	Radiation (n = 27)
5-year overall survival, %*	38.6	29.9

Single treatment modality subgroup			
	Chemotherapy alone (n = 6)	Surgery alone (n = 9)	Radiation alone (n = 9)
3-year overall survival, %*	0	53.8	30.0

*calculated by the Kaplan-Meier method

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Allocation to groups not reported; unclear if different treatment groups were comparable at baseline.
Performance bias: Unclear/unknown risk. No detail on what care was given in addition to intervention/comparison.
Attrition bias: Unclear/unknown risk. Patients were analysed according to treatment in two different ways, neither of which included all patients.
Detection bias: Unclear/unknown risk. Length of follow up unclear.

Additional comments

Not all patients are within the population of interest: 7 of 94 patients had distant metastases.

1

Study, country

Sun, 2012.

Study type, study period

Retrospective cohort study.
January 1976 to December 2005.

Number of patients

51.

Patient characteristics

Patients with oral mucosal melanoma admitted to the centre. All patients underwent surgery within one week of admission.

Gender	n (%)
Male	36 (70.6)
Female	15 (29.4)

Age	n (%)
<55 years	28 (54.9)
≥ 55 years	23 (45.1)

cTNM stage	n (%)
III	12 (23.5)
IV	39 (76.5)

Intervention

Surgery alone (n = 11)

Comparison

Surgery combined with biotherapy (n = 10), consisting of Bacillus Calmette Guerin (skin puncture once per week for seven weeks) in five patients treated from 1980 to 1998 and interleukin 2 (four patients) or IFN-α2B (two patients) treated from 1999 to 2005.

Length of follow-up

Not reported.

Outcome measures and effect size

	Surgery alone (n = 11)	Surgery + biotherapy (n = 10)
3-year overall survival, %*	25.0	70.1
5-year overall survival, %*	12.5	58.4

*calculated by the Kaplan-Meier method

Source of funding

Research foundation grant.

Risks of bias

Selection bias: High risk. Allocation to groups not reported; unclear if different treatment groups were comparable at baseline.
Performance bias: Unclear/unknown risk. No detail on what care was given in addition to intervention/comparison.
Attrition bias: Unclear/unknown risk. Number of patients for whom outcome data is available (and for how long patients were followed up) is unclear.
Detection bias: Unclear/unknown risk. Length of follow up unclear.

Additional comments

The study included 51 patients in total, grouped differently according to treatment in several different analyses. However only the comparison presented above is relevant to the PICO.

1

Study, country

Tanaka, 2004.
Japan, two centres.

Study type, study period

Retrospective cohort study.
1970 to 2001.

Number of patients

35.

Patient characteristics

Patients with primary malignant melanoma arising in the oral region.
Mean age: 65.2 years (range 30 to 92 years).

Gender	n (%)
Male	14
Female	21

Lesion site	n (%)
Maxillary gingiva and palate	17
Palate alone	10
Maxillary gingiva alone	5
Mandibular gingiva or tongue	3

Intervention

Surgery (n = 13) with complete macroscopic resection at the primary site.

Comparison

Radiotherapy (without surgery) (n = 17).

Length of follow-up

Not reported.

Outcome measures and effect size

	Surgery (n = 13)	Radiotherapy (n =17)
Primary lesion controlled after treatment, n (%)	12 (92.3)	9 (52.9)
Incidence of tumour recurrence, n (%)	2 (15.4)	0 (0)
Incidence of distant metastasis, n (%)	10 (77.0)	11 (64.7)
5-year overall survival, %	15.4	35.3

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Allocation to groups not reported; unclear if different treatment groups were comparable at baseline
Performance bias: Unclear/unknown risk. Limited detail of care received other than the intervention. Patients treated at two centres, each of which favoured different primary treatments.
Attrition bias: Low risk.
Detection bias: Unclear/unknown risk. Length of follow up unclear.

Additional comments

Outcomes reported for 30 of a total of 35 patients. Five patients did not received surgery or radiotherapy (three received chemotherapy; two received no treatment).

2

3

Study, country

Temam, 2005.
France, single centre.

Study type, study period

Retrospective cohort study.
1979 to 1997.

Number of patients

69

Patient characteristics

Patients with primary mucosal melanoma of the head and neck treated with surgery alone or surgery plus postoperative radiotherapy.

Mean age: 58 years (range 21-90 years)

	Surgery (n = 30)	**Surgery+RT (n = 39)**
Gender	**n (%)**	**n (%)**
Male	15 (50)	18 (46)
Female	15 (50)	21 (54)
Tumour site	**n (%)**	**n (%)**
Sinonasal	20 (67)	26 (67)
Oral cavity	9 (30)	10 (25)
Pharyngolaryngeal	1 (3)	3 (8)
Stage	**n (%)**	**n (%)**
T1-T2	25 (83)	22 (56)
T3-T4	5 (17)	17 (44)

Intervention

Surgery alone (n = 30).

Comparison

Surgery with postoperative radiotherapy (n = 39).

Length of follow-up

Median 3.8 years (range 8-384 months).

Outcome measures and effect size

	Surgery (n = 30)	**Surgery+RT (n = 39)**
Incidence of local recurrence, n (%)	22 (73.3)	15 (38.5)
Median local disease-free survival, months	9	33
Median overall survival, months	30	17
Incidence of distant metastasis, n (%)	19 (63.3)	28 (71.8)

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Allocation to groups not reported. A greater proportion of patients receiving surgery alone had early stage disease; the results may be biased in favour of this intervention.
Performance bias: Unclear/unknown risk. Limited detail of care received other than the intervention.
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

Survival outcomes also reported in systematic review by Washou et al (2015)

1

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Intervention	Comparison	Outcomes

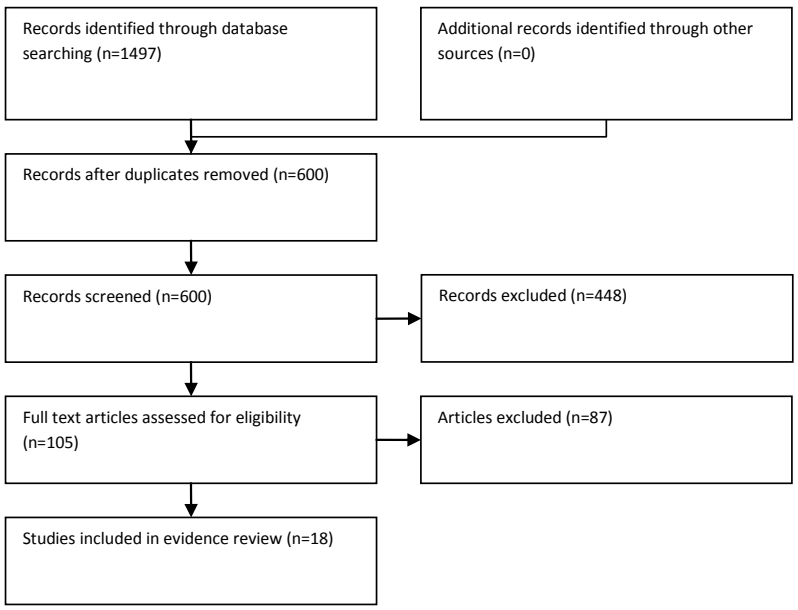
Adults with newly diagnosed upper airways tract mucosal melanoma in the absence of systemic metastases.
 	
Subgroups:
• Primary site
  • sinonasal
  • other sites
	• Primary site surgery
	• Primary site surgery plus post operative radiotherapy
	• Primary site radiotherapy
	• Elective Neck dissection
	• Therapeutic neck dissection
	• Elective radiotherapy to the neck
	• Therapeutic radiotherapy to the neck
	• Adjuvant radiotherapy to the neck
	• Adjuvant biological therapies
	• Chemotherapy
	• Chemoradiotherapy
	• Combinations of the above
		Each other	• Overall survival
			• Disease free survival
			• Progression free survival
			• Treatment related mortality
			• Treatment related morbidity
			• Health related quality of life
			• Locoregional control

3

Additional review protocol details (refer to Section 10 for full review protocol)

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.
Search strategies	None specified
Review strategies	The evidence tables for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Differences in timing or frequency of radiotherapy, and type of surgery, may also be considered within the review.

Figure 6.4. Study flow diagram



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Reason for exclusion: Non comparative study.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Non comparative study.

Brandwein, M. S., Rothstein, A., Lawson, W., Bodian, C., and Urken, M. L. Sinonasal melanoma. A clinicopathologic study of 25 cases and literature meta-analysis. Archives of Otolaryngology -- Head & Neck Surgery 1997. 123(3): 290-296.
Reason for exclusion: Intervention/comparison not relevant to PICO.

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7. Rehabilitation and optimising function

Enteral nutritional support

Clinical question: What criteria should be used at the point of diagnosis to select patients requiring enteral nutritional support during curative treatment?

Background

The importance of nutrition in the CUADT population is well established due to the effects of the disease and its treatment on a patient's ability to eat and drink. Malnutrition affects treatment outcomes, quality of life, and healthcare costs. Existing NICE guidance (Nutrition support in adults) recommends that if enteral feeding is required for longer than four weeks a gastrostomy tube should be used in preference to a nasogastric tube. In CUADT the optimal method of tube feeding remains unclear and complications can occur. Therefore, we need to understand what criteria should be used at diagnosis to select people who may benefit from enteral feeding.

Evidence statements

Weight loss

Moderate quality evidence from six observational studies (Brown et al, 2014; Cho et al, 2013; Kubrak et al, 2010; Lescut et al, 2013; Mallick et al, 2013; Silander et al, 2013) suggests that significant weight loss following treatment for upper aerodigestive tract tumours is common, with reported rates ranging from 38% to 66%. Five other observational studies (Farhangfar et al, 2014; Kubrak et al, 2013; Nourissat et al, 2010; Ottosson et al, 2014a, 2014b) estimated that after treatment such patients lost on average between 4% and 14% of their pretreatment body weight.

These studies reported multivariate models using a wide range of pretreatment factors to predict post treatment weight loss – either as a dichotomous (Brown et al, 2014; Cho et al, 2013; Kubrak et al, 2010; Lescut et al, 2013; Mallick et al, 2013; Silander et al, 2013) or continuous variable (Farhangfar et al, 2014; Kubrak et al, 2013; Nourissat et al, 2010; Ottosson et al, 2014a, 2014b). Pre treatment factors associated with weight loss in multivariate models are reported below.

Patient demographics

Moderate quality from observational studies (including up to 976 patients) suggests that age, sex, smoking and alcohol use are not independent predictive factors for post treatment weight loss in patients with upper aerodigestive tract cancers. Moderate quality evidence from two observational studies (including 1170 patients) suggests that poorer pretreatment performance status is an adverse risk factor for weight loss.

Nutritional factors

Moderate quality evidence from two observational studies (N = 314) suggests that people who are normal body weight before treatment are less likely to experience significant weight loss that those who are overweight or obese (OR 0.83 [95% CI 0.73, 0.93]).

One observational study (including 341 patients) found anorexia to be an independent risk factor for significant weight loss after treatment (OR 3.60 [95% CI 1.7, 7.6]).

There was conflicting evidence from two observational studies (including 314 patients) about the impact of pre-treatment weight loss on post treatment weight loss.

One high quality observational study (Brown et al, 2014; N = 219) evaluated the malnutrition screening tool (MST) as a predictor of weight loss in patients with head and neck cancer. However 56% of patients identified as not at risk of malnutrition (0 or 1 on the MST scale) experienced significant weight loss after treatment, suggesting that a baseline MST alone is not sufficient to identify those at risk of malnutrition.

The same observational study (Brown et al, 2014; N = 72) evaluated the Patient Generated Subjective Global Assessment (PG-SGA) of nutritional status at baseline as a predictor of weight. However 62% of patients identified as well nourished on the PG-SGA experienced significant weight loss after treatment, suggesting that a baseline PG-SGA measurement alone is not sufficient to identify those at risk of malnutrition.

A systematic review (Languis et al, 2013) of two randomised trials (Salas et al 2009; Silander et al, 2012; N = 172) observed no overall differences in the post treatment BMI of patients with advanced head and neck cancer given prophylactic PEG versus those given tube feeding only if required. A subgroup analysis of patients with post treatment weight loss (in Silander et al, 2012) indicated patients with prophylactic PEG lost a smaller amount of their pretreatment weight than those with reactive tube feeding. Both trials reported quality of life after treatment was better with prophylactic PEG, but in the short term only. Silander et al (2012) reported a lower rate of dysphagia with prophylactic PEG.

Tumour site & stage

Moderate quality evidence from two observational studies (including 312 patients) suggests that patients with tumour stage T3 to T4 are more likely to experience significant weight loss and lose more weight overall than patients with T0-T2 disease (OR 2.33 [95% CI 1.18, 4.61]).

One observational study (Cho et al, 2013; N = 226) reported that patients with less than three metastatic lymph nodes were less likely to experience significant weight loss than patients with three or more metastatic lymph nodes.

Although overall clinical stage was examined in two studies it was not an independent prognostic factor for weight loss when other factors were taken into account.

The primary tumour site was examined in three studies, although on univariate analyses an oropharyngeal primary (compared to other sites) was a risk factor for weight loss it did not remain so when other factors were taken into account.

Many studies excluded patients with T1-T2 glottic cancer, however one moderate quality observational study of stage I or II head and neck cancer (Nourissat et al, 2012; N = 535) found patients with glottic cancer had reduced post radiotherapy weight loss compared to those with supraglottic laryngeal, hypopharyngeal, oropharyngeal or oral cancer.

Treatment

Moderate quality evidence from one observational study suggests that treatment with radiotherapy (compared with no radiotherapy) increases the risk of significant weight loss (OR 5.62 [95% CI 2.32,

13.60]). One study (Mallick et al, 2013) evaluated radiotherapy target volume and found it an independent predictor of post radiotherapy weight loss.

Moderate quality evidence from 2 observational studies (including 222 patients) suggests that treatment with chemoradiotherapy (compared to other treatments) increases the risk of significant weight loss (OR 5.88 [95% CI 3.03, 12.50]).

Although patients treated with definitive surgery (compared with other treatments) were at reduced risk of weight loss, definitive surgery was not an independent predictor when other factors were taken into consideration.

Predicted complications of placement

The literature searches did not identify evidence about predicted complications of placement.

Swallowing factors

Moderate quality evidence from two observational studies (including 896 patients) suggests that dysphagia is an adverse risk factor for weight loss (OR 3.90 [95% CI 2.00, 7.60] - for significant weight loss; OR 4.39 [95% CI 1.82, 10.61] – for weight loss in kg).

Although mouth sores or mucositis were associated with significant weight loss in univariate analyses, there was uncertainty about whether mouth sores were an independent prognostic factor in multivariate analysis (OR 1.80 [95% CI 2.00, 7.60]).

Quality of life

One study (Silander et al 2013; N = 119) examined the EORTC QLQ-C30 and EORTC QLQ-HN35 as predictors of malnutrition in advanced head and neck cancer. The global quality of life score, or the functioning or symptom subscores were significant independent predictors of malnutrition in multivariate analysis.

Enteral nutrition

Seven studies reported models to predict the need for (Mangar et al, 2006; Mays et al, 2014; Sachdev et al, 2015; Sanguineti et al, 2013; Wermker et al, 2012; Wopken et al, 2014) or duration of (Jang et al, 2013) enteral nutrition. Two of these studies were limited to patients with oropharyngeal cancer (Jang et al, 2013; Sanguineti et al, 2013). Wopken et al (2014) and Mays et al (2014) used their models to develop a nomogram to predict feeding tube requirement following treatment. The risk factors identified in these studies are largely in agreement with the studies of factors to predict weight loss.

Patient demographics

Age was an independent predictor of need for enteral nutrition in two out of the six observational studies that examined it (Mangar et al, 2006; Mays et al 2014; Sachdev 2015; Sanguineti et al, 2013; Wermker et al, 2012; Wopken et al, 2014). Gender was not a predictor of enteral nutrition (Mays et al 2014; Sachdev 2015; Jang et al, 2013; Sanguineti et al, 2013; Wermker et al, 2012; Wopken et al, 2014)

One observational study (Jang et al, 2013), found alcohol and narcotic abuse as well as living alone were associated with longer duration of enteral nutrition in patients with advanced oropharyngeal cancer.

One study considered baseline performance status and found poor performance status was associated with enteral nutrition (Mangar et al, 2006).

Nutritional factors

Baseline weight loss was an independent predictor of enteral nutrition in three of the four studies that considered it (Mangar et al, 2006; Wopken et al, 2014; Mays et al 2014; Sachdev 2015;).

Tumour site & stage

Tumour stage and nodal stage were independent predictors of enteral nutrition four of the six studies that considered them (Jang et al, 2013; Sanguineti et al, 2013; Wermker et al, 2012; Wopken et al, 2014; Mays et al 2014; Sachdev 2015;). Another study (Mangar et al, 2006) found overall clinical stage to be a predictor of need for enteral nutrition.

Tumour site was considered by Wermker et al (2012) and a posterior mouth floor tumour was an independent predictor of need for enteral nutrition.

Treatment

Two studies considered radiotherapy parameters and reported neck irradiation (Wopken et al 2014) and dose to the oral mucosa, larynx and superior constrictor muscles (Sanguineti et al, 2013) to be predictors of need for enteral nutrition.

One study considered intraoperative parameters (Wermker et al, 2012) and found resection of tongue base, resection of oropharync and neck dissection all independent predictors of enteral nutrition.

Wopken et al (2014) found both accelerated fractionation and chemoradiotherapy increased the risk of enteral nutrition when compared with conventional radiotherapy.

Swallowing factors

Three studies considered baseline dysphagia but only one found it an independent predictor of enteral nutrition (Wopken et al , 2014; Jang et al, 2013; Mays et al 2014).

Quality of life

The literature searches did not identify studies of quality of life as a predictive factor for enteral nutrition.

Study characteristics and quality

Study quality was assessed using the checklist for prognostic studies in the 2012 version of the NICE guidelines manual. Around half the studies were at unclear risk of bias due to the study sample being restricted to a particular treatment type or primary tumour site. It was also unclear whether loss to follow-up was a source of bias because many of the studies were retrospective reviews of patients' medical records. In most studies the prognostic factor of interest and the outcome of interest were adequately measured. Most studies included important potential confounders and used appropriate statistical analysis.

Table 7.1. Characteristics of included studies that treated weight loss as a continuous variable.

STUDY ID	Population, country	N	Outcome	Mean (SD) weight change	Factors considered	Factors included in multivariate model
Farhangfar 2014	Patients treated for head and neck cancer at a single institution 2004-2012. Canada	1022	% weight loss at 6 months post treatment	-3.9% (8.0%)	Not reported	Total symptom score, performance status, T stage
Kubrak 2013	Patients with head and neck cancer scheduled for, RT and not tube fed during RT, 2007-2008 Canada	38	Weight loss in kg, around 2.5 months after RT	-0.42 kg (3.8)	CRP, loss of appetite, pain, dysphagia, mucositis, xerostomia, chemosensory score	For RT treated patients (N = 13): Pain, mucositis For ChemoRT treated patients (N = 25): CRP, loss of appetite, pain, dysphagia, mucositis, xerostomia, chemosensory score
Nourissat 2010	Patients enrolled on a chemoprevention trial for stage I-II head and neck cancer. 1994-2000 Canada	540	Weight loss in kg	-2.2 kg (3.4)	Sex, primary tumour site, clinical stage, weight at baseline, alcohol, smoking, energy intake, RT dose, chemoprevention, oral supplementation, feeding tube, dysphagia/odynophagia, digestive symptoms, constipation, acute adverse effects by site (larynx, pharynx/oesophagus or muscosa)	Cancer site, weight at baseline, clinical stage, dysphagia/ odynophagia, musical adverse events, total energy intake, HNRQ digestive domain, EORTC QLQ-30 constipation
Ottosson 2014	Patients enrolled in the ARTSCAN trial with M0 oropharyngeal cancer. 1998-2006. Sweden	357	% weight loss up to 5 months after RT	-13.66% (7.88)	Clinical stage, treatment type, surgery, tube feeding before RT, tube feeding after RT, RT treated volume	Clinical stage, tube feeding before RT, RT treated volume
Ottosson 2014	Patients enrolled in the ARTSCAN trial with M0 SCC of the head and neck – and complete data. 1998-2006. Sweden	49	% weight loss at 5 years after treatment	-6.6% (10.5%)	Age, gender, primary site, T stage, RT fractionation, surgery, aspiration, BMI at start of RT, earlier tube feeding use	Aspiration, BMI at start of treatment, primary site

1 **Table 7.2. Characteristics of included studies of predictors for enteral nutrition.**

STUDY ID	Population, country	N	Outcome	Enteral nutrition	Factors considered	Factors included in multivariate model
Jang 2013	Patients with advanced oropharyngeal cancer receiving chemoradiotherapy, USA	109	Duration of enteral nutrition	100%	Age, sex, race, comorbidity, mental health, marital status, living alone, employment, income, education, smoking, alcohol, baseline weight loss, use of narcotics, dysphagia, T-stage, N-stage, HPV status	Alcohol abuse, narcotics, living alone, T-stage, N-stage
Mangar 2006	Patients receiving RT for head and neck cancer, UK	160	Enteral nutrition, Reactive enteral nutrition	31%	Weight loss, BMI, serum albumin, protein, stage, tumour site, performance status, smoking, alcohol consumption and co-morbidities	*Enteral nutrition (including proph.):* Age, PS, baseline weight loss, clinical stage, smoking, BMI, albumin *Reactive enteral nutrition:* PS, clinical stage, smoking,
Mays 2014	Patients with upper UADT lesions (6% were benign), treated surgically	540	Gastrostomy tube after surgery	23%	Age, sex, BMI, marital status, weight loss, tobacco use, heavy alcohol use, medical comorbidities, ASA class, depression, chronic pain, poor functional status, preoperative RT, failed swallow study and history of dysphagia. TNM stage, tumour site. Surgical type, type of reconstruction and placement of tracheotomy tube	*Patient characteristics:* preoperative weight loss, dysphagia, preoperative RT *Tumour characteristics:* clinical node stage, T-stage *Surgical resection:* tracheostomy, reconstruction type, supracricoid laryngectomy.
Sachdev 2015	Patients with locally advanced head and neck cancer receiving chemo-RT, USA	100	Enteral nutrition	33%	Age, sex, performance status, BMI, smoking, tumour site, T-stage, N-stage, overall AJCC stage, chemotherapy type, induction, BID treatment, modality	Age

STUDY ID	Population, country	N	Outcome	Enteral nutrition	Factors considered	Factors included in multivariate model
Sanguineti 2013	Patients with oropharyngeal cancer receiving (chemo)RT, USA	179	PEG dependence at 3 months and 7 months	24% (at 3 mths)	Sex, tumour site, T-stage, N-stage, clinical stage, age, chemotherapy, PEG use, symptoms, seen by SLP, RT dose, RT volume	RT dose to oral mucosa, chemotherapy, dose to larynx, dose to superior constrictor muscles
Wermker 2012	Patients with head and neck cancer, treated surgically, Germany	152	PEG required after surgery	17%	Age, sex, BMI, ASA score, smoking, alcohol abuse, tumour site, T-stage, N-stage, tumour grade, area of bone resection, sites of soft tissue resection, neck dissection, reconstruction, tracheotomy	*Preoperative factor model* BMI, T-stage, N-stage posterior mouth floor tumour, tongue base tumour *Pre/intra-operative factor model* T-stage, resection of tongue base, resection of oropharynx, neck dissection
Wopken 2014	Patients receiving (chemo)RT for head and neck cancer, the Netherlands	427	Enteral nutrition at 6 months	13%	Sex, age, T-stage, N-stage, primary site, treatment modality, radiation technique, neck irradiation, baseline swallowing, baseline weight loss	T-stage, N-stage, baseline weight loss, treatment modality, neck irradiation

1

2

Table 7.3. Risk of bias in studies of weight loss predictors

	Low risk of bias	High risk of bias	Unclear risk of bias
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	9/16 studies (56%)	0/16 (0%)	7/16 (44%) Oral cavity/oropharynx only (Cho 2013; Ottosson 2014) Stage I-II only (Nourissat 2010) Stage III-IV only (Silander 2013) RT only (Nourissat 2010, Ottosson 2013, 2014a, 2014b) Poorly reported (Righini, 2013)
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	4/16 (25%)	0/16 (0%)	12/16 (75%) Poorly reported (Cho 2013; Farhangfar 2014; Gourin 2014; Kubrak, 2013; Lescut 2013; Mallick 2013; Ottosson 2014a, 2014b; Righini 2013; Silander 2013; Van den Berg 2006).
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	16/16 (100%)	0/16 (0%)	0/16 (0%)
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	13/16 (81%)	0/16 (0%)	3/16 (19%) Pretreatment weight loss (Gourin 2014) Long term weight loss – 5 years post treatment (Ottosson 2014b) Composite definition of malnutrition (Righini 2013)
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	11/16 (69%)	5/16 (31%) Important counfounders not included (Farhangfar 2014; Kubrak 2010) No multivariate analysis (Munshi 2003 Righini 2013 ; Van den berg 2006)	0/16 (0%)
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	11/16 (69%)	5/16 (31%) Sample size too small (Kubrak 2013; Ottosson 2014b) No multivariate analysis (Munshi 2003 Righini 2013 ; Van den berg 2006)	0/16 (0%)

Outcomes

Table 7.4. Patient, nutritional, disease and treatment factors related to weight loss

	Dichotomous (significant weight loss or not)		Continuous (amount of weigh loss)	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
DEMOGRPAHICS				
Age (<65 vs. ≥65 years)	OR 1.01 [0.71, 1.45] 3 studies (N = 528) Favours neither	-	-1.49% [-2.64%, -0.34%] 2 studies (N = 811) Favours older	-
Sex (male vs. female)	OR 0.80 [0.59, 1.09] 6 studies (N = 976)	-	-0.80% [-2.07%, 0.58%] 2 studies (N = 810)	-
Performance status (worse vs. better)	-	-	5.70% [2.94% , 8.46%] 1 study (N = 672) Favours worse PFS	OR 2.15 [1.17, 2.88] 2 studies (N = 1170) Per 20% KPS increase Favours better PFS
Smoking	OR 1.12 [0.70, 1.78] 2 studies (N = 354) Favours neither	-	0.00kg [-0.64, 0.64kg] 1 study (N = 435) Favours neither	-
Alcohol use	OR 1.00 [0.62, 1.61] 2 studies (N = 354) Favours neither	-	-0.50kg [-1.26, 0.26kg] 1 study (N = 435) Favours neither	-
NUTRITIONAL FACTORS				
BMI (underweight versus normal)	OR 2.37 [1.44, 3.92] 2 studies (N = 491) Favours normal weight	-	5.80% [2.84%, 8.76%] 1 study (N = 184) Favours underweight	
BMI (normal versus overweight/obese)	OR 0.55 [0.31, 0.99] 1 study (N = 198) Favours normal weight	OR 0.83 [0.73, 0.93] 2 studies (N = 314) Favours normal weight	5.20% [3.55%, 6.85%] 1 study (N = 315) Favours normal weight	-
Weight at baseline (kg)	-	-	-	OR 1.06 [1.04, 108] Per 1 kg 1 study (N = 535) Favours lower weight
Weight loss at baseline	-	OR 2.00 [0.88, 4.56] 2 studies (N = 314) Conflicting results	-	-
Prophylactic Tube feeding (feeding vs. no feeding)	OR 1.18 [0.68, 2.02] 1 study (N = 219) Favours neither	OR 1.08 [0.43, 2.71] 1 study (N = 186) Favours neither	5.91% [3.66%, 8.16%] 2 studies (N = 937) Favours proph. tube feeding	-
Anorexia	OR 4.03 [2.06, 7.88] 1 study (N = 341) Favours no anorexia	OR 3.6 [1.7, 7.6] 1 study (N = 341) Favours no anorexia	-	Kubrak (2013)

	Dichotomous (significant weight loss or not)		Continuous (amount of weigh loss)	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
DISEASE CHARACTERISTICS				
T stage (T0-T2 vs. T3-T4)	OR 1.99 [1.45, 2.72] 4 studies (N = 684) Favours lower T stage	OR 2.33 [1.18, 4.61] 2 studies (N = 312) Favours lower T stage	-0.80% [-2.89%, 1.29%] 1 study (N = 103) Favours neither	OR 1.29 [1.05, 1.58] 1 study (N = 635) Favours lower T stage
N stage (N0 vs. N+)	OR 0.46 [0.25, 0.85] 1 study (N = 180) Favours N0	OR 0.36 [0.15, 0.82] 1 study (N = 226) Favours <3 positive nodes	0.20% [-1.99%, 2.39%] 1 study (N = 103) Favours neither	-
Clinical stage (I-II vs. III-IV)	OR 0.31 [0.17, 0.58] 1 study (N = 93) Favours clinical stage I-II	-	1.20% [-0.19, 2.59%] 2 studies (N = 939) Favours neither	-
Oral cavity (versus other sites)	OR 0.41 [0.28, 0.59] 3 studies (N = 522) Favours oral cavity	-	2.40% [0.49%, 4.31%] 1 study (N = 707) Favours oral cavity	OR 1.68 [0.79, 3.59] 1 study (N = 152) Favours neither
Oropharynx (versus other sites)	OR 0.63 [0.59, 0.67) 3 studies (N = 438) Favours other sites	-	-4.56% [-5.65%, -3.47%] 2 studies (N = 810) Favours other sites	
Larynx(versus other sites)	OR 0.22 [0.15, 0.34] 2 studies (N = 712) Favours larynx	-	3.20% [1.76%, 4.64%] 1 study (N = 707) Favours larynx	
TREATMENT				
RT versus no RT	OR 5.11 [2.73, 9.57] 1 study (N = 94) Favours no RT	OR 5.62 [2.32, 13.60] 1 study (N = 132) Favours no RT	-	-
CRT versus other treatment	OR 3.67 [2.45, 5.51] 4 studies (N = 588) Favours no CRT	OR 5.88 [3.03, 12.5] 2 studies (N = 222) Favours no CRT	4.55% [2.71%, 6.39%] 3 studies (N = 163) Favours no CRT	-
Definitive treatment (surgical versus other)	OR 0.65 [0.49, 0.85] 4 studies (N = 498) Favours surgery	-	-	-
SWALLOWING FACTORS				
Dysphagia (versus none)	OR 2.80 [1.83, 4.28] 2 studies (N = 460) Favours no dysphagia	OR 3.90 [2.00, 7.60] 1 studies (N = 341) Favours no dysphagia	4.6% [2.44%, 6.76%] 1 study (N = 707) Favours dysphagia 2.9kg [2.00, 3.80kg] 1 study (N = 535) Favours dysphagia	OR 4.39 [1.82, 10.61] 1 study (N = 535) Favours no dysphagia
Mouth sores/mucositis (versus none)	OR 2.29 [1.28, 4.11] 1 study (N = 341) Favours no mouth sores	OR 1.80 [0.95, 3.40] 1 study (N = 341) Favours neither	2.50kg [1.44, 3.56kg] 1 study (N = 535) Favours no grade 3-4 mucositis	Kubrak (2013)
QOL	-	-	-	-
EORTC QLQ-HN35 global	OR 1.17 [0.99, 1.38]	-		

Evidence tables for all included studies

Study, country
Brown (2014) Australia
Study type, study period
Observational study, prospective, 2007-2008
Number of patients
219
Patient characteristics
Patients with confirmed head and neck cancer, referred to a single tertiary centre, with planned curative treatment and referred to a dietician.
Outcome
Weight loss ≥10%, 3 months after treatment
Univariate analysis
Primary site, age, sex, BMI at diagnosis, T stage, N stage, treatment type, secondary treatment, adherence to guidelines, type of nutritional support, malnutrition screening score at baseline, PG-SGA score at baseline
Multivariate analysis
BMI at diagnosis, weight loss at baseline, T stage, type of nutritional support, primary site, treatment type, H&N guideline risk rating.
Source of funding
Royal Brisbane and Women's Hospital
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Y
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Y
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Y

Additional comments
This study also presents the RBWH swallowing and nutritional management guidelines for H&N cancer – with pre treatment risk stratification and clinical pathways.

Study, country
Cho, 2013; Korea
Study type, study period
Observational study, retrospective, single centre,2005-2010
Number of patients
226
Patient characteristics
Patients with carcinoma of the oral cavity or oropharynx considered curable, aged >18 years, previously untreated, with at least 6 months of follow-up
Outcome
Weight loss ≥10% with 6 months after treatment, disease free survival, overall survival
Univariate analysis
Smoking, alcohol use, BMI, comorbidity, residence, education, occupation, histologic differentiation, resection margin, lymphovascular invasion, perineural invasion, number of metastatic nodes, treatment type, recurrence
Multivariate analysis
Radiotherapy, recurrence, number of metastatic nodes.
Source of funding
Asian Institute for Life Science and National Research Foundation of Korea

Risks of bias (answer yes, no or unclear to each question)	
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear (oral cavity and oropharynx only)
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – patients without follow-up data were excluded
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes
Additional comments	

1

Study, country
Farhangfar 2014, Canada
Study type, study period
Observational study, single centre, retrospective, 2004-2012
Number of patients
635
Patient characteristics
Adult patients with head and neck cancer, entered into the Alberta province cancer registry, referred to a single regional treatment centre, on independent oral nutrition at the time of the study with no use of tube feeding, treated with radiation with or without chemotherapy and/or surgery
Outcome
Percent weight loss at 6 months post treatment, food intake,
Univariate analysis
Total symptom score, age, sex, tumour stage and performance status
Multivariate analysis
Total symptom score, performance status, T stage
Source of funding
Not reported

Risks of bias (answer yes, no or unclear to each question)	
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	y
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – 678/1333 eligible patients were excluded for missing data
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	N (treatment is not included)
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Y
Additional comments	

1

Study, country
Gourin, 2014. USA
Study type, study period
Observational study, multicentre, 2003-2008
Number of patients
93663
Patient characteristics
Adult patients entered into the Nationwide Inpatient Sample database, with cancer of the oral cavity, larynx, hypopharynx or oropharynx, treated with an ablative procedure
Outcome
Pre-treatment weight loss (ICD-9 code), in-hospital death, postoperative surgical complications, acute medical complications, length of stay, hospital costs
Univariate analysis
Primary site, age, race, sex, payer, admission type, comorbidity score, surgical procedure type, procedure severity, dysphagia, alcohol abuse, acute comorbidities, mechanical ventilation, gastrostomy tube, tracheostomy tube, disposition
Multivariate analysis
Urgent/emergent admission, hypopharyngeal primary, major procedure, free or pedicled flap reconstruction, Medicaid, comorbidity score, dysphagia, alcohol abuse, acute cardiac event, acute pulomary edema/failure, acute renal failure, sepsis, UTI, pneumonia, wound healing complications, postop surgical site infection, mechanical ventilatory support, tracheostomy placement, gastrostomy tube placement, short term hospital, other facility, home health care
Source of funding
Not reported
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Y
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – loss to follow up not reported
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear – this study reported pre-treatment weight loss as a predictor for adverse outcome
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y – although (chemo)radiotherapy is not considered as a factor
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Y

Additional comments

2

Study, country
Kubrak, 2010; Canada
Study type, study period
Observational, population based registry, 2004-2007
Number of patients
341
Patient characteristics
Adult patients with newly diagnosed head and neck cancer, entered into the Alberta province cancer registry, referred to a single regional treatment centre, on independent oral nutrition at the time of the study with no use of tube feeding, treated with radiation with or without chemotherapy and/or surgery
Outcome
Grade 1 or more weight loss: ≥2% in 6 months post treatment,
Univariate analysis
Anorexia, dysphagia, pain, dysgeusia, feeling full, nausea, constipation, mouth sores, bothersome smells, dental problems, xerostomia, other nutrition impact symptom
Multivariate analysis
Anorexia, dysphagia, mouth sores, other nutrition impact symptom

Source of funding
Minton Endowment fund, Faculty if Nursing, Alberta University
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Y
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – not reported
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	No – does not include disease characteristics, demographics or treatment factors
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	y

Additional comments

1

Study, country
Kubrak 2013, Canada
Study type, study period
Observational study, prospective, 2007-2008
Number of patients
38
Patient characteristics
Orally fed patients with head and neck cancer treated with radiotherapy or chemoradiotherapy with or without surgery,
Outcome
Weight loss in kg at 2.5 months after RT, energy intake
Univariate analysis
CRP, loss of appetite, pain, dysphagia, mucositis, xerostomia, chemosensory score
Multivariate analysis
For RT treated patients (N = 13): Pain, mucositis For ChemoRT treated patients (N = 25): CRP, loss of appetite, pain, dysphagia, mucositis, xerostomia, chemosensory score
Source of funding
Minton Endowment fund, Faculty if Nursing, Alberta University
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Y
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear 14/52 eligible patient excluded – 6 due to requirement for enteral feeding, 4 due to death and 2 due to toxicity
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	N – very small study size compared to the number of prognostic factors in the model – especially the subgroup (RT, CRT) models

Additional comments
Study, country
Lescut, 2013, France
Study type, study period
Observational, single centre, retrospective, 2007-2010
Number of patients
127
Patient characteristics
Patients with head and neck cancer treated with radiotherapy or chemoradiotherapy
Outcome
Weight loss ≥10% 3 months after treatment
Univariate analysis
T stage, age, BMI, analgesic use, dysphagia, social isolation, smoking, concomitant chemotherapy/cetuximab, albumin, primary site, weight loss before treatment
Multivariate analysis
T stage, weight loss in the 3mths before treatment, analgesic use, albumin
Source of funding
Not reported
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Y
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear - not reported
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Y

Additional comments
French language

1

Study, country
Mallick, 2013, India
Study type, study period
Observational, single centre, retrospective, 2011-2012
Number of patients
103
Patient characteristics
Patients treated with curative intent RT for head and neck cancer (excluding those receiving hypofractionated RT for T1/T2 glottic cancer)
Outcome
Weight loss ≥5% 1 month after treatment, % weight loss
Univariate analysis
Age, sex, primary site, T stage, N stage, treatment indication, concurrent treatment, RT dose, RT modality, planning target volume
Multivariate analysis
planning target volume (prescribed or total), use of chemoradiotherapy
Source of funding
Not reported

Risks of bias (answer yes, no or unclear to each question)	
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Y
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – not reported
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Y
Additional comments	

1

Study, country
Munshi 2003, India
Study type, study period
Observational study, single centre, retrospective, 2002
Number of patients
140
Patient characteristics
Patients with head and neck cancer, treated with curative intent radiotherapy or chemoradiotherapy, with no gaps in RT more than 5 days,
Outcome
Weight loss > 5kg following RT.
Univariate analysis
Sex, age, KPS, primary site, well differentiated histology versus others, surgery versus no surgery, CRT versus RT, mid RT mucosal reaction, field size and RT dose
Multivariate analysis
None
Source of funding
Not reported
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Y
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Y
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	N, no multivariate analysis
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	N, no multivariate analysis – patient numbers within each prognostic group not reported
Additional comments	

1

Study, country
Nourissat, 2010. Canada
Study type, study period
Multicentre randomised trial, 1994-2000
Number of patients
535
Patient characteristics
Patients enrolled on a chemoprevention trial for stage I-II head and neck cancer.
Outcome
Weight loss in kg at the end of RT.
Univariate analysis
Sex, primary tumour site, clinical stage, weight at baseline, alcohol, smoking, energy intake, RT dose, chemoprevention, oral supplementation, feeding tube, dysphagia/odynophagia, digestive symptoms, constipation, acute adverse effects by site (larynx, pharynx/oesophagus or muscosa)
Multivariate analysis
Cancer site, weight at baseline, clinical stage, dysphagia/ odynophagia, musical adverse events, total energy intake, HNRQ digestive domain, EORTC QLQ-30 constipation
Source of funding
Canadian Cancer Society.
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear – stage I-II only, RT only
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Y – all eligible enrolled patients appear to be included in the analysis
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Y

Additional comments

2

Study, country
Ottosson, 2013, Sweden
Study type, study period
Retrospective analysis of multicentre, randomised trial, 1998-2006
Number of patients
712
Patient characteristics
Patients with MO head and neck squamous cell carcinoma of oral cavity, oropharynx, hypopharynx and larynx (excluding T1-T2 glottic carcinoma) entered into the ARTSCAN trial of radiotherapy fractionation, age >18 years.
Outcome
Weight change (%) at 5 months after RT
Univariate analysis
Age, sex, tumour site, clinical stage, BMI, RT fractionation, Surgery (yes/no), KPS, Swallowing problems at the start/end of RT, Mucositis (after RT), use of opioids at the start/end of RT, tube feeding at the start/end of RT
Multivariate analysis
None
Source of funding
Swedish Cancer Society, Lions Cancer Research Foundation at Umea University and the Cancer Research Foundation of Northern Sweden.

Risks of bias (answer yes, no or unclear to each question)	
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear - all RT
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Y – all patients appear to be included
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Y
Additional comments	

1

Study, country
Ottosson, 2014, Sweden
Study type, study period
Retrospective analysis of multicentre, randomised trial, 1998-2006
Number of patients
232
Patient characteristics
Patients with MO oropharyngeal carcinoma entered into the ARTSCAN trial of radiotherapy fractionation, age >18 years.
Outcome
Weight change (%) at 5 months after RT
Univariate analysis
Clinical stage, treatment type, surgery, tube feeding before RT, tube feeding after RT, RT treated volume
Multivariate analysis
Clinical stage, tube feeding before RT, RT treated volume
Source of funding
Swedish Cancer Society, Lions Cancer Research Foundation at Umea University and the Cancer Research Foundation of Northern Sweden.
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	N – oropharyngeal carcinoma only, RT only
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – missing weight data for 125/357 eligible patients meant they were excluded from this study
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Y

Additional comments
Some of these patients may be included in Ottosson 2013.

2

1

Study, country
Ottosson, 2014, Sweden
Study type, study period
Retrospective analysis of randomised trial, 1998-2006
Number of patients
124 (49 analysed)
Patient characteristics
Patients with MO head and neck cancer entered into the ARTSCAN trial of radiotherapy fractionation, age >18 years, no chemotherapy, treated at either of two centres, with no recurrence at 15 months post RT
Outcome
Weight change (%) around 5 years (mean 69.3 months) after RT
Univariate analysis
Age, gender, primary site, T stage, RT fractionation, surgery, aspiration, BMI at start of RT, earlier tube feeding use
Multivariate analysis
Aspiration, BMI at start of treatment, primary site
Source of funding
Swedish Cancer Society, Lions Cancer Research Foundation at Umea University and the Cancer Research Foundation of Northern Sweden.
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear – selected patient group with no recurrent disease
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – missing weight data for 75/124 eligible patients meant they were excluded from this study
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear – this study is of long term weight loss – might not be relevant to stratifying patients for prophylactic enteral feeding.
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Unclear – very low number of patients to develop prognostic model

Additional comments
Some of these patients may be included in Ottosson 2013.

2

Study, country
Righini 2013, France
Study type, study period
Observational study, single centre, prospective, 2010-2011
Number of patients
169
Patient characteristics
Patients with newly diagnosed head and neck cancer (oral cavity, oropharynx, hypopharynx or larynx) admitted to a single centre,
Outcome
Moderately or severely malnourished
Univariate analysis
Sex, Age, smoking, alcohol use, tumour site, tumour stage
Multivariate analysis
None
Source of funding
Not reported

Risks of bias (answer yes, no or unclear to each question)	
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear – selection criteria area not well reported
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – not reported
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear - the definition of malnourished is a composite of weight loss, NRI, BMI and albumin levels.
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	No multivariate analysis
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	No multivariate analysis
Additional comments	

1

Study, country
Silander, 2013
Study type, study period
Additional analysis of patients in a randomised trial, period not reported
Number of patients
134
Patient characteristics
Patients with newly diagnosed untreated phangeal, oral or unknown primary (presumed head and neck) cancer, advanced stage (III or IV), treated with curative intent, entered into a trial of prophylactic PEG
Outcome
Weight loss ≥10% 6 months after diagnosis
Univariate analysis
Age, sex, primary site, clinical stage, treatment modality, weight loss at diagnosis, BMI, fat-free mass index, dysphagia, KPS, PEG, EORTC-QLQ-C30, EORTC QLQ-HN35
Multivariate analysis
Chemoradiotherapy, BMI at diagnosis
Source of funding
Research and development Council Vastra Gotaland County, Assar Garielssons Fund Foundation, Goteborgs Medical Society, Laryngfonden Foundation and Adlerbertska Foundation
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear – advanced stage only
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – some loss to follow up due to death (N = 10) and morbidity (N = 3).
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Y
Additional comments	

2

Study, country
Van den Berg 2006, The Netherlands
Study type, study period
Observational study, prospective, single centre 2002-2004
Number of patients
68 enrolled, 47 analysed
Patient characteristics
Patients with squamous cell carcinoma of the oral cavity, oropharynx and hypopharynx, aged 18 years or more, stage II-IV, treated with curative intent
Outcome
Weight (kg), during diagnosis and treatment
Univariate analysis
Type of treatment (RT, surgery, ChemoRT or surgery+RT)
Multivariate analysis
None
Source of funding
College of Health Care Insurance, Association of Academic Efficiency Programs
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Y – although limited to oral cavity, oropharynx and hypopharynx, no stage I
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear - 21/68 not analysed – but not significantly different to remainder
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	N – not multivariate analysis
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	N – not multivariate analysis

Additional comments

1

Study, country
Jang, 2013, USA
Study type, study period
Observational study, single centre, retrospective, 2000-2009
Number of patients
109
Patient characteristics
Patients with advanced (stage III to IVb) oropharyngeal cancer
Outcome
Length of time patients actively used their feeding tube (continuous variable)
Univariate analysis
Age, sex, race, comorbidity, mental health, marital status, living alone, employment, income, education, smoking, alcohol, baseline weight loss, use of narcotics, dysphagia, T-stage, N-stage, HPV status
Multivariate analysis
Alcohol abuse, narcotics, living alone, T-stage, N-stage
Source of funding
Not reported

Risks of bias (answer yes, no or unclear to each question)	
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear – oropharyngeal only, advanced only, all had feeding tube
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – not reported
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Unclear – small sample size for the number of factors included in the model
Additional comments	

1

Study, country
Mangar, 2006, UK
Study type, study period
Observational study, retrospective, 2001
Number of patients
160
Patient characteristics
Patients referred for radiotherapy for head and neck cancer
Outcome
Enteral nutrition (N = 50): prophylactic enteral nutrition (N = 30, started before RT), reactive enteral nutrition (N = 20, started during RT),
Univariate analysis
Weight loss, BMI, serum albumin, protein, stage, tumour site, performance status, smoking, alcohol consumption and co-morbidities
Multivariate analysis
Enteral nutrition model (including prophylactic nutrition): Age, PS, baseline weight loss, clinical stage, smoking, BMI, albumin *Reactive enteral nutrition (excluding prophylactic nutrition):* PS, clinical stage, smoking,
Source of funding
Not reported
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear – all RT no chemotherapy
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes – all appear accounted for
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	yes

Additional comments
Reports a lookup table (based on – stage 3-4, WHO 2/3, Smoking > 20 cpd) to calculated the predicted probability of enteral nutrition.

1

Study, country
Sanguineti 2013, USA
Study type, study period
Observational study, 2 centre, 2002-2011
Number of patients
171
Patient characteristics
Patients with oropharyngeal cancer treated with IMRT±chemotherapy. All receiving chemotherapy were offered prophylactic PEG, for others PEG was considered during treatment based on clinical judgement.
Outcome
PEG dependence at 3 months and 7 months post IMRT.
Univariate analysis
Sex, tumour site, T-stage, N-stage, clinical stage, age, chemotherapy, PEG use, symptoms, seen by SLP, RT dose, RT volume
Multivariate analysis
RT dose to oral mucosa, chemotherapy, dose to larynx, dose to superior constrictor muscles
Source of funding
Not reported
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear – oropharyngeal only, IMRT only
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – not reported
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Additional comments

2

Study, country
Wermker 2012, Germany
Study type, study period
Observational study, retrospective, single centre, 2005-2010
Number of patients
152
Patient characteristics
Patients with head and neck squamous cell carcinoma, treated surgically
Outcome
PEG required after surgery (N = 26)
Univariate analysis
Age, sex, BMI, ASA score, smoking, alcohol abuse, tumour site, T-stage, N-stage, tumour grade, area of bone resection, sites of soft tissue resection, neck dissection, reconstruction, tracheotomy
Multivariate analysis
Preoperative factor only model BMI, T-stage, N-stage posterior mouth floor tumour, tongue base tumour *Pre & intra-operative factors model* T-stage, resection of tongue base, resection of oropharynx, neck dissection

Source of funding	
Not reported – stated no conflicts of interest	
Risks of bias (answer yes, no or unclear to each question)	
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – not reported
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	yes
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	yes
Additional comments	

1

Study, country
Wopken 2014, The Netherlands
Study type, study period
Observational, prospective, 2 centre
Number of patients
600: 427 for training set and 183 for validation
Patient characteristics
Patients with carcinoma of the mucosal surfaces of the larynx, oropharynx, oral cavity, hypopharynx and nasopharynx, who received curative radiotherapy with or without chemotherapy or cetuximab.
Outcome
Enteral nutrition at 6,12,18 and 24 months. Prophylactic PEG-tubes were placed in patients treated with concomitant chemoradiotherapy or those with pre-treatment weight loss or severe dysphagia, reactive PEG-tubes were placed in patients with significant weight loss or severe dysphagia during treatment.
Univariate analysis
Sex, age, T-stage, N-stage, primary site, treatment modality, radiation technique, neck irradiation, baseline swallowing, baseline weight loss
Multivariate analysis
T-stage, N-stage, baseline weight loss, treatment modality, neck irradiation
Source of funding
Not reported

Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear – all had radiotherapy
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear - not reported
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Y
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Y
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Y
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Y – a validation set of 183 patients was used to test the prediction model.

Additional comments

This study reports a nomogram for the prediction of feeding tube dependence at 6 months.

1

Study, country

Languis (2013), International (France and Sweden)

Study type, study period

Systematic review of RCTs published up to 2012

Number of patients

2 RCTs of prophylactic versus reactive tube feeding including 172 patients.

Patient characteristics

Patients with advanced head and neck cancer

Outcome

BMI and QOL of life

Univariate analysis

Prophylactic PEG versus reactive tube feeding

Multivariate analysis

Not applicable

Source of funding

The review was funded by Nutricia Advanced Medical Nutrition. The Salas (2009) trial was funded by grants from the Programme Hospitalier Recherche Clinique National. Silander (2012) received function from the Research and development Council Vastra Gotaland County, Assar Garielssons Fund Foundation, Goteborgs Medical Society, Laryngfonden Foundation and Adlerbertska Foundation

Risks of bias (answer yes, no or unclear to each question)

From Languis et al (2013) appendix 2:

	Silander 2012	Salas 2009
Random sequence generation	Low risk	Low risk
Allocation concealment	Unclear risk	Unclear risk
Blinding of participants and personnel	High risk	High risk
Blinding of outcome assessment	Unclear risk	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk	Unclear risk
Selective reporting (reporting bias)	Low risk	Low risk
Other bias	Unclear risk	Unclear risk

Additional comments

The review included other comparisons beyond prophylactic PEG – but these are not included here.

2

3

Study, country
Mays 2014; USA
Study type, study period
Retrospective, observational, 2007-2012
Number of patients
540 with upper UADT lesions (30 were benign)
Patient characteristics
Patients with head and neck cancer. Exclusions: preoperative gastrostomy tube (G-tube), G-tube placed more than 3 months post surgery, G-tube placed prophylactically, patients who did not have primary site resection, those with previous CUADT.
Outcome
Postoperative G-tube placement
Univariate analysis
age, sex, BMI, marital status, weight loss, tobacco use, heavy alcohol use, medical comorbidities, ASA class, depression, chronic pain, poor functional status, preoperative RT, failed swallow study and history of dysphagia. TNM stage, tumour site. Surgical type, type of reconstruction and placement of tracheotomy tube
Multivariate analysis
Patient characteristics: preoperative weight loss, dysphagia, preoperative RT *Tumour characteristics:* clinical node stage, T-stage *Surgical resection:* tracheostomy, reconstruction type, supracricoid laryngectomy.
Source of funding
Not reported – no conflicts of interest declared.
Risks of bias (answer yes, no or unclear to each question)

The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear – 203/743 potentially eligible patients were excluded
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	yes
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	yes
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	unclear – no exact definition of post-op G-tube placement (e.g. timing)
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	yes
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	yes – multiple logistic regression

Additional comments
A nomogram to identify patients at risk of G-tube placement was presented – using the variables indentified in the multivariate model.

1

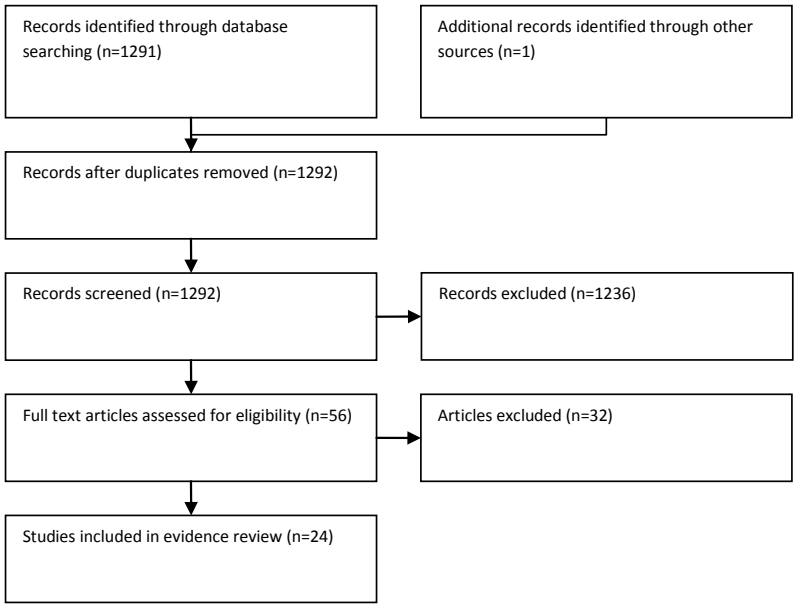
Study, country
Sachdev 2015; USA
Study type, study period
Retrospective observational study, 2005-2010
Number of patients
100
Patient characteristics
Locally advanced stage III or IV head and neck squamous cell carcinoma, treated with IMRT and concurrent chemotherapy.
Outcome
Requirement for enteral feeding
Univariate analysis
Age, sex, performance status, BMI, smoking, tumour site, T-stage, N-stage, overall AJCC stage, chemotherapy type, induction, BID treatment, modality
Multivariate analysis
age
Source of funding
Not reported – no conflicts of interest declared.

Risks of bias (answer yes, no or unclear to each question)	
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	yes – but limited to non-surgical treatment
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear – retrospective chart review
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	yes
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	yes
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	yes
Additional comments	

1

Evidence search details and references

Figure 7.1. Study flow diagram



Additional review protocol details (refer to Section 10 for full review protocol)

Type of review	Prognostic
Language	English only
Study design	No restrictions
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.
Search strategies	Search from 1990. According to the GDG, this is the date of publication for the earliest evidence on this topic.
Review strategies	The evidence table for prognostic studies will be used (NICE Guidelines Manual Appendix J) to extract and present results from individual studies. The quality checklists for prognostic studies from the NICE Guidelines Manual (appendix I) will be used.

Included studies

Brown, T., Ross, L., Jones, L., Hughes, B., & Banks, M. (2014). Nutrition outcomes following implementation of validated swallowing and nutrition guidelines for patients with head and neck cancer. Supportive Care in Cancer, 22, 2381-2391.

Cho, Y. W., Roh, J. L., Jung, J. H., Kim, S. B., Lee, S. W., Choi, S. H. et al. (2013). Prediction of posttreament significant body weight loss and its correlation with disease-free survival in patients with oral squamous cell carcinomas. Nutrition & Cancer, 65, 417-423.

Farhangfar, A., Makarewicz, M., Ghosh, S., Jha, N., Scrimger, R., Gramlich, L. et al. (2014). Nutrition impact symptoms in a population cohort of head and neck cancer patients: multivariate regression analysis of symptoms on oral intake, weight loss and survival. Oral Oncology, 50, 877-883.

Gourin, C. G., Couch, M. E., & Johnson, J. T. (2014). Effect of Weight Loss on Short-Term Outcomes and Costs of Care After Head and Neck Cancer Surgery. Annals of Otology Rhinology and Laryngology, 123, 101-110.

Jang, J. W., Parambi, R. J., McBride, S. M., Goldsmith, T. A., Holman, A. S., & Chan, A. W. (2013). Clinical factors predicting for prolonged enteral supplementation in patients with oropharyngeal cancer treated with chemoradiation. Oral Oncology, 49, 438-442.

Kubrak, C., Olson, K., Jha, N., Scrimger, R., Parliament, M., McCargar, L. et al. (2013). Clinical determinants of weight loss in patients receiving radiation and chemoirradiation for head and neck cancer: A prospective longitudinal view. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck, 35, 695-703.

Kubrak, C., Olson, K., Jha, N., Jensen, L., McCargar, L., Seikaly, H. et al. (2010). Nutrition impact symptoms: key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. Head & Neck, 32, 290-300.

Lescut, N., Personeni, E., Desmarets, M., Puyraveau, M., Hamlaoui, R., Servagi-Vernat, S. et al. (2013). [Evaluation of a predictive score for malnutrition in patients treated by irradiation for head and neck cancer: a retrospective study in 127 patients]. [French]. Cancer Radiotherapie, 17, 649-655.

Langius, J. A., Zandbergen, M. C., Eerenstein, S. E., van Tulder, M. W., Leemans, C. R., Kramer, M. H. et al. (2013). Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. [Review]. Clinical Nutrition, 32, 671-678

The Languis (2013) systematic review includes the following randomised trials:

Salas, S., Baumstarck-Barrau, K., Alfonsi, M., Digue, L., Bagarry, D., Feham, N. et al. (2009). Impact of the prophylactic gastrostomy for unresectable squamous cell head and neck carcinomas treated with radio-chemotherapy on quality of life: Prospective randomized trial. Radiotherapy & Oncology, 93, 503-509.

Silander, E., Nyman, J., Bove, M., Johansson, L., Larsson, S., & Hammerlid, E. (2012). Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer: a randomized study. Head & Neck, 34, 1-9.

Mallick, I., Gupta, S. K., Ray, R., Sinha, T., Sinha, S., Achari, R. et al. (2013). Predictors of Weight Loss during Conformal Radiotherapy for Head and Neck Cancers - How Important are Planning Target Volumes? Clinical Oncology, 25, 557-563.

Mangar, S., Slevin, N., Mais, K., & Sykes, A. (2006). Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer: a retrospective review. Radiotherapy & Oncology, 78, 152-158.

Mays, A. C. (2014). A model for predicting gastrostomy tube placement in patients undergoing surgery for upper aerodigestive tract lesions. JAMA Otolaryngology-- Head & Neck Surgery, 140, 1198-1206.

Munshi, A., Pandey, M. B., Durga, T., Pandey, K. C., Bahadur, S., & Mohanti, B. K. (2003). Weight loss during radiotherapy for head and neck malignancies: what factors impact it? Nutrition & Cancer, 47, 136-140.

Nourissat, A., Bairati, I., Samson, E., Fortin, A., Gelinas, M., Nabid, A. et al. (2010). Predictors of Weight Loss During Radiotherapy in Patients With Stage I or II Head and Neck Cancer. Cancer, 116, 2275-2283.

Ottosson, S., Zackrisson, B., Kjellen, E., Nilsson, P., & Laurell, G. (2013). Weight loss in patients with head and neck cancer during and after conventional and accelerated radiotherapy. Acta Oncologica, 52, 711-718.

Ottosson S., L. (2014). Weight loss and body mass index in relation to aspiration in patients treated for head and neck cancer: A long-term follow-up. Supportive Care in Cancer, 22, 2361-2369.

Ottosson, S., Soderstrom, K., Kjellen, E., Nilsson, P., Zackrisson, B., & Laurell, G. (2014). Weight and body mass index in relation to irradiated volume and to overall survival in patients with oropharyngeal cancer: a retrospective cohort study. Radiation Oncology, 9.

Righini, C. A., Timi, N., Junet, P., Bertolo, A., Reyt, E., & Atallah, I. (2013). Assessment of nutritional status at the time of diagnosis in patients treated for head and neck cancer. European annals of otorhinolaryngology, head & neck diseases, 130, 8-14.

Sachdev S & Refaat (2015). Age most significant predictor of requiring enteral feeding in head-and-neck cancer patients. Radiation Oncology, 10, 93.

Sanguineti, G., Rao, N., Gunn, B., Ricchetti, F., & Fiorino, C. (2013). Predictors of PEG dependence after IMRT+chemotherapy for oropharyngeal cancer. Radiotherapy & Oncology, 107, 300-304.

Silander, E., Nyman, J., & Hammerlid, E. (2013). An exploration of factors predicting malnutrition in patients with advanced head and neck cancer. Laryngoscope, 123, 2428-2434.

Van Den Berg, M. G. A. (2006). A prospective study on weight loss and energy intake in patients with head and neck cancer, during diagnosis, treatment and revalidation. Clinical Nutrition, 25, 765-772.

Wermker, K., Jung, S., Huppmeier, L., Joos, U., & Kleinheinz, J. (2012). Prediction model for early percutaneous endoscopic gastrostomy (PEG) in head and neck cancer treatment. Oral Oncology, 48, 355-360.

Wopken, K., Bijl, H. P., van der Schaaf, A., Christianen, M. E., Chouvalova, O., Oosting, S. F. et al. (2014). Development and validation of a prediction model for tube feeding dependence after curative (chemo-) radiation in head and neck cancer. PLoS ONE [Electronic Resource], 9, e94879.

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Alshadwi, A., Nadershah, M., Carlson, E. R., Young, L. S., Burke, P. A., & Daley, B. J. (2013). Nutritional considerations for head and neck cancer patients: a review of the literature. [Review]. Journal of Oral & Maxillofacial Surgery, 71, 1853-1860. *Expert review*

Barrios, R. (2014). Oral health-related quality of life and malnutrition in patients treated for oral cancer. Supportive Care in Cancer, 22, 2927-2933. *Outcomes not in PICO*

Britton, B., Clover, K., Bateman, L., Odelli, C., Wenham, K., Zeman, A. et al. (2012). Baseline depression predicts malnutrition in head and neck cancer patients undergoing radiotherapy. Supportive Care in Cancer, 20, 335-342. *Reports a prognostic model for malnutrition including depression, time and tumour site – 29% of patients had skin cancer*

Burkitt, P., Carter, L. M., Smith, A. B., & Kanatas, A. (2011). Outcomes of percutaneous endoscopic gastrostomy and radiologically inserted gastrostomy in patients with head and neck cancer: a systematic review. [Review]. British Journal of Oral & Maxillofacial Surgery, 49, 516-520. *Does not report prognostic factors for malnutrition*

Casas, R. P., de Luis, D. A., Gomez, C. C., & Culebras, J. M. (2012). Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a systematic review. [Review]. Nutricion Hospitalaria, 27, 681-690. *Systematic review comparing nutritional interventions*

Collins, M. M., Wight, R. G., & Partridge, G. (1999). Nutritional consequences of radiotherapy in early laryngeal carcinoma. Annals of the Royal College of Surgeons of England, 81, 376-381. *Does not report prognostic factors for malnutrition*

Egestad, H. (2015). Differences in quality of life in obese and normal weight head and neck cancer patients undergoing radiation therapy. Supportive Care in Cancer, 23, 1081-1090.*Outcomes not in PICO*

Elia, M., Van der Schueren, M. A. E. V., Garvey, J., Goedhart, A., Lundholm, K., Nitenberg, G. et al. (2006). Enteral (oral or tube administration) nutritional support and eicosapentaenoic acid in patients with cancer: A systematic review. International Journal of Oncology, 28, 5-23. *Systematic review comparing nutritional interventions*

Florez Almonacid, C. I. (2013). Evaluation of the nutritional profile of patients with total laryngectomy. e-SPEN Journal, 8, e229-e234. *Does not report prognostic factors for malnutrition*

Garg, S., Yoo, J., & Winquist, E. (2010). Nutritional support for head and neck cancer patients receiving radiotherapy: a systematic review. [Review] [20 refs] DARE structured abstract available. Supportive Care in Cancer, 18, 667-677. *Does not report prognostic factors for malnutrition*

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Lin, A., Jabbari, S., Worden, F. P., Bradford, C. R., Chepeha, D. B., Teknos, T. N. et al. (2005). Metabolic abnormalities associated with weight loss during chemoirradiation of head-and-neck cancer. International Journal of Radiation Oncology Biology Physics, 63, 1413-1418. *Does not report prognostic factors for malnutrition*

Martin, S., Jordan, Z., & Carney, A. S. (2013). The effect of early oral feeding compared to standard oral feeding following total laryngectomy: a systematic review (Provisional abstract). JBI.Database of Systematic Reviews and Implementation.Reports, 11, 140-182. *Post laryngectomy, does not report prognostic factors for malnutrition*

Moore, K. A., Ford, P. J., & Farah, C. S. (2014). Support needs and quality of life in oral cancer: a systematic review. International Journal of Dental Hygiene, 12, 36-47. *does not report prognostic factors for malnutrition*

Murono S & Tsuji (2015). Factors associated with gastrostomy tube dependence after concurrent chemoradiotherapy for hypopharyngeal cancer. Supportive Care in Cancer, 23, 457-462. *Predictors for duration of G-tube use – all patients had G-tube fitted*

Orell-Kotikangas, H. (2015). NRS-2002 for pre-treatment nutritional risk screening and nutritional status assessment in head and neck cancer patients. Supportive Care in Cancer, 23, 1495-1502. *Reports the accuracy of nutritional risk screening assessment*

Paillaud E., L. (2014). Impact of comprehensive geriatric assessment on survival, function, and nutritional status in elderly patients with head and neck cancer: protocol for a multicentre randomised controlled trial (EGeSOR). BMC cancer, 14. *Trial protocol*

Nourissat, A., Bairati, I., Fortin, A., Gelinas, M., Nabid, A., Brochet, F. et al. (2012). Factors associated with weight loss during radiotherapy in patients with stage I or II head and neck cancer. Supportive Care in Cancer, 20, 591-599. *Duplicate of Nourissat 2010*

Nugent, B., Lewis, S., & O'Sullivan, J. M. (2013). Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy. [Review][Update of Cochrane Database Syst Rev. 2010;(3):CD007904; PMID: 20238358]. Cochrane Database of Systematic Reviews, 1, CD007904. *Does not report prognostic factors for malnutrition*

Orphanidou, C., Biggs, K., Johnston, M. E., Wright, J. R., Bowman, A., Hotte, S. J. et al. (2011). Prophylactic feeding tubes for patients with locally advanced head-and-neck cancer undergoing combined chemotherapy and radiotherapy-systematic review and recommendations for clinical practice. Current oncology, 18, E191-E201. *Evidence based review and guideline about prophylactic feeding tubes – does not quantify the effect of such interventions on malnutrition*

Paleri, V., Roe, J. W., Strojan, P., Corry, J., Gregoire, V., Hamoir, M. et al. (2014). Strategies to reduce long-term postchemoradiation dysphagia in patients with head and neck cancer: an evidence-based

review. Head & Neck, 36, 431-443. *Evidence based review for improving swallowing outcomes following chemoradiotherapy*

Paleri, V. & Patterson, J. (2010). Use of gastrostomy in head and neck cancer: a systematic review to identify areas for future research. [Review]. Clinical Otolaryngology, 35, 177-189. *Does not report predictive factors for weightloss. Potentially relevant information about prophylactic gastrostomy*

Poulsen, M. G., Riddle, B., Keller, J., Porceddu, S. V., & Tripcony, L. (2008). Predictors of acute grade 4 swallowing toxicity in patients with stages III and IV squamous carcinoma of the head and neck treated with radiotherapy alone. Radiotherapy & Oncology, 87, 253-259. *Does not report prognostic factors for malnutrition*

Rabinovitch, R., Grant, B., Berkey, B. A., Raben, D., Ang, K. K., Fu, K. K. et al. (2006). Impact of nutrition support on treatment outcome in patients with locally advanced head and neck squamous cell cancer treated with definitive radiotherapy: a secondary analysis of RTOG trial 90-03. Head & Neck, 28, 287-296. *Does not report prognostic factors for malnutrition – models the impact of baseline nutritional support on survival*

So, W. K., Chan, R. J., Chan, D. N., Hughes, B. G., Chair, S. Y., Choi, K. C. et al. (2012). Quality-of-life among head and neck cancer survivors at one year after treatment--a systematic review. [Review]. European Journal of Cancer, 48, 2391-2408. *Does not report prognostic factors for malnutrition*

Stableforth, W. D., Thomas, S., & Lewis, S. J. (2009). A systematic review of the role of immunonutrition in patients undergoing surgery for head and neck cancer. [Review] [23 refs] DARE structured abstract available. International Journal of Oral & Maxillofacial Surgery, 38, 103-110. *Systematic review comparing nutritional interventions*

Suzuki, M. (2015). Risk factors for body weight loss following reconstructive surgery for tongue cancer. Japanese Journal of Head and Neck Cancer, 41, 30-34. *Full text could not be obtained.*

Takenaka, Y., Yamamoto, M., Nakahara, S., Yamamoto, Y., Yasui, T., Hanamoto, A. et al. (2014). Factors associated with malnutrition in patients with head and neck cancer. Acta Oto-Laryngologica, 134, 1079-1085. *Factors associated with initial (pre-treatment) BMI.*

Toyama, A. F., Dedivitis, R. A., Picado-Petrarolha, S. M., Marques, B. W., Cernea, C. R., & Garcia, B. L. (2014). Early oral feeding following total laryngectomy: a systematic review (Provisional abstract). Database.of Abstracts.of Reviews.of Effects. *Does not report predictors for malnutrition*

Udd, M. (2015). Assessment of indications for percutaneous endoscopic gastrostomy--development of a predictive model. Scandinavian Journal of Gastroenterology, 50, 245-252. *Includes only patients with a PEG.*

van der Molen, L., van Rossum, M. A., Burkhead, L. M., Smeele, L. E., & Hilgers, F. J. (2009). Functional outcomes and rehabilitation strategies in patients treated with chemoradiotherapy for advanced head and neck cancer: a systematic review. [Review][Erratum appears in Eur Arch Otorhinolaryngol. 2009 Jun;266(6):901-2]. European Archives of Oto-Rhino-Laryngology, 266, 889-900. *Systematic review of functional outcome post CRT – does not report predictors for malnutrition*

Wang, J., Liu, M., Liu, C., Ye, Y., & Huang, G. (2014). Percutaneous endoscopic gastrostomy versus nasogastric tube feeding for patients with head and neck cancer: a systematic review. Journal of Radiation Research, 55, 559-567. *Systematic review comparing PEG versus nasogastric feeding – does not report predictors for malnutrition*

Speech and language therapy interventions

Clinical question: Which active speech and language therapy interventions are of most benefit to patients with cancer of the upper aerodigestive tract?

Background

The management of CUADT can have a significant impact on speech, voice and swallowing function particularly with the increasing use of chemotherapy and organ preservation. The role of the speech and language therapist in the MDT is well established but there is a lack of consensus about the timing, duration and type of intervention and to whom it is offered.

Evidence statements

Swallowing/nutrition

Moderate quality evidence from a single randomised trial (Carnaby-Mann 2012, 28 patients) suggests uncertainty over whether high-intensity swallowing therapy during cancer treatment improves swallowing and nutrition outcomes in patients undergoing treatment for oropharyngeal cancer. High-intensity swallowing therapy was beneficial compared to either usual care or sham therapy in terms of rates of return to normal diet (risk ratio (RR) 2.5, 95% confidence interval (CI) 0.58, 10.8, and RR 2.32, 95% CI 0.54, 9.95, respectively), functional swallowing (RR 3, 95% CI 0.73, 12.39 and RR 2.79, 95% CI 0.68, 11.42, respectively), rates of nonoral feeding (RR 0.5, 95% CI 0.15, 1.61 and RR 0.93, 95% CI 0.23, 3.81, respectively), and the proportion of patients with greater than 10% weight loss (RR 0.67, 95% CI 0.24, 1.86 and RR 0.62, 95% CI 0.22, 1.71), but the differences between groups did not reach statistical significance.

Low quality evidence from a single randomised trial (Tang 2010, 69 patients) suggests that in patients who have had radiotherapy for nasopharyngeal cancer, swallow function is improved by rehabilitation exercises (RR 2.06, 95% CI 1.07, 3.97, compared with no rehabilitation), but the period over which swallow function was measured in this study is not clear.

The effects of preventative speech and language therapy in patients being treated for cancer of the upper aerodigestive tract was investigated in a single randomised trial (Kotz 2012, 26 patients) and two observational studies (Ahlberg 2011, 205 patients, and Carroll 2008, 18 patients). Low quality evidence suggests that over 12 months of follow up, normalcy of diet and functional oral intake scale both returned to normal more quickly in patients who received preventative therapy compared to those who received usual care (Kotz 2012), but the differences between groups at each time point were very small. Very low quality evidence suggests uncertainty over the benefit of preventative therapy. One trial (Carroll 2008, 18 patients) found no statistically significant benefit in terms of aspiration, posterior tongue base movement, or vertical hyoid movement. Very low quality evidence from a second observational study (Ahlberg 2011) found no difference in rates of PEG tube use after 6 months between patients receiving preventative therapy and those who did not (RR 1.15, 95% CI 0.57, 2.34), whilst patients who had received preventative swallowing therapy were less likely to be free of swallowing difficulties after 6 months (RR 0.79, 95% CI 0.63, 0.98). A third trial (Virani 2015, 50 patients) found that fewer patients who performed preventative exercises required a PEG tube 3

months after finishing their cancer treatment (RR 0.31, 95% CI 0.11, 0.82), but there was no significant difference between groups in terms of PEG tube use at completion of treatment, or in terms of change in functional intake scale (FOIS) scores.

Two observational studies provided very low quality evidence on the effect of timing/amount of therapy on swallow outcomes. One study (Kulbersh 2006, 37 patients) suggests that in patients with cancer of the upper aerodigestive tract treated with chemotherapy or chemoradiotherapy, those who receive swallowing therapy before their cancer treatment suffer from less long-term dysphagia symptoms than those who receive posttreatment swallowing therapy (follow up 6–20 months). A second study (Cavalot 2009, 43 patients) suggests that in patients undergoing partial laryngectomy for larynx carcinoma, the use of both pre- and post-surgery swallowing therapy reduces the time to resumption of swallowing when compared to patients receiving only post-surgery swallowing therapy (mean difference 11.38 days shorter, 95% CI 8.72, 14.04 shorter).

Two observational studies (Duarte 2013 and Hutcheson 2013, 85 and 497 patients, respectively) provided very low quality evidence about the effect of patients' adherence to their swallowing therapy on outcomes. The results suggest that patients who comply with their prescribed swallowing therapy are more likely to return to a normal diet (Hutcheson 2013, follow up median 22 months, RR 1.12, 95% CI 1.02, 1.22), and require a gastrostomy tube for a shorter time after their treatment (median duration of gastrostomy tube dependence 68 days and 113 days for adherent and non adherent patients, respectively, p = 0.007). However, results of the second trial suggest uncertainty over whether adherence to treatment reduced weight loss or swallowing pain 1 month after treatment (Duarte 2013, 85 patients).

Trismus/mouth opening

Moderate quality evidence from a single randomised trial (Hogdal 2015, 97 patients) suggests uncertainty over whether preventative jaw exercises reduce the incidence (RR 1.15, 95 % CI 0.60, 21.9) or severity (mean difference in maximum interincisal opening 0.83 mm greater, 95% CI, 3.64, 5.29 mm) of trismus in the 12 months after radiotherapy treatment in patients with oral cavity or oropharynx cancer. However, low quality evidence from a second randomised trial (Tang 2010, 69 patients) suggests that in patients who have had radiotherapy for nasopharyngeal cancer, mean intercisor distance after treatment is greater in patients who receive trismus rehabilitation training during hospitalisation for their cancer treatment (mean difference 0.6 cm greater, 95% CI 0.34, 0.86 greater, follow up period not clear).

Very low quality evidence from a single randomised trial (van der Molen 2014, 29 patients) suggests that in patients with cancer of the upper aerodigestive tract, mouth opening outcomes are similar in patients using stretch exercises (using a Therabite device) and strengthening exercises, or in patients following a programme of range-of-motion and strengthening exercises. After two years of follow up, and at intermediate time points, the change in the incidence of trismus and the degree of mouth opening were similar between the two types of therapy.

Very low quality evidence from a single observational study (Ahlberg 2011, 205 patients) suggests that patients receiving early preventative therapy are more likely to experience mouth opening difficulties 6 months after treatment (mouth opening difficulties absent or minor at 6 months: RR 0.77, 95% CI 0.61, 0.97).

Very low quality evidence from a single observational study (Pauli 2014, 100 patients) suggests that compared with standard care, a programme of jaw exercises using a jaw device may improve mouth opening outcomes in patients treated with radiotherapy (with or without chemotherapy) for cancer of the upper aerodigestive tract. Patients who used jaw exercises had greater maximal interincisal opening after 3 months (6.4 and 0.7 mm increase for jaw exercises and standard care, respectively, p <0.001) Patient-reported limitation in mouth opening after 3 months also favoured the use of jaw exercises, but the difference between groups did not reach statistical significance for some methods of measurement.

Voice quality

Two randomised trials (low quality evidence) investigated the effect of voice rehabilitation on voice quality. One study (Tuomi 2014b, 69 patients) found no significant difference in voice acoustic measurements between people with laryngeal cancer who did or did not receive voice rehabilitation. However, in the same group, patient reported outcomes of voice quality (hoarseness, loudness, and Self Evaluation of Communication after Laryngeal Cancer score) significantly improved after 6 months in patients who received voice rehabilitation compared to those who did not. A second study (van Gogh 2006, 23 patients) investigated the effect of voice therapy in people who had received treatment for glottic carcinoma and developed voice impairment. The results of this study suggest uncertainty in the benefit of voice therapy in this patient group: patients having voice therapy had greater improvements in acoustic measurements and patient-reported voice outcomes than control patients, but some measurements of voice quality were worse in the voice therapy group at baseline.

Very low quality evidence from a single observational study (Ahlberg 2011, 205 patients) suggests that patients receiving early preventative therapy are more likely to experience speech difficulties 6 months after treatment (speech difficulties absent or minor at 6 months: RR 0.71, 95% CI 0.57, 0.89).

Study characteristics and quality

The review identified 18 studies of relevance; their characteristics are summarised in Table 7.5. There were 7 randomised controlled trials (RCTs) and 11 observational studies. All of the RCTs included small numbers of patients (median = 29; range 18–69 patients), and all but one were rated as at a serious or very serious risk of bias; risks of bias included lack of evidence of rigorous randomisation, unexplained loss of patients to follow up, and incomplete reporting of results. The observational studies included larger, but still relatively small, numbers of patients (median = 45, range 18-497 patients). Due to differences in study design, interventions, type of outcomes measured, and the methods used to measure outcomes, few studies were sufficiently similar to allow results to be pooled.

In several studies, the timing of speech and language intervention in relation to the patients' primary cancer treatment is not clear. Some studies also did not state for how long speech and language therapy continued, or how long outcomes were assessed for after the beginning of treatment.

Table 7.5. Characteristics of included studies

STUDY ID	Design	Patient characteristics	Cancer treatment	N	Interventions	Follow up period	Outcomes
Ahlberg 2011	PCS	H&N cancer	External beam radiotherapy ± surgery/chemotherapy	205	Preventative speech and physiotherapy rehabilitation versus standard care	6 months	Incidence of PEG tube Swallowing difficulties Chewing difficulties Mouth opening Speech difficulties
Carnaby-Mann 2012	RCT	Oropharyngeal cancer	External beam radiotherapy ± chemotherapy/neck dissection	58	Standardised high intensity swallowing therapy (pharyngocise) versus either usual care or standardised sham therapy	6 weeks	Mouth opening Swallowing ability Weight loss Normal/nonoral diet
Carroll 2008	RCS	Oropharynx, hypopharynx or larynx SCC	Combined chemotherapy and radiotherapy	18	Pretreatment swallowing exercises versus control	Maximum 12 months	Aspiration Tongue base position/movement Hyoid position/movement PEG tube use
Cavalot 2009	RCS	Larynx carcinoma	Partial laryngectomy	43	Pre- and post-surgery swallowing therapy vs. post-surgery swallowing therapy only	10–150 months	Time to resumption of swallowing
Duarte 2013	RCS	H&N cancer	Radiotherapy or chemoradiotherapy	85	Compliance vs. non compliance with a swallowing preservation protocol	2 months	Weight loss Oral diet Use of G-tube Pain on swallowing
Hogdal 2015	RCT	Oral cavity or oropharyngeal cancer	Radiotherapy	97	Preventative jaw exercises vs. usual care	12 months	Mouth opening
Hutcheson 2013	RCS	Pharyngeal cancer	Radiotherapy or chemoradiotherapy	497	Compliance vs. non compliance with swallowing exercises	22 months	Gastrostomy dependence Return to normal diet

STUDY ID	Design	Patient characteristics	Cancer treatment	N	Interventions	Follow up period	Outcomes
Kotz 2012	RCT	H&N cancer	Concurrent chemotherapy	26	Prophylactic swallowing exercises vs. standard care	12 months	Normalcy of diet Functional oral intake scale
Kulbersh 2006	RCS	Hypopharyngeal, laryngeal, or oropharyngeal cancer	Primary radiation or chemoradiation	37	Pretreatment swallowing exercises vs. posttreatment swallowing exercises	9-14 months	Quality of life
Lazarus 2014	RCT	Oral or oropharyngeal cancer, stage II to IV	Undergoing radiotherapy with or without chemotherapy	18	Tongue strengthening exercises vs. normal care	6 weeks	Swallowing function Tongue strength Quality of life
Pauli 2014	PCS	Newly diagnosed head and neck cancer patients who develop trismus	Radiation therapy ± chemotherapy	101	Structured trismus exercises using a jaw device vs. standard care	3 months	Mouth opening Quality of life
Rose 2009	RCS	H&N cancer	Radical radiotherapy ± chemotherapy	45	Jaw exercises during radiotherapy vs. control (no exercises)	Up to 36 months	Mouth opening
Tang 2010	RCT	Nasopharyngeal cancer	Radiotherapy	46	Rehabilitation exercises for dysphagia and trismus vs. control (no exercises)	Unclear	Mouth opening Swallow function
Tuomi 2014a	PCS	T1–T3 glottic and supraglottic cancer	Radiotherapy	20	Voice rehabilitation after cancer treatment vs. control (no rehabilitation)	6 months	Speech intelligibility
Tuomi 2014b	RCT	Laryngeal cancer	Radiotherapy ± chemotherapy	69	Voice rehabilitation vs. control (no rehabilitation)	6 months	Speech intelligibility Quality of life
van der Molen 2014	RCT	Oral cavity, oropharynx, hypopharynx, larynx, nasopharynx SCC	Concomitant chemoradiotherapy	29	Stretch and strengthening exercises vs. range of motion and strengthening exercises	2 years	Aspiration Feeding tube use Normalcy of diet Trismus

STUDY ID	Design	Patient characteristics	Cancer treatment	N	Interventions	Follow up period	Outcomes
van Gogh 2006	RCT	Glottic carcinoma patients who developed voice impairment	Radiotherapy or endoscopic laser surgery	23	Voice therapy vs. no voice therapy	3 months	Speech intelligibility
Virani 2014	PCS	Oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx cancer	Radiotherapy/chemotherapy	50	Preventative swallowing exercises vs. repetitive swallowing	3 months	PEG tube use Oral intake
Zhen 2011	PCS	Tongue cancer patients who developed dysphagia	Tongue resection	46	Swallowing therapy vs. control (no swallowing therapy)	Unclear	Dysphagia
Abbreviations: H&N: head and neck; NR: not reported; PCS: prospective cohort study; RCT: randomised controlled trial; RCS: retrospective cohort study; SCC: squamous cell carcinoma.							

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GRADE evidence tables

Table 7.6. GRADE evidence profile: high intensity swallowing therapy during cancer treatment versus usual care

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High intensity swallowing therapy during cancer treatment	Usual care	Relative (95% CI)	Absolute	
Normal diet at last follow up (6 weeks)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	5/14 (35.7%)	2/14 (14.3%)	RR 2.5 (0.58, 10.8)	214 more per 1000 (from 60 fewer to 1000 more)	⊕⊕⊕O MODERATE
Functional swallowing at last follow up (6 weeks)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	6/14 (42.9%)	2/14 (14.3%)	RR 3 (0.73, 12.39)	286 more per 1000 (from 39 fewer to 1000 more)	⊕⊕⊕O MODERATE
Nonoral feeding at last follow up (6 weeks)											
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	3/14 (21.4%)	6/14 (42.9%)	RR 0.5 (0.15, 1.61)	214 fewer per 1000 (from 364 fewer to 261 more)	⊕⊕⊕O MODERATE
Greater than 10% weight loss at last follow up (6 weeks)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	4/14 (28.6%)	6/14 (42.9%)	RR 0.67 (0.24, 1.86)	141 fewer per 1000 (from 326 fewer to 369 more)	⊕⊕⊕O MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High intensity swallowing therapy during cancer treatment	Usual care	Relative (95% CI)	Absolute	
Change in swallowing ability (MASA score) (follow-up 6 weeks; better indicated by higher values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	14	14	-	MD 6.46 higher (2.33 lower to 15.25 higher)	⊕⊕⊕O MODERATE

[1] Carnaby-Mann 2012.
[2] Small study population size.

Table 7.7. GRADE evidence profile: high intensity swallowing therapy during cancer treatment versus sham therapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High intensity swallowing therapy during cancer treatment	Sham therapy	Relative (95% CI)	Absolute	
Normal diet at last follow up (6 weeks)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	5/14 (35.7%)	2/13 (15.4%)	RR 2.32 (0.54, 9.95)	203 more per 1000 (from 71 fewer to 1000 more)	⊕⊕⊕O MODERATE
Functional swallowing at last follow up (6 weeks)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	6/14 (42.9%)	2/13 (15.4%)	RR 2.79 (0.68, 11.42)	275 more per 1000 (from 49 fewer to 1000 more)	⊕⊕⊕O MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High intensity swallowing therapy during cancer treatment**	**Sham therapy**	**Relative (95% CI)**	**Absolute**	
Nonoral feeding at last follow up (6 weeks)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	3/14 (21.4%)	3/13 (23.1%)	RR 0.93 (0.23, 3.81)	16 fewer per 1000 (from 178 fewer to 648 more)	⊕⊕⊕O MODERATE
Greater than 10% weight loss at last follow up (6 weeks)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	4/14 (28.6%)	6/13 (46.2%)	RR 0.62 (0.22, 1.71)	175 fewer per 1000 (from 360 fewer to 328 more)	⊕⊕⊕O MODERATE
Change in swallowing ability (MASA score) (follow up 6 weeks; better indicated by higher values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	14	13	-	MD 3.1 higher (5.68 lower to 11.88 higher)	⊕⊕⊕O MODERATE

[1] Carnaby-Mann 2012.
[2] Small study population size.

Table 7.8. GRADE evidence profile: exercises for trismus and dysphagia versus control (no exercises)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercises for trismus and dysphagia	Control (no exercises)	Relative (95% CI)	Absolute	
Mean intercisor distance after treatment, cm (follow-up period unclear; Better indicated by higher values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	33	36	-	MD 0.6 higher (0.34 to 0.86 higher)	⊕⊕OO LOW
Swallow function improved (follow-up period unclear)											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	17/33 (51.5%)	9/36 (25%)	RR 2.06 (1.07, 3.97)	265 more per 1000 (from 18 more to 743 more)	⊕⊕OO LOW

[1] Tang 2010.

[2] Method of randomisation not reported; unclear whether allocation was adequately concealed. Very limited information on patient baseline characteristics.

[3] Small study population size.

Table 7.9. GRADE evidence profile: therapeutic exercises versus repetitive swallowing

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Therapeutic exercises	Repetitive swallowing	Relative (95% CI)	Absolute	
PEG tube use at completion of treatment											
1[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	8/26 (30.8%)	13/24 (54.2%)	RR 0.57 (0.29, 1.13)	233 fewer per 1000 (from 385 fewer to 70 more)	⊕OOO VERY LOW
PEG tube use at 3 months post-treatment											
1[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	4/26 (15.4%)	12/24 (50%)	RR 0.31 (0.11, 0.82)	345 fewer per 1000 (from 90 fewer to 445 fewer)	⊕OOO VERY LOW
Post-treatment FOIS score (Better indicated by lower values)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	26	24	Post-treatment FOIS scores: mean 3.8 and 3.7 for intervention and control groups, respectively		⊕OOO VERY LOW

[1] Virani 2014

[2] Small study population size

Table 7.10. GRADE evidence profile: early preventative therapy versus control (usual care/no preventative therapy)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early preventative therapy	Control	Relative (95% CI)	Absolute	
Incidence of PEG tube use at last follow up (6 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	12/84 (14.3%)	15/121 (12.4%)	RR 1.15 (0.57, 2.34)	19 more per 1000 (from 53 fewer to 166 more)	⊕OOO VERY LOW
Swallowing difficulties absent or minor at last follow up (6 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	47/84 (56%)	86/121 (71.1%)	RR 0.79 (0.63, 0.98)	149 fewer per 1000 (from 14 fewer to 263 fewer)	⊕OOO VERY LOW
Chewing difficulties absent or minor at last follow up (6 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	49/84 (58.3%)	76/121 (62.8%)	RR 0.93 (0.74, 1.17)	44 fewer per 1000 (from 163 fewer to 107 more)	⊕OOO VERY LOW
Mouth opening difficulties absent or minor at last follow up (6 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	45/84 (53.6%)	84/121 (69.4%)	RR 0.77 (0.61, 0.97)	160 fewer per 1000 (from 21 fewer to 271 fewer)	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early preventative therapy	Control	Relative (95% CI)	Absolute	
Speech problems absent or minor at last follow up (6 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	46/84 (54.8%)	93/121 (76.9%)	RR 0.71 (0.57, 0.89)	223 fewer per 1000 (from 85 fewer to 330 fewer)	⊕OOO VERY LOW
Aspiration, Rosenbeck score at last follow up (3 months; better indicated by lower values)											
1[4]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	9	9	-	MD 0.23 higher (2.12 lower to 2.58 higher)	⊕OOO VERY LOW
Posterior tongue base movement, mm (3 months; better indicated by higher values)											
1[4]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	9	9	-	MD 0.99 higher (3.93 lower to 5.91 higher)	⊕OOO VERY LOW
Vertical hyoid movement, mm (3 months; better indicated by higher values)											
1[4]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	9	9	-	MD 0.91 higher (5.11 lower to 6.93 higher)	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early preventative therapy	Control	Relative (95% CI)	Absolute	
Normalcy of diet (patient reported, scale 1-100) (follow-up 12 months; better indicated by higher values)											
1[7]	randomised trials	serious[5,6]	no serious inconsistency	no serious indirectness	serious[3]	none	13	13	**Normalcy of diet** / **Pre-CRT**: Intervention 100 (50-100), Control 100; **Immediately after**: 20 (0-100), 20 (0-80); **3 Mo**: 100 (40-100), 80 (30-100); **6 Mo**: 100 (50-100), 50 (30-100); **9 Mo**: 100 (50-100), 80 (30-100); **12 Mo**: 100 (50-100), 80 (30-100)		⊕⊕OO LOW
Functional oral intake scale (FOIS), 1-7 (follow-up 12 months; better indicated by higher values)											
1[7]	randomised trials	serious[5,6]	no serious inconsistency	no serious indirectness	serious[3]	none	13	13	**FOIS scores** / **Pre-CRT**: Intervention 7 (6-7), Control 7 (6-7); **Immediately after**: 3 (1-7), 4 (1-6); **3 Mo**: 7 (5-7), 5 (3-7); **6 Mo**: 7 (6-7), 6 (3-7); **9 Mo**: 7 (6-7), 6 (5-7); **12 Mo**: 6 (5-7), 6 (5-7)		⊕⊕OO LOW

[1] Ahlberg 2011.
[2] Outcome data reported only for patients who responded to a survey. A greater proportion of patients in the control group responded (and therefore have outcome data available) than for the intervention group.
[3] Small study population size.
[4] Carroll 2008.
[5] Method of randomisation not reported.
[6] Unclear whether allocation was adequately concealed.
[7] Kotz 2012.

Table 7.11. GRADE evidence profile: pre- and post-surgery swallowing therapy versus post-surgery swallowing therapy alone

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre- and post-surgery swallowing therapy	Post-surgery swallowing therapy only	Absolute	
Time to resumption of swallowing, days (follow-up median 65 months; Better indicated by lower values)										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	18	25	MD 11.38 lower (8.72, 14.04 lower)	⊕OOO VERY LOW

[1] Cavalot 2009.
[2] Allocation to treatment based on time of recruitment into the study. Limited details of patient characteristics reported.
[3] Small study population size.

Table 7.12. GRADE evidence profile: adherence with swallowing exercises versus nonadherence

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adherence with swallowing exercises	Nonadherence	Relative (95% CI)	Absolute	
Weight loss 1 month after end of cancer treatment, % (Better indicated by lower values)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	57	28	-	MD 0.6 lower (4.62 lower to 3.42 higher)	⊕OOO VERY LOW
Weight loss 2 months end of after cancer treatment, % (Better indicated by lower values)											
1[1]	observational studies	very serious[2,4]	no serious inconsistency	no serious indirectness	serious[3]	none	23	24	-	MD 5.5 higher (3.13 lower to 14.13 higher)	⊕OOO VERY LOW
Return to regular (chewable) diet (follow-up median 22 months)											
1[5]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	242/286 (84.6%)	160/211 (75.8%)	RR 1.12 (1.02, 1.22)	91 more per 1000 (from 15 more to 167 more)	⊕OOO VERY LOW
Chewable diet tolerated 1 month after end of cancer treatment											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	31/57 (54.4%)	6/28 (21.4%)	RR 2.54 (1.2, 5.36)	330 more per 1000 (from 43 more to 934 more)	⊕OOO VERY LOW
Gastrostomy tube dependence 1 month after end of cancer treatment											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	13/57 (22.8%)	15/28 (53.6%)	RR 0.43 (0.24, 0.77)	305 fewer per 1000 (from 123 fewer to 407 fewer)	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adherence with swallowing exercises**	**Nonadherence**	**Relative (95% CI)**	**Absolute**	
Duration of gastrostomy tube dependence, days (follow-up median 22 months; Better indicated by lower values)											
1[5]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	286	211	Median 68 days (range 0–1815 days) for intervention group; median 113 days (range 0–1594 days) for control group. p = 0.007.		⊕OOO VERY LOW
Swallowing pain 1 month after end of cancer treatment, scale 1-10, better indicated by lower values (Better indicated by lower values)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	57	28	-	MD 0.1 higher (0.99 lower to 1.19 higher)	⊕OOO VERY LOW
Swallowing pain 2 months after end of cancer treatment, scale 1-10, better indicated by lower values (Better indicated by lower values)											
1[1]	observational studies	very serious[2,4]	no serious inconsistency	no serious indirectness	serious[3]	none	23	24	-	MD 1.7 higher (0.52 to 2.88 higher)	⊕OOO VERY LOW

[1] Duarte 2013.
[2] Patients allocation based on compliance with treatment.
[3] Small study population size.
[4] Number of dropouts at two months was higher for the intervention group. The number of patients for whom outcome data is available at two months is not clear.
[5] Hutcheson 2013.

Table 7.13. GRADE evidence profile: pre-cancer treatment versus posttreatment swallowing exercises

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-cancer treatment swallowing exercises	Posttreatment swallowing exercises	Relative (95% CI)	Absolute	
MD Anderson Dysphagia Inventory survey scores (follow-up 6 to 20 months; Better indicated by higher values)											
1[3]	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	12			⊕OOO VERY LOW

	Pretreatment group (n = 25)	Posttreatment group (n = 12)	P value
MDADI for Patients with Head and Neck Cancer scores*, unadjusted, mean (95% CI)			
Global assessment	71.7 (62.0, 81.3)	45.0 (31.3, 58.7)	0.003
Emotional	71.5 (66.0, 77.0)	57.5 (49.7, 65.3)	0.005
Functional	68.3 (62.4, 74.2)	61.3 (53.0, 69.7)	0.172
Physical	65.1 (57.8, 72.4)	49.0 (38.6, 59.3)	0.014
MDADI for Patients with Head and Neck Cancer scores, adjusted for age, T stage, site (tongue and tonsil vs. other), follow up time, treatment, race, and gender, mean (95% CI)			
Global assessment	74.4 (64.5, 84.3)	32.9 (17.0, 48.7)	0.0002
Emotional	72.1 (66.1, 78.0)	53.9 (44.3, 63.5)	0.005
Functional	68.7 (62.4, 75.1)	58.6 (48.5, 68.8)	0.114
Physical	66.4 (58.5, 74.3)	43.2 (30.6, 55.7)	0.005
*0 to 100 scale, 100 representing normal swallowing ability.			

[1] Patients allocated to treatment based on the time of their treatment. Longer follow up period in the control group.
[2] Small study population size.
[3] Kulbersh 2006.

Table 7.14. GRADE evidence profile: tongue and laryngeal range of motion exercises, with or without tongue strengthening exercises

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tongue and laryngeal range of motion exercises, with tongue strengthening exercises	Tongue and laryngeal range of motion exercises, without tongue strengthening exercises	Relative (95% CI)	Absolute	
Swallowing function (measured with oropharyngeal swallowing efficiency (OPSE) score; better indicated by higher values; follow-up 6 weeks)											
1[1]	randomised trials	very serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	8	8	**OPSE score** **Baseline** **Post-treatment**	**Intervention group** 44.63 ± 16.69 46.50 ± 14.85	**Control group** 59.60 ± 8.85 54.56 ± 20.08	⊕OOO VERY LOW
Tongue strength (follow-up 6 weeks; Better indicated by higher values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	8	10	**Tongue strength, Kpa** **Baseline** **Post-treatment**	**Intervention group** 44.63 ± 13.39 46.50 ± 16.50	**Control group** 49.30 ± 10.53 52.40 ± 10.78	⊕⊕OO LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tongue and laryngeal range of motion exercises, with tongue strengthening exercises	Tongue and laryngeal range of motion exercises, without tongue strengthening exercises	Relative (95% CI)	Absolute	
Quality of life, Head and Neck Cancer Inventory scores (follow-up 6 weeks; better indicated by higher values)											
1[1]	randomised trials	very serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	8	10	**Quality of life, HNCI scores, mean ± SD** **Speech, pretreatment** 53.33 ± 19.04 **Speech, posttreatment** 70.55 ± 24.68 **Eating, pretreatment** 36.90 ± 18.98 **Eating, posttreatment** 53.13 ± 22.29 **Social disruption, pretreatment** 37.96 ± 24.69 **Social disruption, posttreatment** 54.63 ± 29.20	**Intervention group** **Control group** 72.27 ± 25.43 72.00 ± 26.26 40.71 ± 20.36 49.60 ± 21.28 62.12 ± 27.22 66.67 ± 20.78	⊕OOO VERY LOW

[1] Lazarus 2014.
[2] Unclear whether allocation was adequately concealed.
[3] Measurements taken at baseline showed differences between the two treatment groups that may be partially responsible for the observed effects.
[4] Small study population size.

Table 7.15. GRADE evidence profile: jaw exercises versus usual care (randomised trials)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jaw exercises	Usual care	Relative (95% CI)	Absolute	
Maximum interincisal opening, mm (follow-up 12 months; Better indicated by higher values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	47	Mean difference 0.83 (−3.64, 5.29)	not reported	⊕⊕⊕O MODERATE
Incidence of trismus (follow-up 12 months)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	14/40 (35%)	11/36 (30.6%)	RR 1.15 (0.60, 2.19)	46 more per 1000 (from 122 fewer to 364 more)	⊕⊕⊕O MODERATE

[1] Hogdal 2015

[2] Small study population size.

1 **Table 7.16. GRADE evidence profile: jaw exercises versus standard care (control): observational studies**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jaw exercises	Standard care (control)	Relative (95% CI)	Absolute	
Maximum interincisal opening (MIO), mm (follow-up 3 months; better indicated by higher values)											
1[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	50	**MIO (mm)** / **Before intervention, mean (CI)** / **3-month follow-up, mean (CI)** / **Change in MIO (mm) (CI)** / **Change in MIO (%)** **Study group**: 32.2 (31.2, 33.2) / 38.6 (36.8, 40.4) / Δ 6.4 (4.8, 8.0) / Δ 20.2 (15.1, 25.3) **Control group**: 33.2 (32.0, 34.4) / 33.9 (32.7, 35.1) / Δ 0.7 (< 0.3, 1.7) / Δ 3.2 (1.4, 7.8) **p-value**: p <0.05 / p <0.001 / p <0.001 / p <0.001	⊕OOO VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jaw exercises	Standard care (control)	Relative (95% CI)	Absolute	
Facial pain (patient reported, 0-100) (follow-up 3 months)											
1[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	50	See nested table below		⊕OOO VERY LOW

	Before study group exercise			3-month follow-up				
	Intervention Mean (CI)	Control group Mean (CI)	p	Intervention Mean (CI)	Control Mean (CI)	p	Intervention Diff Δ	Control Diff Δ
Facial pain								
Facial pain right now	24.3 (17.8, 30.8)	20.7 (14.1, 27.3)	ns	9.0 (4.5, 13.5)	20.7 (15.0, 26.3)	***	−15.3	0.0
Facial pain when worst	43.0 (35.5, 50.5)	40.3 (33.0, 47.6)	ns	22.7 (16.3, 29.0)	30.7 (23.8, 37.5)	ns	−20.3	−9.7
last month (lm)								
Facial pain average value (lm)	38.3 (31.9, 44.8)	35.3 (28.1, 42.5)	ns	21.0 (15.2, 26.8)	30.0 (23.2, 36.8)	ns	−17.3	−5.3
Facial pain interfering with social, leisure and family activities (lm)	24.0 (16.1, 31.9)	23.5 (15.5, 31.4)	ns	15.0 (7.1, 22.9)	20.0 (13.1, 26.9)	ns	−9.0	−3.6
Facial pain affecting ability to work (lm)	25.0 (16.8, 33.2)	23.5 (15.1, 31.8)	ns	13.5 (5.9, 21.1)	21.0 (13.6, 28.4)	*	−11.5	−3.6
Domains and single items range 0–100, where 100 indicates maximal amount of symptoms and 0 is equal to no symptoms; P-values indicate difference in mean scores between the intervention group and the control group, before intervention and at 3-month follow-up. *p < 0.05, **p < 0.01, ***p < 0.001. GTQ, Gothenburg Trismus Questionnaire.								

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jaw exercises	Standard care (control)	Relative (95% CI)	Absolute	
Limitation in mouth opening (patient reported, 0-100) (follow-up 3 months)											
1[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	50			⊕OOO VERY LOW

	Before study group exercise			3-month follow-up				
	Intervention group Mean (CI)	Control group Mean (CI)	p	Intervention group Mean (CI)	Control group Mean (CI)	p	Intervention Diff Δ	Control Diff Δ
Limitation in opening mouth (LOM)	49.0 (42.7, 55.3)	45.0 (36.4, 53.6)	ns	33.0 (25.9, 40.1)	40.0 (33.1, 46.9)	ns	−16.0	−5.0
LOM interfering with social, leisure and family activities (lm)	24.0 (17.7, 30.3)	24.5 (16.8, 32.2)	ns	16.5 (8.3, 24.7)	26.5 (19.7, 33.3)	**	−7.5	+2.0
LOM affecting ability to work (lm)	24.5 (16.4, 32.6)	25.0 (17.0, 33.0)	ns	14.0 (6.2, 21.8)	22.0 (14.5, 29.5)	*	−10.5	−3.0
Domains and single items range 0–100, where 100 indicates maximal amount of symptoms and 0 is equal to no symptoms; P-values indicate difference in mean scores between the intervention group and the control group, before intervention and at 3-month follow-up. *p < 0.05, **p < 0.01, ***p < 0.001. GTQ, Gothenburg Trismus Questionnaire.								

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jaw exercises	Standard care (control)	Relative (95% CI)	Absolute	
Dental gap, cm (Better indicated by higher values)											
1[3]	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	29	16	<table><tr><th></th><th>Jaw exercises</th><th>No jaw exercises</th></tr><tr><td colspan="3">**Dental gap, cm**</td></tr><tr><td>**Baseline**</td><td>4.12</td><td>3.73</td></tr><tr><td>**1 month**</td><td>4.30</td><td>3.52</td></tr><tr><td>**2-3 months**</td><td>3.50</td><td>4.02</td></tr><tr><td>**6-7 months**</td><td>3.94</td><td>3.74</td></tr><tr><td>**10-12 months**</td><td>3.77</td><td>3.33</td></tr><tr><td>**18-24 months**</td><td>3.73</td><td>3.00</td></tr><tr><td>**24-36 months**</td><td>4.42</td><td>2.73</td></tr></table>		⊕OOO VERY LOW

[1] Pauli 2014.
[2] Small study population size.
[3] Rose 2009.
[4] Unclear whether all patients were followed up for the full 36-month time period. Exact timing of outcome measurement is not clear.

Table 7.17. GRADE evidence profile: voice rehabilitation versus control

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Voice quality (acoustic measures) (follow-up 3-6 months)								
2[1,6]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	Outcomes from Tuomi 2014b: **Changes from baseline to follow up in:** — **Intervention group (n = 33)** — **Control group (n = 36)** — **p value** **Harmonics-to-noise ratio, mean (SD)** — 0.1 (7.1) — -1.4 (6.8) — 0.329 **Jitter, mean (SD)** — 0.36 (1.91) — 0.14 (2.49) — 0.640 **Shimmer, mean (SD)** — 0.09 (0.58) — 0.09 (0.47) — 0.741 **Fundamental frequency, mean (SD)** — -16.05 (20.38) — -17.0 (29.5) — 0.735 **Maximum phonation time, mean (SD)** Change from baseline to follow up — -0.4 (6.1) — 1.3 (6.6) — 0.243 **S-SECEL score, environmental domain, mean (SD)** — -6.8 (6.7) — 1.6 (7.7) — <0.001 **Hoarseness (patient-reported 100-mm visual analogue scale), mean (SD)** — 18.3 (26.8) — 2.1 (19.3) — 0.002 **Adequate loudness (patient-reported 100-mm visual analogue scale), mean (SD)** — 19.0 (24.6) — 4.7 (20.5) — 0.009	⊕⊕OO LOW

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		

Outcomes from van Gogh et al:

	Control group (n = 11)		Voice-therapy group (n = 12)	
	Study entry assessment	Study exit assessment	Study entry assessment	Study exit assessment
Voice Handicap Index, mean (SD)				
Total score	29.45 (13.34)	26.82 (15.04)	39.67 (16.17)	24.42 (10.26)
Acoustic analyses, mean (SD)				
Fundamental frequency	131 (27)	127 (19)	118 (44)	124 (33)
Noise-to harmonics ratio	0.18 (0.042)	0.18 (0.057)	0.20 (0.064)	0.14 (0.021)
Jitter	1.39 (0.59)	1.70 (1.15)	2.20 (1.50)	1.39 (1.32)
Shimmer	8.56 (5.82)	7.48 (2.09)	7.26 (3.20)	5.09 (1.12)
Voice-Range Profile, mean (SD)				
Intensity range	28.4 (6.6)	30.4 (6.3)	32.2 (8.02)	31.8 (7.9)
Pitch range	20.7 (6.1)	21.9 (4.8)	23.7 (5.2)	21.9 (3.3)

Quality assessment							Effect				Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations					
Voice quality (patient reported) (follow-up 3 months[5])											
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none		**Control group (n = 11)**		**Voice-therapy group (n = 12)**	⊕⊕OO LOW
								Study entry assessment	**Study exit assessment**	**Study entry assessment**	**Study exit assessment**
							Communicative suitability, mean (SD)				
							Talking with a friend	6.45 (1.15)	6.37 (1.51)	6.19 (1.23)	6.26 (1.53)
							Asking a passer-by	6.44 (1.11)	6.53 (1.30)	6.23 (1.07)	6.29 (1.31)
							Giving a lecture	5.85 (1.31)	5.65 (1.53)	5.71 (1.30)	5.64 (1.50)
							Perceptual voice quality scores, median				
							Breathiness	1	1	0.5	0
							Roughness	1	1	1	1
							Vocal fry	2	2	3	2

[1] Tuomi 2014b.
[2] Acoustic measurements taken at baseline showed differences between the two treatment groups.
[3] Small study population size.
[4] Unclear whether allocation was concealed in either study. Van Gogh did not use a method of allocation that is truly random.
[5] The time at which outcomes were assessed is stated as either three months, or after a patient's course of voice therapy. The length of the voice therapy course, and whether this varied between patients, is not reported.
[6] van Gogh 2006.
[7] Patients were allocated to treatment in the order of presentation; this is not a truly random method of allocation. Unclear whether allocation was concealed. Exact timing of outcome measurement (and whether this varied) is not clear (see footnote 5).

Table 7.18. GRADE evidence profile: stretch (Therabite) (intervention) and strengthening exercise versus range of motion and strengthening exercises (control)

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Aspiration or penetration rates, % (follow-up median 114 weeks)								
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	**Intervention group (n = 14)** / **Control group (n = 11)** Baseline: 0 / 18 10 weeks: 18 / 9 1 year: 9 / 18 2 years: 0 / 9	⊕OOO VERY LOW
Feeding tube rates, % (follow-up median 114 weeks)								
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	**Intervention group (n = 15)** / **Control group (n = 14)** Baseline: 0 / 0 10 weeks: 40 / 43 1 year: 7 / 0 2 years: 0 / 0	⊕OOO VERY LOW

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Abnormal diet (FOIS score 1-6), % (follow-up median 114 weeks)								
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	**Intervention group (n = 15)** / **Control group (n = 14)** Baseline: 0 / 21 10 weeks: 67 / 43 1 year: 13 / 0 2 years: 17 / 14	⊕OOO VERY LOW
Incidence of trismus, % (follow-up median 114 weeks)								
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	**Intervention group (n = 15)** / **Control group (n = 14)** Baseline: 0 / 21 10 weeks: 13 / 7 1 year: 0 / 7 2 years: 0 / 14	⊕OOO VERY LOW
Mouth opening, mm (follow-up median 114 weeks; better indicated by higher values)								
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	**Intervention group (n = 15)** / **Control group (n = 14)** Baseline: 53.7 (45-69) / 49.7 (26-67) 10 weeks: 49.5 (27-65) / 48.3 (12-65) 1 year: 52.1 (38-70) / 49.6 (20-70) 2 years: 53.1 (38-70) / 48.7 (20-65)	⊕OOO VERY LOW

[1] van der Molen 2014.

[2] Method of randomisation not reported; unclear whether allocation was adequately concealed. Some outcomes differed between groups at baseline. Data not reported for all patients: only patients who were followed up for the entire 2 years are included in the analysis, i.e. patients who have 10-week/1-year data available are excluded.

[3] Small study population size.

Table 7.19. GRADE evidence profile: postoperative swallowing therapy versus control for cancer of the upper aerodigestive tract

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative swallowing therapy	Control	Relative (95% CI)	Absolute	
MD Anderson Dysphagia (MDADI) score at last follow up (follow-up 1 to 4 months[1]). Subgroup: tongue rehabilitation ≥50%											
1[4]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	**Intervention group (n = 9)** / **Control group (n = 10)** / **p** **MDADI scores, median** **Global** 64.56 ± 3.28 / 60.60 ± 2.84 / 0.012 **Emotional** 61.22 ± 2.95 / 57.50 ± 2.27 / 0.006 **Functional** 69.78 ± 3.77 / 68.60 ± 4.33 / 0.537 **Physical** 67.00 ± 2.87 / 62.00 ± 3.56 / 0.004				⊕OOO VERY LOW
MDADI score at last follow up (follow-up 1 to 4 months[1]). Subgroup: tongue rehabilitation <50%											
1[4]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	**Intervention group (n = 14)** / **Control group (n = 13)** / **p** **MDADI scores, median** **Global** 57.07 ± 4.14 / 52.92 ± 5.12 / 0.029 **Emotional** 54.36 ± 6.11 / 48.85 ± 4.56 / 0.014 **Functional** 61.50 ± 3.25 / 60.77 ± 4.51 / 0.632 **Physical** 58.07 ± 3.29 / 52.92 ± 4.01 / 0.001				⊕OOO VERY LOW

[1] Length of follow up is not clearly described.

[2] Limited details of patient characteristics reported. Unclear if measured outcomes were comparable at baseline. It is also unclear whether patients in each treatment group were followed up for comparable lengths of time.

[3] Small study population size.

[4]. Zhen 2012.

Evidence tables for all included studies

Study, country

Ahlberg 2011.
Sweden, single centre.

Study type, study period

Prospective cohort study.
January 2004 to July 2007.

Number of patients

205.

Patient characteristics

Inclusion criteria: patients diagnosed with head and neck cancer who were to receive external beam radiotherapy with curative intent.

	Intervention group (n = 84)	Control group (n = 121)
Mean age, years	63.6 (13.1)	64.1 (12.0)
Gender, n (%)		
Male	56 (67)	82 (68)
Female	28 (33)	39 (32)
Tumour site, n (%)		
Oral cavity	22 (26)	25 (21)
Oropharynx	26 (31)	33 (27)
Epipharynx	2(2)	5 (4)
Hypopharynx	6(7)	4(3)
Larynx	8 (10)	14 (12)
Salivary gland	8 (10)	11 (9)
Nose and sinus	0(0)	6(5)
Other	12 (14)	23 (19)
Treatment, n (%)		
Preoperative radiotherapy	26 (31)	36 (30)
Postoperative radiotherapy	33 (39)	52 (43)
Radiotherapy alone	25 (30)	32 (27)
Any surgery	59 (70)	89 (74)
No surgery	5 (30)	32 (26)
Major surgery	6(7)	12 (10)
Chemotherapy	10 (12)	35 (29)

Patients received radiotherapy treatment at one of two units (both in Stockholm).All patients treated at one unit were allocated to the intervention group; all patients treated at the second unit received control treatment.

Intervention

Early preventative speech and physiotherapy rehabilitation (n = 84).

All patients in the study group were examined by the speech/language pathologist before radiotherapy and 3 months after completion of therapy. The patients were instructed, both verbally and with written information, on how to perform mobility exercises for the tongue and larynx (Mendelson's manoeuvre) at least once and preferably twice a day at home during the course of radiotherapy, and for 3 months after termination of treatment. The tongue mobility exercises consisted of five repetitions of extending the tongue as far as possible straight out, up, down, and laterally and then moving the tongue over the whole inside of the oral cavity and teeth. Mendelson's manoeuvre, holding the larynx at its most superior position for 2-3 s during swallowing, was to be repeated 10 times.

Patients had an appointment with the physiotherapist before the start of radiotherapy and follow-ups were performed at 2, 6, and 12 months after termination of treatment. The patients received written and verbal instructions about exercises and stretching of muscles of the head and neck to maintain mobility in the radiotherapy-exposed areas. The exercises for preventing stiffness of the neck consisted of active rotation of the head in both directions, flexion/ extension of the head in a neutral position, and lateral flexions of the head, 3×10 times in each direction. They also involved stretching of the platysma and muscles of the neck. The patients were told that the program should be performed twice a day and performed before, during, and after radiotherapy until follow-up at 6 months, and later if required.

Prevention of trismus consisted of exercises with the 'Acute Medic Jaw Trainer and Stretcher'. The program of active mouth opening was done as active maximal mouth opening assisted with the Jaw Trainer and Stretcher for 10 × 20 s, twice a day. At follow-ups, the directions could sometimes be changed to a 'hold and release' technique, depending on the need and/or compliance of the patient.

Comparison

Control treatment (n = 121): standard care, with no preventative speech or physiotherapy rehabilitation.

Length of follow-up

Outcomes reported 6 months after end of treatment.

Outcome measures and effect size

All outcomes were self-reported via a questionnaire sent to patients 6 months after the end of their treatment.

	Intervention group (n = 84)	Control group (n = 121)	
Incidence of PEG tube, n (%)	12 (18)	15 (15)	
Swallowing difficulties, n (%)			
Not at all	20 (26)	51 (47)	
A little	27 (36)	35 (32)	
Quite a bit	23 (30)	16 (15)	
Very much	6 (8)	7 (6)	P = 0.003. Proportional OR of 2.3 (95% CI 1.3, 4.0) in favour of control group
Chewing difficulties, n (%)			
Not at all	28 (38)	45 (40)	
A little	21 (29)	31 (27)	
Quite a bit	18 (25)	22 (20)	
Very much	6 (8)	15 (13)	P = 0.94. Proportional OR not reported
Reduced ability to open mouth, n (%)			
Not at all	25 (34)	56 (50)	
A little	20 (27)	28 (25)	
Quite a bit	21 (28)	23 (20)	
Very much	8 (11)	6 (5)	P = 0.018. Proportional OR of 1.9 (95% CI 1.1, 1.3) in favour of control group
Speech problems, n (%)			
Not at all	20 (28)	54 (48)	
A little	26 (36)	39 (35)	
Quite a bit	16 (22)	11 (10)	
Very much	10 (14)	8 (7)	P = 0.001. Proportional OR of 2.5 (95% CI 1.4, 4.4) in favour of control group

Source of funding

Not reported; authors declared no conflicts of interest.

Risks of bias

Selection bias: Unclear/unknown risk. Allocation based on treatment unit.
Performance bias: Unclear/unknown risk. Type of cancer treatments varied between groups. Details of background care not reported and it is unclear if this was standardised across the two treatment units.
Attrition bias: High risk. Outcome data is only available for patients who responded to a survey sent to them. A greater proportion of patients in the control group responded (and therefore have outcome data available) than for the intervention group.
Detection bias: Low risk.

Additional comments

374 patients were initially included; results are available only for patients who answered a questionnaire sent to them 6 months after the end of treatment.

1

Study, country

Carnaby-Mann 2012
United States, single centre.

Study type, study period

Randomised controlled trial.
2001 to 2004.

Number of patients

58 patients were randomised to three different treatments. Outcome data at 6 weeks and 6 months was available for 41 and 31 patients, respectively. Reasons for missing patient data were death (3 patients) or loss to follow up (16 patients).

2

Patient characteristics

Inclusion criteria:
Head and neck cancer of the oropharyngeal regions, confirmed by the clinical history and examination findings, with positive cross-sectional imaging studies and histopathologic biopsy, excluding other pathologic factors
Planned external beam radiotherapy treatment
No history of nonoral feeding for cancer-related illness
Able to undergo MRI procedures

	Usual care group (n = 20)	Sham group (n = 18)	Pharyngocise group (n = 20)
Mean age, years (SD)	54 ± 11.3	60 ± 12.2	59 ± 10.4
Gender, n (%)			
Male	15 (75)	11 (61)	18 (90)
Female	5 (25)	7 (39)	2 (10)
Radiotherapy, n (%)			
Conventional radiotherapy	9 (45)	6 (33)	9 (45)
IMRT	11 (55)	12 (67)	11 (55)
Other treatment, n (%)			
Radiotherapy (any) plus chemotherapy	10 (50)	6 (33)	6 (30)
Neck dissection, n (%)	8 (40)	6 (33)	8 (40)
Mean radiotherapy dose, Gy (SD)	67.5 ± 2.5	69.2 ± 1.4	72.5 ± 1.2

Intervention

Standardised high intensity swallowing therapy (pharyngocise). This included a battery of exercises (e.g. falsetto, tongue press, hard swallow, and jaw resistance/strengthening using the Therabite Jaw Motion Rehabilitation system) and dietary modification, under the direction of the study speech pathologist, twice daily for the duration of treatment (up to a maximum of 6 weeks). Patients assigned to this group completed the four swallowing exercises in 10 repetitions over four cycles, each of 10 minutes in duration. The treatment sessions were 45 minutes in duration.

Comparison

Either:

(i) Usual care. This included patient management by the attending radiation oncologist "as usual". Treatment, if offered, consisted of supervision for feeding and precautions for safe swallowing (e.g. positioning, slowed rate of feeding) by the hospital speech pathology service. Patients in this group received focussed attentions sessions during the course of treatment from a research assistant, consisting of weekly telephone calls to monitor swallowing outcome.

(ii) Standardised sham therapy. This included a buccal extension manoeuvre ("valchuff") and appropriate dietary modification, under the direction of the study speech pathologist, twice daily for the duration of treatment. Patients assigned to this group completed the exercise for 10 repetitions over 4 cycles, each of 10 minutes duration. Treatment sessions were 45 minutes in duration.

Length of follow-up

6 months, but most outcomes are reported 6 weeks after baseline (no clear definition of "baseline" is given, but it is assumed to coincide with the beginning of (chemo)radiotherapy).

Outcome measures and effect size

	Usual care group (n = 14)	Sham group (n = 13)	Pharyngocise group (n = 14)
Mean change in swallowing ability, MASA score (± SD)	−24.16 ± 13.4	−20.8 ± 12.9	−17.7 ± 10.1
Mean change in mouth opening*	−4.3	−5.1	−1.6
Normal diet, n (%)	2 (14.3)	2 (15.4)	5 (35.7)
Nonoral feeding, n (%)	6 (42.9)	3 (23.1)	3 (21.4)
Functional swallowing, n (%)	2 (14.3)	2 (15.4)	6 (42.9)
> 10% weight loss, n (%)	6 (42.9)	6 (46.2)	4 (28.6)

MASA: Mann assessment of swallowing ability
*units/methods of measurement not reported.

All outcomes were measured 6 weeks after baseline; or as the change from baseline to 6 weeks.

Source of funding

Not reported; authors declared no conflicts of interest.

Risks of bias

Selection bias: Low risk
Performance bias: Low risk
Attrition bias: Low risk
Detection bias: Unclear/unknown risk

Additional comments

Study, country

Carroll 2008
United States, single centre.

Study type, study period

Retrospective cohort study.
Study period not reported.

Number of patients

18.

Patient characteristics

Inclusion criteria: patients with advanced squamous cell carcinoma of the oropharynx, hypopharynx or larynx treated with combined chemotherapy and radiotherapy to a minimum dose of 70 Gy.

All patients had PEG tubes placed prior to treatment.

	Intervention group (n = 9)	Control group (n = 9)
Mean age, years	57.5	60.7
Gender, n (%)		
Male	7 (77.8)	5 (55.6)
Female	2 (22.2)	4 (44.4)
Tumour site, n (%)		
Oropharynx	7 (77.8)	7 (77.8)
Larynx	2 (22.2)	1 (11.1)
Hypopharynx	0	1 (11.1)
Treatment, n (%)		
Concurrent CRT	3 (33.3)	4 (44.4)
Neoadjuvant CRT	5 (55.6)	3 (33.3)
Celecoxib protocol CRT	1 (11.1)	2 (22.2)

Intervention

Pretreatment swallowing exercises. Patients began swallowing exercises approximately two weeks prior to chemoradiotherapy.
Swallowing exercises included tongue-hold, tongue resistance, effortful swallow, Mendelsohn manoeuvre, and Shaker exercises.

Exercise schedule was 10 repetitions, 5 times per day (with the exception of the Shaker exercises; schedule not reported by the authors)

Comparison

Control group: patients were seen by the speech pathologist after completing chemoradiotherapy, and received posttreatment swallowing exercises as swallowing problems arose.

When exercises were assigned, it is assumed that the same exercise schedule was used as for the intervention group, but this is not made explicitly clear by the study authors.

Length of follow-up

Minimum 12 months. Most outcomes were assessed after 3 months.

Outcome measures and effect size

All outcomes were measured at 3 months by videofluoroscopy, with the exception of PEG tube placement.

	Intervention group (n = 9)	Control group (n = 9)
Aspiration, Rosenbeck score, mean ± SD (scale 1 to 8, better indicated by lower values)	4.11 ± 2.84	3.88 ± 2.20
Mean posterior tongue base position at rest, mm ± SD	26.48 ± 4.28	32.2 ± 7.99
Mean posterior tongue base position during swallow, mm ± SD	15.2 ± 5.47	22.0 ± 6.23
Mean posterior tongue base movement, mm ± SD	11.28 ± 3.69	10.29 ± 6.56
Mean vertical hyoid position at rest, mm ± SD	43.73 ± 5.90	42.8 ± 7.52
Mean vertical hyoid position during swallow, mm ± SD	24.97 ± 6.26	24.96 ± 5.59
Mean vertical hyoid movement, mm ± SD	18.75 ± 4.21	17.84 ± 8.19
Epiglottis inversion, n (%)	8 (89)	3 (33)
Mean cricopharyngeal opening, mm ± SD	8.07 ± 3.86	7.62 ± 3.95
PEG tube use 12 months after CRT, n (%)	3 (33)	4 (44)

Source of funding

Not reported.

Risks of bias

Selection bias: Low risk
Performance bias: Low risk
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

1

Study, country

Cavalot 2009
Italy, single centre.

Study type, study period

Retrospective cohort study.
1990 to 2000

Number of patients

43.

Patient characteristics

Inclusion criteria: patients with larynx carcinoma undergoing subtotal laryngectomy.

All patients had a nasogastric tube inserted immediately after surgery.

Average age: 62 years (range 44–82 years).

Gender	n (%)
Male	40 (93)
Female	3 (7)

T/N stage	n (%)
T1NO	29 (67)
T1N1	3 (7)
T2NO	2 (5)
T2N1	9 (21)

Intervention

Pre- and post-surgery swallowing therapy.

Comparison

Post-surgery swallowing therapy only.

Length of follow-up

Average 65 months (range 10–150 months).

Outcome measures and effect size

	Intervention group (n = 18)	Control group (n = 25)
Time to resumption of swallowing*, days ± SD	16.38 ± 2.9	27.76 ± 5.2

*All patients were able to resume swallowing and had their nasogastric tube removed.

Source of funding

Not reported.

Risks of bias

Selection bias: Unclear/unknown risk. Allocation to treatment based on time of recruitment into the study. Limited details of patient characteristics reported.
Performance bias: Low risk
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

1

2

Study, country

Duarte 2013
United States, single centre.

Study type, study period

Retrospective cohort study.
2007 to 2012.

Number of patients

85.

Patient characteristics

Inclusion criteria: head and neck cancer patients treated with either radiotherapy or chemoradiotherapy and who participated in a swallow preservation protocol.
Exclusion criteria: previous surgery; inadequate follow up; significant missing data.

	Compliant group (n = 57)	Noncompliant group (n = 28)
Mean age, years	60	61
Gender, n (%)		
Male	42 (73.7)	24 (85.7)
Female	15 (26.3)	4 (14.3)
Tumour site, n (%)		
Nasopharynx	12 (21.1)	3 (10.7)
Oral cavity	2 (3.5)	3 (10.7)
Oropharynx	33 (57.9)	20 (71.4)
Larynx	7 (12.3)	1 (3.6)
Unknown primary	3 (5.3)	1 (3.6)
Treatment, n (%)		
Radiotherapy	13 (22.8)	5 (17.9)
Chemoradiotherapy	44 (77.2)	23 (82.1)
Stage, n (%)		
0	1 (1.8)	0 (0)
1	1 (1.8)	1 (3.6)
2	2 (3.5)	1 (3.6)
3	9 (15.8)	5 (17.9)
4	37 (64.9)	16 (57.1)
Unknown/data missing	7 (12.3)	5 (17.9)
Pretreatment diet, n (%)		
Chew	49 (86.0)	20 (71.4)
Puree	5 (8.8)	4 (14.3)
Liquid	1 (1.8)	1 (3.6)
G-tube	2 (3.5)	3 (10.7)

All patients were assigned to a swallowing preservation protocol. Two weeks prior to cancer treatment, patients underwent swallow assessment that included education about expected treatment side effects, assessment for pretreatment dysphagia, and the introduction of an exercise programme. A swallow preservation exercise set was used, consisting of gargling liquid for 10 seconds, 10 times; effortful swallow 10 times; Mendelsohn manoeuvre 10 times; chug-a-lug 3 ounces at once; tongue protrusion 10 times; tongue press 10 times; and Shaker head lift 3 times. This set of exercises was to be performed three times daily except for the Shaker exercise (once daily). The last swallow preservation protocol clinical visit was at 2 months posttreatment.

Intervention

Compliance with swallowing preservation protocol. This was self-reported; patients used a form to track their exercises and brought this to each clinic visit. Compliance was defined as performing at least one full set of exercises per day.

Comparison

Noncompliance with swallowing preservation protocol. This was self-reported; patients used a form to track their exercises and brought this to each clinic visit. Noncompliance was defined as performing less than one full set of exercises per day.

Length of follow-up

Maximum 2 months.

Outcome measures and effect size

	Compliant group (n = 57)		Noncompliant group (n = 28)	
	1 month posttreatment	2 months posttreatment	1 month posttreatment	2 months posttreatment
Weight loss, % ± SD	8 ± 7.5	14.1 ± 19.1	8.6 ± 9.5	8.6 ± 9.2
Pain level on swallowing, scale 1–10 ± SD	3.5 ± 2.2	4.4 ± 2.6	3.4 ± 2.5	2.7 ± 1.3
Chewable diet tolerated, n (%)	31/57 (54.4)	NR	6/28 (21.4)	NR
Oral diet tolerated (chewable, liquid or puree), n (%)	NR	23/23 (71.9)	NR	12/24 (50%)
G-tube dependent	13/57 (22.8)	NR	15/28 (53.6)	NR

NR: not reported.

Source of funding

Public body grant.

Risks of bias

Selection bias: High risk. Patients 'self-allocated' to treatment group based on their compliance.
Performance bias: Low risk
Attrition bias: High risk. Number of patients in each group is not clear: Inconsistently reported as either 57 or 58 for the compliant group, and 28 or 31 for the noncompliant group. For some outcomes, it is unclear how many patients had data available. Dropout rate in compliant patients was high between months 1 and 2, possibly introducing bias into the outcome measurements recorded at 2 months.
Detection bias: Unclear/unknown risk. For some outcomes, the length of follow up is not clear.

Additional comments

1

Study, country

Hogdal 2015.
Denmark, single centre.

Study type, study period

Randomised controlled trial. February 2009 to November 2010.

Number of patients

100 recruited; 70 completed the study. In the usual care group, two patients withdrew consent and one died before the baseline assessment. Baseline data is therefore available for 47 patients in this group.

Patient characteristics

Inclusion criteria:

- Diagnosis of cancer of the oral cavity or oropharynx
- Aged 18 years or over
- Referred for curative radiotherapy
- Gave informed consent

Exclusion criteria:

- Operative reconstruction of bone or skin transplant
- Damage to neck or shoulder function during surgery
- Any other disease that could influence symptoms or adverse events in the temporomandibular joint
- Poor general condition that would impair ability to participate in the trial
- Inability to understand Danish
- Referral for palliative radiotherapy
- Lack of informed consent

	Exercise group (n = 50)	Usual care group (n = 47)
Gender, n (%)		
Male	37 (74)	33 (70)
Female	13 (26)	14 (30)
Tumour site, n (%)		
Oral cavity	8 (16	12 (26)
Oropharynx	42 (84)	35 (74)
Age, mean (SD)	58.6 (8.6)	58.5 (10.7)
Radiotherapy dose, mean Gy (SD)	67.2 (1.1)	66.8 (1.0)

For all patients, radiotherapy treatment lasted for 5–6 weeks, with either 5 or 6 weekly fractions and a dosage of 66–70 Gy.

Intervention

Preventative exercises (n = 50), including frequent daily slow dynamic exercises, stretching exercises, chewing gum and instructions in

lymphoedema self-drainage.

Patients received individual guidance and physiotherapist supervised exercises once a week for 45 minutes during the radiotherapy treatment period. The supervised physiotherapy sessions included exercises and instructions in lymphoedema self-drainage. For home training, all patients in the exercise group performed a standard programme consisting of seven exercises. Each exercise was carried out with five repetitions and should be performed five times per day. The patients were also instructed to use sugar free chewing gum five times a day for up to 10 minutes. Two months after the end of radiotherapy, the patients were instructed in self-administered lymph drainage and exercises for the following 10 months.

Comparison

Usual care (n = 47), consisting of treatments and advice offered by the oncologist and other healthcare providers, including instructions in mouth opening exercises by a nurse for approximately 10 minutes prior to the onset of radiotherapy.

Length of follow-up

12 months.

Outcome measures and effect size

	Exercise group	Usual care group	
Maximal intercisor distance at 12 months, unadjusted mean difference, mm (95% CI) (positive value favours exercise group)	-	-	0.83 (−3.64, 5.29)
Patients with trismus after 12 months, n (%)	14/40 (35)	11/36 (31)	p = 0.31

Source of funding

Public body research grants.

Risks of bias

Selection bias: Low risk.
Performance bias: Low risk.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

Study, country

Hutcheson 2013
United States

Study type, study period

Retrospective cohort study
2002 to 2008.

Number of patients

497.

Patient characteristics

Inclusion criteria: patients treated with definitive RT or CRT for pharyngeal cancer.

Subsite	n (%)
Oropharynx	458 (92%)
Hypopharynx	39 (8%)
Gastrostomy placed	**n (%)**
No	184 (37%)
Yes	313 (63%)

T-classification	n (%)
1	98 (20%)
2	170 (34%)
3	129 (26%)
4	100 (20%)
N-classification	**n (%)**
N0	31 (6%)
N1	55 (11%)
≥N2	370 (81%)
NX	5 (1%)

RT technique	n (%)
IMRT	452 (91%)
3D conformal	45 (9%)
RT schedule	**n (%)**
Standard	376 (76%)
Concomitant boost	121 (24%)
Chemotherapy	**n (%)**
None	116 (23%)
Induction	69 (14%)
Concurrent	234 (47%)
Induction + concurrent	78 (16%)

All patients were referred to a speech pathologist prior to treatment, and prescribed a standard swallowing exercise regimen targeting hyolaryngeal excursion, airway protection, and tongue base retraction. Specific exercises prescribed included a modified Shaker exercise, jaw stretch, supraglottic, Valsava manoeuvre, falsetto, lingual protrusion and retraction, yawn, gargle, Masako manoeuvre, and effortful swallows. Patients were asked to demonstrate competency with swallowing exercises to the speech pathologist and report their adherence to a daily exercise regimen. These details were recorded in the medical record by the speech pathologist.

Intervention

Adherence to swallowing exercises (n = 286). Patients who reported any (partial [<4 times/day] or full [≥4 times/day], per institutional protocols) exercise adherence were coded adherent.

Comparison

Nonadherence to swallowing exercises (n = 211). Patients who reported no swallowing exercise or did not keep their speech pathology appointment for exercise training (i.e., those who never saw the speech pathologist) were coded as nonadherent.

Length of follow-up

Median 22 months.

Outcome measures and effect size

	Intervention group (n = 286)	Control group (n = 211)	
Median duration of gastrostomy dependence, days (range)	68 (0–1815)	113 (0–1594)	p = 0.007[1]
Return to long-term regular diet, n (%)	242 (85)	160 (76)	p < 0.001[2]

[1]adjusted for T-classification, age, and baseline diet
[2]adjusted for T-classification, tumour site, age, and baseline diet

Source of funding

Public body grants. Authors declared no conflicts of interest.

Risks of bias

Selection bias: High risk. Grouping patients by adherence introduces potential bias in other patient characteristics. Any other differences between groups at baseline are not reported. Some attempts made to account for baseline differences by multivariate analysis, but the methods used are not clearly reported.
Performance bias: Low risk
Attrition bias: Unclear/unknown risk.
Detection bias: Low risk

Additional comments

1

Study, country

Kotz 2012
United States, single centre.

Study type, study period

Randomised trial.
July 2007 to January 2010.

Number of patients

26.

Patient characteristics

Inclusion criteria: patients scheduled for concurrent chemotherapy for newly diagnosed head and neck cancer.
Exclusion criteria: patients with a history of head and neck surgery, including tracheostomy, those who had previously undergone radiation treatment, and those with a history of neurological diseases that could affect swallowing function.

	Intervention group (n = 13)	Control group (n = 13)
Age, mean (SD), years	57 (10)	62 (11)
Gender, n (%)		
Male	10 (77)	10 (77)
Female	3 (23)	3 (23)
Primary site of tumour		
Base of tongue	6 (46)	5 (38)
Tonsil	4 (31)	7 (54)
Glottic larynx	0	1 (8)
Nasopharynx	1 (8)	0
Oropharyngeal wall	1 (8)	0
Unknown primary	1 (8)	0
Tumour stage		
2	1 (8)	0
3	3 (23)	2 (15)
4	9 (69)	11 (85)

Intervention

Prophylactic swallowing exercises (effortful swallow, two tongue base retraction exercises, the Super Supraglottic Swallow technique, and the Mendelssohn manoeuvre) initiated prior to the start of radiation. Patients were instructed to continue these specific swallowing exercises for the duration of their CRT.

Comparison

Standard care: referral to a head and neck speech pathologist for swallowing assessment and treatment if dysphagic symptoms were present after the completion of cancer treatment.

Length of follow-up

12 months.

Outcome measures and effect size

All figures are presented as median (range).

Assessment	Arm	Pre-CRT	Immediately after	3 Mo	6 Mo	9 Mo	12 Mo
Eating in public	**Intervention**	100	50 (0-100)	100 (75-100)	100	100 (75-100)	100 (75-100)
	Control	100	25 (0-100)	100 (25-100)	100 (25-100)	100 (75-100)	100 (75-100)
Normalcy of diet	**Intervention**	100 (50-100)	20 (0-100)	100 (40-100)	100 (50-100)	100 (50-100)	100 (50-100)
	Control	100	20 (0-80)	80 (30-100)	50 (30-100)	80 (30-100)	80 (30-100)
FOIS	**Intervention**	7 (6-7)	3 (1-7)	7 (5-7)	7 (6-7)	7 (6-7)	6 (5-7)
	Control	7 (6-7)	4 (1-6)	5 (3-7)	6 (3-7)	6 (5-7)	6 (5-7)

FOIS: functional oral intake scale.

Source of funding

Not reported. Authors declared no conflicts of interest.

Risks of bias

Selection bias: Unclear/unknown risk. Method of randomisation not reported; unclear whether allocation was adequately concealed.
Performance bias: Low risk.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

Study, country

Kulbersh 2006.
United States, single centre.

Study type, study period

Retrospective cohort study.
1999 to 2004.

Number of patients

37.

Patient characteristics

Inclusion criteria: patients undergoing primary radiation or chemoradiation treatment for previously untreated hypopharyngeal, laryngeal, or oropharyngeal cancer.

	Pretreatment group (n = 25)	Posttreatment group (n = 12)
Gender, n (%)		
Male	19 (76.0)	9 (75.0)
Female	6 (24.0)	3 (25.0)
Stage at diagnosis, n (%)		
T1	0 (0)	0 (0)
T2	7 (29.2)	5 (41.7)
T3	8 (33.3)	4 (33.3)
T4	9 (37.5)	1 (8.3)
Not reported	0 (0)	2 (16.7)
Primary site, n (%)		
Base of tongue	12 (48.0)	1 (8.3)
Tonsil	7 (28.0)	2 (16.7)
Oropharynx	2 (8.0)	1 (8.3)
Pharyngeal wall	2 (8.0)	3 (25.0)
Supraglottis/larynx	2 (8.0)	3 (25.0)
Nasopharynx	0 (0)	1 (8.3)
Neck	0 (0)	1 (8.3)
Age	55.1 ± 9.6	60.3 ± 10.0

All patients followed the same protocol of swallowing exercises, beginning 2 weeks prior to the start of radiotherapy: Mendelsohn manoeuvre, Shaker exercises, tongue hold, and tongue resistance. Falsetto phonation was also used in some patients. Exercises were performed for 10 repetitions, five times per day. The sustained Shaker exercise was performed three times and the repetitive Shaker exercise 30 times, five times per day.

Intervention

Pretreatment swallowing exercises (n = 25). Patients began the exercise protocol two weeks prior to the start of radiation therapy and returned to the clinic at two and six weeks into treatment to monitor progress and compliance.

Comparison

Posttreatment swallowing exercises (n = 12). Patients received the swallowing exercises at the first visit after initiation of their treatment.

Length of follow-up

Pretreatment group: median 9 months (range 6 to 12 months). Posttreatment group: median 14 months (range 6 to 20 months). Follow up period was defined as the time from completion of therapy to the time patients completed the MD Anderson Dysphagia Inventory (MDADI) survey.

Outcome measures and effect size

	Pretreatment group (n = 25)	Posttreatment group (n = 12)	P value
MDADI for Patients with Head and Neck Cancer scores*, unadjusted, mean (95% CI)			
Global assessment	71.7 (62.0, 81.3)	45.0 (31.3, 58.7)	0.003
Emotional	71.5 (66.0, 77.0)	57.5 (49.7, 65.3)	0.005
Functional	68.3 (62.4, 74.2)	61.3 (53.0, 69.7)	0.172
Physical	65.1 (57.8, 72.4)	49.0 (38.6, 59.3)	0.014
MDADI for Patients with Head and Neck Cancer scores, adjusted for age, T stage, site (tongue and tonsil vs. other), follow up time, treatment, race, and gender, mean (95% CI)			
Global assessment	74.4 (64.5, 84.3)	32.9 (17.0, 48.7)	0.0002
Emotional	72.1 (66.1, 78.0)	53.9 (44.3, 63.5)	0.005
Functional	68.7 (62.4, 75.1)	58.6 (48.5, 68.8)	0.114
Physical	66.4 (58.5, 74.3)	43.2 (30.6, 55.7)	0.005

*0 to 100 scale, 100 representing normal swallowing ability.

Source of funding

Not reported.

Risks of bias

Selection bias: Unclear/unknown risk. Patients allocated to treatment groups in a time-dependent manner.
Performance bias: Unclear/unknown risk. Unclear if treatment protocols were standardised throughout the study period
Attrition bias: High risk. Longer follow up period in the posttreatment group.
Detection bias: Low risk.

Additional comments

1

Study, country

Lazarus 2014.
United States, multiple centres.

Study type, study period

Randomised controlled trial.
Study period not reported.

Number of patients

23 randomised; results available for 18.

Patient characteristics

Inclusion criteria: patients with newly diagnosed AJCC stage II to IV oral or oropharyngeal cancer, undergoing radiotherapy with or without chemotherapy.

	n (%)
Gender	
Male	22 (96)
Female	1 (4)
AJCC stage	
II	1 (4)
III	3 (13)
IVA	16 (70)
IVB	3 (13)
Primary site	
Tonsil	11 (48)
Base of tongue	9 (39)
Lateral pharyngeal wall	2 (9)
Soft palate	1 (4)
Treatment type	
Chemoradiation	21 (91)
Radiation only	2 (9)

Both groups were instructed to perform prophylactic swallowing exercises once daily during radiotherapy. Patients then underwent six weeks of exercise starting one month after (chemo)radiotherapy.

Intervention

Tongue strengthening exercises with traditional therapy. Patients performed the same traditional therapy exercises as the control group, plus an isometric lingual resistance exercise programme utilizing active resistance in all directions with the tongue against a tongue depressor.

Comparison

Traditional therapy, consisting of tongue and laryngeal range of motion exercises (Mendelsohn manoeuvre).

Length of follow-up

6 weeks.

Outcome measures and effect size

	Intervention group (n = 8)	Control group (n = 10)*
OPSE score, mean ± SD		
Baseline	44.63 ± 16.69	59.60 ± 8.85
Post-treatment	46.50 ± 14.85	54.56 ± 20.08
Tongue strength, Kpa, mean ± SD		
Baseline	44.63 ± 13.39	49.30 ± 10.53
Post-treatment	46.50 ± 16.50	52.40 ± 10.78
Quality of life, HNCI scores, mean ± SD		
Speech, pretreatment	53.33 ± 19.04	72.27 ± 25.43
Speech, posttreatment	70.55 ± 24.68	72.00 ± 26.26
Eating, pretreatment	36.90 ± 18.98	40.71 ± 20.36
Eating, posttreatment	53.13 ± 22.29	49.60 ± 21.28
Social disruption, pretreatment	37.96 ± 24.69	62.12 ± 27.22
Social disruption, posttreatment	54.63 ± 29.20	66.67 ± 20.78

*OPSE score was recorded for 8/10 patients in the control group.
OPSE: oropharyngeal swallowing efficiency.
Pretreatment assessment was performed four weeks after chemoradiotherapy. Posttreatment assessment was performed 10 weeks after radiotherapy.

Source of funding

Public body grant.

Risks of bias

Selection bias: High risk. Unclear whether allocation was adequately concealed. For some outcomes, measurements taken at baseline showed differences between the two treatment groups.
Performance bias: Low risk.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

Study, country

Pauli 2014.
Sweden, five centres.

Study type, study period

Prospective cohort study.
2007 to 2012

Number of patients

101.

Patient characteristics

Inclusion criteria: patients newly diagnosed with head and neck cancer and treated with radiation therapy ± chemotherapy who developed trismus (defined as maximum interincisal opening (MIO) ≤ 35 mm)
Exclusion criteria: recurrent tumour, poor general health, difficulties in filling out questionnaires and edentulous patients.

	Intervention group (n = 50)	Control group n = 50 Mean (range)
Age mean (range)	57.9 (30–75)	58.0 (29–80)
Gender, n (%)		
Male	31 (62)	31 (62)
Female	19 (38)	19 (38)
Treatment regimen, n (%)		
Radiotherapy only	7 (14)	8 (16)
Radiochemotherapy	39 (78)	38 (76)
Radiotherapy + surgery	4 (8)	4 (8)
Time from radiation therapy, n (%)		
3 months	44 (88)	38 (76)
6 months	6 (12)	12 (24)
Tumour location, n (%)		
Oropharynx	38 (76)	38 (76)
Tumour colli	6 (12)	6 (12)
Oral cavity	1 (2)	1 (2)
Nasopharynx	5 (10)	5 (10)
Tumour staging, n (%)		
I	1 (2.3)	0 (0.0)
II	8 (18.2)	4 (9.1)
III	8 (18.2)	12 (27.3)
IV	27 (61.4)	28 (63.6)

Patients living in Gothenburg were included in the intervention group. The control group was comprised of patients living outside the

Gothenburg catchment area and was matched according to gender, tumour location, tumour stage, comorbidity, radiation dosage and age.

Intervention

Structured trismus exercises using a jaw device (n = 51). Patients followed a 10-week structured exercise program with exercise five times per day. The program consisted of three steps: 1) warm up movements consisting of jaw opening 10 times and small sideway movements of the jaws 10 times without using the jaw device; 2) passive stretching, with the jaw mobilizing device, 30 seconds (if possible), repeated five times; 3) five repetitions of active exercise (bite towards resistance). Patients were instructed to relax in between the sessions. Patients were instructed to gradually increase the amount and intensity of the exercises to avoid pain or injury. During the program, patients were evaluated by an oral surgeon with measurement of MIO after four and 10 weeks and in addition, three months after intervention commencement.

The patients in the intervention group were randomized into two exercise groups; one using the Therabite and one using the Engström jaw mobilizing device

Comparison

Standard care (n = 50). Patients followed their regional hospitals schedule for follow-up visits according to local guidelines, which included regular MIO measurements by the hospital dentist. No structured intervention program addressing trismus existed in the region at the time of the study. Any amount of exercise, any device used or attempt of improving the mouth opening performed in the control group was registered by the study coordinator.

Length of follow-up

3 months.

1

Outcome measures and effect size

MIO (mm)	Before intervention, mean (CI)	3-month follow-up, mean (CI)	Change in MIO (mm) (CI)	Change in MIO (%)
Study group	32.2 (31.2–33.2)	38.6 (36.8–40.4)	Δ 6.4 (4.8–8.0)	Δ 20.2 (15.1–25.3)
Control group	33.2 (32.0–34.4)	33.9 (32.7–35.1)	Δ 0.7 (< 0.3–1.7)	Δ 3.2 (1.4–7.8)
p-value	p <0.05	p <0.001	p <0.001	p <0.001

CI: confidence interval; MIO: maximum interincisal opening

	Before study group exercise			3-month follow-up				
	Intervention group Mean (CI)	Control group Mean (CI)	p	Intervention group Mean (CI)	Control group Mean (CI)	p	Intervention Diff Δ	Control Diff Δ
Jaw-related problems	41.4 (35.7–47.2)	41.5 (34.6–48.4)	ns	22.9 (17.3–28.6)	43.1 (36.9–49.3)	***	−18.5	+1.6
Eating limitation	46.5 (37.4–55.6)	40.0 (33.2–46.8)	ns	28.1 (21.4–34.9)	39.5 (32.7–46.2)	*	−18.4	−0.5
Muscular tension	26.3 (21.9–30.8)	23.8 (18.4–29.3)	ns	13.2 (9.5–16.9)	27.5 (21.9–33.1)	***	−13.2	+3.7
Facial pain								
Facial pain right now	24.3 (17.8–30.8)	20.7 (14.1–27.3)	ns	9.0 (4.5–13.5)	20.7 (15.0–26.3)	***	−15.3	0.0
Facial pain when worst last month (lm)	43.0 (35.5–50.5)	40.3 (33.0–47.6)	ns	22.7 (16.3–29.0)	30.7 (23.8–37.5)	ns	−20.3	−9.7
Facial pain average value (lm)	38.3 (31.9–44.8)	35.3 (28.1–42.5)	ns	21.0 (15.2–26.8)	30.0 (23.2–36.8)	ns	−17.3	−5.3
Facial pain interfering with social, leisure and family activities (lm)	24.0 (16.1–31.9)	23.5 (15.5–31.4)	ns	15.0 (7.1–22.9)	20.0 (13.1–26.9)	ns	−9.0	−3.6
Facial pain affecting ability to work (lm)	25.0 (16.8–33.2)	23.5 (15.1–31.8)	ns	13.5 (5.9–21.1)	21.0 (13.6–28.4)	*	−11.5	−3.6
Limitation in opening mouth (LOM)	49.0 (42.7–55.3)	45.0 (36.4–53.6)	ns	33.0 (25.9–40.1)	40.0 (33.1–46.9)	ns	−16.0	−5.0
LOM interfering with social, leisure and family activities (lm)	24.0 (17.7–30.3)	24.5 (16.8–32.2)	ns	16.5 (8.3–24.7)	26.5 (19.7–33.3)	**	−7.5	+2.0
LOM affecting ability to work (lm)	24.5 (16.4–32.6)	25.0 (17.0–33.0)	ns	14.0 (6.2–21.8)	22.0 (14.5–29.5)	*	−10.5	−3.0

Domains and single items range 0–100, where 100 indicates maximal amount of symptoms and 0 is equal to no symptoms; P-values indicate difference in mean scores between the intervention group and the control group, before intervention and at 3-month follow-up. *p < 0.05, **p < 0.01, ***p < 0.001. GTQ, Gothenburg Trismus Questionnaire.

Source of funding

Public body grants. Authors declared no conflicts of interest.
Risks of bias
Selection bias: Low risk. Performance bias: Low risk. Attrition bias: Low risk. Detection bias: Low risk.
Additional comments

1

Study, country
Rose 2009. Canada, single centre.
Study type, study period
Cohort study, assumed to be retrospective. Study took place over a three year period (dates not reported).
Number of patients
45.
Patient characteristics
Inclusion criteria: • Patients were newly referred, belonging to one of two radiation oncologists specializing in head and neck cancer. • Treatment was prescribed with a radical intent. All patients received radical radiotherapy either with or without chemotherapy. • Treatment plans included were bilateral to the head and neck, with or without electron boosts.

	Intervention group (n = 29)	Control group (n = 16)
Gender, %		
Male	72	75
Female	28	25
Age, %		
40-59	59	56
60-79	38	38
80-99	3	6
Primary site, %		
Tonsil	31	38
Tongue	31	17
Oropharynx	6	10
Larynx	6	14
Primary unknown	13	7
Floor of mouth/alveolus	6	10
Other	6	3

Intervention
Jaw exercises during radiotherapy treatment (n = 29). Patients were given standard instructions on a set of four jaw exercises by their radiation oncologist. The time at which patients commenced the exercises during their treatment is not clear. Patients were asked to perform the exercises twice a day and to continue doing them until their first follow-up appointment, wherein the radiation oncologist would encourage them to continue using the exercises indefinitely.
Comparison
No jaw exercises performed (n = 16).
Length of follow-up
Up to 36 months.
Outcome measures and effect size

	Jaw exercises (n = 29)	No jaw exercises (n = 16)
Dental gap, cm		
Baseline	4.12	3.73
1 month	4.30	3.52
2-3 months	3.50	4.02
6-7 months	3.94	3.74
10-12 months	3.77	3.33
18-24 months	3.73	3.00
24-36 months	4.42	2.73

Source of funding
Not reported.
Risks of bias
Selection bias: Unclear/unknown risk. Limited details of patient characteristics reported. Unclear if groups were comparable at baseline.

Performance bias: Unclear/unknown risk. Unclear if patients in different treatment groups received similar care other than for the intervention.
Attrition bias: Unclear/unknown risk. Unclear whether all patient were followed up for the full 36-month time period.
Detection bias: Unclear/unknown risk. Timing of outcome measurement is not clear: measurement of outcome is grouped into monthly ranges, rather than specific precise times.

Additional comments

1

Study, country

Tang 2010.
China, single centre.

Study type, study period

Randomised controlled trial.
November 2006 to November 2007.

Number of patients

46 patients recruited; results for three patients were excluded from the results due to poor compliance.

Patient characteristics

Inclusion criteria: patients diagnosed with nasopharyngeal cancer who received radiotherapy.
Exclusion criteria: patients with cancer relapse, metastases, other malignancies, neurovascular disease, demyelinating disease, infection of the nervous system, or any other oral or temporomandibular disease.

Mean age: 49 years (range 17 to 69 years).

	Intervention group (n = 22)	Control group (n = 21)
Gender, n (%)		
Male	32 (74)	
Female	11 (26)	
Post radiotherapy interval, years	4.6 ± 1.8	4.8 ± 1.6

Intervention

Rehabilitation exercises for dysphagia and trismus (n = 22). Patients receiving rehabilitation training during hospitalisation and continued exercises after discharge. Exercises included passive and active range of motion tongue exercises, therapeutic postures for swallowing, effortful swallow, Mendelsohn manoeuvre, active and passive jaw movement exercises.

Rehabilitation exercises were to be performed three times per day. Each exercise was repeatedly practised for 15 cycles for a total of 45 cycles per day. To encourage continued exercise once patients were discharged from hospital, patients were given a guideline booklet describing their exercise schedule, appointed a family member as a guardian to assist and encourage them with their exercise schedule, and recorded their training exercises using a specially designed calendar

Comparison

No rehabilitation exercises (n = 21).

Length of follow-up

Unclear. Outcomes are described as measured 'posttreatment' but it is unclear if this refers to the end of primary cancer treatment or the end of rehabilitative treatment.

Outcome measures and effect size

	Intervention group (n = 22)	Control group (n = 21)
Mean interincisor distance, cm ± SD		
Pretreatment	1.89 ± 0.69	1.8 ± 0.56
Posttreatment	1.7 ± 0.68	1.1 ± 0.36
Difference	-0.19 ± 0.5	-0.69 ± 0.56
Swallow function improved, n	17	9
Swallow function unchanged, n	5	8
Swallow function deteriorated, n	0	4

Source of funding

Government and public body grants.

Risks of bias

Selection bias: Unclear/unknown risk. Method of randomisation not reported; unclear whether allocation was adequately concealed. Very limited information on patient baseline characteristics.
Performance bias: Low risk.
Attrition bias: Unclear/unknown risk. Patients who were less than 85% compliant with the exercise programme were excluded from the results for the intervention group. It is not clear whether this was prespecified as part of the study protocol.
Detection bias: Unclear/unknown risk. Length of follow up is not clear

Additional comments

2

Study, country

Tuomi 2014a.
Sweden, multiple centres.

Study type, study period

Prospective cohort study.
Study period not reported.

Number of patients

20.

Patient characteristics

Inclusion criteria: male patients with stages T1–T3 glottic and supraglottic cancer treated with irradiation; good cognitive abilities; fluent Swedish speakers; able to complete questionnaires.

Characteristics	Study Group (n = 10)	Control Group (n = 10)
Age, years (range)	59 (38–79)	53 (35–67)
Radiation dose, Gy (range)	64.5 Gy (62.4–68)	63.2 Gy (62.4–64.6)
Tumour site, n (%)		
Glottic	7 (70)	8 (80)
Supraglottic	3 (30)	2 (20)
T-stage, n (%)		
T1	7 (70)	4 (40)
T2	2 (20)	4 (40)
T3	1 (10)	2 (20)
Smoking habits, n (%)		
Nonsmoker	5 (50)	5 (50)
Smoker	3 (30)	3 (30)
Quit smoking >12 months ago	2 (20)	2 (20)
Comorbidity (assessed with Adult Comorbidity Evaluation-27), n (%)		
None	6 (60)	5 (50)
Mild	2 (20)	4 (40)
Moderate	2 (20)	1 (10)
Severe	0 (0)	0 (0)

Intervention

Voice rehabilitation (n = 10). This was conducted according to a structured protocol and started approximately 1 month after completion of oncologic treatment. It included 10 specified voice rehabilitation sessions of 30 minutes each, spread over 10 weeks, and consisted of relaxation, respiration, posture, and phonation exercises. Patients were asked to follow-up with voice training at home between sessions.

Comparison

No voice rehabilitation (n = 10). Patients were followed with recordings and self-assessment of voice in parallel with the study group. The control group also received vocal hygiene advice.

Length of follow-up

6 months.

Outcome measures and effect size

	Intervention group (n = 10)	Control group (n = 10)
Fundamental frequency, Hz, median		
Pretreatment	105	140
Posttreatment	111	140
Difference	6	0
Jitter, median		
Pretreatment	0.5	0.625
Posttreatment	0.4	0.6
Difference	-0.1	-0.025
Shimmer, dB, median		
Pretreatment	0.49	0.48
Posttreatment	0.36	0.42
Difference	−0.13	−0.06
Harmonics-to-noise ratio, median		
Pretreatment	17	20
Posttreatment	18.1	17.8
Difference	1.1	−2.2
Maximum phonation time, seconds, median		
Pretreatment	14	8
Posttreatment	15.1	6.2
Difference	1.1	−1.8
Vocal fatigue, 100-mm visual analogue scale, median		
Pretreatment	68	44
Posttreatment	84	87
Difference	16	43
Loudness, 100-mm visual analogue scale, median		
Pretreatment	61	45
Posttreatment	78	52
Difference	17	7
Hoarseness, 100-mm visual analogue scale, median		
Pretreatment	75	42
Posttreatment	68	82
Difference	-9	40

Source of funding

Public body grants.

Risks of bias

Selection bias: High risk. For some outcomes, measurements taken at baseline showed differences between the two treatment groups.
Performance bias: Unclear/unknown risk. Patients were treated across different centres. Intervention followed a standard protocol, but it is not clear if patients' other care differed.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

Study, country

Tuomi 2014b.
Sweden, multiple centres.

Study type, study period

Randomised controlled trial.
2000 to 2011.

Number of patients

79 randomised, results available for 69.

Patient characteristics

Inclusion criteria:

- Male patients with laryngeal cancer who were to receive radiation therapy with curative intent, with or without chemotherapy
- Good cognitive ability
- Able to complete written questionnaires (in Swedish)
- Normal airways

	Intervention group (n = 33)	Control group (n = 36)
Age, years, mean (SD)	66.0 (12.7)	64.0 (9.9)
Comorbidity (assessed with Adult Comorbidity Evaluation-27), n (%)		
None	14 (42.5)	16 (44)
Mild	10 (30.5)	15 (42)
Moderate	9 (27)	5 (14)
Severe	0 (0)	0 (0)
Smoking, n (%)		
Smoker	12 (36)	18 (50)
Nonsmoker	21 (64)	18 (50)
Radiation therapy, n (%)		
Conventional	24 (73)	26 (72)
Hyperfractionated	9 (27)	10 (28)
Chemotherapy, n (%)		
Induction	2 (6)	1 (3)
T stage, n (%)		
Tis	0 (0)	2 (5.5)
T1	23 (69.7)	19
T2	8 (24.2)	10
T3	1 (3.0)	5
T4	1 (3.0)	0 (0)

Intervention

Voice rehabilitation (n = 33). A study-specific protocol was used consisting of a combination of direct and indirect therapy approaches including, but not limited to, diaphragmatic breathing, coordination of breathing and phonation, control and variation of pitch, general relaxation, and vocal hygiene. Between voice rehabilitation sessions, patients were instructed to perform the exercises at home.

Comparison

The control group (n = 36) did not receive and voice rehabilitation but were given vocal hygiene advice.

Length of follow-up

6 months

Outcome measures and effect size

	Intervention group (n = 33)	Control group (n = 36)	p value
Harmonics-to-noise ratio, mean (SD)			
Baseline	17.1 (5.4)	17.7 (5.0)	0.822
At follow up	17.2 (6.9)	15.4 (6.2)	0.165
Change from baseline to follow up	0.1 (7.1)	-1.4 (6.8)	0.329
Jitter, mean (SD)			
Baseline	0.98 (0.91)	1.03 (1.77)	0.445
At follow up	1.34 (1.90)	1.43 (2.23)	0.758
Change from baseline to follow up	0.36 (1.91)	0.14 (2.49)	0.640
Shimmer, mean (SD)			
Baseline	0.54 (0.35)	0.52 (0.28)	0.807
At follow up	0.63 (0.52)	0.66 (0.52)	0.679
Change from baseline to follow up	0.09 (0.58)	0.09 (0.47)	0.741
Fundamental frequency, mean (SD)			
Baseline	124.6 (27.5)	122.8 (26.0)	0.908
At follow up	106.8 (19.0)	107.3 (23.6)	0.735
Change from baseline to follow up	-16.05 (20.38)	-17.0 (29.5)	0.735
Maximum phonation time, mean (SD)			
Baseline	15.3 (8.7)	10.5 (8.3)	0.015
At follow up	14.9 (9.2)	13.5 (13.4)	0.152
Change from baseline to follow up	-0.4 (6.1)	1.3 (6.6)	0.243
S-SECEL score, environmental domain, mean (SD)			
Baseline	16.4 (7.5)	10.5 (8.1)	0.002
At follow up	9.6 (7.3)	12.0 (8.3)	0.206
Change from baseline to follow up	-6.8 (6.7)	1.6 (7.7)	<0.001
Hoarseness (patient-reported 100-mm visual analogue scale), mean (SD)			
Baseline	39.0 (24.5)	47.9 (26.2)	0.112
At follow up	56.0 (23.1)	47.8 (24.2)	0.158
Change from baseline to follow up	18.3 (26.8)	2.1 (19.3)	0.002
Adequate loudness (patient-reported 100-mm visual analogue scale), mean (SD)			
Baseline	43.5 (22.9)	51.3 (25.8)	0.136
At follow up	61.0 (24.4)	55.2 (20.9)	0.303
Change from baseline to follow up	19.0 (24.6)	4.7 (20.5)	0.009

Source of funding

Public body grants.

Risks of bias

Selection bias: High risk. Unclear whether allocation was adequately concealed. For some outcomes, measurements taken at baseline showed differences between the two treatment groups.
Performance bias: Unclear/unknown risk. Patients were treated across different centres. Intervention followed a standard protocol, but it is not clear if patients' other care differed.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

Study, country

van der Molen 2014
Netherlands, single centre.

Study type, study period

Randomised controlled trial.
Patients were recruited within a 20 month period beginning in the second half of 2006.

Number of patients

55 randomised. At 10-weeks, 1-year, and 2-years results were available for 49, 37, and 29 patients, respectively. However, all results (even those at earlier time points) presented are assumed to represent the 29 patients followed for the whole 2-year period (see additional comments/risks of bias).

Patient characteristics

Inclusion criteria: patients with advanced (stages III and IV) squamous cell carcinoma of the head and neck (oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx tumours) treated with concomitant chemoradiotherapy.

	Control group (standard treatment, n = 25)	Intervention group (experimental treatment, n =24)	Total
Age (years)			
Mean	57	56	57
Range	32–75	37–78	32–78
Gender			
Male	16	23	39 (80)
Female	9	1	10 (20)
T Classification			
T1	5 (20)	3 (13)	8 (16)
T2	8 (32)	7 (29)	15 (31)
T3	8 (32)	11 (46)	19 (39)
T4	4 (16)	3 (13)	7 (14)
N Classification			
N0	1 (4)	3 (13)	4 (8)
N1	9 (36)	5 (21)	14 (29)
N2	13 (52)	13 (53)	26 (53)
N3	2 (8)	3 (13)	5 (10)
Stage (UICC)			
III	9 (36)	7 (29)	16 (33)
IV	16 (64)	17 (71)	33 (67)
Tumour site			
Oral cavity/oropharynx	12 (47)	12 (50)	24 (49)
Tongue	2 (8)		2 (4)
Retromolar trigone	1 (4)		1 (2)
Base of tongue	4 (16)	6 (25)	10 (20)
Tonsil	3 (12)	3 (13)	6 (12)
Soft palate	1 (4)		1 (2)
Pharynx posterior wall		3 (13)	3 (6)
Valleculae	1 (4)		1 (2)
Laryngo/hypopharynx	9 (37)	9 (37)	18 (37)
Pyriform sinus	8 (32)	8 (33)	16 (33)
Hypopharynx posterior wall		1 (4)	1 (2)
Supraglottic larynx	1 (4)		1 (2)
Nasopharynx	4 (16)	3 (13)	7 (14)

Intervention

Experimental rehabilitation. Stretch exercise (passive and slow opening of the mouth using a TheraBite device) and strengthening exercise (swallowing with the tongue elevated to the palate while maintaining mouth opening at 50% of its maximum).

Comparison

Standard rehabilitation, consisting of range-of-motion exercises and three strengthening exercises, i.e., the effortful swallow, the Masako manoeuvre, and the super-supraglottic swallow.

Length of follow-up

Median 114 weeks, range 102 to 155 weeks.

Outcome measures and effect size

	Intervention group (n = 15)	Control group (n = 14)
Aspiration or penetration rates*, %		
Baseline	0	18
10 weeks	18	9
1 year	9	18
2 years	0	9
Feeding tube, %		
Baseline	0	0
10 weeks	40	43
1 year	7	0
2 years	0	0
Abnormal diet (FOIS score 1-6), %		
Baseline	0	21
10 weeks	67	43
1 year	13	0
2 years	17	14
Trismus, %		
Baseline	0	21
10 weeks	13	7
1 year	0	7
2 years	0	14
Mouth opening, mm (range)		
Baseline	53.7 (45-69)	49.7 (26-67)
10 weeks	49.5 (27-65)	48.3 (12-65)
1 year	52.1 (38-70)	49.6 (20-70)
2 years	53.1 (38-70)	48.7 (20-65)

*results available for 14 and 11 patients in the intervention group and control group, respectively

Source of funding

Partially funded by an unrestricted research grant from Atos Medical.

Risks of bias

Selection bias: High risk. Method of randomisation not reported; unclear whether allocation was adequately concealed. Some outcomes differed between groups at baseline.
Performance bias: Low risk.
Attrition bias: High risk. Data not reported for all patients (see additional comments below).
Detection bias: Low risk.

Additional comments

The most recently published results for this study (van der Molen 2014) include outcomes at 10 weeks, 1 year and 2 years. Only patients who were followed up for the entire 2 years are included in the analysis, i.e. patients who have 10-week/1-year data available are excluded. Reasons for this approach are not made clear by the study authors. An earlier publication (van der Molen 2011) focuses on outcomes at 10 weeks, but does not include any comparison of the two intervention groups.

For dichotomous outcomes, the results are reported as percentages rather than a proportion of overall patient numbers.

1

Study, country

van Gogh 2006.
Netherlands, single centre.

Study type, study period

Quasi-randomised controlled trial (patients allocated to treatment in the order of presentation).
One year study period (dates not specified).

Number of patients

29 patients randomised, results available for 23.

Patient characteristics

Inclusion criteria: patients who received treatment for early (carcinoma in situ [Tis], T1N0M0, or T2N0M0) glottic carcinoma at least 6 months previously with either radiotherapy or endoscopic laser surgery, and who had developed voice impairment.

	Intervention group (n = 12)	Control group (n = 11)
Gender, n (%)		
Male	12 (100)	11 (100)
Female	0 (100)	0 (100)
Treatment, n (%)		
Radiotherapy	9 (75)	8 (72)
Laser surgery	3 (25)	3 (28)
Age, mean (range)	67 (55-80)	58 (40-80)
Average posttreatment time, months (range)	31 (6-81)	42 (6-120)

Intervention

Voice therapy (n = 12), up to 24 sessions (lasting 30 minutes) with a speech pathologist. The type of voice therapy could be chosen freely according to the patient's needs. Therapeutic sessions mainly consisted of voice and breathing exercises and vocal hygiene. Specific voice exercises took up > 50% of the treatment time.

Comparison

No voice therapy (n = 11)

Length of follow-up

Maximum of 3 months. Patients were assessed at baseline and again either at 3 months or at the end of their course of voice therapy.

Outcome measures and effect size

	Control group		Voice-therapy group	
	Study entry assessment	Study exit assessment	Study entry assessment	Study exit assessment
Voice Handicap Index, mean (SD)				
Total score	29.45 (13.34)	26.82 (15.04)	39.67 (16.17)	24.42 (10.26)
Acoustic analyses, mean (SD)				
Fundamental frequency	131 (27)	127 (19)	118 (44)	124 (33)
Noise-to harmonics ratio	0.18 (0.042)	0.18 (0.057)	0.20 (0.064)	0.14 (0.021)
Jitter	1.39 (0.59)	1.70 (1.15)	2.20 (1.50)	1.39 (1.32)
Shimmer	8.56 (5.82)	7.48 (2.09)	7.26 (3.20)	5.094 (1.12)
Voice-Range Profile, mean (SD)				
Intensity range	28.4 (6.6)	30.4 (6.3)	32.2 (8.02)	31.8 (7.9)
Pitch range	20.7 (6.1)	21.9 (4.8)	23.7 (5.2)	21.9 (3.3)

	Control group		Voice-therapy group	
	Study entry assessment	Study exit assessment	Study entry assessment	Study exit assessment
Communicative suitability, median (SD)				
Talking with a friend	6.45 (1.15)	6.37 (1.51)	6.19 (1.23)	6.26 (1.53)
Asking a passer-by	6.44 (1.11)	6.53 (1.30)	6.23 (1.07)	6.29 (1.31)
Giving a lecture	5.85 (1.31)	5.65 (1.53)	5.71 (1.30)	5.64 (1.50)
Perceptual voice quality scores, median				
Breathiness	1	1	0.5	0
Roughness	1	1	1	1
Vocal fry	2	2	3	2

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Patients were allocated to treatment in the order of presentation; this is not a truly random method of allocation. Unclear whether allocation was concealed.
Performance bias: Low risk.
Attrition bias: Unclear/unknown risk. The time at which outcomes were assessed after intervention is not clear. This is stated as either three months, or after a patient's course of voice therapy (the length of the voice therapy course, and whether this varied between patients, is not reported
Detection bias: Low risk.

Additional comments

1

Study, country

Virani 2014
United States, single centre.

Study type, study period

Prospective cohort study. December 2010 to January 2012.

Number of patients

50.

Patient characteristics

Inclusion criteria:

- Diagnosis of cancer of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, and/or nodal disease
- Evidence of functional swallowing ability before initiation of radiotherapy/chemotherapy
- No prophylactic PEG tube placement

Exclusion criteria:

- Diminished ability to comprehend and perform therapy tasks
- Dysphagia warranting PEG tube placement before initiation of radiotherapy/chemotherapy

	Exercise group (n = 26)	Swallow group (n = 24)
Gender, n (%)		
Male	19 (73)	21 (87.5)
Female	7 (27)	3 (12.5)
Tumour site, n (%)		
Oral cavity	2 (8)	2 (9)
Nasopharynx	1 (4)	1 (4)
Oropharynx	9 (34)	12 (50)
Hypopharynx	2 (8)	1 (4)
Larynx	7 (27)	6 (25)
Unknown	5 (19)	2 (8)
Age, mean (range)	64 (24-90)	60 (43-85)

All patients attended 45-minute swallowing therapy sessions once weekly during radiotherapy/chemotherapy. During the session, patients completed 50% of their allocated therapy for the day under the study coordinator's supervision and clarified any questions regarding their swallowing.

Intervention

Exercise group (n = 26). Exercises included the Masako exercise (10 repetitions, 7 sets daily), pharyngeal squeeze (10 repetitions, 7 sets daily), and Shaker exercise (3 sets daily).

Comparison

Swallowing group (n = 24). Thirty-four swallows of saliva and/or water, 7 sets daily.

Length of follow-up

3 months.

Outcome measures and effect size

	Exercise group (n = 26)	Swallow group (n = 24)	
PEG tube use at completion of treatment	8 (31)	13 (54)	p = 0.094
PEG tube use at 3 months post-treatment	4 (16)	12 (50)	P = 0.016
Post-treatment FOIS score, mean	3.8	3.7	P = 0.571

FOIS: functional oral intake scale

Source of funding

Not reported

Risks of bias

Selection bias: Unclear/unknown risk. Patients allocated to alternate treatment groups in the order of recruitment.
Performance bias: Unclear/unknown risk. The cancer treatment received by patients was not reported.
Attrition bias: Low risk.
Detection bias: Unclear/unknown risk. Unclear if 3 months of follow up is sufficient. Methods used to measure outcomes are not clearly defined.

Additional comments

2

Study, country

Zhen 2012.
China, single centre.

Study type, study period

Prospective cohort study.
September 2007 to December 2009.

Number of patients

46.

Patient characteristics

Inclusion criteria:

- Tongue cancer patients who had undergone tongue resection and rehabilitation
- Complete would healing after surgery, allowing for functional training
- Able to receive oral nutrition and hydration
- MD Anderson Dysphagia Inventory (MDADI) score of 60 or lower

	Intervention group (n = 23)	Control group (n = 23)
Gender, n (%)		
Male	17 (73.9)	14 (60.9)
Female	6 (26.1)	9 (39.1)
Tumour stage, n (%)		
I	3 (13.0)	3 (13.0)
II	5 (21.7)	5 (21.7)
III	11 (47.8)	10 (43.5)
IV	4 (17.4)	5 (21.7)
Level of tongue resection and rehabilitation, n (%)		
≥50%	10 (43.5)	9 (39.1)
<50%	13 (56.5)	14 (60.9)

Intervention

Swallowing therapy and training (n = 23). General swallowing therapy sessions, each lasting 30 minutes, 6 days per week for 2 weeks. Therapy commenced 2 to 3 weeks after surgery and included compensatory swallowing strategies and indirect therapies.

Comparison

No swallowing therapy (n = 23).

Length of follow-up

Not clear. Authors state that "postoperative studies were performed 2 to 3 weeks and 1 to 4 months following surgery". It is therefore assumed that patients were followed up for 1 to 4 months.

Outcome measures and effect size

Subgroup: tongue rehabilitation ≥50%

	Intervention group (n = 9)	Control group (n = 10)	p
MDADI scores, median			
Global	64.56 ± 3.28	60.60 ± 2.84	0.012
Emotional	61.22 ± 2.95	57.50 ± 2.27	0.006
Functional	69.78 ± 3.77	68.60 ± 4.33	0.537
Physical	67.00 ± 2.87	62.00 ± 3.56	0.004

Subgroup: tongue rehabilitation <50%

	Intervention group (n = 14)	Control group (n = 13)	p
MDADI scores, median			
Global	57.07 ± 4.14	52.92 ± 5.12	0.029
Emotional	54.36 ± 6.11	48.85 ± 4.56	0.014
Functional	61.50 ± 3.25	60.77 ± 4.51	0.632
Physical	58.07 ± 3.29	52.92 ± 4.01	0.001

MDADI: MD Anderson Dysphagia Inventory.

Data were presented according to subgroup only. The authors state that MDADI scores were significantly ($p < 0.05$) higher in controls than in the experimental group, but individual MDADI scores are not presented.

Source of funding

Not stated; authors declared no conflicts of interest and no competing funding interest.

Risks of bias

Selection bias: Unclear/unknown risk. Limited details of patient characteristics reported. Unclear if measured outcomes were comparable at baseline.
Performance bias: Low risk.
Attrition bias: Unclear/unknown risk. Length of follow up is not clearly described. It is unclear whether patients in each treatment group were followed up for comparable lengths of time.
Detection bias: Low risk.

Additional comments

1

Evidence search details and references

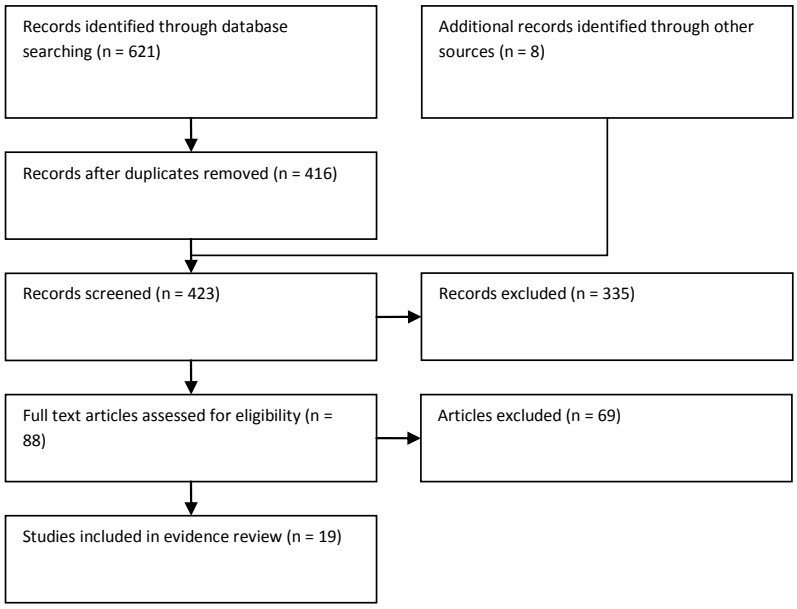
Review question in PICO format

Population	Intervention	Comparison	Outcomes
Adults with a diagnosis of cancer of the upper aerodigestive tract. Subgroups: • site • tumour stage • point on care pathway • treatment modality	Active speech and language support • FEES (functional endoscopic evaluation of swallowing) • Swallowing exercises • Range of motion exercises	Each other Nothing	• Voice quality • Speech intelligibilty • Oral diet • Good mouth opening • Reduced aspiration rates • Safe swallow • Dysphagia • Quality of life • Enteral feeding

Additional review protocol details (refer to Section 10 for full review protocol)

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.
Search strategies	Search from 2000 onwards
Review strategies	The evidence tables for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, and duration of treatment will be important considerations for the review.

Figure 7.2. Study flow diagram



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Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

Logemann, J. A., Rademaker, A., Pauloski, B. R., Kelly, A., Stangl-McBreen, C., Antinoja, J., Grande, B., Farquharson, J., Kern, M., Easterling, C., and Shaker, R. A randomized study comparing the Shaker exercise with traditional therapy: a preliminary study. Dysphagia 2009. 24(4): 403-411.
Reason for exclusion: Population not relevant to PICO.

McCabe, D. Ashford. Evidence-based systematic review: Oropharyngeal dysphagia behavioral treatments. Part IV - Impact of dysphagia treatment on individuals' postcancer treatments. Journal of Rehabilitation Research and Development 2009. 46(2): 205-214.
Reason for exclusion: Systematic review. Included studies not relevant to PICO.

Mittal, B. B., Pauloski, B. R., Haraf, D. J., Pelzer, H. J., Argiris, A., Vokes, E. E., Rademaker, A., Logemann, J. A. Swallowing dysfunction--preventative and rehabilitation strategies in patients with head-and-neck cancers treated with surgery, radiotherapy, and chemotherapy: a critical review. [Review] [125 refs]. International Journal of Radiation Oncology, Biology, Physics 2003. 57(5): 1219-1230.
Reason for exclusion: Editorial/narrative review.

Molen, L., Rossum, M. A., Burkhead, L. M., Smeele, L. E., Rasch, C. R., and Hilgers, F. J. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia 2011. 26: 155-170.
Reason for exclusion: Superceded by later study results.

Molen, L., Rossum, M. A., Rasch, C. R. N., Smeele, L. E., and Hilgers, F. J. M. A randomized controlled trial investigating preventive swallowing exercises in advanced head and neck cancer treated with chemoradiotherapy: 1-year functional outcomes*. Dysphagia 2011. 26: 483.
Reason for exclusion: Superceded by results from van der Molen, 2014.

Ouyoung, L., V. Improved swallowing outcomes in tongue cancer patients using exercise-based dysphagia training and neuromuscular electrical stimulation (NMES). Dysphagia 2011. Conference(var.pagings): 475.
Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

Paleri, V., Roe, J. W. G., Strojan, P., Corry, J., Gregoire, V., Hamoir, M., Eisbruch, A., Mendenhall, W. M., Silver, C. E., Rinaldo, A., Takes, R. P., and Ferlito, A. Strategies to reduce long-term postchemoradiation dysphagia in patients with head and neck cancer: An evidence-based review. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck 2014. 36(3): 431-443.
Reason for exclusion: Editorial/narrative review.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Editorial/narrative review.

Peng, K. A. W. A swallow preservation protocol improves function for veterans receiving chemoradiation for head and neck cancer. Otolaryngology - Head and Neck Surgery (United States) 2014. Conference(var.pagings): P66.
Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

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Reason for exclusion: Comparison not relevant to PICO.

Perry, A. R., Shaw, M. A. Evaluation of functional outcomes (speech, swallowing and voice) in patients attending speech pathology after head and neck cancer treatment(s): development of a multi-centre database. Journal of Laryngology & Otology 2000. 114(8): 605-615.
Reason for exclusion: Superceded by later study results.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Unclear if included population is relevant to PICO.

Roe, J. W. G. Prophylactic swallowing exercises for patients receiving radiotherapy for head and neck cancer. Current Opinion in Otolaryngology and Head and Neck Surgery 2011. 19(3): 144-149.
Reason for exclusion: Editorial/narrative review.

Sahin, M. A novel esophageal speech retraining method in patients with total laryngectomy: The role of bio-feedback by intraesophageal impedance. Gastroenterology 2012. Conference(var.pagings): S36.
Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

Sanfilippo, N. J. and Lazarus, C. Tongue Strength and Swallowing Dysfunction in Head and Neck Cancer Patients after Radiation Therapy. International Journal of Radiation Oncology Biology Physics 2010. 78(3): S452-S452.
Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

Scherpenhuizen A, van Waes AM, Janssen LM, Van Cann EM, Stegeman I. The effect of exercise therapy in head and neck cancer patients in the treatment of radiotherapy-induced trismus: A systematic review. Oral Oncol 2015;epub ahead of print.
Reason for exclusion: Systematic review. Inclusion criteria differ from those of this review. Studies within checked for relevance.

Schindler, A., Ginocchio, D., Peri, A., Felisati, G., and Ottaviani, F. FEESST in the rehabilitation of dysphagia after partial laryngectomy. Ann Otol Rhinol Laryngol 2010. 119(2): 71-76.
Reason for exclusion: Non comparative study.

Shinn E. The effect of adherence to swallowing exercises on swallowing outcomes in head and neck cancer patients treated with radiotherapy. Dysphagia 2011. Conference(var.pagings): 443.
Reason for exclusion: Conference abstract only - full study results subsequently published.

Shinn, E. H., Basen-Engquist, K., Baum, G., Steen, S., Bauman, R. F., Morrison, W., Garden, A. S., Sheil, C., Kilgore, K., Hutcheson, K. A., Barringer, D., Yuan, Y., Lewin, J. S. Adherence to preventive exercises and self-reported swallowing outcomes in post-radiation head and neck cancer patients. Head & Neck 2013. 35(12): 1707-1712.
Reason for exclusion: Comparison not relevant to PICO.

Singer, S., Merbach, M., Dietz, A., and Schwarz, R. Psychosocial determinants of successful voice rehabilitation after laryngectomy. Journal of the Chinese Medical Association 2007. 70(10): 407-423.
Reason for exclusion: Editorial/narrative review.

Singer, S., Wollbruck, D., Dietz, A., Schock, J., Pabst, F., Vogel, H. J., Oeken, J., Sandner, A., Koscielny, S., Hormes, K., Breitenstein, K., Richter, H., Deckelmann, A., Cook, S., Fuchs, M., and Meuret, S. Speech rehabilitation during the first year after total laryngectomy. Head & Neck 2013. 35(11): 1583-1590.
Reason for exclusion: Comparison not relevant to PICO.

Speyer, R. Effects of Voice Therapy: A Systematic Review. Journal of Voice 2008. 22(5): 565-580.
Reason for exclusion: Systematic review. No quantitative outcome data included. References checked for relevance.

Speyer, R., Baijens, L., Heijnen, M., and Zwijnenberg, I. Effects of Therapy in Oropharyngeal Dysphagia by Speech and Language Therapists: A Systematic Review. Dysphagia 2010. 25(1): 40-65.
Reason for exclusion: Systematic review. No quantitative outcome data included. References checked for relevance.

Starmer, H. M., Gourin, C. G. Is speech language pathologist evaluation necessary in the nonoperative treatment of head and neck cancer?. [Review]. Laryngoscope 2013. 123(7): 1571-1572.
Reason for exclusion: Editorial/narrative review.

Starmer, H. M. Dysphagia in head and neck cancer: prevention and treatment. Current Opinion in Otolaryngology & Head & Neck Surgery 2014. 22(3): 195-200.
Reason for exclusion: Editorial/narrative review.

Tuomi, L. Vocal rehabilitation after radiotherapy for laryngeal cancer-pilot study. Otolaryngology - Head and Neck Surgery (United States) 2012. Conference(var.pagings): August.
Reason for exclusion: Conference abstract only - full study results subsequently published.

Tuomi, L. Voice rehabilitation: Is it effective in the patient's point of view? Otolaryngology - Head and Neck Surgery (United States) 2013. Conference(var.pagings): P161.
Reason for exclusion: Study design not relevant.

van der Molen, L. A randomized controlled trial investigating preventive swallowing exercises in advanced head and neck cancer treated with chemoradiotherapy: 1-year functional outcomes*. Dysphagia 2011. Conference(var.pagings): 483.
Reason for exclusion: Duplicate record.

van der Molen, L., van Rossum, M. A., Burkhead, L. M., Smeele, L. E., and Hilgers, F. J. M. Functional outcomes and rehabilitation strategies in patients treated with chemoradiotherapy for advanced head and neck cancer: a systematic review. European Archives of Oto-Rhino-Laryngology 2009. 266(6): 889-900.
Reason for exclusion: Systematic review - inclusion criteria not relevant to this evidence review.

van der Molen, L., van Rossum, M. A., Rasch, C. R., Smeele, L. E., Hilgers, F. J. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. European Archives of Oto-Rhino-Laryngology 2014. 271(5): 1257-1270.
Reason for exclusion: Duplicate record.

van Gogh, C. D., Verdonck-de Leeuw, I. M., Langendijk, J. A., Kuik, D. J., and Mahieu, H. F. Long-term efficacy of voice therapy in patients with voice problems after treatment of early glottic cancer. Journal of Voice 2012. 26(3): 398-401.
Reason for exclusion: No comparative outcome data reported.

Varghese, B. T., Mathew, A., Sebastian, P., Iype, E. M., Vijay, A. Comparison of quality of life between voice rehabilitated and nonrehabilitated laryngectomies in a developing world community. Acta Oto-Laryngologica 2011. 131(3): 310-315.
Reason for exclusion: Intervention/comparison not relevant to PICO.

Virani, A. Kunduk. Effects of performing two different prophylactic swallowing exercise protocols on swallowing outcomes post-chemoradiation therapies for head and neck cancers. Dysphagia 2013. Conference(var.pagings): 605.
Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

Xi, S. Effectiveness of voice rehabilitation on vocalisation in postlaryngectomy patients: a systematic review. [Review]. International Journal of Evidence-Based Healthcare 2010. 8(4): 256-258.
Reason for exclusion: Systematic review - insufficient outcome data reported. References checked for relevance.

Economic evidence - The most appropriate nutritional and speech and language support for people having treatment for cancer of the upper aerodigestive tract.

Review question

Which active speech and language therapy interventions are of most benefit to patients with cancer of the upper aerodigestive tract?

Table 7.20. PICO table for the most appropriate nutritional and speech and language support for people having treatment for cancer of the upper aerodigestive tract

Population	Intervention	Comparison	Outcomes
Adults with a diagnosis of cancer of the upper aerodigestive tract. Subgroups: • Site • Tumour stage • Point on care pathway • Treatment modality	Active speech and language support • FEES (functional endoscopic evaluation of swallowing) • Swallowing exercises • Range of motion exercises	Each other Nothing	• Voice quality • Speech intelligibility • Oral diet • Good mouth opening • Reduced aspiration rates • Safe swallow • Dysphagia • Quality of life • Enteral feeding

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO
- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

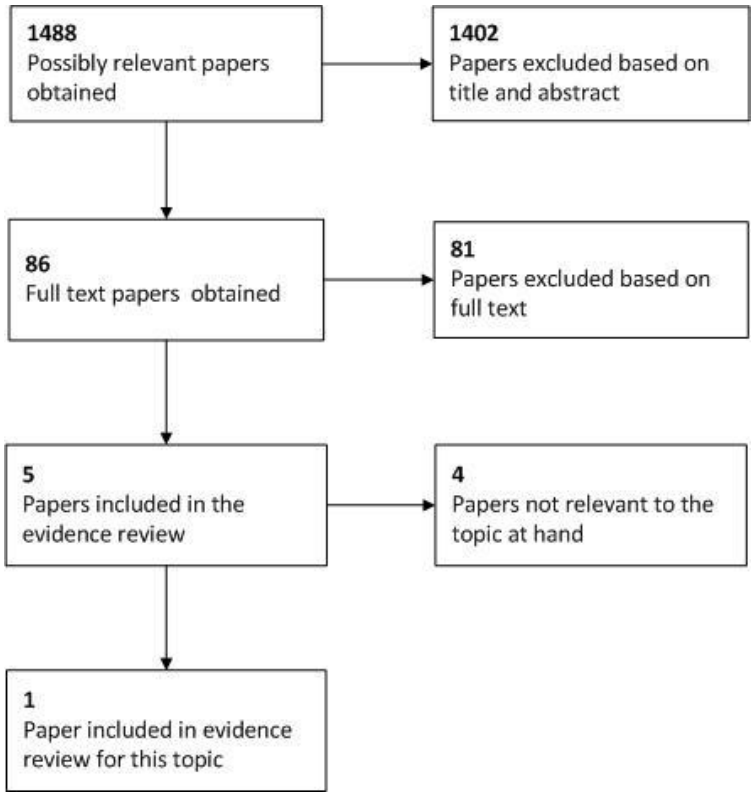
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below shows the search results and sifting process.

Figure 7.3. Summary of evidence search and sifting process for this topic



It can be seen that, in total, 1488 possibly relevant papers were identified. Of these, 1402 papers were excluded at the initial sifting stage based on the title and abstract while 86 full papers were obtained for appraisal. A further 81 papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, five papers were included in the systematic review of the economic evidence for this guideline.

One of these five papers related to the topic at hand and was thus included in the review of published economic evidence for this topic; Retel et al. 2011. The study included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

Quality and applicability of the included study

Retel et al. 2011 was deemed to be only partially applicable to the decision problem that we are evaluating because a healthcare system other than the UK was considered (Netherlands) and not all utility values were directly reported by patients (as recommended by NICE).

Potentially serious limitations were identified with the analysis, including the use of assumptions to quantify the QoL benefit associated with preventive swallowing exercise program (PREP) and the use of non-comparative data to inform the effectiveness of each strategy (each arm was informed from a separate phase III trial). In addition, further sensitivity analysis could have been conducted to better explore uncertainty.

Table 7.21. Methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		
Potentially serious limitations		Retel et al. 2011
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Retel et al. 2011 are summarised in the modified GRADE table below.

Table 7.22. Summary table showing the included evidence on the optimal active speech and language therapy interventions for patients with cancer of the upper aerodigestive tract.

Study	Population	Comparators:	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Retel et al. 2011	Patients with advanced head and neck cancer treated with concomitant chemo-radiotherapy.	Usual care (UC	€41,986	0.68 QALYs	Reference standard			Series of one- and two-way sensitivity analysis were conducted. PREP was found to have an ICER below €20,000 per QALY in the majority of analyses. However, model appears to be particularly sensitive to changes in DBC tariffs. In probabilistic sensitivity analysis (PSA), PREP was found to have a 83% probability of being cost-effective at a threshold of €20,000 per QALY. Expected value of perfect information (EVPI) was also conducted. The EVPI for the base case was found to be €398,063.	***Partially applicable.*** The evaluation does not consider the UK health care system (Netherlands). Furthermore not all utility values were sourced directly from patients. ***Potentially serious limitations.*** Treatment effects are based on non-comparative data and, in some instances, assumptions.
		Preventive (swallowing) exercise program (PREP	€42,271	0.77 QALYs	€285	0.09 QALYs	€3,197		
	Comments:								

Evidence statements

The base case results of the cost-effectiveness analysis showed that, in comparison to usual care, a preventive swallowing exercise program (PREP) provided one additional QALY at a cost of €3,197. Probabilistic sensitivity analysis showed that at a threshold of €20,000 per QALY, PREP had an 83% probability of being cost-effective in comparison to usual care.

However, the analysis was deemed to be only partially applicable to the decision problem in the UK setting as it was based on the health care perspective of the Netherlands. Furthermore, some potentially serious limitations were identified including the use of assumptions to quantify the QoL benefit associated with PREP and the use of non-comparative data to inform the effectiveness of each strategy.

Overall, the analysis can be considered to show the potential cost-effectiveness of preventive exercise programs. However, the credibility of the results is highly dependent upon the credibility of the assumptions and the data that has been used. Further evidence is required to conclusively demonstrate the cost-effectiveness of preventive exercise programs.

Reference

1. Retel, V. P., van der Molen, L., Hilgers, F. J., Rasch, C. R., L'Ortye, A. A., Steuten, L. M., van Harten, W. H., Retel, Valesca P., van der Molen, Lisette, Hilgers, Frans J. M., Rasch, Coen R. N., L'Ortye, Annemiek A. A. M., Steuten, Lotte M. G., and van Harten, Wim H. A cost-effectiveness analysis of a preventive exercise program for patients with advanced head and neck cancer treated with concomitant chemo-radiotherapy. BMC Cancer 2011. 11: 475

Full evidence table

The full details of the study included in the evidence review are presented in the evidence table below.

Table 7.23. Full evidence table showing the included evidence on the optimal active speech and language therapy interventions for patients with cancer of the upper aerodigestive tract.

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
Author: Retel et al. **Year:** 2011 **Country:** Netherlands **Funding:** **Comments**	**Type of analysis:** Cost-effectiveness analysis with quality adjusted life years (QALYs) used as the effectiveness measure (cost-utility analysis). **Interventions** 1. Usual care (UC) 2. Preventive (swallowing) exercise program (PREP) **Model structure:** Markov decision model, consisting of three mutually exclusive health states: "complete remission", "recurrent disease" and "death". **Cycle length:** One month. **Time horizon:** 1 year. **Perspective:** Health care perspective of the Netherlands	**Included population:** Patients with advanced (stage III and IV) functional or anatomical inoperable head and neck cancer treated with concomitant chemo-radiotherapy. **Sample size:** Hypothetical cohort of 1000 patients was modelled. **Age:** 55 years old. **Gender:** Not reported. In the clinical trial upon which CUA is based 68% and 76% were male in the usual care and PREP arms respectively. **Subgroup analysis:** No subgroup analyses were conducted.	**Source of base-line data:** Data on treatment success rates (with chemo-radiotherapy) and probability of recurrence were based on published outcome data from a NKI-AVL phase III trial. Patient characteristics from the clinical trials are presented in the report but they do not appear to have been directly used in the model. **Source of effectiveness data:** Data for the usual care arm were derived from a multi-centre RCT comparing intra-arterial and intravenous chemo-radiation in advanced head and neck cancer (Ackerstaff et al. 2009). Data for the PREP arm were derived from another RCT, in which the effects of preventive strength and stretch exercises as an adjunct to usual care were assessed. The RCT compared two types of exercise regimens but, for the purposes of this evaluation, the data were combined. Aspiration rates for PREP were based on data from the clinical trial. However, data were not available for the usual care arm and so the rate was based on an assumption (appears to have been assumed that it is double the PREP	**Base case** **Effectiveness (QALYs):** Usual care PREP Incremental **Costs** Usual care PREP Incremental **ICER (cost per QALY):** **Sensitivity analysis:** **One-way sensitivity analyses** Lower utility estimates Higher utility estimates Lower resource use Higher resource use **Two-way sensitivity analyses** Two-way sensitivity analyses were explored with variations in utilities combined with variations in DBC tariffs and aspiration rates.	 0.68 QALYs 0.77 QALYs 0.09 QALYs €41,986 €42,271 €285 €3,197 per QALY €6,393 per QALY €2,131 per QALY PREP dominant €45,906 per QALY

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
	Cancer Institute – Antoni van Leeuwenhoek Hospital (NKI-AVL). **Currency unit:** Euros (€) **Cost year:** 2008 **Discounting:** Future costs and effects were discounted at a rate of 4% and 1.5% per year respectively.		aspiration rate). The authors note that the key outcomes of interest in this analysis are tube dependency at 12 months (25% with usual care and 3% with PREP) and the number of hospital days after completion of chemoradiation (4.5 with usual care and 3.2 with PREP). PREP was assumed to have no direct influence on survival. **Source of utility data:** Utilities for patients treated with concomitant chemo-radiotherapy were sourced from the phase III trial by Ackerstaff et al. 2009 (see above). For the usual care arm, the QoL results at 7 weeks and 12 months were used to inform the utility values during and after treatment, respectively. For the PREP arm, assumptions were made as to how the QoL values would differ in comparison to the usual care arm. These assumptions were based on published literature and informal expert elicitation. **Source of cost data:** Treatment costs were estimated using data from the NKI-AVL on the clinical pathways that patients follow when receiving concomitant chemo-radiotherapy.	**DBC tariff = €1,214** Utility = 0.80 Utility = 0.85 Utility = 0.90 **DBC tariff = €3,252** Utility = 0.80 Utility = 0.85 Utility = 0.90 **DBC tariff = €7,058** Utility = 0.80 Utility = 0.85 Utility = 0.90 **Aspiration rate = 0.02** Utility = 0.80 Utility = 0.85 Utility = 0.90 **Aspiration rate = 0.04** Utility = 0.80 Utility = 0.85 Utility = 0.90 **Aspiration rate = 0.06** Utility = 0.80 Utility = 0.85 Utility = 0.90 **Probabilistic sensitivity analysis (PSA)** Probability of PREP being cost-	 -€39,349 -€19,674 -€13,116 €6,394 *€3,197 (base case)* €2,131 €91,814 €45,907 €30,605 €23,442 €11,721 €7,814 €13,430 €6,715 €4,477 €3,417 €1,709 €1,139

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
			The cost of feeding substitutes, pneumonia as an adverse event and hospital days were derived from the NKI-AVL hospital charts and administration. Use of feeding substitutes was calculated per disease severity and it was assumed that in patients requiring tube feeding, 50% received nasal tube and 50% received gastronomy tube. Professional costs of PREP were derived from the Dutch Diagnosis Treatment Combination (DBC) tariff list.	effective at threshold of €20,000 per QALY: Authors noted that PREP has a higher probability of being cost-effective compared to usual care as long as the threshold was higher than €3,200 per QALY. **Expected value of perfect information (EVPI)** EVPI for base case Authors conclude there is potential value in additional research to reduce uncertainty.	83% €398,063

1

Shoulder rehabilitation

Clinical question: What are the most effective interventions for shoulder rehabilitation following neck dissection in people with cancer of the upper aerodigestive tract?

Background

The spinal accessory nerve is potentially at risk of damage during neck dissection. Shoulder function may be compromised by nerve injury leading to pain and restriction in movement which adversely affects quality of life.

There is no consensus as to the most effective way of managing this complication.

Evidence statements

Therapeutic exercises

Moderate quality evidence from a systematic review of randomised controlled trials (three studies, 104 patients) suggests that progressive resistance training is beneficial in head and neck cancer patients with treatment-induced shoulder dysfunction (Carvalho 2012). Compared to head and neck cancer patients receiving standard care, patients participating in progressive resistance training (PRT) had better range of motion (6.2 to 14.51 degrees greater with PRT, depending on the measure used) and muscle strength (1-repetition maximum weight 6.5 to 18.9 kg greater with PRT, depending on the measure used) after 12 weeks of treatment. Quality of life, pain, and shoulder disability were also better in the progressive resistance training group, but the differences between groups were not significant for these outcomes.

Low quality evidence from a single randomised controlled trial (24 patients) suggests that there is uncertainty regarding the benefits of outpatient physiotherapy on shoulder function in patients receiving neck dissection (Lauchlan 2011). One year after treatment, there was no significant difference in shoulder function or quality of life between patients who had received a 3-month course of outpatient physiotherapy and those who had received only routine inpatient physiotherapy care.

Two observational studies (very low quality evidence) also compared postoperative outpatient physiotherapy to standard care in patients who had undergone neck dissection. One study (50 patients) found that motor recovery was similar whether or not patients received outpatient physiotherapy (Baggi 2014). On the other hand, a second observational study (60 patients) demonstrated that 6 months post-surgery, shoulder function and pain were significantly better in patients who had received physiotherapy than in those who had received standard care (outcomes one month after surgery were similar between groups) (Salerno 2002).

Nerve exploration/repair

No evidence was identified on the effectiveness of this intervention in the population of interest.

Study characteristics and quality

Table 7.24 summarises the characteristics of the studies included in the review. One systematic review, three randomised trials, and three observational studies were identified. All three randomised trials were included in the systematic review, but for one of these (Lauchlan 2011) the authors only reported a narrative summary of the results. Quantitative analysis based on the original study is therefore also presented here.

All of the identified studies included relatively small patient numbers: the systematic review included 104 patients from three studies, but no single outcome had data for more than 69 patients. Observational studies ranged in size from 50 to 298 participants. With the exception of two studies (McNeely 2004 and Mcneely 2008, both included as part of the systematic review by Carvalho (2012)), all of the trials included patients with cancer of the upper aerodigestive tract undergoing neck dissection, regardless of whether they had a diagnosis of shoulder dysfunction. The proportion of patients with pre-existing shoulder dysfunction in each trial is not clear.

Studies were conducted in Japan (one observational study), Canada (two randomised trials), and Europe (one randomised trial and two observational studies). Outcomes were assessed between 2 and 12 months after surgery.

Table 7.24. Characteristics of included studies

STUDY ID	DESIGN	PATIENTS	N	TREATMENT COMPARISON	OUTCOMES REPORTED
Carvalho 2012	SRMA	Any head and neck cancer patients with treatment-induced shoulder dysfunction	104	Progressive resistance training (two studies) or early physiotherapy interventions (one study) versus standard care	Shoulder pain and disability Range of motion Adverse events Quality of life Shoulder strength
Lauchlan 2011*	RCT	Head and neck cancer patients treated with neck dissection	34	3 months postoperative physiotherapy versus standard inpatient care and advice.	Shoulder function Quality of life
Baggi 2014	PCS	Head and neck cancer patients treated with neck dissection	50	Physiotherapist-assisted rehabilitation versus self-led rehabilitation	Shoulder function Pain
Nibu 2010	RCS	Head and neck cancer patients treated with neck dissection	224	Postoperative shoulder rehabilitation versus no rehabilitation	Shoulder function
Salerno 2002	PCS†	Patients undergoing total laryngectomy with functional neck dissection	60	Outpatient physical therapy versus no outpatient physical therapy	Shoulder function Pain Quality of life

Abbreviations: NR: not reported; RCT: randomised controlled trial; RCS: retrospective cohort study; prospective cohort study

*This study is included in the systematic review by Carvalho et al, but the authors only reported a narrative summary of the results. Quantitative analysis based on the original study is therefore also presented here. †It is assumed that this study was conducted prospectively, but this is not explicitly stated by the study authors.

GRADE evidence tables

Table 7.25. GRADE evidence profile: progressive resistance training (PRT) versus standard care for shoulder dysfunction in patients treated for head and neck cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PRT	Standard care	Relative (95% CI)	Absolute	
Shoulder Pain and Disability Index (pain score) at 12 weeks (Better indicated by lower values)											
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 6.26 lower (12.2 to 0.31 lower)	⊕⊕⊕O MODERATE
Shoulder Pain and Disability Index (disability subscale) at 12 weeks (Better indicated by lower values)											
2[1,3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 8.48 lower (15.07 to 1.88 lower)	⊕⊕⊕O MODERATE
Shoulder Pain and Disability Index (total score) at 12 weeks (Better indicated by lower values)											
2[1,3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 5.77 lower (14 lower to 2.46 higher)	⊕⊕⊕O MODERATE
Active range of motion (abduction) (Better indicated by lower values)											
2[1,3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 9.45 higher (6.26 lower to 25.17 higher)	⊕⊕⊕O MODERATE
Active range of motion (forward flexion) (Better indicated by lower values)											
2[1,3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 7.01 higher (1.93 lower to 15.95 higher)	⊕⊕⊕O MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PRT	Standard care	Relative (95% CI)	Absolute	
Active range of motion (external rotation) (Better indicated by lower values)											
2[1,3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 14.51 higher (7.87 to 21.14 higher)	⊕⊕⊕O MODERATE
Passive range of motion (abduction) (Better indicated by lower values)											
2[1,3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 7.65 higher (0.64 to 14.66 higher)	⊕⊕⊕O MODERATE
Passive range of motion (forward flexion) (Better indicated by lower values)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 6.2 higher (0.69 to 11.71 higher)	⊕⊕⊕O MODERATE
Passive range of motion (external rotation) (Better indicated by lower values)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 7.17 higher (2.2 to 12.14 higher)	⊕⊕⊕O MODERATE
Passive range of motion (horizontal abduction) (Better indicated by lower values)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 7.34 higher (2.86 to 11.83 higher)	⊕⊕⊕O MODERATE
Quality of life (FACT-G) (Better indicated by lower values)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 5.05 higher (3.01 lower to 13.12 higher)	⊕⊕⊕O MODERATE

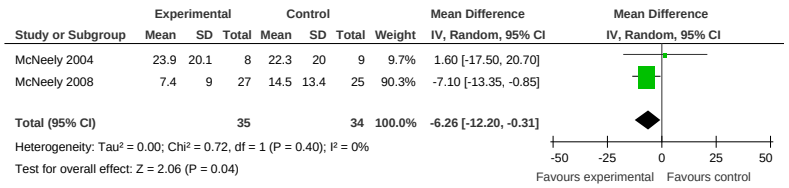
Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PRT	Standard care	Relative (95% CI)	Absolute	
Adverse event - Pain increase											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	1/27 (3.7%)	0/25 (0%)	RR 2.79 (0.12, 65.38)	Not estimable	⊕⊕OO LOW
Adverse event – Nausea											
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	None	1/8 (12.5%)	0/9 (0%)	RR 3.33 [0.15, 71.90]	Not estimable	⊕⊕OO LOW
Quality of life measured by FACT-An scale (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	27	25	-	MD 8 higher (8.77 lower to 24.77 higher)	⊕⊕⊕O MODERATE
Quality of life measured by FACT-H&N questionnaire (Better indicated by lower values)											
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	8	9	-	MD 3.9 higher (16.3 lower to 24.1 higher)	⊕⊕⊕O MODERATE
Quality of life assessed by NDII questionnaire (Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	27	25	-	MD 8.4 higher (3.54 lower to 20.34 higher)	⊕⊕⊕O MODERATE
Endurance of scapular muscles (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	27	25	-	MD 320 higher (89.75 to 550.25 higher)	⊕⊕⊕O MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PRT	Standard care	Relative (95% CI)	Absolute	
Strength of scapular muscles (seated row, 1-RM with two arms) (Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	27	25	-	MD 18.9 higher (6.84 to 30.96 higher)	⊕⊕⊕O MODERATE
Strength of scapular muscles (seated row, 1-RM affected shoulder) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	27	25	-	MD 7 higher (1.17 to 12.83 higher)	⊕⊕⊕O MODERATE
Strength of scapular muscles (chest press, 1-RM with two arms) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	27	25	-	MD 14.4 higher (3.05 to 25.75 higher)	⊕⊕⊕O MODERATE
Strength of scapular muscles (chest press, 1-RM affected shoulder) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	27	25	-	MD 6.5 higher (0.93 to 12.07 higher)	⊕⊕⊕O MODERATE

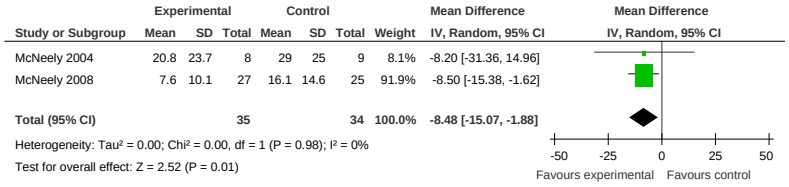
[1] McNeely 2008
[2] Small sample size.
[3] McNeely 2004
[4] Small sample size; very low number of events

Figure 7.4. Forest plots of progressive resistance training versus standard care for the outcomes as listed. Experimental denotes progressive resistance training; control denotes standard care.

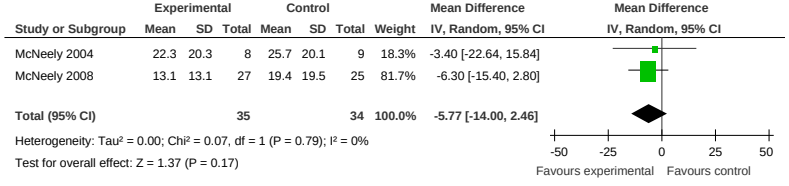
A. Shoulder Pain and Disability Index (pain score) at 12 weeks



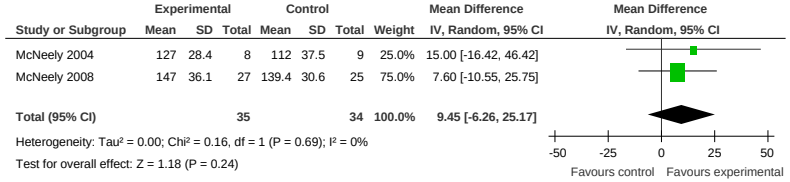
B. Shoulder Pain and Disability Index (disability subscale) at 12 weeks



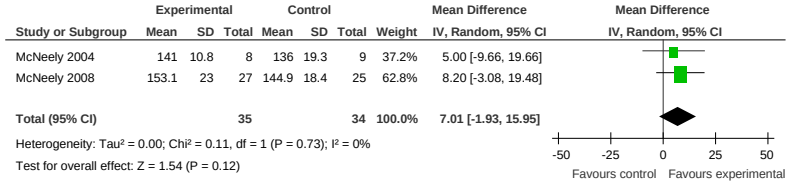
C. Shoulder Pain and Disability Index (total score) at 12 weeks



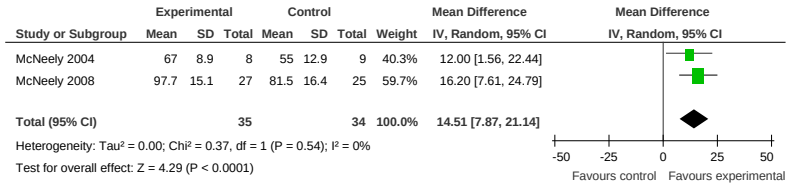
D. Active range of motion (abduction)



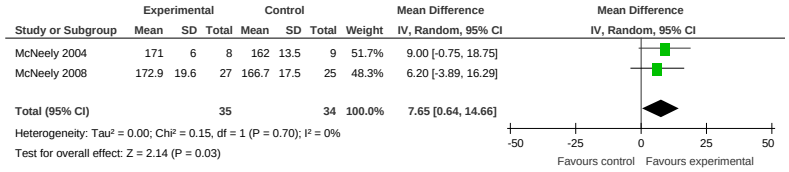
E. Active range of motion (forward flexion)



F. Active range of motion (external rotation)



G. Passive range of motion (abduction)

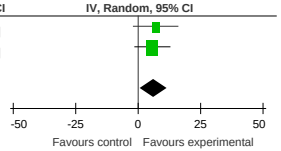


H. Passive range of motion (forward flexion)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
McNeely 2004	164	7.7	8	157	10.9	9	38.3%	7.00 [-1.90, 15.90]
McNeely 2008	170	13.4	27	164.3	12.4	25	61.7%	5.70 [-1.31, 12.71]
Total (95% CI)			**35**			**34**	**100.0%**	**6.20 [0.69, 11.71]**

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

Test for overall effect: Z = 2.21 (P = 0.03)

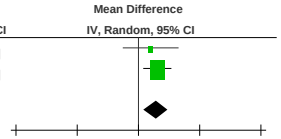


I. Passive range of motion (external rotation)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
McNeely 2004	79	8.4	8	74	14.6	9	19.8%	5.00 [-6.17, 16.17]
McNeely 2008	93.7	11	27	86	9.4	25	80.2%	7.70 [2.15, 13.25]
Total (95% CI)			**35**			**34**	**100.0%**	**7.17 [2.20, 12.14]**

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%

Test for overall effect: Z = 2.83 (P = 0.005)

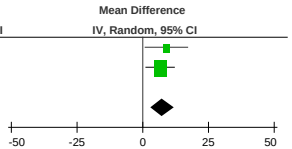


J. Passive range of motion (horizontal abduction)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
McNeely 2004	87	7.1	8	78	9.8	9	30.9%	9.00 [0.93, 17.07]
McNeely 2008	93.2	9.6	27	86.6	10.2	25	69.1%	6.60 [1.21, 11.99]
Total (95% CI)			**35**			**34**	**100.0%**	**7.34 [2.86, 11.83]**

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%

Test for overall effect: Z = 3.21 (P = 0.001)

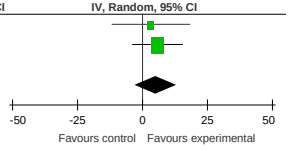


K. Quality of life (FACT-G)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
McNeely 2004	78.75	15.3	8	75.51	16.1	9	29.2%	3.24 [-11.69, 18.17]
McNeely 2008	83.9	15.6	27	78.1	19.3	25	70.8%	5.80 [-3.78, 15.38]
Total (95% CI)			**35**			**34**	**100.0%**	**5.05 [-3.01, 13.12]**

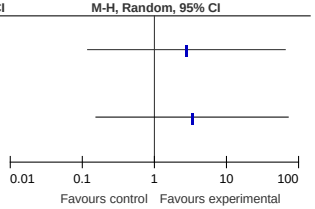
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%

Test for overall effect: Z = 1.23 (P = 0.22)



L. Incidence of adverse events

Study or Subgroup	Experimental Events	Total	Control Events	Total	Risk Ratio M-H, Random, 95% CI
1.12.1 Pain increase					
McNeely 2008	1	27	0	25	2.79 [0.12, 65.38]
1.12.2 Nausea					
McNeely 2004	1	8	0	9	3.33 [0.15, 71.90]

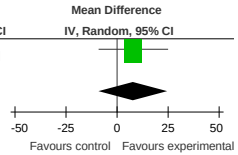


M. Quality of life measured by FACT-An scale

Study or Subgroup	Favours experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
McNeely 2008	142.4	27	27	134.4	34	25	100.0%	8.00 [-8.77, 24.77]
Total (95% CI)			**27**			**25**	**100.0%**	**8.00 [-8.77, 24.77]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.93 (P = 0.35)

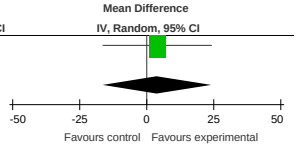


N. Quality of life measured by FACT-H&N questionnaire

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
McNeely 2004	104.8	18.5	8	100.9	23.9	9	100.0%	3.90 [-16.30, 24.10]
Total (95% CI)			**8**			**9**	**100.0%**	**3.90 [-16.30, 24.10]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.38 (P = 0.71)

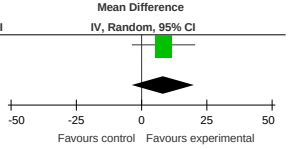


O. Quality of life assessed by NDII questionnaire

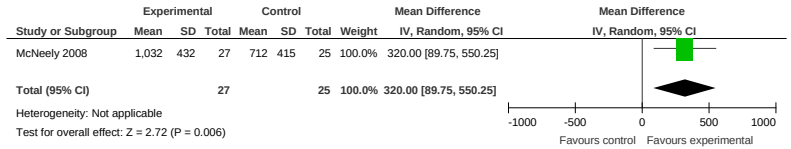
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
McNeely 2008	68.6	22	27	60.2	21.9	25	100.0%	8.40 [-3.54, 20.34]
Total (95% CI)			**27**			**25**	**100.0%**	**8.40 [-3.54, 20.34]**

Heterogeneity: Not applicable

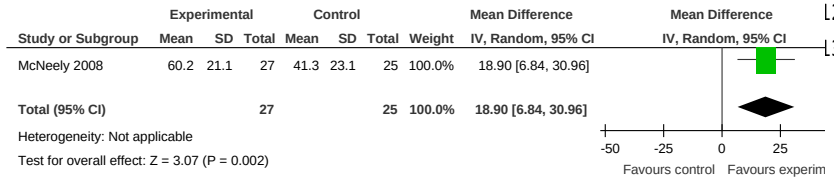
Test for overall effect: Z = 1.38 (P = 0.17)



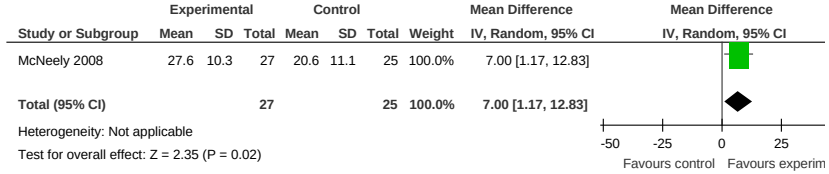
P. Endurance of scapular muscles



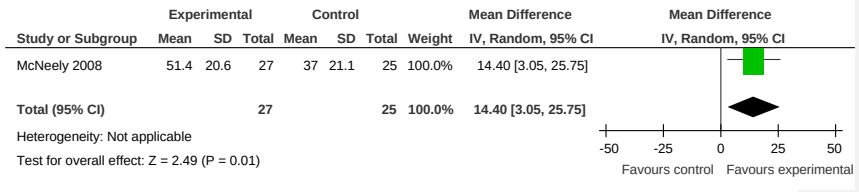
Q. Strength of scapular muscles (seated row, 1-repetition maximum with two arms)



R. Strength of scapular muscles (seated row, 1-repetition maximum affected shoulder)



S. Strength of scapular muscles (chest press, 1-repetition maximum with two arms)



T. Strength of scapular muscles (chest press, 1-repetition maximum affected shoulder)

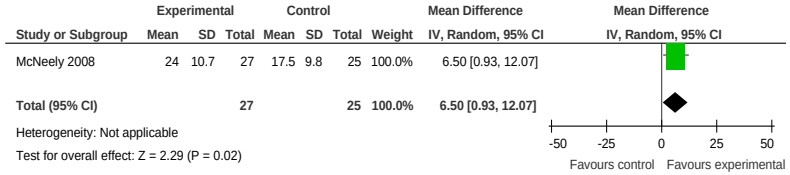


Table 7.26. GRADE evidence profile: outpatient physiotherapy versus standard postoperative care for shoulder dysfunction in patients treated for head and neck cancer

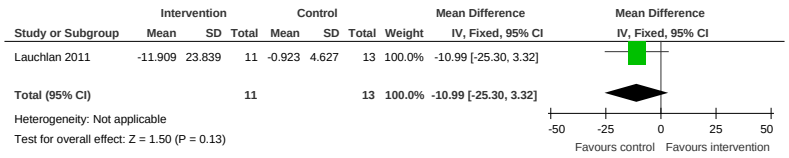
Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outpatient physiotherapy	Standard postoperative care	Relative (95% CI)	Absolute	
Shoulder function (ASSESSA FCS), change at one year (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	11	13	-	MD 10.99 lower (25.3 lower to 3.32 higher)	⊕⊕⊕O MODERATE
Shoulder function (CONSTANT), change at one year (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	11	13	-	MD 3.69 lower (20.21 lower to 12.83 higher)	⊕⊕⊕O MODERATE
SF-12 PCS, change at one year (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	11	13	-	MD 4.88 higher (1.67 lower to 11.42 higher)	⊕⊕⊕O MODERATE
SF-12 MCS, change at one year (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	11	13	-	MD 2.29 lower (13.06 lower to 8.48 higher)	⊕⊕⊕O MODERATE

[1] Lauchlan 2011

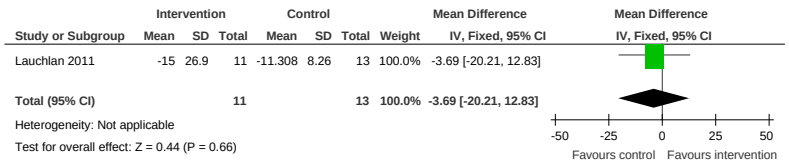
[2] Small sample size.

Figure 7.5. Forest plots of physiotherapy intervention versus standard postoperative care for the outcomes as listed. Intervention denotes physiotherapy; control denotes standard care.

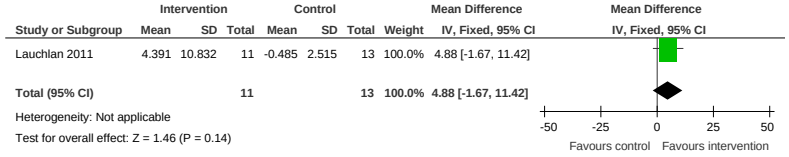
A. Shoulder function (ASSESSA FCS), change at one year



B. Shoulder function (CONSTANT), change at one year



C. Quality of life (SF-12 PCS), change at one year



D. Quality of life (SF-12 MCS), change at one year

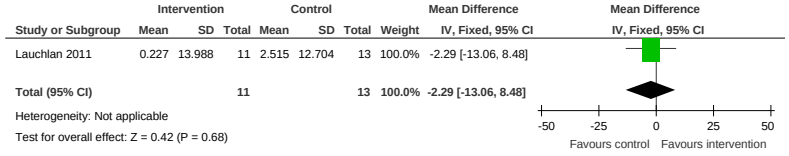


Table 7.27. GRADE evidence profile: physiotherapist-led rehabilitation versus autonomous rehabilitation for shoulder dysfunction after neck dissection

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physiotherapist-led rehabilitation	Autonomous rehabilitation	Relative (95% CI)	Absolute	
≥90% recovery of passive abduction of arm (follow-up 2 months)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	23/25 (92%)	23/25 (92%)	RR 1 (0.85, 1.18)	0 fewer per 1000 (from 138 fewer to 166 more)	⊕OOO VERY LOW
100% recovery of arm strength (follow-up 2 months)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	8/25 (32%)	7/25 (28%)	RR 1.14 (0.49, 2.67)	39 more per 1000 (from 143 fewer to 468 more)	⊕OOO VERY LOW
≥90% recovery of head rotation (follow-up 2 months)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	11/25 (44%)	15/25 (60%)	RR 0.73 (0.42, 1.27)	162 fewer per 1000 (from 348 fewer to 162 more)	⊕OOO VERY LOW
Composite endpoint: good motor recovery (follow-up 2 months)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	5/25 (20%)	5/25 (20%)	RR 1 (0.33, 3.03)	0 fewer per 1000 (from 134 fewer to 406 more)	⊕OOO VERY LOW

[1] Baggi 2014

[2] Follow up period may be insufficiently short.

[3] Small sample size.

Table 7.28. GRADE evidence profile: postoperative rehabilitation versus standard care for shoulder dysfunction after neck dissection

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative rehabilitation	No rehabilitation	Absolute	
Arm abduction score (follow-up 12 months; Better indicated by higher values)										
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	224	74	<table><tr><th></th><th>Rehabilitation group</th><th>No rehabilitation group</th><th>P value</th></tr><tr><td colspan="4">Arm abduction test score</td></tr><tr><td>Level III ND</td><td>4.2</td><td>3.8</td><td>NS</td></tr><tr><td>Level IV ND</td><td>3.7</td><td>3.5</td><td>NS</td></tr><tr><td>Level V ND</td><td>3.9</td><td>3.2</td><td>0.06</td></tr><tr><td>Level VI ND</td><td>2.2</td><td>1.6</td><td>0.03</td></tr><tr><td colspan="4">ND: neck dissection; NS: not significant.</td></tr></table>	⊕OOO VERY LOW

[1] Nibu 2010

[2] Historical control group used, with long (22 years) accrual period. Very limited details reported of the care patients received, or what constituted 'rehabilitation'. Numbers of patients in each ND level subgroup were not reported, nor were pooled results for the entire population.

Table 7.29. GRADE evidence profile: outpatient physical therapy versus standard care for shoulder dysfunction after neck dissection

Quality assessment							No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outpatient physical therapy	Control	Absolute			
Passive forward elevation (0–10) (Better indicated by higher values)												
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	30	30		**Physical therapy.**	**No physical therapy.**	⊕OOO VERY LOW
									1 month post-surgery	7.8 ± 1.69	7.53 ± 1.69	
									6 months post-surgery	9.33 ± 0.96	6.87 ± 1.63	
Global shoulder active motility (0–40) (Better indicated by higher values)												
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	30	30		**Physical therapy.**	**No physical therapy.**	⊕OOO VERY LOW
									1 month post-surgery	25.93 ± 5.57	25.80 ± 5.39	
									6 months post-surgery	36.27 ± 4.19	28.07 ± 6.63	

Pain (0–15) (Better indicated by higher values)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	30	30		**Physical therapy.**	**No physical therapy.**	⊕OOO VERY LOW
									1 month post-surgery	5.03 ± 3.77	5.07 ± 3.77	
									6 months post-surgery	13 ± 2.75	8.57 ± 4.48	
Working and recreational activity (0–20) (Better indicated by higher values)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	30	30		**Physical therapy.**	**No physical therapy.**	⊕OOO VERY LOW
									1 month post-surgery	9.93 ± 3.83	9.97 ± 3.94	
									6 months post-surgery	18.8 ± 1.88	12.7 ± 5.30	
Shoulder functional assessment (measured with: Constant score (0–85); Better indicated by higher values)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	30	30		**Physical therapy.**	**No physical therapy.**	⊕OOO VERY LOW
									1 month post-surgery	48.7 ± 10.51	48.37 ± 10.43	
									6 months post-surgery	77.4 ± 7.50	56.2 ± 14.58	

[1] Salerno 2002
[2] The care received by the control group, and whether this was the same for all patients, is not reported.
[3] Small sample size.

1 Evidence tables for all included studies

Study

Carvalho 2012.

Study type, study period

Systematic review of randomised controlled trials.
Literature searches were conducted in July 2011.

Trial characteristics

Inclusion criteria:

- Participants: adults with a clinical and histological diagnosis of head and neck cancer (any stage) with dysfunction of the shoulder as a result of any type of cancer treatment of the head and neck region.
- Intervention: active or active-assisted range of motion exercises, passive range of motion exercises, stretching exercises, resistance exercises, proprioceptive neuromuscular facilitation, or any other exercises with a focus on shoulder dysfunction treatment or prevention.
- Control: any other intervention, such as no treatment, standard treatment, placebo, sham exercises, and pharmacological interventions.

Number of trials/patients included

Three trials identified, including a total of 104 patients.

Intervention

Progressive resistance training (two studies) with range of motion and stretching exercises. One study used early physiotherapy intervention for 3 months; the spectrum of techniques included free active exercises, stretching, postural care, re-education of scapulothoracic postural muscles and strength of shoulder muscles.

Comparison

Standard care, consisting of active and passive range of motion exercises and stretching exercises (two studies) or routine inpatient physiotherapy and advice (one study).

Outcome measures and effect size

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Shoulder Pain and Disability Index (pain score) 12 weeks	2	69	Mean Difference (IV, Random, 95% CI)	-6.26 [-12.20, -0.31]*
1.2 Shoulder Pain and Disability Index (disability subscale) 12 weeks	2	69	Mean Difference (IV, Random, 95% CI)	-8.48 [-15.07, -1.88]*
1.3 Shoulder Pain and Disability Index (total score) 12 weeks	2	69	Mean Difference (IV, Random, 95% CI)	-5.77 [-14.00, 2.46]*
1.4 Active range of motion (abduction)	2	69	Mean Difference (IV, Random, 95% CI)	9.45 [-6.26, 25.17]†
1.5 Active range of motion (forward flexion)	2	69	Mean Difference (IV, Random, 95% CI)	7.01 [-1.93, 15.95]†
1.6 Active range of motion (external rotation)	2	69	Mean Difference (IV, Random, 95% CI)	14.51 [7.87, 21.14]†
1.7 Passive range of motion (abduction)	2	69	Mean Difference (IV, Random, 95% CI)	7.65 [0.64, 14.66]†
1.8 Passive range of motion (forward flexion)	2	69	Mean Difference (IV, Random, 95% CI)	6.20 [0.69, 11.71]†
1.9 Passive range of motion (external rotation)	2	69	Mean Difference (IV, Random, 95% CI)	7.17 [2.20, 12.14]†
1.10 Passive range of motion (horizontal abduction)	2	69	Mean Difference (IV, Random, 95% CI)	7.34 [2.86, 11.83]†
1.11 Quality of life (FACT-G)	2	69	Mean Difference (IV, Random, 95% CI)	5.05 [-3.01, 13.12]†
1.12.1 Adverse event: Pain increase	1	52	Risk Ratio (M-H, Random, 95% CI)	2.79 [0.12, 65.38]*
1.12.2 Adverse event: Nausea	1	17	Risk Ratio (M-H, Random, 95% CI)	3.33 [0.15, 71.9]*
1.13 Quality of life measured by FACT-An scale	1	52	Mean Difference (IV, Random, 95% CI)	8.00 [-8.77, 24.77]†
1.14 Quality of life measured by FACT-H&N questionnaire	1	17	Mean Difference (IV, Random, 95% CI)	3.90 [-16.30, 24.10]†
1.15 Quality of life assessed by NDII questionnaire	1	52	Mean Difference (IV, Random, 95% CI)	8.40 [-3.54, 20.34]†
1.16 Endurance of scapular muscles	1	52	Mean Difference (IV, Random, 95% CI)	320.00 [89.75, 550.25]†
1.17 Strength of scapular muscles (seated row, 1-RM with two arms)	1	52	Mean Difference (IV, Random, 95% CI)	18.90 [6.84, 30.96]†
1.18 Strength of scapular muscles (seated row, 1-RM affected shoulder)	1	52	Mean Difference (IV, Random, 95% CI)	7.00 [1.17, 12.83]†

1.19 Strength of scapular muscles (chest press, 1-RM with two arms)	1	52	Mean Difference (IV, Random, 95% CI)	14.40 [3.05, 25.75]†
1.20 Strength of scapular muscles (chest press, 1-RM affected shoulder)	1	52	Mean Difference (IV, Random, 95% CI)	6.50 [0.93, 12.07]†
*lower/negative values favour the intervention. †higher values favour the intervention.				

Source of funding

None reported.

Additional comments

The studies included in the review were assessed as at low risk of bias for all parameters, with the exception of performance bias in McNeely 2004 (high risk of bias due to lack of blinding and no detail on whether treatment other than intervention was standardised).

1

Study, country

Lauchlan, 2011
United Kingdom, single centre.

Study type, study period

Randomised controlled trial.
Study recruitment period was 2 years, dates not reported.

Number of patients

34 recruited; outcome data available for 24.

Patient characteristics

Inclusion criteria: head and neck cancer patients receiving selective or radical neck dissection.

Exclusion criteria:

- Severe cardiac or respiratory disease
- Inability to give informed consent
- Previous significant injury to arm/shoulder/neck/chest
- Pre-existing adhesive capsulitis of the glomerohumeral joint

Patient characteristics not reported.

Intervention

3 months of outpatient physiotherapy in addition to standard care.

Comparison

Standard care: routine inpatient post-operative physiotherapy care.

Length of follow-up

12 months

Outcome measures and effect size

	Intervention (n = 11)		Comparison (n = 13)			
Outcome	**Mean**	**SD**	**Mean**	**SD**	**Mean difference**	**P value**
Shoulder function (ASSESSA FCS), change at one year	-11.909	23.839	-0.923	4.627	-10.99 [-25.30, 3.32]	0.13
Shoulder function (CONSTANT), change at one year	-15	26.9	-11.308	8.26	-3.69 [-20.21, 12.83]	0.66
Quality of life, SF-12 PCS, change at one year	4.391	10.832	-0.485	2.515	4.88 [-1.67, 11.42]	0.14
Quality of life, SF-12 MCS, change at one year	0.227	13.988	2.515	12.704	-2.29 [-13.06, 8.48]	0.68

Source of funding

Risks of bias

Selection bias: Unclear/unknown risk. No details of patient characteristics reported
Performance bias: Unclear/unknown risk. Limited detail is reported of the treatment that each group of patients received.
Attrition bias: Low risk. High dropout rate, but this was similar across treatment arms and the reasons for patients leaving the trail were accounted for by the authors.
Detection bias: Low risk.

Additional comments

2

3

Study, country

Baggi 2014.
Italy, single centre.

Study type, study period

Observational study (prospective).
August 2006 to December 2008.

Number of patients

97 enrolled. 50 patients (25 per treatment group) completed the study and have available results.

Patient characteristics

Inclusion criteria:

- Patients with head and neck cancer scheduled for unilateral or bilateral neck dissection
- ECOG performance status 0–2
- Age ≤65 years
- Life expectancy >3 months
- Ability to rotate the head by ≥60°
- Ability to perform complete passive abduction of the involved arm (by 180°)
- Strength of complete arm abduction in the frontal plane ≥3 on the MRC scale

Exclusion criteria:

- Patients undergoing immediate reconstruction with a pectoralis major flap
- Existing cervical or shoulder injury
- Ongoing concomitant illness likely to compromise compliance

	Autonomous group	Physio group
Age, median (range)	49 (16–64)	56 (30–65)
Gender, n (%)		
Male	21 (84)	14 (56)
Female	4 (16)	11 (44)
Side of neck, n (%)		
Right	10 (40)	12 (48)
Left	5 (20)	9 (36)
Bilateral	10 (40)	4 (16)

	Autonomous group	Physio group
Type of neck dissection, n (%)		
Radical	0 (0)	0 (0)
Modified type I	1 (4)	0 (0)
Modified type II	1 (4)	2 (8)
Modified type III	14 (56)	10 (40)
Selective (sup. to hyoid; no level V)	0 (0)	1 (4)
Selective (posterolateral)	8 (32)	10 (40)
Selective (no level V)	1 (4)	2 (8)

Intervention

Autonomous rehabilitation (n = 25). Patients received an instruction session with a physiotherapist on the day before surgery. Patients were given a series of exercises to be performed twice a day, starting as soon as possible after surgery and continued at least until evaluation two months post-surgery.

Comparison

Physiotherapy-assisted rehabilitation (n = 25). In addition to performing exercises at home as described for the autonomous group, patients participated in a physical therapy programme consisting of four once-weekly physiotherapy sessions of 50 minutes each, starting 5 days after surgery.

Length of follow-up

Outcomes were assessed two months after surgery.

Outcome measures and effect size

Pain scores (assessed by 10-point visual analogue scale)

	Autonomous group	Physio group	
Before surgery, median (range)	0 (0–7)	0 (0–7)	
Two months after surgery, median (range)	0 (0–5)	0 (0–8)	P = 0.26

Recovery of arm and neck function at two months

	Autonomous group	Physio group	
≥90% recovery of passive abduction of arm, n/N (%)	23/25 (92)	23/25 (92)	P = 1.0
100% recovery of arm strength, n/N (%)	8/25 (33)	7/25 (28)	P = 0.76
≥90% recovery of head rotation, n/N (%)	11/25 (44)	15/25 (60)	P = 0.26
Composite endpoint: good motor recovery*, n/N (%)	5/25 (20)	5/25 (20)	P = 1.0
*≥90% recovery of arm mobility, ≥90% recovery of neck mobility, and complete recovery of arm strength.			

Quality of life was assessed using the QLQ-C30 and QLQ-H&N35 scales. Outcomes were significantly better in autonomous patients for 2/6 QLQ-C30 functional scales. There was no significant difference in other functional scales, QLQ-C30 global health status, or any of seven measured QLQ-H&N35 symptom scales.

Source of funding

Not reported.

Risks of bias

Selection bias: Unclear/unknown risk. Patients allocated to treatment based on their geographical location (those further from the treatment centre were allocated to autonomous treatment).
Performance bias: Unclear/unknown risk. It is not clear whether patients in the physio-assisted group were instructed to exercise at home as regularly as the autonomous group.
Attrition bias: Low risk. High dropout rate, but this is evenly distributed between the two intervention groups and clearly documented.
Detection bias: High risk. Short follow up period.

Additional comments

Study, country

Nibu 2010
Japan, two centres.

Study type, study period

Observational study (retrospective).
Recruitment period for intervention group not reported. Recruitment period for control group was 1981 to 2003.

Number of patients

298.

Patient characteristics

Inclusion criteria: patients who had undergone neck dissection for the treatment of head and neck cancer.

	Rehabilitation (n = 224)	No rehabilitation (n = 74)
Mean age, years (range)	62 (31–84)	61 (39–84)
Primary tumour site, n (%)		
Oral cavity	81 (36.2)	24 (32.4)
Hypopharynx	50 (22.3)	20 (27.0)
Larynx	38 (17.0)	8 (10.8)
Oropharynx	26 (11.6)	16 (21.6)
Salivary gland	8 (3.6)	-
Thyroid	8 (3.6)	-
Other	13 (5.8)	6 (8.1)
Type of neck dissection, n (%)		
Unilateral	140 (62.5)	33 (44.6)
Bilateral	84 (37.5)	41 (55.4)

Intervention

Patients underwent a rehabilitation programme designed for neck dissection according to the protocol of the institution at which they were treated (n = 224).

Comparison

Patients did not participate in the neck dissection rehabilitation programme (n = 74).

Length of follow-up

12 months.

Outcome measures and effect size

	Rehabilitation group	No rehabilitation group	P value
Arm abduction test score			
Level III ND	4.2	3.8	NS
Level IV ND	3.7	3.5	NS
Level V ND	3.9	3.2	0.06
Level VI ND	2.2	1.6	0.03
ND: neck dissection; NS: not significant.			

Source of funding

Not reported. Authors declared no conflicts of interest.

Risks of bias

Selection bias: High risk. Historical control group used, with long (22 years) accrual period.
Performance bias: Unclear/unknown risk. Care received in addition to the intervention is not clear.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

Study, country

Salerno 2002
Italy, single centre.

Study type, study period

Observational study. Assumed to be prospectively conducted, but this is not explicitly stated by the authors.
January 1998 to July 2000.

Number of patients

60.

Patient characteristics

Inclusion criteria: patients undergoing total laryngectomy with functional neck dissection.

	Physical therapy	No physical therapy
Age, mean (range)	60.8 (41–80)	58.4 (41–78)
Gender, n (%)		
Male	26 (86.7)	26 (86.7)
Female	4 (13.3)	4 (13.3)

	Physical therapy	No physical therapy
T Stage, n (%)		
T2	2 (6.7)	1 (3.3)
T3	18 (60.0)	18 (60.0)
T4	10 (33.3)	11 (36.7)
N Stage, n (%)		
N0	9 (30.0)	10 (33.3)
N1	3 (10.0)	3 (10.0)
N2	12 (40.0)	13 (43.3)

Intervention

Physical therapy (n = 30). Patients attended a postoperative self-rehabilitation training course for the functional recovery of the shoulder, as soon as possible (usually 15–30 days after surgery). Patients also received three sessions per week of assisted physiotherapy. After hospital discharge, further physical therapy was carried out on an outpatient basis for an average of 97 days.

Comparison

Patients received no outpatient physical therapy (n = 30).

Length of follow-up

6 months.

Outcome measures and effect size

	1 month post-surgery			6 months post-surgery		
	Physical therapy.	**No physical therapy.**	**P value**	**Physical therapy.**	**No physical therapy.**	**P value**
Passive forward elevation (0–10)	7.8 ± 1.69	7.53 ± 1.69	0.5	9.33 ± 0.96	6.87 ± 1.63	<0.001
Global shoulder active motility (0–40)	25.93 ± 5.57	25.80 ± 5.39	0.9	36.27 ± 4.19	28.07 ± 6.63	<0.001
Pain (0–15)	5.03 ± 3.77	5.07 ± 3.77	1	13 ± 2.75	8.57 ± 4.48	<0.001
Working and recreational activity (0–20)	9.93 ± 3.83	9.97 ± 3.94	1	18.8 ± 1.88	12.7 ± 5.30	<0.001
Shoulder functional assessment, Constant score* (0–85)	48.7 ± 10.51	48.37 ± 10.43	0.9	77.4 ± 7.50	56.2 ± 14.58	<0.001

*Assessed using the method of Constant and Murley (1987).

Source of funding

Not reported.

Risks of bias

Selection bias: Unclear/unknown risk. Patients allocated to treatment based on their geographical location (those further from the treatment centre were allocated to autonomous treatment).
Performance bias: Unclear/unknown risk. It is not clear what inpatient care the 'no physical therapy' group received.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

2

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Intervention	Comparison	Outcomes
Adults with cancer of the upper aerodigestive tract and shoulder dysfunction following neck dissection.	Therapeutic exercises: • Range of motion exercise • Progressive resistance training • Proprioceptive neuromuscular facilitation exercise Standard physiotherapy/standard care Nerve exploration +/- repair	Each other	• Shoulder function • Shoulder pain • Shoulder disability • Quality of life • Adverse events

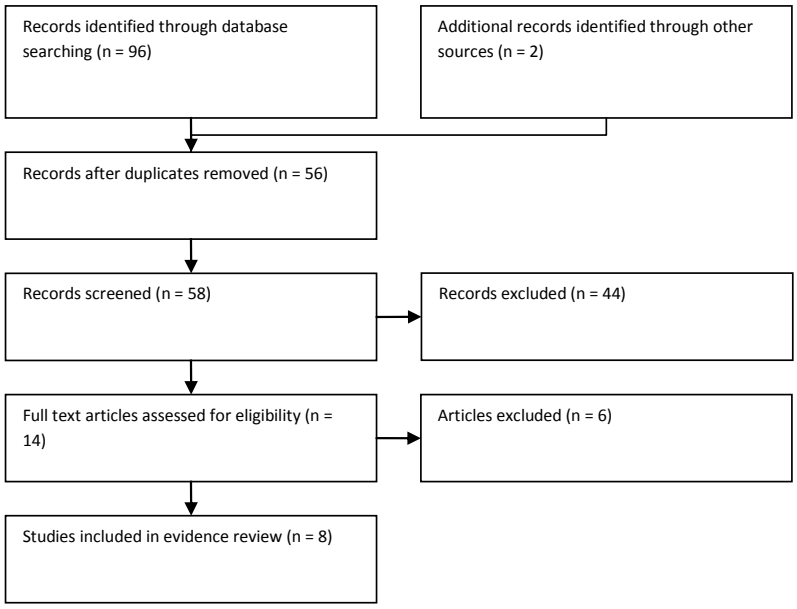
3

4 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.
Search strategies	Search from 1994 onwards.
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Quality checklists for RCTs, observational studies (NICE manual Appendix C) and meta-analysis and systematic reviews (NICE manual Appendix B) will be used Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review

5

Figure 7.6. Study flow diagram



Included studies

Baggi, F., Santoro, L., Grosso, E., Zanetti, C., Bonacossa, E., Sandrin, F., Massaro, M. A., Tradati, N., and Simoncini, M. C. Motor and functional recovery after neck dissection: comparison of two early physical rehabilitation programmes. Acta Otorhinolaryngologica Italiano 2014. 34(4): 230-240

Carvalho, A. P., Vital, F. M., and Soares, B. G. Exercise interventions for shoulder dysfunction in patients treated for head and neck cancer. Cochrane Database of Systematic Reviews 2012. 4

Inoue, H., Nibu, K., Saito, M., Otsuki, N., Ishida, H., Onitsuka, T., Fujii, T., Kawabata, K., and Saikawa, M. Quality of life after neck dissection. Otolaryngology—Head & Neck Surgery 2006. 132(6): 662-666.
Used as source of information regarding historical control group used in Nibu 2010.

Lauchlan, D. T., McCaul, J. A., McCarron, T., Patil, S., McManners, J., and McGarva, J. An exploratory trial of preventative rehabilitation on shoulder disability and quality of life in patients following neck dissection surgery. European Journal of Cancer Care 2011. 20(1): 113-122.
Included in review by Carvalho et al; some additional outcomes reported separately here.

McNeely, M. L., Parliament, M., Courneya, K. S., Seikaly, H., Jha, N., Scrimger, R., and Hanson, J. A pilot study of a randomized controlled trial to evaluate the effects of progressive resistance exercise training on shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy in head and neck cancer survivors. Head and Neck 2004. 26(6): 518-530.
Included as part of review by Carvalho et al.

McNeely, M. L., Parliament, M. B., Seikaly, H., Jha, N., Magee, D. J., Haykowsky, M. J., and Courneya, K. S. Effect of exercise on upper extremity pain and dysfunction in head and neck cancer survivors: a randomized controlled trial. Cancer 2008. 113(1): 214-222.
Included as part of review by Carvalho et al.

Nibu, K., Ebihara, Y., Ebihara, M., Kawabata, K., Onitsuka, T., Fujii, T., Saikawa, M., Nibu, Ken ichi, Ebihara, Yasuhiro, Ebihara, Mitsuru, Kawabata, Kazuyoshi, Onitsuka, Tetsuro, Fujii, Takashi, and Saikawa, Masahisa. Quality of life after neck dissection: a multicenter longitudinal study by the Japanese Clinical Study Group on Standardization of Treatment for Lymph Node Metastasis of Head and Neck Cancer. International Journal of Clinical Oncology 2010. 15(1): 33-38

Salerno, G., Cavaliere, M., Foglia, A., Pellicoro, D. P., Mottola, G., Nardone, M., and Galli, V. The 11th nerve syndrome in functional neck dissection. Laryngoscope 2002. 112(7 Pt 1): 1299-1307

Excluded studies

Eden, M. M. F. Recommendations for patient-reported outcome measures for head and neck cancer-related shoulder dysfunction: A systematic review. Rehabilitation Oncology 2014. 32(3): 6-19.
Reason for exclusion: Systematic review; inclusion criteria not relevant to PICO. References within checked for relevance.

Goldstein, D. P., Ringash, J., Bissada, E., Jaquet, Y., Irish, J., Chepeha, D., and Davis, A. M. Scoping review of the literature on shoulder impairments and disability after neck dissection. Head & Neck 2014. 36(2): 299-308.
Reason for exclusion: Outcomes not relevant to PICO.

Kimura S.Aoki. Rehabilitation for accessory nerve syndrome following neck lymph node dissection for head and neck cancers. Neurorehabilitation and Neural Repair 2012. Conference(var.pagings): 662-August.
Reason for exclusion: Insufficient data reported (conference abstract only).

McGarvey, A. C., Chiarelli, P. E., Osmotherly, P. G., and Hoffman, G. R. Physiotherapy for accessory nerve shoulder dysfunction following neck dissection surgery: a literature review. Head & Neck 2011. 33(2): 274-280.
Reason for exclusion: Systematic review; inclusion criteria not relevant to PICO. References within checked for relevance.

McNeely ML, Parliament MB, Seikaly, and McNeely, Margaret L. Sustainability of outcomes after a randomized crossover trial of resistance exercise for shoulder dysfunction in survivors of head and neck cancer. Physiotherapy Canada 2015. 67(1): 85-93
Reason for exclusion: Updated results of McNeely (2008). Non-comparative results: all control patients crossed over onto active treatment.

Mishra, S. I., Scherer, R. W., Snyder, C., Geigle, P., and Gotay, C. Are exercise programs effective for improving health-related quality of life among cancer survivors? A systematic review and meta-analysis. Oncology Nursing Forum 2014. 41(6): E326-E342.
Reason for exclusion: Systematic review. Inclusion criteria not relevant to PICO. References within checked for relevance.

Rogers, S. N., Ferlito, A., Pellitteri, P. K., Shaha, A. R., and Rinaldo, A. Quality of life following neck dissections. Acta Otolaryngologica 2004. 124(3): 231-236.
Reason for exclusion: Narrative review.

Other references

Constant, C. R. and Murley, A. H. A clinical method of functional assessment of the shoulder. Clin Orthop Relat Res 1987. (214): 160-164.

8. Follow-up of people with cancer of the upper aerodigestive tract and management of osteoradionecrosis (ORN)

Follow-up

Clinical question: In people who are clinically disease free and who have undergone treatment for squamous cell cancer of the upper aerodigestive tract with curative intent, what is the optimal method(s), frequency, and duration of follow-up?

Background

Patients who have undergone treatment for CUADT are commonly followed-up in order to provide support, rehabilitation, identify recurrence or new primary cancers and manage complications of treatment.

There is variation in the duration, frequency and delivery of follow-up in the UK.

Evidence statements

Very low quality evidence (one observational study, 247 patients) suggests that the addition of narrow band imaging (NBI) investigations to routine follow up protocols may increase the detection rate of second primary head and neck tumours (risk ratio [RR] 2.0, 95% confidence interval [CI] 1.03, 3.9) and allow their detection at an earlier stage of disease (lesions detected at a precancer stage: 50% and 0% for patients receiving and not receiving NBI, respectively).

Very low quality evidence (one observational study, 286 patients) suggests that the addition of ultrasound (US) investigations to a routine systematic follow up protocol results in earlier detection of recurrence or metastasis (7.4 months versus 10.4 months). Evidence from the same study also suggests that recurrence or metastasis is detected earlier in patients whose follow up visits adhere to a systematic protocol compared with those whose frequency of follow up visits is left to the discretion of the treating surgeon (10.4 months versus 11.9 months). The stage of disease at detection was similar regardless of the follow up protocol or investigations used.

Very low quality evidence (one observational study, 913 patients) suggests that in people treated for larynx cancer who have recurrent disease, there is no relationship between surveillance intensity prior to disease recurrence and subsequent mortality. Similarly, a second observational study (very low quality evidence, 100 patients) suggests that in people treated for larynx, pharynx and oral cavity cancers, intensity of surveillance does not affect the probability of overall survival.

Very low quality evidence (one observational study, 160 patients) suggest uncertainty over whether the addition of nurse-led consultations to routine follow up improves the psychosocial adjustment and quality of life of patients with cancer of the upper aerodigestive tract. Patients who experienced nurse-led consultations showed greater improvements from baseline for a number of measures of quality of life and psychosocial adjustment, but it is unclear if this effect is due to the intervention, as there were significant differences between the two groups at baseline.

No evidence was identified regarding the effect of different follow up protocols on any of the following outcomes:

- Progression free survival
- Disease-specific survival
- Process related complications

Study characteristics and quality

Of the five relevant studies identified, three used a retrospective design, one was conducted prospectively and one was a historically controlled trial (data for the intervention group was prospectively collected, whilst data for the comparison group was retrospective). Study populations ranged in size from 100 to 913 patients and study results were published between 2003 and 2013.

A lack of reported detail meant that none of the studies could be fully assessed for quality, leading to many risks of bias being rated as unclear/unknown. For example, detail of what follow up care other than the intervention patients received was limited (many studies simply reported this as 'routine' or 'standard' follow up), as was the detail of patient's baseline characteristics, and therefore whether these were comparable across groups receiving different interventions. For one study (Leeuw, 2013) there were statistically significant differences between groups at baseline, including for some of the measured outcomes. Although the authors reported that patients who received nurse-led consultations in addition to visits to their surgeon had greater improvements in quality of life and psychosocial adjustment than patients who only visited their surgeon, these outcome measures were significantly lower at baseline in the group receiving nurse-led consultation.

Table 8.1. Characteristics of included studies

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	N	FOLLOW UP/COMPARISON	LENGTH OF FOLLOW UP	OUTCOMES MEASURED
Chu, 2012	HCT	Oral squamous cell carcinoma, treated surgically	247	Routine follow up versus routine follow up in combination with narrow band imaging	Median 30 months and 48 months for NBI and no NBI groups respectively	Detection of second primary tumour; tumour stage at detection of second primary
Leeuw, 2013	PCS	Head and neck cancer treated with curative intent	160	Surgeon and nurse consultation at each follow up visit, versus consultation with a surgeon alone	12 months	Changes in health related quality of life after treatment; psychosocial adjustment after treatment
Lucev, 2012	RCS	Oral or pharyngeal cancer treated surgically, with local recurrence and/or neck metastases within 2 years after surgery	286	Follow up (physical examination) with frequency of visits at surgeon's discretion), versus visits at a predetermined frequency, versus visits at a predetermined frequency with neck ultrasound performed at each visit	2 years	Time to detection of recurrence or metastasis; stage of disease at detection of recurrence/metastasis
Francis, 2009	RCS	Larynx cancer, with recurrence of disease	913	Intensity of surveillance in the 9 months prior to diagnosis of recurrence (no visits vs. less visits than recommended vs. equal to or more than recommended)	NR	One year mortality; five year mortality
Schwartz, 2003	RCS	Squamous cell carcinoma of the larynx, pharynx or oral cavity treated with curative intent	100	Intensity of surveillance (high intensity vs. low intensity)	Median 28.5 months	Overall survival
Abbreviations: HCT: historically controlled trial; NR: not reported; PCS: prospective cohort study; RCS: retrospective cohort study						

GRADE evidence tables

Table 8.2. GRADE evidence profile: outcomes for routine follow up in combination with narrow band imaging versus routine follow up without narrow band imaging

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Routine follow up + NBI	Routine follow up without NBI	Relative (95% CI)	Absolute	
Detection of second primary head and neck tumour											
1[1,2]	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	18/101 (17.8%)	13/146 (8.9%)	RR 2.0 (1.03, 3.9)	89 more per 1000 (from 3 more to 258 more)	⊕OOO VERY LOW
Detection of second primary tumour (any anatomical site)											
1[1,2]	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	18/101 (17.8%)	18/146 (12.3%)	RR 1.45 (0.79, 2.64)	55 more per 1000 (from 26 fewer to 202 more)	⊕OOO VERY LOW
Tumour stage at detection of second primary											
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	18[5]	13[5]	**Stage of second primary tumour** / **NBI** / **No NBI** Precancer / 13 (50%) / 0 (0%) Tis + T1 + T2 / 12 (46%) / 10 (63%) T3 + T4 / 1 (4%) / 6 (38%)		⊕OOO VERY LOW

[1] Chu 2012
[2] Hsu 2008
[3] Control group treated 8-19 years prior to intervention group. Unclear if overall patient care will have remained comparable within this timescale.
[4] Overall number of events is low.
[5] Some patients had more than one tumour. Results in the effect column represent the results for each tumour rather than for each patient.

Table 8.3. GRADE evidence profile: outcomes for surgeon + nurse-led consultation versus surgeon-led consultation alone

Quality assessment							No of patients		Effect[3]			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgeon + nurse-led consultation	Surgeon-led consultation				
Change in HRQOL (global health status, baseline to 12 months)												
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	80	Intervention group significantly better	Comparison group significantly better	No significant difference between groups	⊕OOO VERY LOW
									1	0	0	
Change in HRQOL (EORTC functional scales, baseline to 12 months)												
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	80	Intervention group significantly better	Comparison group significantly better	No significant difference between groups	⊕OOO VERY LOW
									2	0	3	
Change in HRQOL (ORTC QLQ-H&N35 symptom scales, baseline to 12 months)												
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	80	Intervention group significantly better	Comparison group significantly better	No significant difference between groups	⊕OOO VERY LOW
									10	0	8	

Quality assessment							No of patients		Effect[3]			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgeon + nurse-led consultation	Surgeon-led consultation				
Change in HRQOL (EORTC symptom scales, baseline to 12 months)												
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	80	Intervention group significantly better	Comparison group significantly better	No significant difference between groups	⊕OOO VERY LOW
									6	0	3	
Psychosocial adjustment (baseline to 12 months)												
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	80	Intervention group significantly better	Comparison group significantly better	No significant difference between groups	⊕OOO VERY LOW
									1	0	6	

[1] Leeuw 2013

[2] Patients allocated based on time of recruitment. Significant differences between groups at baseline, including several quality of life parameters.

[3] 'intervention group significantly better' indicates an improvement (from baseline to 12 months) in the measured outcome that was statistically significantly greater in the intervention group than in the comparison group (and vice versa for the comparison group)

Table 8.4. GRADE evidence profile: outcomes for systematic versus discretionary frequency of follow up

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Systematic frequency of follow up	Discretionary frequency of follow up	Absolute	
Time to detection of recurrence/metastasis (mean)										
1[1]	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	105	92	10.45 versus 11.91 months (p = 0.0027)	⊕OOO VERY LOW
Stage of disease at detection of recurrence/metastasis										
1[1]	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	105	92	SYS / DIS Stage 1, n (%): 13 (12.4) / 14 (13.7) Stage 2, n (%): 32 (30.5) / 28 (27.5) Stage 3, n (%): 35 (33.3) / 30 (32.6) Stage 4, n (%): 25 (23.8) / 20 (21.7)	⊕OOO VERY LOW
DIS: discretionary frequency of follow up; SYS: systematic frequency of follow up										

[1] Lucev 2012

[2] No details of method of patient allocation reported. No baseline patient characteristics reported. Limited detail of care received by patients reported.

[3] No detail of cancer histologies reported. It is therefore unclear what proportion of tumours were squamous cell carcinoma (in line with the population of interest to the review).

Table 8.5. GRADE evidence profile: outcomes for follow up with or without neck ultrasound

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Routine follow up + neck ultrasound	Routine follow up alone	Absolute	
Time to detection of recurrence/metastasis										
1[1]	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	89	105	7.42 versus 10.45 months (p < 0.0001)	⊕OOO VERY LOW
Stage of disease at detection of recurrence/metastasis										
1[1]	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	89	105	Stage 1, n (%): +US 13 (12.4), −US 14 (13.7) Stage 2, n (%): +US 32 (30.5), −US 28 (27.5) Stage 3, n (%): +US 35 (33.3), −US 30 (32.6) Stage 4, n (%): +US 25 (23.8), −US 20 (21.7)	⊕OOO VERY LOW

+US: routine follow up + neck ultrasound; −US: routine follow up alone.

[1] Lucev 2012

[2] No details of method of patient allocation reported. No baseline patient characteristics reported. Limited detail of care received by patients reported.

[3] No detail of cancer histologies reported. It is therefore unclear what proportion of tumours were squamous cell carcinoma (in line with the population of interest to the review).

Table 8.6. GRADE evidence profile: outcomes for relative frequency of surveillance in the 9 months prior to recurrence

Quality assessment							No of patients[4]	Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)			
1-year mortality											
1[1]	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	913	Surveillance intensity	Odds ratio	95% CI	⊕OOO VERY LOW
								Larynx			
								No visits	1.00		
								<recommended	0.88	0.64, 1.20	
								≥recommended	0.90	0.55, 1.46	
								Glottis			
								No visits	1.00		
								<recommended	0.78	0.52, 1.17	
								≥recommended	0.60	0.29, 1.25	
								Supraglottis			
								No visits	1.00		
								<recommended	1.18	0.66, 2.12	
								≥recommended	1.98	0.86, 4.56	
								Other			
								No visits	1.00		
								<recommended	0.90	0.34, 2.35	
								≥recommended	0.45	0.12, 1.60	

Quality assessment							No of patients[4]	Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)		
5-year mortality										
1[1]	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	913	Surveillance intensity	Odds ratio	95% CI	⊕OOO VERY LOW
								Larynx		
								No visits	1.00	
								<recommended	0.74	0.56, 0.99
								≥recommended	0.97	0.63, 1.51
								Glottis		
								No visits	1.00	
								<recommended	0.64	0.45, 0.91
								≥recommended	0.82	0.46, 1.44
								Supraglottis		
								No visits	1.00	
								<recommended	1.10	0.61, 1.97
								≥recommended	1.21	0.49, 2.99
								Other		
								No visits	1.00	
								<recommended	0.73	0.25, 2.10
								≥recommended	0.89	0.24, 3.33

[1] Francis 2009
[2] Criteria for patient allocation and inclusion in the final analysis are unclear. Details of follow up care (e.g. methods of surveillance) not reported.
[3] No detail of cancer histologies reported. It is therefore unclear what proportion of tumours were squamous cell carcinoma (in line with the population of interest to the review).
[4] The number of patients according to frequency of surveillance was not reported.

Table 8.7. GRADE evidence profile: outcomes for high versus low intensity surveillance

Quality assessment							No of patients[4]	Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Absolute			
3-year overall survival											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	100		High intensity follow up	Low intensity follow up	⊕OOO VERY LOW
								Probability of 3 year overall survival, months	0.927	0.973	
5-year overall survival											
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	100		High intensity follow up	Low intensity follow up	⊕OOO VERY LOW
								Probability of 5 year overall survival, months	0.907	0.947	

[1] Schwartz 2003

[2] Unclear whether intervention and comparison groups were comparable at baseline. Details of follow up care (e.g. methods of surveillance) not reported. How and whether any eligible patients were omitted from the analysis is unclear.

[3] Overall number of events is low.

[4] The number of patients in the high and low intensity surveillance groups was not reported.

Evidence tables for all included studies

Study, country

Chu 2012
Taiwan, single centre.

Study type, study period

Historically controlled trial.
Patients in the intervention group were initially treated between September 2008 and August 2009. Patients in the control group were initially treated between January 1990 and December 2000.

Number of patients

247

Patient characteristics

Inclusion criteria for intervention group: consecutive patients with oral squamous cell carcinoma treated surgically (with or without adjuvant therapy).

Inclusion criteria for historical control group: patients with previously untreated squamous cell carcinoma of the tongue treated surgically and with curative intent.

Factor	Intervention group (n = 101)	Control group (n = 146)
Median age, years	52	51
Median follow up, months	30	48
Gender		
Male	92 (91%)	121 (83%)
Female	9 (9%)	25 (17%)
Site of primary tumour		
Oral tongue	51 (50%)	146 (100%)
Other*	50 (50%)	0 (0%)
Tobacco consumption		
Yes	71 (70%)	106 (72%)
No	30 (30%)	40 (28%)
Betel quid consumption		
Yes	55 (54)	72 (49%)
No	46 (46)	74 (51%)
Pathologic T classification		
T1 + T2	73 (72%)	117 (80%)
T3 + T4	28 (28%)	29 (20%)
Pathologic N classification		
N0	76 (75%)	112 (77%)
N+	25 (25%)	34 (23%)
Pathologic TNM stage		
Stage I + stage II	60 (59%)	101 (69%)
Stage III + stage IV	41 (41%)	45 (31%)

*sites included: buccal mucosa (n = 32), mouth floor (n = 7), retromolar trigone (n = 4), hard palate (n = 4), low gingival (n = 2), lip (n = 1).

Intervention

Narrow band imaging examination in addition to routine follow up (complete head and neck examination) at each follow up. Follow up schedule (i.e. frequency and timings of follow up visits) not reported.

Tissues examined with NBI: buccal mucosa; retromolar trigone; anterior tonsillar pillar; hard and soft palate; upper and lower gingival; tongue, floor of mouth; nasopharynx; oropharynx; hypopharynx, larynx.

Comparison

Routine follow up only (recent medical history and detailed head and neck examination). Follow up visits every month during the first year, every two months during the second year, every three months in the third year and every six months thereafter.

Outcome measures and effect size

Outcome	NBI (n= 101)	No NBI (n =146)
Detection of second primary tumour at any anatomical site (number of patients)	18 (18%)	18 (12%)
Detection of second primary tumour in the head and neck area (number of patients)	18 (18%)	13 (9%)
Detection of second primary tumour in the head and neck area (number of tumours)	26 (26%)	16 (11%)
Stage of second primary tumour	**NBI**	**No NBI**
Precancer	13 (50%)	0 (0%)
Tis + T1 + T2	12 (46%)	10 (63%)
T3 + T4	1 (4%)	6 (38%)

Source of funding

Not reported.

Risks of bias

Selection bias: Unclear/unknown risk. All patients in the control group had tongue cancer; patients in the intervention group had a mixture of oral cancer subtypes.
Performance bias: Unclear/unknown risk. Control group treated 8-19 years prior to intervention group. Unclear if overall patient care will have remained comparable within this timescale.
Attrition bias: Unclear/unknown risk. Patients in the control group were followed up for a median of 18 months longer than the intervention group. The implication of this discrepancy on the outcomes is unclear.
Detection bias: Low risk.

Additional comments

1

Study, country

Leeuw 2013.
Netherlands, single centre.

Study type, study period

Prospective cohort study
Control group patients were recruited from November 2007 to July 2008; intervention group patients were recruited from January 2009 to February 2010.

Number of patients

160.

Patient characteristics

Inclusion criteria: informed of a diagnosis of head and neck cancer; to be treated with curative intent; able to provide informed consent.
Exclusion criteria: overt psychology; alcohol addiction; life expectancy of less than six months.

Mean patient age: 58.8 years (range 22-86 years)

	Intervention group, n (%)	Comparison group, n (%)
Gender		
Male	54 (67.5)	60 (75.0)
Female	26 (32.5)	20 (25.0)
Ethnicity		
Caucasian	79 (98.8)	80 (100)
Cancer site		
Larynx	14 (17.5)	23 (28.8)
Hypopharynx	7 (8.8)	1 (1.3)
Oropharynx	15 (18.8)	10 (12.5)
Oral cavity	32 (40.0)	34 (42.5)
Other	10 (12.5)	10 (12.5)

	Intervention group, n (%)	Comparison group, n (%)
Stage		
I	24 (30.0)	30 (37.5)
II	19 (23.8)	22 (27.5)
III	10 (12.5)	7 (8.8)
IV	24 (30.0)	12 (15.0)
No stage	2 (2.5)	0 (0)
Treatment modality		
Surgery only	34 (42.5)	50 (62.5)
Surgery + radiotherapy	11 (28.8)	9 (22.5)
Radiotherapy only	23 (13.8)	18 (11.3)
Chemoradiotherapy	12 (15.0)	1 (1.3)
Laser surgery	0 (0)	2 (2.5)

Intervention

In parallel with conventional follow up care (see comparison group for details), six 30-minute nursing follow up consultations in the first year post-treatment. The aim of consultations was to give advice and support, addressing the physical and psychosocial consequences of treatment. Patients completed a 13-item checklist prior to each consultation. Nurses also performed simple medical checks during each consultation.

Comparison

Conventional follow up care, consisting of a 5-year routine control schedule with six bimonthly 10 minute visits to a head and neck surgeon in the first year post-treatment.

Length of follow-up

12 months.

Outcome measures and effect size

Psychosocial adjustment after treatment, measured using the Psychosocial Adjustment to Illness Scale – Self Report (PAIS-SR) questionnaire.
Health-related quality of life (HRQOL) was measured using the European Organization of Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) with an additional head and neck module (QLQ-H&N35).

Number of statistically significant differences between treatment groups for each symptom/scale at baseline, 6 months and 12 months.

	Baseline			6 months			12 months		
Scale/measure (total number of measures)	Intervention group significantly better	Comparison group significantly better	No significant difference between groups	Intervention group significantly better	Comparison group significantly better	No significant difference between groups	Intervention group significantly better	Comparison group significantly better	No significant difference between groups
Psychosocial adjustment (PAIS-SR) (7)	0	3	4	0	0	7	0	1	6
Functional scales (EORTC) (5)	0	3	2	0	0	5	0	0	5
Global health status/QOL (EORTC) (1)	0	1	0	0	0	1	0	0	1
Symptom scales (EORTC) (9)	0	6	3	0	0	9	0	0	9
Symptom scales (ORTC QLQ-H&N35) (18)	0	13	5	0	0	18	0	0	18
Total	0	26	14	0	0	40	0	1	39

Number of statistically significant differences between groups in the degree of change from baseline

	6 months			12 months		
Scale/measure (total number of measures)	Intervention group significantly better	Comparison group significantly better	No significant difference between groups	Intervention group significantly better	Comparison group significantly better	No significant difference between groups
Psychosocial adjustment (PAIS-SR) (7)	1	0	6	1	0	6
Functional scales (EORTC) (5)	2	0	3	2	0	3
Global health status/QOL (EORTC) (1)	1	0	0	1	0	0
Symptom scales (EORTC) (9)	6	0	3	6	0	3
Symptom scales (ORTC QLQ-H&N35) (18)	8	0	10	10	0	8
Total	18	0	22	20	0	20

Source of funding

Not reported.

Risks of bias

Selection bias: High risk. Patients were allocated to different interventions based on their time of recruitment into the study. There are significant differences between groups at baseline for many characteristics, including several of the measured quality of life and

psychosocial parameters.
Performance bias: Unclear/unknown risk. Details of other follow up care not clearly reported.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

Study, country

Lucev 2012
Croatia, three centres.

Study type, study period

Retrospective cohort study.
1991 to 2007.

Number of patients

286

Patient characteristics

Inclusion criteria: patients surgically treated for oral or pharyngeal cancer who experienced local recurrence and/or neck metastases within 2 years after surgery.

Patients' baseline characteristics were not reported.

Intervention/comparison

Group 1 (n = 92): conventional follow up. Inspection and palpation of the oral cavity and neck. Frequency of follow up visits was at the discretion of the surgeon, typically every 2 to 3 months.

Group 2 (n = 105): systematic follow up. Inspection and palpation of the oral cavity and neck (as group 1), once a month during the first year and once every two months during the second year.

Group 3 (n = 89): systematic follow up. In addition to inspection and palpation of the oral cavity and neck, neck ultrasound was performed at very follow up visit. Patients were seen every four to six weeks during the first year and once every two months during the second year.

In all groups further diagnostic tests were performed when symptoms or results of examination indicated the possibility of recurrence or metastasis.

Length of follow-up

2 years.

Outcome measures and effect size

Mean time to detection of recurrence/metastasis:

	Group 1	Group 2	Group 3
Mean time to detection of recurrence or metastasis, months	11.91[a,b]	10.45[a,c]	7.42[b,c]

[a]Group 1 vs. Group 2: p = 0.0027
[b]Group 1 vs. Group 3: p < 0.0001
[c]Group 2 vs. Group 3: p < 0.0001

Stage of disease (International Union Against Cancer, 1987) at detection:

	Group 1 (n =92)	Group 2 (n = 105)	Group 3 (n =89)
Stage 1, n (%)	14 (13.7)	13 (12.4)	12 (13.5)
Stage 2, n (%)	28 (27.5)	32 (30.5)	26 (29.2)
Stage 3, n (%)	30 (32.6)	35 (33.3)	32 (36.0)
Stage 4, n (%)	20 (21.7)	25 (23.8)	19 (21.3)

Subgroup analysis: mean time to detection of recurrence/metastasis according to type of surgical treatment received.

Mean time to detection of recurrence/metastasis, months	Group 1	Group 2	Group 3
Local excision	13.0	12.0	9.2
Local excision + unilateral neck dissection	12.2	10.6	7.0
Local excision + bilateral neck dissection	9.6	8.5	6.9

Source of funding

Not reported

Risks of bias

Selection bias: Unclear/unknown risk. No details of method of patient allocation reported. No baseline patient characteristics reported.

Performance bias: Unclear/unknown risk. Limited detail of care received by patients was reported.
Attrition bias: Low risk.
Detection bias: Unclear/unknown risk. Protocol used to establish recurrence/metastasis, and the therefore measure time to detection, was not reported.

Additional comments

1

Study, country

Francis, 2009
United States, multiple centres (patients identified from the Surveillance Epidemiology and End Results (SEER) and Medicare databases).

Study type, study period

Retrospective cohort study.
1992 to 2002.

Number of patients

913.

Patient characteristics

Inclusion criteria: patients with larynx cancer and recurrent disease
Exclusion criteria: any previous cancer diagnosis.

Gender	n (%)
Male	755 (82.7)
Female	158 (17.3)

Primary tumour subsite	n (%)
Glottis	579 (63.4)
Supraglottis	244 (26.7)
Other/not specified	90 (9.9)

Treatment	n (%)
Surgery	142 (15.6)
Radiation	418 (45.8)
Surgery + RT	273 (29.9)
Chemotherapy + RT	44 (4.8)
Other	36 (3.9)

Intervention/comparison

Intensity of surveillance in the 9 months before diagnosis of recurrence. Surveillance intensity was defined by comparing the actual frequency to American Head and Neck Society/National Cancer Care Guidelines (2001). Intensity was categorised into no visits; less visits than recommended; or equal to or more than recommended.

Length of follow-up

Not reported.

Outcome measures and effect size

Unadjusted odds of mortality, stratified by surveillance intensity and tumour subsite.

One-year mortality			
Surveillance intensity	Odds ratio	95% CI	*P* value
Larynx			
No visits	1.00		
<recommended	0.88	0.64, 1.20	0.414
≥recommended	0.90	0.55, 1.46	0.674
Glottis			
No visits	1.00		
<recommended	0.78	0.52, 1.17	0.229
≥recommended	0.60	0.29, 1.25	0.174
Supraglottis			
No visits	1.00		
<recommended	1.18	0.66, 2.12	0.570
≥recommended	1.98	0.86, 4.56	0.107
Other			
No visits	1.00		
<recommended	0.90	0.34, 2.35	0.830
≥recommended	0.45	0.12, 1.60	0.215

Five-year mortality			
Surveillance intensity	Odds ratio	95% CI	*P* value
Larynx			
No visits	1.00		
<recommended	0.74	0.56, 0.99	0.040
≥recommended	0.97	0.63, 1.51	0.899
Glottis			
No visits	1.00		
<recommended	0.64	0.45, 0.91	0.013
≥recommended	0.82	0.46, 1.44	0.489
Supraglottis			
No visits	1.00		
<recommended	1.10	0.61, 1.97	0.748
≥recommended	1.21	0.49, 2.99	0.674
Other			
No visits	1.00		
<recommended	0.73	0.25, 2.10	0.559
≥recommended	0.89	0.24, 3.33	0.865

Source of funding

American Academy of Otolaryngology Head and Neck Surgery Foundation, Health Service Research CORE grant.

Risks of bias

Selection bias: Unclear/unknown risk. Criteria for patient allocation unclear.
Performance bias: Unclear/unknown risk. Details of follow up care (e.g. methods of surveillance) not reported.
Attrition bias: Unclear/unknown risk. Length of follow up and how patients were chosen for included in the analysis is unclear.
Detection bias: Unclear/unknown risk. Length of follow up is unclear. Recurrence measured using a surrogate outcome (time to further ablative treatment after initial treatment).

Additional comments

1

Study, country

Schwartz, 2003.
United States, multiple centres.

Study type, study period

Retrospective cohort study.
1994 to 1998.

Number of patients

100.

Patient characteristics

Inclusion criteria: patients treated with curative intent for squamous cell carcinoma of the larynx, pharynx or oral cavity, treated with either definitive or postoperative radiotherapy.
Exclusion criteria: prior aerodigestive tract cancer diagnosis within the six months before diagnosis of the index tumour; patients without clearance of disease six weeks after therapy; patients not complying with scheduled follow up.

Gender	n (%)
Male	83 (83)
Female	17 (17)

Primary tumour site	n (%)
Larynx	23 (23)
Hypopharynx	8 (8)
Oropharynx	51 (51)
Oral cavity	18 (18)

Disease stage (AJCC criteria)	n (%)
I	13 (13)
II	12 (12)
III	18 (18)
IV	57 (57)

Type of radiotherapy	n (%)
Definitive	57 (57)
Postoperative	43 (43)

AJCC: American Joint Criteria on Cancer

Intervention/comparison

Intensity of surveillance. Mean surveillance intensity across the study population was 5.1 visits per year. Intensity was categorised into high intensity follow up (greater than mean number of visits) and low intensity follow up (fewer than mean number of visits).

Length of follow-up

Median 28.5 months (range 2-91 months).

Outcome measures and effect size

	High intensity follow up	Low intensity follow up
Probability of 3 year overall survival, months	0.927	0.973
Probability of 5 year overall survival, months	0.907	0.947

Survival estimated from Kaplan-Meier curves.

Source of funding

US government grant.

Risks of bias

Selection bias: Unclear/unknown risk. Unclear whether intervention and comparison groups were comparable at baseline.
Performance bias: Unclear/unknown risk. Details of follow up care (e.g. methods of surveillance) not reported.
Attrition bias: Unclear/unknown risk. How and whether any eligible patients were omitted from the analysis is unclear.
Detection bias: Low risk.

Additional comments

2

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Intervention	Comparison	Outcomes

Adults who have undergone curative treatment for squamous cell cancer of the upper aerodigestive tract.
 	
Subgroups:
 	
• HPV status
• Smokers
• Site
• Staging
• Treatment modality
	• Protocols involving:
	  • MRI
	  • CT
	  • PET/PET-CT
	  • US
	  • chest X-ray
	  • thyroid function testing
	  • oesophagoscopy
	  • clinical examination
	  • with or without narrow band imaging
	• Non-medic led clinic
	• Remote surveillance (e.g. telephone/online/postal consultation)
		Each other	• Stage of disease at recurrence
			• Detection of second primary
			• Overall survival
			• Progression free survival
			• Disease-specific survival
			• Process related complications
			• Health-related quality of life

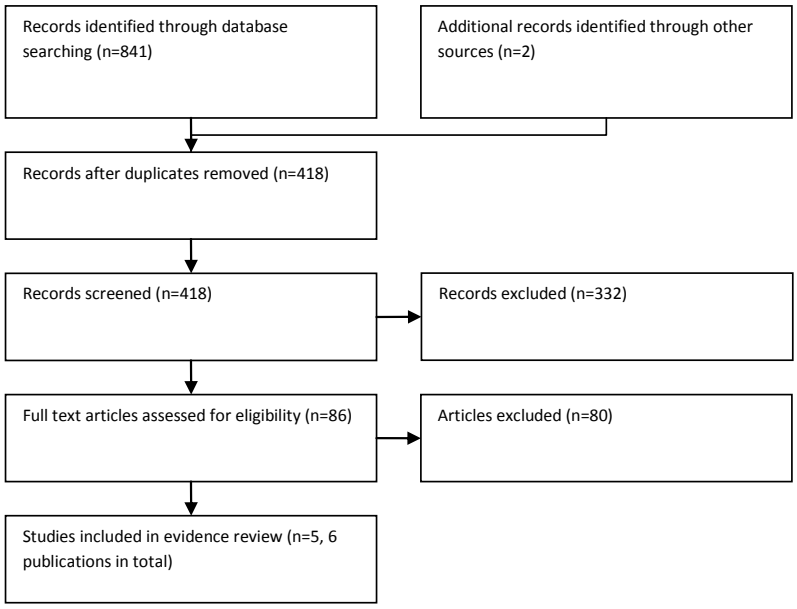
3

1 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.
Search strategies	
Review strategies	The evidence tables for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Additionally, any differences in timing, frequency and duration of follow up protocol will be considered within the review and subgroup analyses conducted where possible.

2

Figure 8.1. Study flow diagram



Included studies

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Note: used for extra data on control arm of Chu 2012 only.

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Excluded studies

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posttreatment recurrence of head and neck squamous cell carcinoma in patients negative for disease on clinical follow-up? Journal of Nuclear Medicine 2009. 50(1): 24-29.
Reason for exclusion: Non comparative study.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Population not relevant to PICO.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

de, Leeuw J. and Larsson, M. Nurse-led follow-up care for cancer patients: what is known and what is needed. Supportive Care in Cancer 2013. 21(9): 2643-2649.
Reason for exclusion: Editorial/narrative review.

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Reason for exclusion: Editorial/narrative review.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Systematic review. Inclusion criteria not relevant to PICO.

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Reason for exclusion: Study design not relevant.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Non comparative study.

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Iyengar, N. M. Routine versus clinically indicated post-treatment surveillance in head and neck cancer. Journal of Clinical Oncology 2010. Conference(var.pagings): 15.
Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Non English publication.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Systematic review. Inclusion criteria and outcomes not relevant to PICO.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Editorial/narrative review.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Conference abstract only. Full article subsequently published.

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Reason for exclusion: Study design not relevant.

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Reason for exclusion: Insufficient outcome data reported.

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Reason for exclusion: Population not relevant to PICO.

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Reason for exclusion: Population not relevant to PICO.

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Reason for exclusion: Population not relevant to PICO.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Intervention/comparison not relevant to PICO.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Study design not relevant.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Outcomes not relevant to PICO.

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Reason for exclusion: Editorial/narrative review.

Szmeja, Z., Wierzbicka, M., and Kordylewska, M. The value of ultrasound examination in preoperative neck assessment and in early diagnosis of nodal recurrences in the follow-up of patients operated for laryngeal cancer. European Archives of Oto-Rhino-Laryngology 1999. 256(8): 415-417.
Reason for exclusion: Non comparative study.

Takenaka, R., Kawahara, Y., Okada, H., Hori, K., Kita, M., Tsuzuki, T., Tanioka, D., Kawano, S., Inoue, M., Yagi, S., Uemura, M., Nomiya, S., Onoda, T., Tominaga, S. O., and Yamamoto, K. Narrow band Imaging for esophageal surveillance in patients with head and neck cancers. Gastrointestinal Endoscopy 2008. 67(5): AB134-AB134.
Reason for exclusion: Population not relevant to PICO.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Population not relevant to PICO.

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Reason for exclusion: Non comparative study.

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Reason for exclusion: Outcomes not relevant to PICO.

Yun, M., Ryu, Y. H., Kim, G. E., and Lee, J. D. FDG PET in the evaluation of treatment response and follow up of patients with nasopharyngeal carcinoma (NPC). Journal of Nuclear Medicine 2003. 44(5): 404P-404P.
Reason for exclusion: Non comparative study.

Management of ORN

Clinical question: What are the most effective methods of managing osteoradionecrosis following treatment of cancer of the upper aerodigestive tract?

Background

Osteoradionecrosis most commonly affects the mandible and can have significant consequences for the patient. Treatment options include surgery, hyperbaric oxygen therapy (HBO), and drugs such as tocopherol and pentoxyphylline. These interventions have costs and potential side effects, and have uncertain efficacy.

Evidence statements

Hyperbaric oxygen (HBO) therapy

Very low quality evidence from a systematic review (Bennett 2012) of three randomised controlled trials including a total of 246 patients suggests that in people who have or at risk of osteoradionecrosis (ORN) of the jaws, treatment with HBO improves the likelihood of complete mucosal cover in the affected area (risk ratio [RR] 1.30, 95% confidence interval [CI] 1.09, 1.55; RR >1 favours HBO). However, this analysis included some patients receiving HBO for the prevention or ORN, rather than as an ORN treatment. Excluding these patients from the analysis suggests that there is uncertainty about whether HBO therapy improves the incidence of complete mucosal cover in people undergoing treatment for ORN of the jaws (RR 1.22, 95% CI 0.85, 1.76).

Low quality evidence from a single randomised controlled trial (Annane 2004) compared the effectiveness of HBO and placebo in the treatment of ORN of the jaws (68 patients). There was no significant difference between HBO and placebo in terms of the rate of recovery from ORN one year post-treatment (RR 0.60, 95 CI 0.25, 1.40). The authors used a stringent definition of “recovery”, whereby any case requiring surgery was deemed as a treatment failure. Nevertheless, rates of recovery were also not significantly different between patients who had surgery after treatment with HBO or placebo (RR 0.94, 95% CI 0.75, 1.17).

Surgical interventions

Three observational studies were identified that investigated the effectiveness of adding sequestrectomy to ORN treatment protocols (very low quality evidence, 102 patients in total). Due to differences between studies in the control treatments used and the way outcomes were measured, the results could not be pooled. Results from one trial (Cheng 2006; 45 patients) suggest that patients treated with sequestrectomy are more likely to achieve a stable clinical condition for the duration of follow up (RR 1.67, 95% CI 1.09, 2.55), but the length of follow up was not reported. In the second trial (Wong 1997; 28 patients), more patients treated with sequestrectomy had improvement or resolution of their ORN at the end of follow up (RR 2.22, 95% CI 0.82, 6.05), but the number of patients studied was small and the difference between groups did not reach statistical significance. In a third trial (David 2001; 39 patients), similar proportions of patients in each treatment group achieved at least some improvement in ORN after treatment (RR 1.00 95% CI 0.87,

1.16). However, rates of complete treatment success were higher in patients treated with sequestrectomy (RR 2.57, 95% CI 1.39, 4.76).

David et al also investigated the addition of resection to ORN treatment (very low quality evidence, 31 patients). Similar proportions of patients in each treatment group achieved at least some improvement in ORN after treatment (RR 0.97 95% CI 0.79, 1.18). However, rates of complete treatment success were higher in patients treated with resection (RR 2.49, 95% CI 1.35, 4.59).

Other interventions

No relevant evidence was identified on the effectiveness of nutritional support, medical management (with tocopherol or pentoxyphylline), or smoking cessation in the treatment of ORN of the jaws.

Study characteristics and quality

The search identified one systematic review (including three relevant randomised trials) and four observational studies relevant to the review. Details of study design are summarised in Table 8.8. For one randomised trial, some outcomes that were not included in the systematic review are also reported separately here.

The systematic review had a broader scope than that of this evidence review: it included studies investigating the effects of HBO on the treatment or prevention of any form of late radiation tissue injury. Only the results for studies investigating the use of HBO as a treatment for ORN are reported here. More specifically, this evidence review includes only the treatment, and not the prevention, of ORN. The published systematic review, however, makes no distinction between treatment and prevention in the reporting of their results. Of the three trials of ORN included in the review, one investigates ORN treatment, one investigates ORN prevention, and in the third trial some outcomes pertaining to ORN treatment are reported, but it is unclear whether all patients in this trial had a diagnosis of ORN at baseline. To attempt to deal with this problem, exploratory analysis has been conducted here that excludes the trial of patients receiving HBO as prophylaxis.

In the published systematic review, data from all three trials have been pooled for the outcome 'complete mucosal cover'. However, due to differences in methods of reporting between the trials, it is unclear whether it is appropriate to pool this outcome data. Notwithstanding the issues discussed above regarding the grouping together of patients regardless of whether they received HBO as treatment or prophylaxis, the three studies used varied definitions of outcome. Event rates were often reported for 'treatment success' or 'treatment failure' using several criteria to measure this that were not limited to mucosal cover alone. The use of event rates for failure/success as a surrogate for mucosal cover (as the authors appear to have done) introduces the risk of under- or over-reporting of the true event rates for this outcome.

All four observational trials have been rated as very low quality evidence. All of these trials were small (including between 32 and 51 patients) and conducted retrospectively. All observational studies had a high risk of bias: issues included clear imbalances between treatment groups at baseline (three out of four studies), a lack of detail on the care received by patients alongside the studies treatment and whether this care was standardised (three out of four studies), and unclear reporting of follow up (one trial).

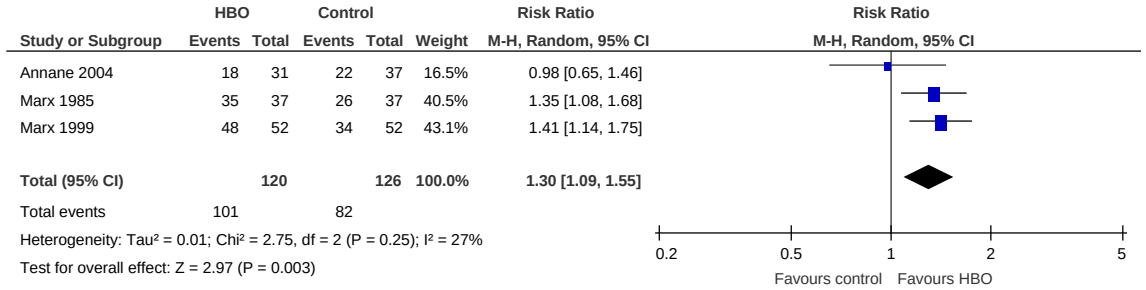
Table 8.8. Characteristics of included studies

AUTHOR	YEAR	DESIGN	PATIENT CHARACTERISTICS	N	INTERVENTION	COMPARISON	OUTCOMES MEASURED
Annane	2004	RCT	Mandibular ORN persisting after >2 months of conservative treatment	68	HBO	Placebo	Rate of recovery after 1 year; rate of recovery after first surgery; rate of recovery after second surgery; rate of treatment failure; incidence of mucosal coverage
Bennett	2002	SRMA	Any late radiation tissue injury (osteoradionecrosis results only reported here)	Maximum of 246	HBO	Any control treatment	Rate of complete recovery; mucosal coverage; establishment of bony continuity; successful healing of tooth sockets after tooth extraction
Cheng	2006	OBS	Maxillary ORN after treatment for nasopharyngeal cancer	48	Conservative therapy	Localized sequestrectomy	Rates of treatment success/failure
David	2001	OBS	Mandibular ORN treated with HBO	51	Sequestrectomy or resection (with HBO)	HBO alone	Success or improvement after treatment
Maier	2000	OBS	Severe mandibular ORN after treatment for oral cancer	41	HBO	No HBO	Treatment success rate
Wong	1997	OBS	ORN after head and neck radiotherapy	32	Conservative management in combination with sequestrectomy	Conservative management alone	ORN status (resolved/improving/stable) at last follow up
Abbreviations: HBO: hyperbaric oxygen; OBS: observational study; ORN: osteoradionecrosis; RCT: randomised controlled trial; SRMA: systematic review and meta-analysis							

GRADE evidence tables and meta-analysis

Figure 8.2. Forest plot of HBO versus control for the outcome 'complete mucosal cover'. (A) pooled data from the systematic review by Bennett et al (2012). (B) exploratory analysis excluding the study by Marx (1985) which studied HBO solely for ORN prevention.

(A)



(B)

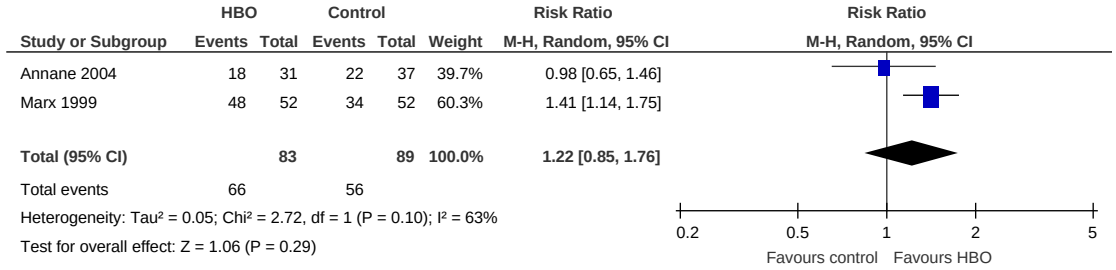


Figure 8.3. Forest plot of HBO versus placebo for the treatment of ORN

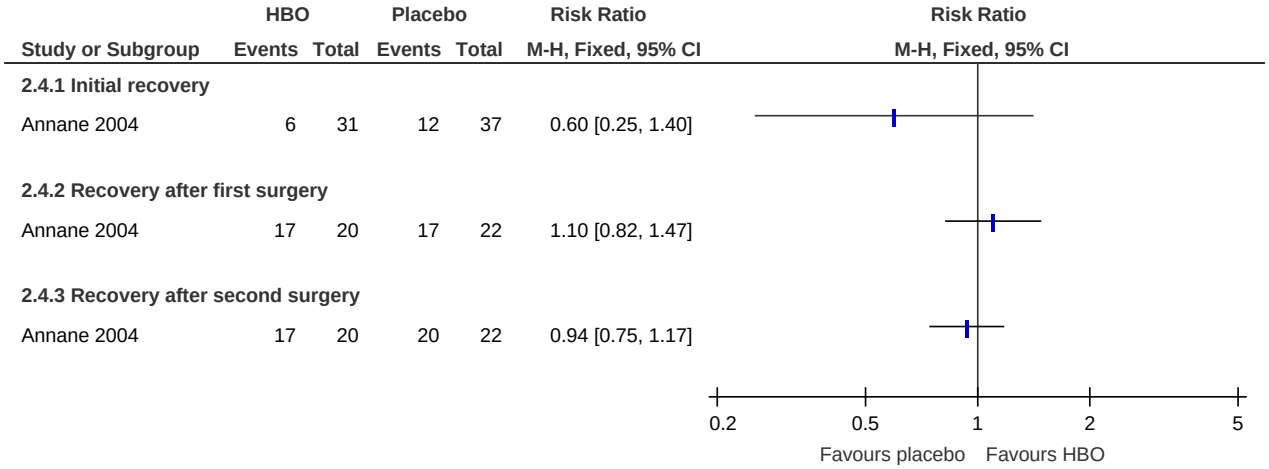


Table 8.9. GRADE evidence profile: HBO versus control for treatment or prevention of osteoradionecrosis

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBO	Control	Relative (95% CI)	Absolute	
Complete mucosal cover											
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	101/120 (84.2%)	82/126 (65.1%)	RR 1.3 (1.09, 1.55)	195 more per 1000 (from 59 more to 358 more)	⊕OOO VERY LOW
Complete mucosal cover (excluding patients receiving HBO for ORN prevention)											
2	randomised trials	serious[4]	no serious inconsistency	serious[2]	serious[3]	none	66/83 (79.5%)	56/89 (62.9%)	RR 1.22 (0.85, 1.76)	138 more per 1000 (from 94 fewer to 478 more)	⊕OOO VERY LOW

[1] Two out of three trials contained no details of method of randomisation, and were unblinded. The same trials also did not report any details of care received in addition to the intervention, or whether patient characteristics were comparable between treatment groups.

[2] One trial investigated prevention of ORN rather than its treatment, meaning patients did not have a diagnosis of ORN at baseline. In a second trial some treatment outcomes were reported, but it is unclear whether all patients in this trial had a diagnosis of ORN at baseline.

[3] Low overall number of events.

[4] One out of two trials contained no details of method of randomisation, and was unblinded. The same trial did not report any details of care received in addition to the intervention, or whether patient characteristics were comparable between treatment groups.

Table 8.10. GRADE evidence profile: HBO versus placebo for treatment of ORN of the jaws

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBO	Placebo	Relative (95% CI)	Absolute	
Recovery at end of follow up (follow-up 12 months)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[2]	none	6/31 (19.4%)	12/37 (32.4%)	RR 0.6 (0.25, 1.4)	130 fewer per 1000 (from 243 fewer to 130 more)	⊕⊕OO LOW
Recovery after 1st surgery (follow-up 12 months)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[2]	none	17/20 (85%)	17/22 (77.3%)	RR 1.1 (0.82, 1.47)	77 more per 1000 (from 139 fewer to 363 more)	⊕⊕OO LOW
Recovery after 2nd surgery (follow-up 12 months)											
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[2]	none	17/20 (85%)	20/22 (90.9%)	RR 0.94 (0.75, 1.17)	55 fewer per 1000 (from 227 fewer to 155 more)	⊕⊕OO LOW

[1] Annane 2004

[2] Small population size. Study recruited only about one-third of the study size planned (by power calculation) due to early stopping rules.

[3]. Although patients are described as having "overt mandibular osteoradionecrosis," it is unclear whether all patients truly meet this definition: according to study inclusion criteria, patients had received at least 2 months of conservative treatment prior to the study and where required to meet only limited clinical and radiographic criteria (which may not be representative of overt ORN) in order to be include in the study.

Table 8.11. GRADE evidence profile: surgery and postoperative HBO versus surgery alone for treatment of ORN of the jaws

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery and postoperative HBO	Surgery alone	Relative (95% CI)	Absolute	
Treatment success (follow-up 18 to 59 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	13/20 (65%)	20/21 (95.2%)	RR 0.68 (0.49, 0.95)	305 fewer per 1000 (from 48 fewer to 486 fewer)	⊕OOO VERY LOW

[1] Maier 2000

[2] Patient characteristics are not clearly reported, but methods suggest that patients treated with HBO had already failed at least one treatment, whereas this was not necessarily the case for patients in the surgery only group. Length of follow up was longer for the surgery group (59 months) than the HBO group (18 months).

[3] Small population size.

Table 8.12. GRADE evidence profile: localized sequestrectomy versus conservative therapy for treatment of ORN of the jaws

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Localized sequestrectomy	Conservative therapy	Relative (95% CI)	Absolute	
Treatment success rate (follow-up length not reported)											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	25/27 (92.6%)	10/18 (55.6%)	RR 1.67 (1.09, 2.55)	372 more per 1000 (from 50 more to 861 more)	⊕OOO VERY LOW

[1] Cheng 2006

[2] Treatment groups are imbalanced in terms of disease severity. Unclear what treatments patients received in addition to the intervention. Length of follow up not reported.

[3] Small population size.

Table 8.13. GRADE evidence profile: conservative management, with or without sequestrectomy, for treatment of ORN of the jaws

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conservative management + sequestrectomy	Conservative management w/out sequestrectomy	Relative (95% CI)	Absolute	
Resolution of ORN (follow-up 36 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	10/18 (55.6%)	3/10 (30%)	RR 1.85 (0.66, 5.2)	255 more per 1000 (from 102 fewer to 1000 more)	⊕OOO VERY LOW
Improvement or resolution of ORN (follow-up 36 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	12/18 (66.7%)	3/10 (30%)	RR 2.22 (0.82, 6.05)	366 more per 1000 (from 54 fewer to 1000 more)	⊕OOO VERY LOW
Resection or HBO required (follow-up 36 months)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	3/18 (16.7%)	6/10 (60%)	RR 0.28 (0.09, 0.88)	432 fewer per 1000 (from 72 fewer to 546 fewer)	⊕OOO VERY LOW

[1] Wong 1997

[2] Text suggests (but does not confirm) that any patient with sequestrum formation was treated with sequestrectomy. If this is the case, this introduces an imbalance between treatment groups. Follow up of "at least 3 years" for the majority of patients. Exact length of follow up, and whether this was the same for each treatment group, is not clear. Outcome data for four eligible patients is not reported, and the reasons for this are not explained.

[3] Small population size.

Table 8.14. GRADE evidence profile: HBO plus sequestrectomy versus HBO alone for treatment of ORN of the jaws

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBO + sequestrectomy	HBO alone	Relative (95% CI)	Absolute	
Treatment success (follow-up mean 1.8 years)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	18/20 (90%)	7/19 (36.8%)	RR 2.44 (1.33, 4.48)	531 more per 1000 (from 122 more to 1000 more)	⊕OOO VERY LOW
Treatment success or improvement (follow-up mean 1.8 years)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	19/20 (95%)	18/19 (94.7%)	RR 1 (0.87, 1.16)	0 fewer per 1000 (from 123 fewer to 152 more)	⊕OOO VERY LOW

[1] David 2001

[2] Study states that "the final treatment of ORN depended on the severity of the condition". No detail of care other than the intervention was reported.

[3] Small population size.

Table 8.15. GRADE evidence profile: HBO plus resection versus HBO alone for treatment of ORN of the jaws

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBO + resection	HBO alone	Relative (95% CI)	Absolute	
Treatment success (follow-up mean 1.8 years)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	11/12 (91.7%)	7/19 (36.8%)	RR 2.49 (1.35, 4.59)	549 more per 1000 (from 129 more to 1000 more)	⊕OOO VERY LOW
Treatment success or improvement (follow-up mean 1.8 years)											
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	11/12 (91.7%)	18/19 (94.7%)	RR 0.97 (0.79, 1.18)	28 fewer per 1000 (from 199 fewer to 171 more)	⊕OOO VERY LOW

[1] David 2001

[2] Study states that "the final treatment of ORN depended on the severity of the condition". No detail of care other than the intervention was reported.

[3] Small population size.

1 ## Evidence tables for all included studies

Study

Bennett, 2012

Study type, study period

Systematic review and meta-analysis of randomised trials.
Searches to identify studies were conducted in March 2011. No date limits were used.

Trial characteristics

Inclusion criteria:

- Randomised controlled trials and pseudo-randomised controlled trials that compared the effect of a regimen including HBO on any form of late radiation tissue injury, with any treatment regimen not including HBO.
- Any person with LRTI (including necrosis) of any tissue, or patients treated with large-dose radiotherapy likely to induce relatively early necrosis.
- Trials comparing regimens that included HBO with similar regimens that excluded HBO.

This review studied the effects of HBO on the treatment or prevention of any form of late radiation tissue injury. Only the results for studies investigating the use of HBO as a treatment for ORN are reported here.

Number of trials/patients included

Three trials relevant to the treatment of osteoradionecrosis were identified, including 246 relevant patients (120 treated with HBO; 126receiving control treatment)..

Intervention

Trials were accepted if they used HBO administered in a compression chamber between pressures of 1.5 ATA and 4.0 ATA and treatment times between 30 minutes and 120 minutes daily or twice daily. These parameters were chosen to exclude trivial exposure at one end of the scale, or highly toxic exposure at the other.

Comparison

Any standard treatment regimen designed to promote tissue healing or prevent further deterioration

Patient and treatment characteristics

No details of patient characteristics reported.

In all trials, patients received 30 treatment sessions using 2.4 ATA HBO. In Marx 1985 and Marx 1999, 20 sessions were preoperative and 10 were postoperative.

One trial (Annane 2004) used sham/placebo treatment as the comparison. One trial (Marx 1985) used standard treatment without HBO as the comparison. In one trial, no details of control treatment were reported.

Outcome measures and effect size

Outcome (number of studies)	HBO		No HBO		Risk ratio [95% CI]
	Events	Total	Events	Total	
Complete resolution of ORN after 12 months (1)	6	31	12	37	0.60 [0.25, 1.40]
Establishment of complete mucosal cover (3)	101	120	82	126	1.30 [1.09, 1.55]
Establishment of bony continuity (1)	48	52	34	52	1.41 [1.14, 1.75]
Successful healing of tooth sockets after tooth extraction (1)	35	37	26	37	1.35 [1.08, 1.68]

Source of funding

None reported.

Additional comments

2

Study, country

Annane, 2004.
France, 12 centres.

Study type, study period

Randomised controlled trial.
Patient enrolled between October 1997 and November 2001.

Number of patients

68. Original planned sample size was 222 (see additional comments).

Patient characteristics

Inclusion criteria:

- Past history of radiation
- Overt mandibular ORN
- Patients who met the following criteria after at least 2 months of optimal conservative treatment (antibiotics, local irrigation,

surgery),:

1. Presence of pain, dysthesia in the distribution of the inferior alveolar nerve, areas of trismus, or fistula
2. Presence of increased density, periosteal thickening, diffuse radiolucency, mottled areas of osteoporosis, or sclerosis sequestration

Exclusion criteria:

- Fracture or radiographic evidence of bone reabsorption to the inferior border
- Ongoing cancer
- Previous treatment with HBO
- Any contraindication to HBO

	HBO group	Control group
Gender, n (%)		
Male	25 (80.7)	34 (91.9)
Female	6 (19.3)	3 (8.1)
Median time since cancer diagnosis, months	48	34
Tumour site		
Floor of mouth	11 (35.5)	15 (40.5)
Tongue	13 (41.9)	11 (29.7)
Tonsil	5 (16.1)	5 (13.5)
Soft palate	6 (19.3)	9 (24.3)
Solid palate	1 (3.2)	3 (8.1)
Lips	1 (3.2)	0 (0)
Buccal mucosa	7 (22.6)	4 (10.8)

	HBO group	Control group
Median diameter of exposed bone area, mm	13.5	18
Site of necrosis		
Symphysis	2 (7)	4 (13)
Body	22 (78)	25 (81)
Angle	8 (28)	3 (10)
Ramus	3 (11)	1 (3)

Intervention

HBO. 100% oxygen breathed at 2.4 ATA for 90 minutes, 30 times over 3 weeks.

Comparison

Placebo. As for intervention, except patients breathed gas containing 9% oxygen and 91% nitrogen (designed to yield similar arterial oxygenation to breathing room air at 1 ATA).

Length of follow-up

12 months.

Outcome measures and effect size

	HBO group	Control group	
Rate of recovery from ORN after 1 year	6/31	12/37	RR 0.60 [95 CI 0.25, 1.40]
Recovery after 1st surgery	17/20	17/22	RR 0.60 [95 CI 0.25, 1.40]
Recovery after 2nd surgery	17/20	20/22	RR 0.94 [95% CI 0.75, 1.17]
Complete mucosal coverage after 12 months	18/31	22/37	RR 0.98 [95% CI 0.65, 1.46]

Source of funding

Not reported. Authors indicated no potential conflicts of interest.

Risks of bias

Selection bias: Low risk
Performance bias: Low risk
Attrition bias: Low risk
Detection bias: Low risk

Additional comments

Based on estimates of numbers required to give sufficient statistical power to detect a difference between treatment groups, the study originally planned to recruit 222 patients. Interim analyses were scheduled after inclusion of every 30 patients. At the second interim analysis, the independent safety and efficacy monitoring board advised stopping enrolment as recovery rates were worse in the hyperbaric oxygen arm. Therefore the study population comprises patients analysed up to this point, and eight additional patients whose follow up period ended after the second interim analysis.

1

Study, country

Cheng 2006
Taiwan, single centre.

Study type, study period

Observational study.
January 1988 to December 1998.

Number of patients

48.

Patient characteristics

Inclusion criteria:
Patients with nasopharyngeal carcinoma who had received radiotherapy and in whom ORN of the maxilla was subsequently identified. Maxillary ORN was recorded when bone of the maxilla was exposed within the radiation treatment volume after completion of radiotherapy and persisted for more than 3 months.

Exclusion criteria
ORN confined to the mandible.

In addition to the intervention/comparison, 11 out of 48 patients were treated with HBO. No data were reported on the outcomes of HBO treatment vs. no HBO treatment.

Gender	n (%)
Male	27
Female	21

Age, years	n (%)
<51	12
51–60	31
>60	5

Time after radiotherapy, months	n (%)
<24	10
24–60	28
>60	10

ORN stage*	Localized sequestrectomy, n (%)	Conservative therapy, n (%)
Stage I	1 (4)	9 (50)
Stage II	13 (48)	5 (28)
Stage III	13 (48)	4 (22)
*authors' own staging system, measuring exposure, infection and bleeding		

Intervention

Localized sequestrectomy (n = 27): removal of loose sequestrum and localized debridement without reconstruction of soft and hard tissues

Comparison

Conservative therapy (n = 18): oral hygiene instruction, daily mouth rinsing with 0.2% chlorhexidine, and antibiotics if indicated.

Length of follow-up

Not reported.

Outcome measures and effect size

Treatment success: 25/27 in the localized sequestrectomy group; 10/18 in the conservative therapy group. Risk ratio 1.67 [95% CI 1.09, 2.55].

Treatment success was defined as a stable clinical condition during the follow up period:

- Absence of pain and symptoms and signs of infection
- No signs of bleeding
- Stabilization or decrease of bone exposure area
- Stabilization or regression of radiographic bone destruction

Source of funding

Not reported.

Risks of bias

Selection bias: high risk. Treatment groups are imbalanced, with a greater proportion of late-stage disease patients receiving sequestrectomy.
Performance bias: unclear/unknown risk. Some patients received HBO as additional treatment, but the number of patients in each treatment arm receiving this is not reported.
Attrition bias: unclear/unknown risk. No information on length of follow up reported
Detection bias:

Additional comments

Three out of 48 patients were treated with maxillectomy. Due to small patient numbers, outcomes are not reported for these patients.

1

Study, country

David 2001
Canada, single centre.

Study type, study period

Observational study.
1985 to 1997.

Number of patients

51.

Patient characteristics

Inclusion criteria: all patients treated for mandibular ORN using HBO.

Mean age 62.2 years (range 37 to 88 years).

Gender	n (%)
Male	29 (56.9)
Female	22 (43.1)

Anatomical site of original disease	n	%
Tongue	1	2.0
Floor of mouth	8	15.7
Palate	5	9.8
Oropharynx/pharynx	5	9.8
Buccal/lingual mucosa	4	7.8
Nose/nasopharynx	3	5.9
Oral cavity	3	5.9
Retromolar trigone	2	3.9
Mandible	2	3.9
Lymphoma	2	3.9
Actinomycotic infection	1	2.0
Submandibular gland tumour	1	2.0
Not reported	14	27.5

Intervention (1)

HBO and sequestrectomy (n = 20)

Intervention (2)

HBO and resection plus reconstruction (n = 12)

Comparison

HBO alone (n = 19)

Length of follow-up

Mean 1.8 years (range 0.5 to 9 years).

Outcome measures and effect size

Success or improvement after HBO therapy. Success was recorded when all of the following criteria were met:

- No bone exposure
- Closure of fistula (if originally present)
- Asymptomatic status

Improvement was assigned to patients in whom one or two of these criteria was met.

	Success, n (%)	Improvement, n (%)	No improvement, n (%)
HBO and sequestrectomy	18 (90)	1 (5)	1 (5)
HBO and resection	11 (91.7)	0 (0)	1 (8.3)
HBO alone	7 (36.9)	11 (57.9)	1 (5.3)

Source of funding

Not reported. Authors declared that they have no relevant conflicts of interest.

Risks of bias

Selection bias: High risk. Study states that "the final treatment of ORN depended on the severity of the condition".
Performance bias: Unclear/unknown risk. No detail of care other than the intervention was reported.
Attrition bias: Low risk.
Detection bias: Low risk.

Additional comments

1

Study, country

Maier 2000.
Denmark, single centre.

Study type, study period

Observational study.
Study period not reported.

Number of patients

41.

Patient characteristics

Inclusion criteria: oral cancer patients, originally treated with surgery and postoperative radiotherapy, with severe osteoradionecrosis of the mandible

Mean age 56 years (range 46 to 68 years).

Intervention

Surgery and postoperative HBO (n = 20). Surgery was either debridement or partial mandibulectomy followed by microvascular transplantation. HBO (2.5 ATA/ hour) was given for a mean of 29 sessions (range 15 to 57).

Comparison

Surgery alone (n = 19): either debridement or partial mandibulectomy followed by microvascular transplantation.

Length of follow-up
HBO group: mean 18 months. Surgery group: 59 months.
Outcome measures and effect size
Treatment success: 13/20 (65%) in the postoperative HBO group; 20/21 (95.2%) in the surgery only group. Risk ratio 0.68 [95% CI 0.49, 0.95].
Source of funding
Not reported.
Risks of bias
Selection bias: High risk. Patient characteristics are not clearly reported, but methods suggest that patients treated with HBO had already failed at least one treatment, whereas this was not necessarily the case for patients in the surgery only group. Performance bias: Unclear/unknown risk. No detail of care other than the intervention was reported. Attrition bias: High risk. Length of follow up differed between treatment groups Detection bias: Unclear/unknown risk. No definition given for "treatment success".
Additional comments

1

Study, country
Wong 1997. Canada, single centre.
Study type, study period
Observational study. August 1960 to September 1995.
Number of patients
32.
Patient characteristics
Inclusion criteria: patients with bone exposure after head and neck radiotherapy, resultant from either oral surgical/dental interventions, or without apparent cause apart from radiation exposure. Exclusion criteria: bone exposure resulting from tumour necrosis or tumour recurrence. Mean age: 67 years (range 46 to 92 years). **Gender**: Male 23 (72); Female 9 (28) **Primary tumour origin**: Floor of mouth 10 (31.3); Tongue 2 (6.3); Gingival 2 (6.3); Alveolus 1 (3.1); Soft palate 1 (3.1); Tonsillar area 5 (15.6); Retromolar trigone 2 (6.3); Oropharynx 4 (12.5); Epiglottis 1 (3.1); Larynx 1 (3.1); Pyriform sinus 2 (6.3); Neck 1 (3.1)
Intervention
"Simple management" consisting of gentle removal of sequestrum from sequestrating lesions, in addition to conservative management (see below). Twenty patients treated, data available for 18.
Comparison
"Conservative management" consisting of local irrigation (saline solution, $NaHCO_3$, or chlorhexidine), systemic antibiotics in acute infectious episodes, and oral hygiene instruction. Twelve patients treated, data available for 10.
Length of follow-up
At least 3 years, except for one patient who was monitored for one year up to commencement of the study. No further details provided.
Outcome measures and effect size
ORN resolved, n (%): Simple management 10 (55.6); Conservative management 3 (30) **ORN improving, n (%)**: Simple management 2 (11.1); Conservative management 0 (0 **ORN stable, n (%)**: Simple management 3 (16.7); Conservative management 1 (10) **Resection ± HBO, n (%)**: Simple management 3 (16.7); Conservative management 6 (60) Cases were counted as resolved if mucosal cover was re-established. Cases were counted as improving if there was a decrease in mucosal exposure and symptoms. Cases were counted as stable where there was persistent bony exposure until the end of follow up or death.

Source of funding
Not reported.
Risks of bias
Selection bias: High risk. Text suggests (but does not confirm) that any patient with sequestrum formation was treated with sequestrectomy. If this is the case, this introduces an imbalance between treatment groups. Performance bias: Low risk. Attrition bias: Unclear/unknown risk. Follow up of "at least 3 years" for the majority of patients. Exact length of follow up, and whether this was the same for each treatment group, is not clear. Outcome data for four eligible patients is not reported, and the reasons for this are not explained. Detection bias: Low risk.
Additional comments

1

1 Evidence search details and references

2 ***Review question in PICO format***

Population	Intervention	Comparison	Outcomes

Adults who have been treated for cancer of the upper aerodigestive tract and have developed osteoradionecrosis of the jaws	• Hyperbaric oxygen
	• Surgical intervention:
	  • Debridement
	  • Sequestrectomy
	  • Segmental resection
	  • Rim resection
	  • Free flap reconstruction +/- implant rehabilitation
	• Nutritional support:
	  • Oral nutrition
	  • Enteral nutrition
	• Medical management:
	  • Tocopherol
	  • Pentoxyphylline
	• Smoking cessation
	• Observation
	• Combinations of the above
		Each other
		
		Placebo/sham treatment
			• Symptom control
			• Quality of life
			• Treatment related morbidity
			• Jaw preservation rates
			• Mucosal integrity
			• Fistula closure
			• Trismus
			• Oral intake
			• Nutritional status

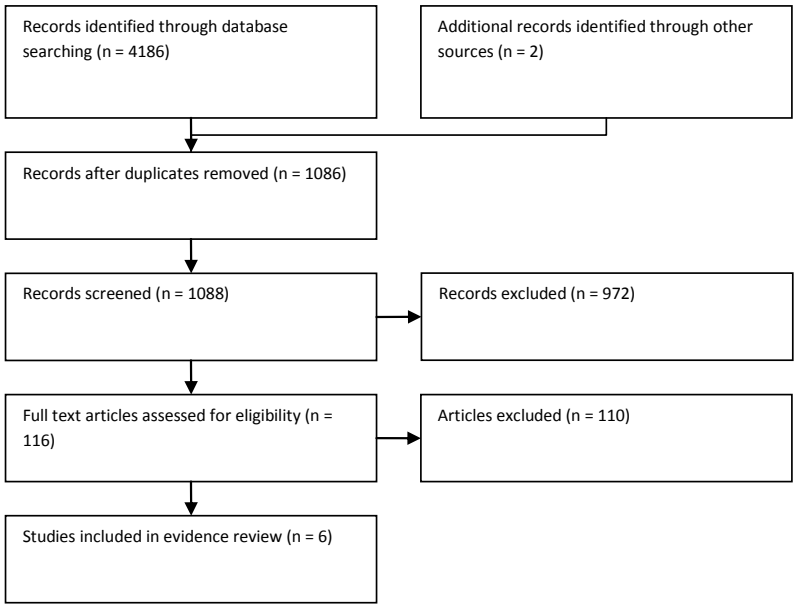
3

1 ***Additional review protocol details (refer to Section 10 for full review protocol)***

Type of review	Intervention
Language	English only
Study design	Randomised controlled trials and observational studies.
Status	Published data only
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Retrospective case series that use more than one intervention will be included only where results are reported for a mimimum of 10 patients per intervention.
Search strategies	Search from 1981 onwards – this was the date of publication of a key paper which began research in this field (see identified papers).
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.

2

Figure 8.4. Study flow diagram



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Excluded studies

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Reason for exclusion: Published before specified date limit.

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Reason for exclusion: Editorial/narrative review.

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Reason for exclusion: Health technology assessment with systematic review. No relevant outcome data reported. References checked for relevance.

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Reason for exclusion: Individual case report.

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Reason for exclusion: Non English publication.

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Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

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Marunick, M. T., Donat, T. L., Ahmad, S., and Jacobs, J. R. Total maxillary osteoradionecrosis after adjuvant neutron radiotherapy: A clinical report. Journal of Prosthetic Dentistry 1998. 79(6): 617-620.
Reason for exclusion: Individual case report.

Marx, R. E. A new concept in the treatment of osteoradionecrosis. Journal of Oral & Maxillofacial Surgery 1983. 41(6): 351-357.
Reason for exclusion: Non comparative study.

Mathew Iype E., Kumar. Changing the phase of cancer therapy - Surgical cure for post radiation sequelae in head and neck cancer. European Journal of Surgical Oncology 2010. Conference(var.pagings): 9.
Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

Maurer, P. and Meyer, L. Osteoradionecrosis of the mandible - Resection aided by measurement of partial pressure of oxygen (pO(2)): A technical report. Journal of Oral and Maxillofacial Surgery 2006. 64(3): 560-562.
Reason for exclusion: Individual case report.

McKenzie, M. R., Wong, F. L., Epstein, J. B., and Lepawsky, M. Hyperbaric oxygen and postradiation osteonecrosis of the mandible. European Journal of Cancer 1993. Part B, Oral Oncology. 29B(3): 201-207.
Reason for exclusion: Small population size.

McLeod, N. M., Pratt, C. A., Mellor, T. K., and Brennan, P. A. Pentoxifylline and tocopherol in the management of patients with osteoradionecrosis, the Portsmouth experience. British Journal of Oral & Maxillofacial Surgery 2012. 50(1): 41-44.
Reason for exclusion: Non comparative study.

Meghji, S., Reher, P., Doan, N., Ghazali, N., Raml, R., and Harris, M. The effect of therapeutic ultrasound on bone remodelling: Role in osteoradionecrosis. Bone 2001. 28(5): S155-S155.
Reason for exclusion: Study design not relevant.

Mirante, J. P., Urken, M. L., Aviv, J. E., Brandwein, M., Buchbinder, D., and Biller, H. F. Resistance to Osteoradionecrosis in Neovascularized Bone. Laryngoscope 1993. 103(10): 1168-1173.
Reason for exclusion: Individual case report.

Morton, M. E. Osteoradionecrosis: a study of the incidence in the North West of England. British Journal of Oral & Maxillofacial Surgery 1986. 24(5): 323-331.
Reason for exclusion: Outcomes not relevant to PICO.

Mucke, T., Koschinski, J., Rau, A., Loeffelbein, D. J., Deppe, H., Mitchell, D. A., Kanatas, A., and Wolff, K. D. Surgical outcome and prognostic factors after treatment of osteoradionecrosis of the jaws. Journal of Cancer Research & Clinical Oncology 2013. 139(3): 389-394.
Reason for exclusion: No comparative outcome data reported.

Murray, C. G., Herson, J., Daly, T. E., and Zimmerman, S. Radiation necrosis of the mandible: a 10 year study. Part II. Dental factors; onset, duration and management of necrosis. International Journal of Radiation Oncology, Biology, Physics 1980. 6(5): 549-553.
Reason for exclusion: Editorial/narrative review.

Nabil, S. and Samman, N. Osteoradionecrosis of the jaws: Analysis of the evidence. Oral Oncology 2011. 47: S51-S51.
Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

Nagler, R., Kuten, A., Rosenblatt, E., and Laufer, D. Mandibular osteoradionecrosis clinical characteristics and therapy. Journal of Dental Research 1996. 75(5): 1249-1249.
Reason for exclusion: Non comparative study.

Nolen, D., Cannady, S. B., Wax, M. K., Scharpf, J., Puscas, L., Esclamado, R. M., Fritz, M., Freiberger, J., and Lee, W. T. Comparison of complications in free flap reconstruction for osteoradionecrosis in

patients with or without hyperbaric oxygen therapy. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck 2014. 36(12): 1701-1704.
Reason for exclusion: Intervention/comparison not relevant to PICO.

Notani, K., Yamazaki, Y., Kitada, H., Sakakibara, N., Fukuda, H., Omori, K., and Nakamura, M. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. Head & Neck 2003. 25(3): 181-186.
Reason for exclusion: Inappropriate study design.

O'Quigley, S. Hyperbaric oxygen therapy. Irish Medical Journal 1983. 76(4): 193-194.
Reason for exclusion: Editorial/narrative review.

Obwegeser, H. L. and Sailer, H. F. Experience with intraoral resection and immediate reconstruction in cases of radio-osteomyelitis of the mandible. Journal of Maxillofacial Surgery 1978. 6(4): 257-265.
Reason for exclusion: Non comparative study.

Ohba, S., Yoshimura, H., Kobayashi, J., Ishimaru, K., Matsuda, S., Katase, N., Imamura, Y., Ueno, T., and Sano, K. The Influence of Radiation Therapy and Hyperbaric Oxygen Therapy on Osteoradionecrosis of the Jaw. Journal of Hard Tissue Biology 2013. 22(1): 147-152.
Reason for exclusion: Small population size.

Pasquier, D., Hoelscher, T., Schmutz, J., Dische, S., Mathieu, D., Baumann, M., and Lartigau, E. Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: a literature review. [Review] [209 refs]. Radiotherapy & Oncology 2004. 72(1): 1-13.
Reason for exclusion: Narrative review.

Patterson, J. Hyperbaric oxygen therapy for central osteoradionecrosis (Structured abstract). Health Technology Assessment Database 2002. (3): 9.
Reason for exclusion: Article unobtainable.

Peleg, M. and Lopez, E. A. The treatment of osteoradionecrosis of the mandible: the case for hyperbaric oxygen and bone graft reconstruction. Journal of Oral & Maxillofacial Surgery 2006. 64(6): 956-960.
Reason for exclusion: Editorial/narrative review.

Peterson, D. E., Doerr, W., Hovan, A., Pinto, A., Saunders, D., Elting, L. S., Spijkervet, F. K., and Brennan, M. T. Osteoradionecrosis in cancer patients: the evidence base for treatment-dependent frequency, current management strategies, and future studies. [Review]. Supportive Care in Cancer 2010. 18(8): 1089-1098.
Reason for exclusion: Systematic review. Insufficient outcome data reported. References within checked for relevance.

Pitak-Arnnop, P., Sader, R., Dhanuthai, K., Masaratana, P., Bertolus, C., Chaine, A., Bertrand, J. C., and Hemprich, A. Management of osteoradionecrosis of the jaws: an analysis of evidence. [Review] [144 refs]. European Journal of Surgical Oncology 2008. 34(10): 1123-1134.
Reason for exclusion: Systematic review. Insufficient outcome data reported. References checked for relevance.

Ramli, R., Karim, F. A., Rahman, R. A. L., Rajandram, R. K., Mohamad, M. S. F., Jabar, M. N. A., and Primuharsa Putra, S. H. A. Management of osteoradionecrosis of the jaw bones following radiotherapy for nasopharyngeal carcinoma. Oral Oncology 2007. 149-149.
Reason for exclusion: Non comparative study.

Ramli, R., Rahman, R. A., and Primuharsa Putra, S. H. A. The use of buccal pad of fat to augment defects caused by osteoradionecrosis. Oral Oncology 2007. 149-149.
Reason for exclusion: Non comparative study.

Ramli, R. and Roslan, A. R. Therapeutic ultrasound improves limitation of mouth opening and heals osteoradionecrosis in patients who received radiotherapy to the head and neck. Oral Oncology 2005. 1(1): 203-203.
Reason for exclusion: Population not relevant to PICO.

Reid, V., Rapidis, A. D., Patel, S. G., Stavrianos, S., and Shah, J. P. Management of osteoradionecrosis of the mandible: combined experience of two tertiary cancer care centers. Oral Oncology 2007. 53-53.
Reason for exclusion: Study design not relevant.

Reuther, T., Schuster, T., Mende, U., and Kubler, A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients--a report of a thirty year retrospective review. International Journal of Oral & Maxillofacial Surgery 2003. 32(3): 289-295.
Reason for exclusion: Outcomes not relevant to PICO.

Saunders, P. J. Hyperbaric oxygen therapy in the management of carbon monoxide poisoning, osteoradionecrosis, burns, skin grafts, and crush injury. [Review] [31 refs]. International Journal of Technology Assessment in Health Care 2003. 19(3): 521-525.
Reason for exclusion: Systematic review. Insufficient reporting of methods and outcomes. References within checked for relevance.

Sawhney, R. and Ducic, Y. Management of pathologic fractures of the mandible secondary to osteoradionecrosis. Otolaryngology - Head & Neck Surgery 2013. 148(1): 54-58.
Reason for exclusion: Intervention/comparison not relevant to PICO.

Seto, V. A synopsis of common oral complications of cancer therapies. Supportive Care in Cancer 2012. Conference(var.pagings): S252.
Reason for exclusion: Study design not relevant.

Shaw, R. J. and Dhanda, J. Hyperbaric oxygen in the management of late radiation injury to the head and neck. Part I: treatment. [Review]. British Journal of Oral & Maxillofacial Surgery 2011. 49(1): 2-8.
Reason for exclusion: Editorial/narrative review.

Silverman, S., Morrish, R. B., and Fu, K. F. Osteonecrosis in Patients Irradiated for Head and Neck-Carcinoma. Journal of Dental Research 1980. 59: 915-915.
Reason for exclusion: Insufficient outcome data reported. Conference abstract only.

Spiegelberg, L., Djasim, U. M., van Neck, H. W., Wolvius, E. B., and van der Wal, K. G. Hyperbaric oxygen therapy in the management of radiation-induced injury in the head and neck region: a review of the literature. [Review] [71 refs]. Journal of Oral & Maxillofacial Surgery 2010. 68(8): 1732-1739.
Reason for exclusion: Systematic review. Insufficient design and outcome date reported. References checked for relevance.

Store, G., Boysen, M., and Skjelbred, P. Mandibular osteoradionecrosis: reconstructive surgery. Clinical Otolaryngology & Allied Sciences 2002. 27(3): 197-203.
Reason for exclusion: Small population size.

Sylvester-Jensen, H. C. Outcome of HBO-treatment of osteoradionecrosis in irradiated patients: a prospective study. Abstract presented at 11th Meeting of the Scandinavian Society for Head and

Neck Oncology, Tampere , Finland , 16 18 April 1999 Clinical Otolaryngology and Allied Sciences 2000. 25(1): 84.
Reason for exclusion: Study design not relevant.

Thornton, J. W., Stevenson, T. R., and Vanderkolk, C. A. Osteoradionecrosis of the Olecranon - Treatment by Radial Forearm Flap. Plastic and Reconstructive Surgery 1987. 80(6): 833-835.
Reason for exclusion: Population not relevant to PICO.

van Merkesteyn, J. P., Bakker, D. J., and Borgmeijer-Hoelen, A. M. Hyperbaric oxygen treatment of osteoradionecrosis of the mandible. Experience in 29 patients. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics 1995. 80(1): 12-16.
Reason for exclusion: No comparative outcome data reported.

Vanmerkesteyn, J. P. R., Bakker, D. J., and Borgmeijerhoelen, A. M. M. J. Hyperbaric-Oxygen Treatment of Osteoradionecrosis of the Mandible - Experience in 29 Patients. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics 1995. 80(1): 12-16.
Reason for exclusion: Duplicate record.

Villanueva, E., Johnston, R., Clavisi, O., Burrows, E., Bernath, V., Rajendran, M., Wasiak, J., Fennessy, P., Anderson, J., Harris, A., and Yong, K. Hyperbaric oxygen therapy (Structured abstract). Health Technology Assessment Database 2000. (3).
Reason for exclusion: Health technology assessment with systematic review. No relevant outcome data reported. References checked for relevance.

Vudiniabola, S., Pirone, C., Williamson, J., and Goss, A. N. Hyperbaric oxygen in the therapeutic management of osteoradionecrosis of the facial bones. International Journal of Oral & Maxillofacial Surgery 2000. 29(6): 435-438.
Reason for exclusion: No comparative outcome data reported.

Wang, C., Schwaitzberg, S., Berliner, E., Zarin, D. A., and Lau, J. Hyperbaric oxygen for treating wounds: a systematic review of the literature. [Review] [75 refs]. Archives of Surgery 2003. 138(3): 272-279.
Reason for exclusion: Systematic review. Design differs from PICO. References checked for relevance.

Wang, C. C. and Doppke, K. Osteoradionecrosis of the temporal bone--consideration of Nominal Standard Dose. International Journal of Radiation Oncology, Biology, Physics 1976. 1(9-10): 881-883.
Reason for exclusion: Population not relevant to PICO.

Wang, L., Su, Y. X., and Liao, G. Q. Quality of life in osteoradionecrosis patients after mandible primary reconstruction with free fibula flap. Oral Oncology 2011. 47: S83-S83.
Reason for exclusion: Non comparative study.

Wurster, C. F., Krespi, Y. P., and Curtis, A. W. Osteoradionecrosis of the Temporal Bone. Otolaryngology-Head and Neck Surgery 1982. 90(1): 126-129.
Reason for exclusion: Population not relevant to PICO.

9. Search strategies

Chapter 1. Information and support

Question title: What are the specific information and support needs reported by patients with cancer of the upper aerodigestive tract and their carers?

Question no: Topic A

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	7647	397	07/03/2014
Premedline	Mar 7, 2014	379	28	10/03/2014
Embase	1974 -	8886	560	12/03/2014
Cochrane Library	As per database	485	44	10/03/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1970 -	7654	331	18/03/2014
AMED	1985 -	70	21	10/03/2014
Psycinfo	1806 -	195	82	10/03/2014
Cinahl	1937 -	162	91	18/03/2014

Total references retrieved (after de-duplication): 880

Medline search strategy *(This search strategy is adapted to each database.)*

1. "head and neck neoplasms"/ or facial neoplasms/ or mouth neoplasms/ or otorhinolaryngologic neoplasms/

2. (("upper respiratory tract" or "upper airway* tract" or "upper aerodigestive tract" or "head and neck" or UAT or UADT or head or neck) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous)).ti.

3. exp Mouth Neoplasms/

4. ((oral or intra-oral or intraoral or mouth or lip* or tongue or cheek* or cheek lin* or gingiv* or gum* or palat* or "roof of mouth" or odontogenic or teeth or tooth or buccal or buccal mucosa or face or facial or maxilla*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous)).ti.

5. exp Lip Neoplasms/

6. exp Gingival Neoplasms/

7. exp Palatal Neoplasms/

8. exp Tongue Neoplasms/

9. exp Tonsillar Neoplasms/

10. exp Mandibular Neoplasms/

11. exp Maxillary Neoplasms/

12. exp Odontogenic Tumors/

13. exp Oropharyngeal Neoplasms/

14. ((oropharyn* or tonsil* or retromolar*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous)).tw.

15. exp Pharyngeal Neoplasms/

16. ((pharyn* or throat) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous)).tw.

17. exp Nasopharyngeal Neoplasms/

18. (nasopharyn* adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous)).tw.

19. exp Hypopharyngeal Neoplasms/

20. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous)).tw.

21. exp Laryngeal Neoplasms/

22. ((laryn* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous)).tw.

23. exp Paranasal Sinus Neoplasms/

24. ((nasal* or nose* or paranasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxillary) adj sinus*)) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous)).tw.

25. or/1-24

26. Choice Behavior/

27. Decision Making/

28. exp Decision Support Techniques/

29. (decision* adj3 (aid* or support*)).tw.

30. ((patient* or consumer*) adj3 (decision* or choic* or prefer* or participat*)).tw.

31. ((personal or interpersonal or individual) adj3 (decision* or choic* or prefer* or participat*)).tw.

32. Pamphlets/

33. pamphlet*.tw.

34. (leaflet* or diary or diaries or booklet* or guidebook* or sheet* or flyer* or flier*).tw.

35. (prompt* or coach*).tw.

36. (checklist* or check list*).tw.

37. (written or write).tw.

38. question*.tw.

39. (card* or helpcard*).tw.

40. (video* or tape* pr cd* or film* or dvd* or telephone* or phone* or computer* or internet or electronic).tw.

41. exp Audiovisual Aids/

42. exp Internet/

43. Communication/

44. communicat*.tw.

45. (information adj3 need*).tw.

46. information material*.tw.

47. (patient* adj3 information).tw.

48. (information adj3 web*).tw.

49. (information adj3 print*).tw.

50. (information adj3 electronic*).tw.

51. ((inform* or support*) adj2 (tool* or method* or group*)).tw.

52. exp Self-Help Groups/

53. (support* adj2 (group* or meet*)).tw.

54. exp Patient Education/mt [Methods]

55. ((patient* or care*) adj pathway*).tw.

56. information deliver*.tw.

57. interactive session*.tw.

58. (face* adj face*).tw.

59. or/26-58

60. 25 and 59

2. Health Economics Literature search details
This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on upper airways cancers.

3. Any further comments
Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search
For the update search, the same search criteria/filters were applied as initial search with a date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	8243 – sifted 686	20	01/06/2015
Premedline	519	27	02/06/2015
Pubmed	30	8	02/06/2015
Embase	9978 – sifted 1449	72	02/06/2015
Cochrane Library	635 – sifted 190	7	01/06/2015
Cinahl	198 – sifted 37	9	02/06/2015
Psychinfo	222 – sifted 27	6	01/06/2015
AMED	77 – sifted 7	1	01/06/2015
Web of Science (SCI & SSCI)	8669 – sifted 1051	49	01/06/2015

Total references retrieved (after de-duplication): 133

1

2

Question title: Does smoking cessation affect outcomes for people with (undergoing treatment or post treatment) cancer of the upper aerodigestive tract?

Question no: Topic P

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-Current	1708	163	14/01/2014
Premedline	As per database	86	6	14/01/2014
Embase	1974-Current	2515	285	20/01/2014
Cochrane Library	As per database	258	8	21/01/2014
Psychinfo	1806-Current	75	23	20/01/2014
Web of Science (SCI & SSCI) and ISI Proceedings	As per database	2182	178	23/01/2014

Total references retrieved (after de-duplication): 409

Medline search strategy *(This search strategy is adapted to each database.)*

1. (("head and neck" or "upper aero-digestive" or "upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

2. exp Mouth Neoplasms/

3. exp Lip Neoplasms/

4. exp Gingival Neoplasms/

5. exp Palatal Neoplasms/

6. exp Tongue Neoplasms/

7. exp Tonsillar Neoplasms/

8. exp Maxillary Neoplasms/

9. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil* or mandib*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or

carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

10. exp Oropharyngeal Neoplasms/

11. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

12. exp Pharyngeal Neoplasms/

13. exp Tracheal Neoplasms/

14. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

15. exp Nasopharyngeal Neoplasms/

16. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

17. exp Hypopharyngeal Neoplasms/

18. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

19. exp Laryngeal Neoplasms/

20. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

21. exp Paranasal Sinus Neoplasms/

22. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or esthesioneuroblastoma*)).tw.

23. exp Carcinoma, Squamous Cell/

24. (oesophag* or esophag* or lung*).tw.

25. 23 not 24

26. or/1-22

27. 25 or 26

28. exp Smoking Cessation/

29. exp "Tobacco Use Cessation"/

30. exp Smoking/pc, th [Prevention & Control, Therapy]

31. (smoking adj (cessation or ceas* or intervention or withdrawal or quit* or stop*)).tw.

32. Tobacco/ or exp "Tobacco Use Disorder"/

33. or/28-32

34. 27 and 33

35. smok*.m_titl.

36. 27 and 35

37. 34 or 36

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on upper airways cancers.

3. Update Searches

For the update searches, the same search criteria/filters were applied as the initial search with a date limit of January 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	120	11	04/06/2015
Premedline	88	10	04/06/2015
Embase	147	22	05/06/2015
Cochrane Library	15	0	08/06/2015
Web of Science (SCI & SSCI)	124	8	11/06/2015
PsycInfo	13	0	12/06/2015
1 additional reference identified in a high level search of Pubmed 15/06/2015			

Total references retrieved (after de-duplication): 38

1

2

Chapter 2. Investigation

Question title: What is the most effective configuration of tests within a rapid access clinic for assessing neck lumps suspected of being cancer of the upper aerodigestive tract?

Question no: Topic B

1. Literature search details

Database name	Dates Covered	No of references found	Finish date of search
Medline	1990- April 2014	1102	11.04.14
Medline in process	16.04.14	43	16.04.14
Embase	1990- April 2014	2472	16.04.14
Cochrane Library	1990-April 2014	119	15.04.14
Web of Science (SCI & SSCI) and ISI Proceedings	1990-April 2014	997	16.04.14

Total references retrieved (after de-duplication): 3497

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp "Head and Neck Neoplasms"/

2. (("head and neck" or "upper aero-digestive" or "upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

3. exp Mouth Neoplasms/

4. exp Lip Neoplasms/

5. exp Gingival Neoplasms/

6. exp Palatal Neoplasms/

7. exp Tongue Neoplasms/

8. exp Tonsillar Neoplasms/

9. exp Maxillary Neoplasms/

10. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

11. exp Oropharyngeal Neoplasms/

12. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or

adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

13. exp Pharyngeal Neoplasms/

14. exp Tracheal Neoplasms/

15. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

16. exp Nasopharyngeal Neoplasms/

17. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

18. exp Hypopharyngeal Neoplasms/

19. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

20. exp Laryngeal Neoplasms/

21. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

22. exp Paranasal Sinus Neoplasms/

23. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or esthesioneuroblastoma*)).tw.

24. or/1-22

25. (neck adj3 (lump* or mass* or bump* or lesion* or metasta*)).tw.

26. exp Neck/

27. exp Neoplasms/

28. exp Neoplasm Metastasis/

29. 27 or 28

30. 26 and 29

31. 25 or 30

32. 24 and 31

33. exp Biopsy, Fine-Needle/

34. (fine needle aspiration cytology or FNAC).tw.

35. exp Endoscopic Ultrasound-Guided Fine Needle Aspiration/

36. ultrasound*.tw.

37. exp Biopsy/

38. biops*.tw.

39. nasendoscop*.tw.

40. exp Esophagoscopy/

41. oesophagoscop*.tw.

42. exp Magnetic Resonance Imaging/

43. (magnetic resonance imag* or MRI).tw.

44. exp Tomography, X-Ray Computed/

45. (CT or CT scan* or comput* tomograph*).tw.

46. or/33-45

47. 32 and 46

48. letter.pt.

49. Letter/

50. letter$/

51. editorial.pt.

52. historical article.pt.

53. anecdote.pt.

54. commentary.pt.

55. note.pt.

56. Case Report/

57. case report$.pt.

58. Case Study/

59. case study.pt.

60. exp animal/ not human/

61. Nonhuman/

62. exp animal experiment/

63. exp Experimental Animal/

64. exp animal model/

65. exp rodent/

66. exp rodentia/

67. Animals, Laboratory/

68. exp rodent/

69. or/48-68

70. 47 not 69

2. Health Economics Literature search details

NOT REQUIRED

3. Update Searches

Database name	No of references found	No of references retrieved	Finish date of search
Medline	177	19	01/06/2015
Premedline	7	1	01/06/2015
Embase	468	5	05/06/2015
Cochrane Library	3	0	08/06/2015
Web of Science (SCI & SSCI) and ISI Proceedings	538	25	09/06/2015
Pubmed	124	5	05/06/2015
Total references retrieved (after de-duplication): 53			

1

2

Question title: What is the most effective investigative pathway for identifying the occult primary site in patients presenting with metastatic neck disease (squamous cell carcinoma)?

Question no: Topic C1

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1995-Current	1427	270	05/03/2014
Premedline	1995-Current	124	8	05/03/2014
Embase	1995-Current	2635	176	10/03/2014
Cochrane Library	1995-Current	38	1	05/03/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1995-Current	825	200	11/03/2014

Total references retrieved (after de-duplication): 556

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp "Head and Neck Neoplasms"/

2. (("head and neck" or "upper aero-digestive" or "upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

3. exp Mouth Neoplasms/

4. exp Lip Neoplasms/

5. exp Gingival Neoplasms/

6. exp Palatal Neoplasms/

7. exp Tongue Neoplasms/

8. exp Tonsillar Neoplasms/

9. exp Maxillary Neoplasms/

10. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

11. exp Oropharyngeal Neoplasms/

12. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

13. exp Pharyngeal Neoplasms/

14. exp Tracheal Neoplasms/

15. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

16. exp Nasopharyngeal Neoplasms/

17. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

18. exp Hypopharyngeal Neoplasms/

19. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

20. exp Laryngeal Neoplasms/

21. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

22. exp Paranasal Sinus Neoplasms/

23. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or esthesioneuroblastoma*)).tw.

24. exp Carcinoma, Squamous Cell/di [Diagnosis]

25. exp Lymph Nodes/di, su [Diagnosis, Surgery]

26. exp Lymphatic Metastasis/di, pa [Diagnosis, Pathology]

27. Neoplasms, Unknown Primary/di [Diagnosis]

28. or/1-27

29. exp Tomography, X-Ray Computed/

30. exp Diagnostic Imaging/

31. CT*.tw.

32. (ct adj scan*).tw.

33. exp Magnetic Resonance Imaging/

34. MRI*.tw.

35. magnetic resonance imag*.tw.

36. exp Positron-Emission Tomography/

37. (PET CT or PET-CT or PETCT).tw.

38. PET.tw.

39. panendoscopy.tw.

40. exp Biopsy/

41. biops*.tw.

42. exp Tonsillectomy/

43. tonsillectomy*.tw.

44. (transoral robotic surgery or TORS).tw.

45. (transoral laser microsurgery or TLM).tw.

46. exp Robotics/

47. exp Narrow Band Imaging/

48. narrow band imaging.tw.

49. nasendoscopy.tw.

50. or/29-49

51. exam*.tw.

52. exp Anesthesia, General/

53. an?esthe*.tw.

54. 52 or 53

55. 51 and 54

56. 50 or 55

57. (neck adj3 (lump* or mass* or bump* or lesion* or metasta*)).tw.

58. exp Neck/

59. exp Neoplasms/

60. exp Neoplasm Metastasis/

61. 59 or 60

62. 58 and 61

63. 57 or 62

64. 28 and 63

65. 64 and 56

66. limit 65 to yr="1995 -Current"

2. Health Economics Literature search details

LOW PRIORITY

3. Update Searches

For the update search, the same search criteria/filters were applied as initial search with a date limit of March 2014 onwards.

Database name	No of references	No of references	Finish date of

	found	retrieved	search
Medline	201	28	05/06/2015
Premedline	47	6	05/06/2015
Embase	427	20	05/06/2015
Cochrane Library	2	0	08/06/2015
Web of Science (SCI & SSCI)	248	45	09/06/2015

Total references retrieved (after de-duplication): 87

1

Question title: Which patients with cancer of the upper aerodigestive tract require systemic staging?

Question no: Topic C2

1. Literature search details

Database name	Dates Covered	No of references found	Finish date of search
Medline	1946-Jan 2015	3274	28/01/2015
Premedline	27 Jan 2015	148	28/01/2015
Embase	1948 – Jan 2015	3694	28/01/2015
Cochrane Library	Issue 2, Feb 2015	294	02/02/2015
Web of Science (SCI & SSCI) and ISI Proceedings	1900-2015	2454	02/02/2015

Total references retrieved (after databases combined, de-duplicated and sifted): 1931

Medline search strategy *(This search strategy is adapted to each database.)*
1. exp "Head and Neck Neoplasms"/

2. (("head and neck" adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)) or (("upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma))).tw.

3. exp mouth neoplasms/

4. exp lip neoplasms/

5. exp gingival neoplasms/

6. exp palatal neoplasms/

7. exp tongue neoplasms/

8. exp tonsillar neoplasms/

9. exp maxillary neoplasms/

10. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

11. exp oropharyngeal neoplasms/

12. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

13. exp pharyngeal neoplasms/

14. exp tracheal neoplasms/

15. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

16. exp nasopharyngeal neoplasms/

17. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

18. exp hypopharyngeal neoplasms/

19. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

20. exp laryngeal neoplasms/

21. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

22. exp paranasal sinus neoplasms/

23. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or

esthesioneuroblastoma*)).tw.

24. or/1-23

25. Tomography, Emission-computed/

26. Tomography, X-Ray Computed/

27. Tomography, Spiral Computed/

28. ((CT or CTS or CAT) adj (scan* or imag*)).tw.

29. comput* tomograph*.tw.

30. exp Positron-Emission Tomography/

31. ((positron emission or computed or computerised or computerized) and tomography*).tw.

32. (PET CT or PET-CT or PETCT).tw.

33. PET.tw.

34. Fluorodeoxyglucose F18/

35. F18.tw.

36. Fluorodeoxyglucose.tw.

37. FDG.tw.

38. Magnetic Resonance Imaging/

39. (Magnetic resonance imaging or MRI).tw.

40. (MR* adj (scan* or imag*)).tw.

41. Diagnostic Imaging/

42. (diagnos* adj (imag* or scan*)).tw.

43. or/25-42

44. 24 and 43

45. Neoplasm Staging/

46. (staging or stage or stages or staged or restaging or restaged or upstaging or upstaged or downstaging or downstaged or classif*).tw.

47. 45 or 46

48. 44 and 47

49. limit 48 to english language

Notes
A general exclusions filter was applied. The search was limited to the English language.

2. Health Economics Literature search details
LOW PRIORITY

3. Update Search

For the update search, the same search criteria/filters were applied as the initial search with a date limit of January 2015 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	69	2	05/06/2015
Premedline	5	3	05/06/2015
Embase	36	2	05/06/2015
Cochrane Library	16	0	08/06/2015
Web of Science (SCI & SSCI)	80	5	09/06/2015
1 additional reference identified in a high level search of Pubmed 15/06/2015			

Total references retrieved (after de-duplication): 13

1

2

Question title: What is the most effective systemic imaging strategy for investigating cancer of the upper aerodigestive tract?

Question no: Topic C3

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 to current	1900	229	25/02/2015
Premedline	Feb 24 2015	20	10	25/02/2015
Embase	1948 to current	179	49	02/03/2015
Cochrane Library	Issue 3, 2015	345	22	02/03/2015
Web of Science (SCI) and ISI Proceedings	1900-2015	244	52	03/03/2015

Total references retrieved (after de-duplication): 273

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp "Head and Neck Neoplasms"/

2. (("head and neck" adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)) or (("upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma))).tw.

3. exp mouth neoplasms/

4. exp lip neoplasms/

5. exp gingival neoplasms/

6. exp palatal neoplasms/

7. exp tongue neoplasms/

8. exp tonsillar neoplasms/

9. exp maxillary neoplasms/

10. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or

buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

11. exp oropharyngeal neoplasms/

12. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

13. exp pharyngeal neoplasms/

14. exp tracheal neoplasms/

15. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

16. exp nasopharyngeal neoplasms/

17. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

18. exp hypopharyngeal neoplasms/

19. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

20. exp laryngeal neoplasms/

21. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

22. exp paranasal sinus neoplasms/

23. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or esthesioneuroblastoma*)).tw.

24. or/1-23

25. Tomography, Emission-computed/

26. Tomography, X-Ray Computed/

27. Tomography, Spiral Computed/

28. ((CT or CTS or CAT) adj (scan* or imag*)).tw.

29. comput* tomograph*.tw.

30. exp Positron-Emission Tomography/

31. ((positron emission or computed or computerised or computerized) and tomography*).tw.

32. (PET CT or PET-CT or PETCT).tw.

33. PET.tw.

34. Fluorodeoxyglucose F18/

35. F18.tw.

36. Fluorodeoxyglucose.tw.

37. FDG.tw.

38. Magnetic Resonance Imaging/

39. (Magnetic resonance imaging or MRI).tw.

40. (MR* adj (scan* or imag*)).tw.

41. exp Ultrasonography/

42. (ultraso* or sonogra*).tw.

43. (chest* adj2 (x-ray or xray or radiogra*)).tw.

44. CXR.tw.

45. (bone* adj3 (scan* or scintigraph* or scintiscan*)).tw.

46. Tomography, X-Ray/

47. Diagnostic Imaging/

48. (diagnos* adj (imag* or scan*)).tw.

49. or/25-48

50. 24 and 49

51. limit 50 to english language

52. limit 51 to yr="1994 -Current"

2. Notes

Due to the volume of results, a systematic reviews filter was applied. The search was also limited to the English language with a date of 1994 onwards applied.

3. Health Economics Literature search details

LOW PRIORITY

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of February 2015 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	33	2	05/06/2015
Premedline	24	3	05/06/2015
Embase	2	0	05/06/2015
Cochrane Library	18	0	08/06/2015
Web of Science (SCI & ISI Index of Conference Proceedings)	16	4	09/06/2015
1 additional reference identified in a high level search of Pubmed 15/06/2015			

Total references retrieved (after de-duplication): 8

1

2

Chapter 3. Treatment of early stage disease

Question title: What is the most effective treatment for newly diagnosed T1 or T2 carcinoma of the larynx?

Question no: Topic D1

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-Current	1404	395	13/03/2014
Premedline	All-Current	71	27	13/03/2014
Embase	All-Current	887	164	17/03/2014
Cochrane Library	All-Current	212	34	17/03/2014
Web of Science (SCI & SSCI) and ISI Proceedings	All-Current	225	58	17/03/2014

Total references retrieved (after de-duplication):539

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Laryngeal Neoplasms/

2. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

3. 1 OR 2

4. exp Early Diagnosis/ or exp "Early Detection of Cancer"/

5. (T1 or T2 or NO).tw.

6. (early adj stage).tw.

7. 4 OR 5 OR 6

8. 3 AND 7

9. exp Radiotherapy/

10. (radiotherap* or radiat* or irradiat*).tw.

11. radical chemoradiation*.tw.

12. trans-oral laser*.tw.

13. exp Laryngectomy/

14. laryngectomy.tw.

15. transoral robotic surgery.tw.

16. transoral laser microsurgery.tw.

17. 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16

13. 8 AND 17

Note: A general exclusion filter was added to the search.

2. Health Economics Literature search details

LOW PRIORITY

3. Update Searches

For the update search, the same search criteria/filters were applied as initial search with a date limit of March 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	116	41	03/06/2015
Premedline	71	17	03/06/2015
Embase	223	30	03/06/2015
Cochrane Library	65	1	08/06/2015
Web of Science (SCI & SSCI)	201	47	10/06/2015

Total references retrieved (after de-duplication): 96

1

Question title: What is the most effective management strategy for the clinically and radiologically N0 neck in patients with early squamous cell carcinoma of the oral cavity?

Question no: Topic F

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1994-2014	910	215	03/09/2014
Premedline	1994-2014	4	1	03/09/2014
Embase	1994-2014	3694	701	17/09/2014
Cochrane Library	1994-2014	385	53	08/09/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1994-2014	1719	523	09/09/2014

Total references retrieved (after de-duplication): 1259

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Mouth Neoplasms/

2. exp Lip Neoplasms/

3. exp Gingival Neoplasms/

4. exp Palatal Neoplasms/

5. exp Tongue Neoplasms/

6. exp Tonsillar Neoplasms/

7. exp Maxillary Neoplasms/

8. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or

adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

9. or/1-8

10. exp Radiotherapy/

11. (radiotherap* or irradiat* or radiat*).tw.

12. chemotherap*.tw.

13. exp Chemoradiotherapy/

14. (chemoradiotherap* or chemoradiat*).tw.

15. exp Neck Dissection/

16. (neck adj3 (dissect* or surg*)).tw.

17. exp Sentinel Lymph Node Biopsy/

18. ((sentinel lymph node or sentinel node) adj3 biops*).tw.

19. (active adj1 surveillance).tw.

20. (active adj1 monitoring).tw.

21. watchful wait*.tw.

22. exp Watchful Waiting/

23. (watch* adj2 wait*).tw.

24. (watchful adj2 (observation or surveillance or monitoring)).tw.

25. (active adj2 (surveillance or monitoring)).tw.

26. (expectant adj2 (monitoring or surveillance)).tw.

27. ((deferred or delayed) adj2 (therap* or treatment*)).tw.

28. conservative monitoring.tw.

29. or/10-28

30. 9 and 29

31. letter.pt.

32. Letter/

33. letter$/

34. editorial.pt.

35. historical article.pt.

36. anecdote.pt.

37. commentary.pt.

38. note.pt.

39. Case Report/

40. case report$.pt.

41. Case Study/

42. case study.pt.

43. exp animal/ not human/

44. Nonhuman/

45. exp animal experiment/

46. exp Experimental Animal/

47. exp animal model/

48. exp rodent/

49. exp rodentia/

50. Animals, Laboratory/

51. exp rodent/

52. or/31-51

53. 30 not 52

2. Any further comments

The search was conducted from 1994 onwards. According to the GC, this is the date of publication for the earliest evidence on this topic. Studies were also limited to the English language. RCTs, Systematic Reviews and Observational Studies filters were applied.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of September 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	185	30	02/06/2015
Premedline	9	2	02/06/2015
Embase	253	23	02/06/2015

Cochrane Library	45	0	08/06/2015
Web of Science (SCI & SSCI)	271	8	10/06/2015

Total references retrieved (after de-duplication): 59

1

Question title: What is the optimal management of T1-2, N0 squamous cell carcinoma of the oropharynx?

Question no: Topic I

1. Literature search details

Database name	Dates Covered	No of references found	Finish date of search
Medline	1946 to Nov 2014	1314	02/12/2014
Premedline	Dec 01 2014	86	02/12/2014
Embase	1946 to Nov 2014	2079	03/12/2014
Cochrane Library	Issue 11, 2014	414	10/12/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1900 to 2014	2138	08/12/2014

Total references retrieved (after sifting and de-duplication): 1780

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Oropharyngeal Neoplasms/

2. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

3. 1 or 2

4. Carcinoma, Squamous Cell/

5. squamous cell.tw.

6. 4 or 5

7. 3 and 6

8. exp Radiotherapy/

9. (radiotherap* or irradiat* or radiat* or brachytherap*).tw.

10. (hyperfractionate* or hyper-fractionate*).tw.

11. (chemotherap* or (cytotoxi* adj (therap* or treatment* or intervention*))).tw.

12. exp Chemoradiotherapy/

13. (chemoradiotherap* or chemoradiat* or chemoirradiat*).tw.

14. Antineoplastic Combined Chemotherapy Protocols/

15. Chemotherapy, Adjuvant/

16. exp Antineoplastic Agents/

17. (adriamycin* or bleomycin or carboplatin or cetuximab or cisplatin* or docetaxel* or doxorubicin* or fluorouracil or hydroxyurea or methotrexa* or paclitaxel or vinblastine).tw.

18. ((epidermal growth factor receptor or EGFR) adj (inhibit* or antagonist*or antibod*)).tw.

19. Surgical Procedures, Operative/

20. Robotics/ and Surgical Procedures, Operative/

21. Laser Therapy/

22. Glossectomy/

23. Pharyngectomy/

24. Lymph Node Excision/

25. (surg* or resect* or dissect* or excis* or glossectom* or pharyngectom* or oropharyngectom*or lymphadenectom*).tw.

26. Combined Modality Therapy/

27. or/8-26

28. 7 and 27

29. limit 28 to (english language and yr="1994 -Current")

2. Health Economics Literature search details

LOW PRIORITY

3. Notes

The search was conducted from 1994 onwards. According to the GC, this is the date of publication for the earliest evidence on this topic. Studies were also limited to the English language**.**

A general exclusions filter was applied.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of December 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	57	5	02/06/2015
Premedline	3	1	02/06/2015
Embase	235	9	02/06/2015
Cochrane Library	2	0	08/06/2015
Web of Science (SCI & SSCI)	96	17	10/06/2015
4 additional references identified in a high level search of Pubmed 15/06/2015			

Total references retrieved (after de-duplication): 32

1

2

Chapter 4. Treatment of advanced disease

Question title: What is the most effective treatment for newly diagnosed T3 and T4 squamous cell carcinoma of the larynx?

Question no: Topic D2

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2015	1521	439	17/02/2015
Premedline	Feb 16, 2015	22	10	17/02/2015
Embase	1948-2015	908	388	24/02/2015
Cochrane Library	Issue 2, 2015	144	65	23/02/2015
Web of Science (SCI & SSCI) and ISI Proceedings	1900-present	1287	426	18/02/2015

Total references retrieved (after de-duplication): 978

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp laryngeal neoplasms/

2. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

3. 1 or 2

4. Carcinoma, Squamous Cell/

5. squamous cell.tw.

6. (OPSCC or HNSCC).tw.

7. or/4-6

8. 3 and 7

9. exp Radiotherapy/

10. (radiotherap* or irradiat* or radiat* or brachytherap*).tw.

11. (hyperfractionat* or hyper-fractionat* or altered-fractionat* or altered fractionat*).tw.

12. chemotherap*.tw.

13. exp Chemoradiotherapy/

14. (chemoradiotherap* or chemoradiat* or chemoirradiat*).tw.

15. Antineoplastic Combined Chemotherapy Protocols/

16. Chemotherapy, Adjuvant/

17. Induction Chemotherapy/

18. Neoadjuvant Therapy/

19. exp Antineoplastic Agents/

20. (bleomycin* or carboplatin* or cisplatin* or docetaxel* or taxotere or fluorouracil or 5FU or Ifosfamide or methotrexa* or paclitaxel or abraxane or taxol).tw.

21. ((epidermal growth factor receptor or EGFR) adj (inhibit* or antagonist*or antibod*)).tw.

22. (lapatinib or tyverb or tykerb).tw.

23. (cetuximab or erbitux).tw.

24. Surgical Procedures, Operative/

25. Robotics/ and Surgical Procedures, Operative/

26. Laser Therapy/

27. Lymph Node Excision/

28. Laryngectomy/

29. (transoral adj2 (microsurg* or resect* or surg*)).tw.

30. (TLM or TORL).tw.

31. (endoscop* adj (surg* or resect* or microsurg*)).tw.

32. Neck Dissection/

33. (surg* or resect* or dissect* or excis* or lymphadenectom* or laryngectom*).tw.

34. Combined Modality Therapy/

35. or/9-34

36. 8 and 35

37. limit 36 to yr="1991 -Current"

38. limit 37 to English language

2. Any further comments

The search was conducted from 1991 onwards. According to the GC, this is the date of publication for the earliest evidence on this topic. Studies were also limited to the English language. RCTs, Systematic Reviews and Observational Studies filters were applied.

3. Health Economics Literature search details

LOW PRIORITY

4. UPDATE SEARCH

For the update search, the same search criteria/filters were applied as initial search with a date limit of February 2015 onwards.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline		21	2	01/06/2015
Premedline		0	0	01/06/2015
Embase		5	0	01/06/2015
Cochrane Library		3	0	08/06/2015
Web of Science (SCI & SSCI) and ISI Proceedings		37	6	10/06/2015
5 additional references identified in a high level search of Pubmed 15/06/2015				

Total references retrieved (after de-duplication): 13

1

2

Question title: What is the most effective treatment for locally advanced squamous cell carcinoma of the hypopharynx (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)?

Question no: Topic E

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline				
Premedline				
Embase				
Cochrane Library				
Web of Science (SCI & SSCI) and ISI Proceedings				

Total references retrieved (after de-duplication):

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Hypopharyngeal Neoplasms/

2. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

3. 1 or 2

4. (surg* or dissect* or resect* or excis* or reconstruct*).tw.

5. exp Reconstructive Surgical Procedures/

6. exp Radiotherapy/

7. (radiotherap* or irradiat* or radiat*).tw.

8. chemotherap*.tw.

9. exp Chemoradiotherapy/

10. chemoradiotherap*.tw.

11. or/4-10

12. 3 and 11

13. letter.pt.

14. Letter/

15. letter$/

16. editorial.pt.

17. historical article.pt.

18. anecdote.pt.

19. commentary.pt.

20. note.pt.

21. Case Report/

22. case report$.pt.

23. Case Study/

24. case study.pt.

25. exp animal/ not human/

26. Nonhuman/

27. exp animal experiment/

28. exp Experimental Animal/

29. exp animal model/

30. exp rodent/

31. exp rodentia/

32. Animals, Laboratory/

33. exp rodent/

34. or/13-33

35. 12 not 34

2. Health Economics Literature search details LOW PRIORITY

3. Update Searches

Database name	No of references found	No of references retrieved	Finish date of search
Medline	114	15	01/06/2015
Premedline	7	0	01/06/2015
Embase	248	37	01/06/2015
Cochrane Library	1	0	08/06/2015
Web of Science (SCI & SSCI) and ISI Proceedings	219	45	10/06/2015
1 additional reference identified in a high level search of Pubmed 15/06/2015			

Total references retrieved (after de-duplication): 68

1

Question title: What are the most effective palliative treatments for people with incurable upper aerodigestive tract cancer experiencing breathing difficulties?

Question no: Topic N

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2014	1213	146	22/12/2014
Premedline	Dec 11 2014	87	5	17/12/2014
Embase	1947 -2014	2783	137	24/12/2014
Cochrane Library	Issue 12 of 12, Dec 2014	99	3	17/12/2014
Web of Science (SCI & SSCI) and ISI Proceedings	All	1373	39	22/12/2014

Total references retrieved (after de-duplication): 293

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp "Head and Neck Neoplasms"/

2. (("head and neck" or "upper aero-digestive" or "upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

3. exp Mouth Neoplasms/

4. exp Lip Neoplasms/

5. exp Gingival Neoplasms/

6. exp Palatal Neoplasms/

7. exp Tongue Neoplasms/

8. exp Tonsillar Neoplasms/

9. exp Maxillary Neoplasms/

10. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

11. exp Oropharyngeal Neoplasms/

12. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

13. exp Pharyngeal Neoplasms/

14. exp Tracheal Neoplasms/

15. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

16. exp Nasopharyngeal Neoplasms/

17. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

18. exp Hypopharyngeal Neoplasms/

19. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

20. exp Laryngeal Neoplasms/

21. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

22. exp Paranasal Sinus Neoplasms/

23. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj

sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or esthesioneuroblastoma*)).tw.

24. or/1-22

25. exp Dyspnea/

26. dyspn?ea*.tw.

27. stridor*.tw.

28. (breath* adj3 (difficult* or impair* or shortness)).tw.

29. breathless*.tw.

30. exp Airway Obstruction/

31. (airway* adj3 (obstruct*or narrow*)).tw.

32. or/25-31

33. 24 and 32

34. letter.pt.

35. Letter/

36. letter$/

37. editorial.pt.

38. historical article.pt.

39. anecdote.pt.

40. commentary.pt.

41. note.pt.

42. Case Report/

43. case report$.pt.

44. Case Study/

45. case study.pt.

46. exp animal/ not human/

47. Nonhuman/

48. exp animal experiment/

49. exp Experimental Animal/

50. exp animal model/

51. exp rodent/

52. exp rodentia/

53. Animals, Laboratory/

54. exp rodent/

55. or/34-54

56. 33 not 55

2. Health Economics Literature search details

LOW PRIORITY

For the update search, the same search criteria/filters were applied as initial search with a date limit of December 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	15	1	03/06/2015
Premedline	8	0	03/06/2015
Embase	170	4	03/06/2015
Cochrane Library	16	0	08/06/2015
Web of Science (SCI & ISI Index of Conference Proceedings)	31	0	11/06/2015

3. Total references retrieved (after de-duplication): 5

1

2

1 Chapter 5. HPV-related disease

Question title: What is the most effective test to identify an HPV-positive tumour in people with cancer of the upper aerodigestive tract?

Question no: Topic K2

1. Literature search details

Database name	Dates Covered	No of references found	Finish date of search
Medline	1996-Jul Wk 2 2014	590	17/07/2014
Premedline	Jul 16 2014	15	17/07/2014
Embase	1996-Jul 16 2014	442	17/07/2014
Cochrane Library	Issue 2, Feb 2014	115	17/07/2014
Web of Science (SCI & SSCI)	1900-2014	1060	17/07/2014

Total references retrieved (after databases combined, de-duplicated and sifted): 983

Medline search strategy *(This search strategy is adapted to each database)*

1. exp "Head and Neck Neoplasms"/

2. (("head and neck" adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)) or (("upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma))).tw.

3. exp mouth neoplasms/

4. exp lip neoplasms/

5. exp gingival neoplasms/

6. exp palatal neoplasms/

7. exp tongue neoplasms/

8. exp tonsillar neoplasms/

9. exp maxillary neoplasms/

10. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

11. exp oropharyngeal neoplasms/

12. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

13. exp pharyngeal neoplasms/

14. exp tracheal neoplasms/

15. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

16. exp nasopharyngeal neoplasms/

17. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

18. exp hypopharyngeal neoplasms/

19. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

20. exp laryngeal neoplasms/

21. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

22. exp paranasal sinus neoplasms/

23. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or esthesioneuroblastoma*)).tw.

24. or/1-23

25. exp Carcinoma, Squamous Cell/di, pa, vi

26. exp Papillomavirus Infections/di, pa, vi

27. HPV positive.tw.

28. (human papilloma virus adj positive).tw.

29. (OPSCC or HNSCC).tw.

30. or/25-29

31. 24 and 30

32. (HPV16 adj2 (test* or investigat*)).tw.

33. Immunohistochemistry/

34. (immunohistochem* or immunolabel* or immunogold* or immunocytochem*).tw.

35. 33 or 34

36. exp Polymerase Chain Reaction/

37. ((polymerase adj chain) or (polymerase adj reaction) or pcr or qpcr).tw.

38. 36 or 37

39. exp RNA/ or exp DNA/

40. (RNA or DNA).tw.

41. (ribonucleic acid or deoxyribonucleic acid).tw.

42. or/39-41

43. 38 and 42

44. exp In Situ Hybridization/

45. ("in situ" adj hybridi?ation*).tw.

46. (nucleic acid adj hybridi?ation*).tw.

47. or/44-46

48. Gene Expression Profiling/

49. (transcript* adj (profiling* or monitor* or analys*)).tw.

50. (gene expression adj (profiling* or monitor* or analys*)).tw.

51. (mrna and differential and display*).tw.

52. or/48-51

53. 32 or 35 or 38 or 43 or 47 or 52

54. 31 and 53

55. limit 54 to yr="2000 –Current

56. limit 55 to english language

2. Any further comments

The search was conducted from 2000 onwards. According to the GC, this is the date of publication for the earliest evidence on this topic. Studies were also limited to the English language
A general exclusions filter was applied.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of July 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	84	21	03/06/2015
Premedline	16	6	03/06/2015
Embase	118	23	03/06/2015
Cochrane Library	1	0	08/06/2015
Web of Science (SCI & SSCI)	139	10	11/06/2015

Total references retrieved (after de-duplication): 41

1

2

Question title: Is there a role for de-intensification of non-surgical treatment in patients with HPV-positive upper aerodigestive tract tumours?

Question no: Topic K3

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000-Current	4216	445	09/06/2014
Premedline	2000-Current	705	32	09/06/2014
Embase	2000-Current	1805	260	11/06/2014
Cochrane Library	2000-Current	1189	95	12/06/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2000-Current	825	29	13/06/2014

Total references retrieved (after de-duplication): 662

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp "Head and Neck Neoplasms"/

2. exp Palatal Neoplasms/

3. exp Tongue Neoplasms/

4. exp Tonsillar Neoplasms/

5. exp Oropharyngeal Neoplasms/

6. exp Pharyngeal Neoplasms/

7. (upper aerodigestive tract adj (cancer or neoplasm* or tumor or carcinoma)).tw.

8. (Orophary* adj (cancer or neoplasm* or tumor or carcinoma)).tw.

9. or/1-8

10. exp Carcinoma, Squamous Cell/

11. exp Papillomavirus Infections/

12. HPV positive.tw.

13. (human papilloma virus adj positive).tw.

14. (OPSCC or HNSCC).tw.

15. 10 or 11 or 12 or 13 or 14

16. 9 and 15

17. (standard therapy or standard treatment).tw.

18. radiation therapy.tw.

19. exp Radiotherapy/ or exp Radiotherapy Dosage/

20. exp Drug Therapy/

21. exp Antineoplastic Combined Chemotherapy Protocols/tu [Therapeutic Use]

22. exp Cisplatin/tu [Therapeutic Use]

23. cetuximab.tw.

24. (concomitant adj chemotherapy).tw.

25. (induction adj chemotherapy).tw.

26. (open adj surgery).tw.

27. ((trans-oral adj surgery) or (transoral adj surgery) or (Neck adj dissection)).tw.

28. reconstruction.tw.

29. Lapatinib.tw.

30. EGFR.tw.

31. ((post operative or adjuvant) adj radiotherapy).tw.

32. chemoradiotherapy.tw.

33. (systemic adj (treatment or therapy)).tw.

34. or/17-33

35. deintensification.tw.

36. de-intensification.tw.

37. de-escalat*.tw.

38. (dose adj3 reduc*).tw.

39. (alteration or modification or modify or optimi*).tw.

40. (altered adj fractionation*).tw.

41. treatment volume.tw.

42. (treatment adj (response or assessment)).tw.

43. (decreas* or overtreatment or undertreatment).tw.

44. intensity modulated.tw.

45. response rate*.tw.

46. relapse.tw.

47. patient management.tw.

48. exp "Quality of Life"/

49. exp Risk Assessment/

50. risk stratification.tw.

51. exp Prognosis/

52. (toxicity or local control or locoregional recurrence or survival).tw.

53. or/35-52

54. 34 and 53

55. 16 and 54

Note:

As advised by the GC, the following filters were applied: Randomised controlled trials and observational studies filter.

The search was conducted from 2000 onwards. According to the GC, this is the date of publication for the earliest evidence on this topic.

2. Health Economics Literature search details

LOW PRIORITY

3. Update Searches

For the update search, the same search criteria/filters were applied as initial search with a date limit of June 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	496	16	04/06/2015
Premedline	23	5	04/06/2015
Embase	595	49	04/06/2015
Cochrane Library	2	0	08/06/2015
Web of Science (SCI & SSCI)	119	26	11/06/2015

Total references retrieved (after de-duplication): 85

1

2 ## Chapter 6. Less-common upper aerodigestive tract cancers

Question title: What is the most effective curative treatment for carcinoma of the nasopharynx (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)?

Question no: Topic G

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 to Jan, week 1 2015	1685	573	12/01/2015
Premedline	Jan 09 2015	64	33	07/01/2015
Embase	1947 - present	1521	567	13/01/2015
Cochrane Library	Issue 1 of 12, Jan 2015	723	309	14/01/2015
Web of Science (SCI & SSCI) and ISI Proceedings	1900 - 2015	1750	589	14/01/2015

Total references retrieved (after de-duplication): 1351

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Nasopharyngeal Neoplasms/

2. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

3. 1 or 2

4. exp Radiotherapy/

5. (radiotherap* or radiat* or irradiat* or radiosurger*).tw.

6. exp Brachytherapy/

7. brachytherap*.tw.

8. exp Chemoradiotherapy/

9. (chemoradiotherap* or chemoradiat* or chemoirradiat*).tw.

10. chemotherap*.tw.

11. (cytotoxi* adj (therap* or treatment* or intervention*)).tw.

12. (bleomycin or carboplatin or paralatin or cetuximab or cisplatin or docetaxel or taxotere or doxorubicin or adriamycin or fluorouracil or 5FU or gemcitabine or gemzar or methotrexate or matrex or paclitaxel or taxol).tw.

13. Surgical Procedures, Operative/

14. (surg* or resect* or dissect* or excis* or nasopharyngectom*).tw.

15. ((epidermal growth factor receptor or EGFR) adj (inhibit* or antagonist*or antibod*)).tw.

16. (lapatinib or tyverb).tw.

17. (Cetuximab or Erbitux).tw.

18. *Combined Modality Therapy/

19. or/4-18

20. 3 and 19

2. NOTES

The search was limited to the English language and with a date of 1994 onwards at the advice of the GC.

Search filters for systematic reviews, randomised controlled trials and observational studies were applied.

3. Health Economics Literature search details

LOW PRIORITY

4. Update Searches

Database name	No of references found	No of references retrieved	Finish date of search
Medline	63	13	02/06/2015
Premedline	2	1	02/06/2015
Embase	15	1	02/06/2015
Cochrane Library	1	0	08/06/2015
Web of Science (SCI & SSCI) and ISI Proceedings	61	16	10/06/2015
4 additional references identified from a high level search of Pubmed 15/06/2015			

Total references retrieved (after de-duplication): 32

1

2

Question title: What is the optimal role and timing (in relation to other treatments) of surgery in the management of nose and paranasal sinus carcinoma?

Question no: Topic H

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1994-2014	1342	779	31/07/2014
Premedline	1994-2014	37	26	31/07/2014
Embase	1994-2014	681	253	06/08/2014
Cochrane Library	1994-2014	88	37	05/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1994-2014	828	372	04/08/2014

Total references retrieved (after de-duplication): 1288

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Paranasal Sinus Neoplasms/

2. ((paranasal* or nasal* or nasosinus* or sinonasal* or nose or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or antibod* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or sarcoma*or chondrosarcoma* or haemangiopericytoma* or hemangiopericytoma*)).tw.

3. 1 or 2

4. Combined Modality Therapy/

5. exp Chemoradiotherapy/

6.(chemoradiotherap* or radiochemotherap* or chemoradiat*).tw.

7. 5 or 6

8. exp Radiotherapy/

9. (radiotherap* or radiat* or irradiat*).tw.

10. 8 or 9

11. Surgical Procedures, Operative/

12. exp Nasal Surgical Procedures/

13. exp Reconstructive Surgical Procedures/

14. (surg* or resect* or dissect* or excis* or reconstruct* or obturat* or maxillectom* or nasopharyngectom*).tw.

15. or/11-14

16. Antineoplastic Combined Chemotherapy Protocols/

17. Chemotherapy, Adjuvant/

18. Consolidation Chemotherapy/

19. Induction Chemotherapy/

20. Maintenance Chemotherapy/

21. chemotherap*.tw.

22. or/16-21

23. ((epidermal growth factor receptor or EGFR) adj (inhibit* or antagonist*or antibod*)).tw.

24. (lapatinib or tykerb or tyverb).tw.

25. (tyrosine kinase adj (inhibit* or antagonist*)).tw.

26. (erlotinib or tarceva).tw.

27. (sunitinib or sutent).tw.

28. (sorafenib or nexavar).tw.

29. (nimotuzumab or theraloc or theracim).tw.

30. or/23-29

31. 4 or 7 or 10 or 15 or 22 or 30

32. 3 and 31

2. Any further comments

The search was conducted from 1994 onwards. According to the GC, this is the date of publication for the earliest evidence on this topic. Studies were also limited to the English language
RCTs, Systematic Reviews and Observational Studies filters were applied.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of July 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	81	9	02/06/2015
Premedline	9	1	02/06/2015
Embase	85	10	02/06/2015
Cochrane Library	3	0	08/06/2015
Web of Science (SCI & SSCI)	121	13	10/06/2015
2 additional references identified from a high level search of Pubmed 15/06/2015			

Total references retrieved (after de-duplication): 33

1

Question title: What is the most effective treatment for unknown primary of presumed upper airways tract origin (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)?

Question no: Topic J

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1994 onwards	1203	203	21/08/2014
Premedline	Aug 20, 2014	91	16	21/08/2014
Embase	1994 onwards	2059	380	03/09/2014
Cochrane Library	As per database	39	5	01/09/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1994 onwards	1270	200	02/09/2014

Total references retrieved (after de-duplication): 521

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp "Head and Neck Neoplasms"/

2. (("head and neck" or "upper aero-digestive" or "upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

3. exp Mouth Neoplasms/

4. exp Lip Neoplasms/

5. exp Gingival Neoplasms/

6. exp Palatal Neoplasms/

7. exp Tongue Neoplasms/

8. exp Tonsillar Neoplasms/

9. exp Maxillary Neoplasms/

10. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

11. exp Oropharyngeal Neoplasms/

12. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

13. exp Pharyngeal Neoplasms/

14. exp Tracheal Neoplasms/

15. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

16. exp Nasopharyngeal Neoplasms/

17. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

18. exp Hypopharyngeal Neoplasms/

19. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

20. exp Laryngeal Neoplasms/

21. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

22. exp Paranasal Sinus Neoplasms/

23. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or

esthesioneuroblastoma*)).tw.

24. or/1-23

25. exp Neoplasms, Unknown Primary/

26. (unknown primar* and (cancer* or neoplas* or tumo?r* or carcinoma* or adenocarcinoma* or metasta* or micrometasta* or malignan* or lymphoma*)).tw.

27. (unknown origin and (cancer* or neoplas* or tumo?r* or carcinoma* or adenocarcinoma* or metasta* or micrometasta* or malignan* or lymphoma*)).tw.

28. (occult adj2 (cancer* or neoplas* or tumo?r* or carcinoma* or adenocarcinoma* or metasta* or micrometasta* or malignan* or lymphoma*)).tw.

29. (undetermined origin and (cancer* or neoplas* or tumo?r* or carcinoma* or adenocarcinoma* or metasta* or micrometasta* or malignan* or lymphoma*)).tw.

30. (undetermined primar* and (cancer* or neoplas* or tumo?r* or carcinoma* or adenocarcinoma* or metasta* or micrometasta* or malignan* or lymphoma*)).tw.

31. (unidentifi* origin and (cancer* or neoplas* or tumo?r* or carcinoma* or adenocarcinoma* or metasta* or micrometasta* or malignan* or lymphoma*)).tw.

32. (unidentif* primar* and (cancer* or neoplas* or tumo?r* or carcinoma* or adenocarcinoma* or metasta* or micrometasta* or malignan* or lymphoma*)).tw.

33. or/25-32

34. 24 and 33

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on upper airways cancers.

3. Any further comments

Basic exclusions filter only and date limit of 1994 onwards applied by GC due to earliest evidence on this topic. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	1242 – sifted 130	4 + 3 (Pubmed)	15/06/2015
Premedline (12 June 2015)	108	11	15/06/2015
Embase	2267 – sifted 429	26	15/06/2015
Cochrane Library	48 – sifted 10	1	15/06/2015
Web of Science (SCI & SSCI)	1374 – sifted 158	16	15/06/2015

Total references retrieved (after de-duplication): 39

1

Question title: What is the optimal locoregional treatment for newly diagnosed upper airways tract mucosal melanoma in the absence of systemic metastases?

Question no: Topic L

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-Current	497	273	06/02/2014
Premedline	As per database	59	31	06/02/2014
Embase	1974-Current	608	326	10/02/2014
Cochrane Library	As per database	27	3	06/02/2014
Web of Science (SCI & SSCI) and ISI Proceedings	As per database	857	297	12/02/2014

Total references retrieved (after de-duplication): 574

1. exp "Head and Neck Neoplasms"/

2. ("head and neck" or "upper aero-digestive" or "upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT).tw.

3. exp Mouth Neoplasms/

4. exp Lip Neoplasms/

5. exp Gingival Neoplasms/

6. exp Palatal Neoplasms/

7. exp Tongue Neoplasms/

8. exp Tonsillar Neoplasms/

9. exp Maxillary Neoplasms/

10. (mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal

or buccal mucosa* or maxilla* or tonsil*).tw.

11. exp Oropharyngeal Neoplasms/

12. (oropharyn* or retromolar trigone).tw.

13. exp Pharyngeal Neoplasms/

14. exp Tracheal Neoplasms/

15. (pharyn* or throat or trachea* or paratrachea* or windpipe*).tw.

16. exp Nasopharyngeal Neoplasms/

17. nasopharyn*.tw.

18. exp Hypopharyngeal Neoplasms/

19. (hypopharyn* or laryngopharyn*).tw.

20. exp Laryngeal Neoplasms/

21. (laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal).tw.

22. exp Paranasal Sinus Neoplasms/

23. (paranasal* or nasal* or nasosinus* or sinonasal* or nose).tw.

24. ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*).tw.

25. or/1-22

26. mucosal melanoma.tw.

27. ((muco* membrane* or muco*) adj3 melanoma*).tw.

28. 26 or 27

29. 25 and 28

30. exp Melanoma/rt, su, th [Radiotherapy, Surgery, Therapy]

31. Oral.tw.

32. 22 or 23 or 31

33. 30 and 32

34. 29 or 33

35. letter.pt.

36. Letter/

37. letter$/

38. editorial.pt.

39. historical article.pt.

40. anecdote.pt.

41. commentary.pt.

42. note.pt.

43. Case Report/

44. case report$.pt.

45. Case Study/

46. case study.pt.

47. exp animal/ not human/

48. Nonhuman/

49. exp animal experiment/

50. exp Experimental Animal/

51. exp animal model/

52. exp rodent/

53. exp rodentia/

54. Animals, Laboratory/

55. exp rodent/

56. or/35-55

57. 34 not 56

Medline search strategy *(This search strategy is adapted to each database.)*

2. Health Economics Literature search details

LOW PRIORITY

3. Update searches

For the update search, the same search criteria/filters were applied as initial search with a date limit of February 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	62	9	05/06/2015
Premedline	8	0	05/06/2015
Embase	96	9	05/06/2015
Cochrane Library	1	0	08/06/2015
Web of Science (SCI & ISI Index of Conference Proceedings)	76	19	11/06/2015
1 additional reference identified in a high level search of Pubmed 15/06/2015			

Total references retrieved (after de-duplication): 26

1

2

1 Chapter 7. Rehabilitation and optimising function

Question title: What criteria should be used at the point of diagnosis to select patients requiring enteral nutritional support during curative treatment?

Question no: Topic Q1

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1990 onwards	948	516	08/10/2014
Premedline	1990 onwards	72	40	03/10/2014
Embase	1990 onwards	1977	786	14/10/2014
Cochrane Library	1990 onwards	248	183	09/10/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1990 onwards	2216	532	21/10/2014

Total references retrieved (after de-duplication): 1211

Medline search strategy *(This search strategy is adapted to each database.)*

1. "head and neck neoplasms"/ or facial neoplasms/ or mouth neoplasms/ or otorhinolaryngologic neoplasms/

2. (("upper respiratory tract" or "upper airway* tract" or "upper aerodigestive tract" or "head and neck" or UAT or UADT or head or neck) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

3. exp Mouth Neoplasms/

4. ((oral or intra-oral or intraoral or mouth or lip* or tongue or cheek* or cheek lin* or gingiv* or gum* or palat* or "roof of mouth" or odontogenic or teeth or tooth or buccal or buccal mucosa or face or facial or maxilla*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

5. exp Lip Neoplasms/

6. exp Gingival Neoplasms/

7. exp Palatal Neoplasms/

8. exp Tongue Neoplasms/

9. exp Tonsillar Neoplasms/

10. exp Mandibular Neoplasms/

11. exp Maxillary Neoplasms/

12. exp Odontogenic Tumors/

13. exp Oropharyngeal Neoplasms/

14. ((oropharyn* or tonsil* or retromolar*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

15. exp Pharyngeal Neoplasms/

16. ((pharyn* or throat) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

17. exp Nasopharyngeal Neoplasms/

18. (nasopharyn* adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

19. exp Hypopharyngeal Neoplasms/

20. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

21. exp Laryngeal Neoplasms/

22. ((laryn* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

23. exp Paranasal Sinus Neoplasms/

24. ((nasal* or nose* or paranasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxillary) adj sinus*)) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

25. or/1-24

26. exp Nutritional Support/

27. ((nutrition* or diet*) adj2 (support* or therap* or manage* or intervent*)).tw.

28. ((enter* or tube or parenteral or intravenous*) adj2 (nutrition* or feed* or nutrient* or nourish*)).tw.

29. exp Feeding Methods/

30. or/26-29

31. 25 and 30

32. nutrition*.ti.

33. 32 and 25

34. 31 or 33

35. 25 and 34

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on upper airways cancers.

3. Any further comments

Basic exclusions filter only and date limit of 1999 onwards applied by GC due to earliest evidence on this topic. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	978 – sifted 51	4	04/06/2015
Premedline (June 3, 2015)	86	22	04/06/2015
Embase	2151 – sifted 406	49	04/06/2015
Cochrane Library	279 – sifted 55	11	04/06/2015
Web of Science (SCI & SSCI)	2380 – sifted 265	34	04/06/2015

Total references retrieved (after de-duplication): 80

1

2

Question title: Which active speech and language therapy interventions are of most benefit to patients with cancer of the upper aerodigestive tract?

Question no: Topic Q2

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1996 to Nov week 2 2014	904	190	19/11/2014
Premedline	Nov 17 2014	42	17	18/11/2014
Embase	1996 – Nov 24 2014	1034	185	24/11/2014
Cochrane Library	Issue 11, Nov 2014	148	33	18/11/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1900-2014	1121	115	25/11/2014
AMED	All	15	8	18/11/2014
PsycInfo	1806 to Nov 2014	23	9	18/11/2014
CINAHL	All	45	5	26/11/2014
Linguistics and Language Behavior Abstracts (LLBA)	All	200	43	26/11/2014
Communication Abstracts	All	121	16	26/11/2014

Total references retrieved (after de-duplication): 402

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp "Head and Neck Neoplasms"/

2. (("head and neck" adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)) or (("upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma))).tw.

3. exp mouth neoplasms/

4. exp lip neoplasms/

5. exp gingival neoplasms/

6. exp palatal neoplasms/

7. exp tongue neoplasms/

8. exp tonsillar neoplasms/

9. exp maxillary neoplasms/

10. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

11. exp oropharyngeal neoplasms/

12. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

13. exp pharyngeal neoplasms/

14. exp tracheal neoplasms/

15. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

16. exp nasopharyngeal neoplasms/

17. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

18. exp hypopharyngeal neoplasms/

19. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

20. exp laryngeal neoplasms/

21. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

22. exp paranasal sinus neoplasms/

23. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or esthesioneuroblastoma*)).tw.

24. or/1-23

25. exp Language Therapy/ or exp Speech Therapy/

26. ((speech or speak* or language or voice or vocal*) adj3 (therap* or rehabilitat* or exercise* or intervention* or support*)).tw.

27. exp "rehabilitation of speech and language disorders"/

28. Voice Training/

29. Voice Disorders/rh

30. Voice/rh

31. exp Fluoroscopy/

32. videofluoroscop*.tw.

33. fluoroscop*.tw.

34. barium swallow.tw.

35. functional endoscopic evaluation of swallow*.tw.

36. ((swallow* or motion* or dysphag* or deglutit*) adj3 (exercise* or therap* or rehabilitat* or technique* or strateg*)).tw.

37. pharyngocise*.tw.

38. (lingual exercis* or effortful swallow* or supraglottic swallow or super glottic swallow* or supra glottic swallow*).tw.

39. exp Deglutition Disorders/rh, th

40. Trismus/rh, th

41. or/25-40

42. 24 and 41

43. limit 42 to yr="2000 -Current"

44. limit 43 to english language

45. letter.pt.

46. Letter/

47. editorial.pt.

48. historical article.pt.

49. Case Report/

50. case reports.pt.

51. Case Study/

52. exp animal/ not human/

53. exp animal experiment/

54. exp animal model/

55. exp rodent/

56. exp rodentia/

57. Animals, Laboratory/

58. or/45-57

59. 44 not 58

2. Health Economics Literature search details LOW PRIORITY

3. NOTES

The search was conducted from 2000 onwards. According to the GC, this is the date of publication for the earliest evidence on this topic. Studies were also limited to the English language**.**

Medline records were excluded in the search of CINAHL

4. Update Searches

For the update searches, the same search criteria/filters were applied as initial search with a date limit of November 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	38	2	03/06/2015
Premedline	2	0	03/06/2015
Embase	84	1	03/06/2015
Cochrane Library	5	0	08/06/2015

Web of Science (SCI & SSCI) and ISI Proceedings	158	8	11/06/2015
AMED	1	0	03/06/2015
PsycInfo	7	0	03/06/2015
CINAHL	2	0	12/06/2015
Linguistics and Language Behavior Abstracts (LLBA)	0	0	12/06/2015
Communication Abstracts	9	1	12/06/2015
2 additional references added from a high level search of Pubmed 15/06/2015			

Total references retrieved (after de-duplication): 13

1

Question title: What are the most effective interventions for shoulder rehabilitation following neck dissection in people with cancer of the upper aerodigestive tract?

Question no: Topic O2

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 – Oct 2014	38	23	10/11/2014
Premedline	Nov 07 2014	2	1	10/11/2014
Embase	1947 to present	50	31	10/11/2014
Cochrane Library	Issue 11 of 12, Nov 2014	10	6	11/11/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1900-2014	31	18	11/11/2014
AMED	All	4	4	10/11/2014
PsycInfo	1806 – Nov 2014	3	2	10/11/2014
PEDro	All	4	4	10/11/2014
CINAHL Plus	1937 to present	239	7	11/11/2014

Total references retrieved (after de-duplication): 56

1 additional reference identified 24/11/14

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp "Head and Neck Neoplasms"/

2. (("head and neck" adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)) or (("upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma))).tw.

3. exp mouth neoplasms/

4. exp lip neoplasms/

5. exp gingival neoplasms/

6. exp palatal neoplasms/

7. exp tongue neoplasms/

8. exp tonsillar neoplasms/

9. exp maxillary neoplasms/

10. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

11. exp oropharyngeal neoplasms/

12. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

13. exp pharyngeal neoplasms/

14. exp tracheal neoplasms/

15. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

16. exp nasopharyngeal neoplasms/

17. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

18. exp hypopharyngeal neoplasms/

19. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

20. exp laryngeal neoplasms/

21. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

22. exp paranasal sinus neoplasms/

23. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or esthesioneuroblastoma*)).tw.

24. or/1-23

25. exp neck dissection/

26. ((neck and dissect*) or hnscc).tw.

27. neck surger*.tw.

28. or/25-27

29. 24 and 28

30. exp Shoulder/

31. shoulder pain/

32. (shoulder* or scapul* or trapezius or glenohumeral or (adhesive and capsulitis) or (accessory and nerve*) or ((11th or eleventh) and nerve*)).tw.

33. (morbidit* or disabilit* or function* or dysfunction* or pain* or syndrome or droop* or lesion*or impair*or injur*).tw.

34. 32 and 33

35. (neuropraxi* or axonotmes*).tw.

36. 30 or 31 or 34 or 35

37. 29 and 36

38. neck dissection/rh [Rehabilitation]

39. exp Rehabilitation/

40. exp Physical Therapy Modalities/

41. exp Manipulative Medicine/

42. exp exercise/

43. ((physical and therap*) or physio* or exercise* or movement* or aerobic* or pilates or stretch* or tai or yoga or (resistance and training) or rehab*).tw.

44. (nerve and (repair* or explor*)).tw.

45. or/38-44

46. 37 and 45

47. limit 46 to yr="1994 -Current"

2. NOTES

The search was conducted from 1994 onwards. According to the GC, this is the date of publication for the earliest evidence on this topic. Studies were also limited to the English language.
Medline records were excluded in the search of CINAHL.

3. Health Economics Literature search details - Low priority for this topic

4. Update Searches
For the update search, the same search criteria/filters were applied as initial search with a date limit of November 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	2	1	03/06/2015
Premedline	1	1	03/06/2015
Embase	4	0	03/06/2015

Cochrane Library	0	0	08/06/2015
Web of Science (SCI & SSCI)	7	2	11/06/2015
AMED	0	0	03/06/2015
PsycInfo	0	0	03/06/2015
PEDro	0	0	12/06/2015
CINAHL	6	1	12/06/2015

Total references retrieved (after de-duplication): 2

1

2

Chapter 8. Follow-up of people with cancer of the upper aerodigestive tract and management of osteoradionecrosis (ORN)

Question title: In people who are clinically disease free and who have undergone treatment for squamous cell cancer of the upper aerodigestive tract with curative intent, what is the optimal method(s), frequency, and duration of follow-up?

Question no: Topic M

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	955	254	19/03/2014
Premedline	Mar 18, 2014	50	16	19/03/2014
Embase	1974 -	1168	312	21/03/2014
Cochrane Library	As per database	78	4	19/03/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1970 -	922	255	21/03/2014

Total references retrieved (after de-duplication): 416

Medline search strategy *(This search strategy is adapted to each database.)*

1. "head and neck neoplasms"/ or facial neoplasms/ or mouth neoplasms/ or otorhinolaryngologic neoplasms/

2. (("upper respiratory tract" or "upper airway* tract" or "upper aerodigestive tract" or "head and neck" or UAT or UADT or head or neck) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

3. exp Mouth Neoplasms/

4. ((oral or intra-oral or intraoral or mouth or lip* or tongue or cheek* or cheek lin* or gingiv* or gum* or palat* or "roof of mouth" or odontogenic or teeth or tooth or buccal or buccal mucosa or face or facial or maxilla*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

5. exp Lip Neoplasms/

6. exp Gingival Neoplasms/

7. exp Palatal Neoplasms/

8. exp Tongue Neoplasms/

9. exp Tonsillar Neoplasms/

10. exp Mandibular Neoplasms/

11. exp Maxillary Neoplasms/

12. exp Odontogenic Tumors/

13. exp Oropharyngeal Neoplasms/

14. ((oropharyn* or tonsil* or retromolar*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

15. exp Pharyngeal Neoplasms/

16. ((pharyn* or throat) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

17. exp Nasopharyngeal Neoplasms/

18. (nasopharyn* adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

19. exp Hypopharyngeal Neoplasms/

20. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

21. exp Laryngeal Neoplasms/

22. ((laryn* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

23. exp Paranasal Sinus Neoplasms/

24. ((nasal* or nose* or paranasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxillary) adj sinus*)) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous or teratoma* or keratini?* or non-keratini?* or non keratini?* or differentiat* or undifferentiat* or basaloid* or neuroendocrin* or adenoid cystic or plasmacytoma* or esthesioneuroblastoma*)).tw.

25. or/1-24

26. exp Aftercare/

27. (follow up or followup or follow-up or surveillance or after-care or after care or aftercare).ti.

28. ((post treatment or post-treatment or posttreatment) adj2 (evaluat* or monitor* or care* or follow up or follow-up or

followup or surveillance or after care or after-care or aftercare)).tw.

29. or/26-28

30. 25 and 29

2. Health Economics Literature search details
This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on upper airways cancer.

3. Any further comments
Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search
For the update search, the same search criteria/filters were applied as initial search with a date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	1023 – sifted 73	8 + 3 (Pubmed)	12/06/2015
Premedline (11 June 2015)	83	20	12/06/2015
Embase	1281 - sifted 155	34	12/06/2015
Cochrane Library	90 – sifted 19	2	12/06/2015
Cinahl	15	3	12/06/2015
Psychinfo	9	4	12/06/2015
AMED	41	1	12/06/2015
Web of Science (SCI & SSCI)	1064 – sifted 188	26	12/06/2015

Total references retrieved (after de-duplication): 55

1

2

Question title: What are the most effective methods of managing osteoradionecrosis following treatment of cancer of the upper aerodigestive tract?

Question no: Topic O1

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1440	673	25/09/2014
Premedline	Sept 24, 2014	85	33	25/09/2014
Embase	1974 -	1512	636	01/10/2014
Cochrane Library	As per database	51	25	25/09/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1970 -	1093	459	30/09/2014
Psycinfo	1806 -	3	2	25/09/2014
AMED	1985 -	2	0	25/09/2014

Total references retrieved (after de-duplication): 1090

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp "Head and Neck Neoplasms"/

2. (("head and neck" or "upper aero-digestive" or "upper aerodigestive" or "upper airway*" or "upper respiratory" or UAT or UADT) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

3. exp Mouth Neoplasms/

4. exp Lip Neoplasms/

5. exp Gingival Neoplasms/

6. exp Palatal Neoplasms/

7. exp Tongue Neoplasms/

8. exp Tonsillar Neoplasms/

9. exp Maxillary Neoplasms/

10. ((mouth or oral or intra-oral or intraoral or oral mucos* or lip* or tongue or cheek* or gingiva* or gum* or palat* or buccal or buccal mucosa* or maxilla* or tonsil*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

11. exp Oropharyngeal Neoplasms/

12. ((oropharyn* or retromolar trigone) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

13. exp Pharyngeal Neoplasms/

14. exp Tracheal Neoplasms/

15. ((pharyn* or throat or trachea* or paratrachea* or windpipe*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

16. exp Nasopharyngeal Neoplasms/

17. (nasopharyn* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

18. exp Hypopharyngeal Neoplasms/

19. ((hypopharyn* or laryngopharyn*) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

20. exp Laryngeal Neoplasms/

21. ((laryng* or glotti* or epiglotti* or subglotti* or supraglotti* or vocal cord* or vocal fold* or voice box* or cordal) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma)).tw.

22. exp Paranasal Sinus Neoplasms/

23. ((paranasal* or nasal* or nasosinus* or sinonasal* or ((nasal* or frontal or ethmoidal or spheroid or maxilla*) adj sinus*)) adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma* or metasta* or adenocarcinoma* or oncolog* or melanoma or squamous or teratoma or lymphoma or plasmacytoma* or neuroendocrine or neuroblastoma* or esthesioneuroblastoma*)).tw.

24. or/1-23

25. exp Osteoradionecrosis/

26. osteoradionecrosis*.tw.

27 ((postradiation or postradiotherap* or radiation or radiotherap*) adj2 osteonecros*).tw.

28 radionecros*.tw.

29 Osteonecrosis/

30 osteonecros*.tw.

31 or/25-27

32 or/28-30

33 24 and 32

34 31 or 33

2. Health Economics Literature search details
This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on upper airways cancers.

3. Any further comments
Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search
For the update search, the same search criteria/filters were applied as initial search with a date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	1338 – sifted 37	2 + 8 (Pubmed)	09/06/2015
Premedline (8 June 2015)	98	19	09/06/2015
Embase	1600 – sifted 208	18	09/06/2015
Cochrane Library	60	3	09/06/2015
Web of Science (SCI & SSCI)	1235 – sifted 213	22	09/06/2015
AMED	2	0	09/06/2015
Psycinfo	4 – sifted 1	0	09/06/2015
Cinahl	64	29 (all duplicates)	09/06/2015

Total references retrieved (after de-duplication): 51

1

2

3

10. Review protocols

Chapter 1. Information and support

Review question	What are the specific information and support needs reported by patients with cancer of the upper aerodigestive tract and their carers? (Review question A1)
Subgroup members	**Lead**: Sarah Orr **Subgroup**: Stephen Spraggett, Tony Smith, Leah Cox
Economic priority	N/A

Background

The diagnosis and treatment of UADGT cancer is complex, often involving multi-modality treatment resulting in significant side-effects and life-altering outcomes, both short and long term. Patients are required to give informed consent to their treatment but currently there is no gold standard of information giving across the UADGT cancer centres. Patients and carers report either too little or too much information at diagnosis, during treatment and at end of treatment (including follow-up) leading to poor patient experience during and after completion of treatment. While it is important to understand the information needs at an individual level, it is also important that there is consensus across all centres on the minimum information given, by whom and at what point during treatment to ensure that informed consent, and patient understanding, is achieved at each stage.

A lack of understanding of the treatment options and outcomes can lead to ill-informed patient decisions which may result in sub-optimum treatment being given and poor patient experience. An overload of information may cause increased stress leading to an inability to make a decision thus leading to a delay in treatment starting; this is particularly the case when the patient is presented with a choice of treatment options.

Information should be tailored to the individual but provided at defined points during the patient pathway regardless of where they are receiving treatment. The appropriate healthcare professional is identified at the MDT to give initial information i.e. SLT would be responsible for providing information in addition to the consultant to all patients undergoing a laryngectomy before a consent form is signed. Information should be available in all forms including verbal, written, DVD, information prescriptions and on-line according to patient need. The information available should be standardised across all UADGT cancer centres. As standard practice all patients should have an information session with the CNS prior to consenting to treatment to ensure patient understanding and it is at this consultation that the patient should be asked how they prefer to receive information and a note made of this in the patient record. The patient's key worker is then responsible for ensuring that the patient has access to information from the appropriate healthcare professional as required during their cancer treatment pathway. Qualified volunteers who have experienced cancer treatment could be well utilised to support information needs in the absence of or in addition to a key worker.

PICO table

Population	Themes
Adults with cancer of the upper aerodigestive tract & their carers: • At diagnosis • Pre-treatment • During treatment	Information, communication and support needs associated with upper aerodigestive tract cancer diagnosis and treatment e.g. psychological difficulties; disfigurement; pain; nutrition/tube feeding; treatment complications and toxicity; rehabilitation; work and social impact; speech and swallowing problems; therapeutic decision making. The role of individuals, such as volunteers, in supporting people with upper aerodigestive tract

• End of treatment/discharge/follow up • During end of life • During palliative care	cancers.

Additional comments on PICO		
	Details	**Additional Comments**
Type of review	Qualitative (any relevant quantitative data will also be included).	
Language	English only	
Study design	Any relevant qualitative or quantitative (or mixed methods) study.	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies		Excluded: studies validating QoL measures, evaluations of specific interventions or services where patient information/support needs not reported, conference abstracts, studies reporting factors associated with QoL, studies with no patient/carer reported outcomes.
Search strategies		
Useful search terms		
Review strategies	We will extract qualitative and quantitative data (depending on what studies are found from the search) and present the results using the relevant evidence tables (NICE Guidelines Manual appendix J) according to study type. Consideration will be given to the timing, delivery (by who), and format of the information. The quality checklist for qualitative data (NICE guidelines manual appendix H) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Data will be presented according to the stage of disease and the management options available to patients, where possible and appropriate.	

Identified papers	
Amendments	Details added to clarify inclusion/exclusion criteria during review.

1

Review question	Does smoking cessation affect outcomes for people with (undergoing treatment or post treatment) cancer of the upper aerodigestive tract? (Review question P1)
Subgroup members	**Lead:** Sarah Orr **Subgroup:** Stephen Spraggett; Leah Cox
Economic priority	Low

Background

Cancers of the UADGT are linked to smoking yet there is little consistency in the information about and provision of smoking cessation support to this patient cohort. The presence of trained smoking cessation counsellors in UADGT cancer units is sparse and many patients are expected to travel to attend generalist smoking cessation clinics at a time when they are also attending hospital for staging and treatment preparation leading to a high non-attendance rate and the provision in primary care of smoking cessation units is inconsistent. There is also a group of patients who succeed in quitting during treatment but recommence on completion of treatment increasing the risk of recurrence.

The benefits of quitting are both long and short term. Smokers are at a higher risk of post-operative complications including chest infections and poor wound healing leading to increased length of stay and potential delay in starting post-operative radiotherapy resulting in sub-optimum treatment. Smoking increases the toxicity of the side-effects of radiotherapy which may include severe oral mucositis, increased pain and smoking directly reduces the efficacy of the radiotherapy itself. Long term benefits of smoking cessation are a reduction in the risk of secondary cancers and recurrence leading to increased survival rates. The smoker may feel guilt at diagnosis due to lifestyle habits which can lead to remorse, alternatively the smoker may feel there is 'no point' to cessation as they already have cancer. Both of these groups of patients need to be educated in a sensitive manner to increase likelihood of successful quitting. Many smokers live in a household where more than one other member also smokes making it more difficult to give up and potentially leading to isolation within the home and social settings. Continued smoking has an effect on health economics with increased input from the healthcare system to manage side-effects, length of stay and treatment of recurrence or secondary cancers.

A diagnosis of cancer is well known as a teachable moment for many people to stop smoking. Research by Humphries has shown that fear of recurrence is a driving force for patients to quit smoking so statistics relating to smoking, side-effects and recurrence may have a positive impact on smoking cessation. As a minimum all patients who smoke and have a diagnosis of UADGT cancer should have a brief intervention at the point of diagnosis with further intervention by a trained smoking cessation counsellor with skills in motivational interviewing and knowledge of the UADGT patient cohort shortly after a diagnosis has been made. This intervention pre-treatment should be embedded in the patient pathway and happen in a hospital setting to avoid patients attending multiple healthcare settings. The patient details can be picked up by the smoking cessation

counsellor at the MDT to ensure timely referral in to the service. The importance of continued smoking cessation should be integral to the end of treat consultation as standard practice. The end of treat summary should detail smoking cessation interventions and provide the primary care team and patient with contact details should the patient relapse and require further intervention. All MDT members should be educated in the importance of the 'brief intervention'. Family and friends should also have access to the specialist smoking cessation service.

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults with cancer of the upper aerodigestive tract who are smokers at the time of diagnosis. Subgroups: • Patients undergoing treatment • Post-treatment • Treatment type • Tumour site.	Smoking cessation after cancer diagnosis	Non-cessation of smoking	• Overall survival • Progression free survival (including second primary cancers) • Tumour recurrence • Quality of life • Treatment-related morbidity
Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.	
Search strategies		
Useful search terms		
Review strategies	The evidence tables for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison	

	will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Consideration will be given to the effect of delivery of smoking cessation interventions (use of generalist smoking cessation clinics or head and neck-specific services; specific methods used to help patients quit) and the timescale over which people stop smoking (only for the duration of treatment, or for longer periods) on the outcomes listed in the PICO.	
Identified papers		
Amendments		

1

2

Chapter 2. Investigation

Review question	What is the most effective configuration of tests within a rapid access clinic for assessing neck lumps suspected of being cancer of the upper aerodigestive tract? (Review question B1)
Subgroup members	**Lead**: Selvam Thavaraj **Subgroup**: Wai Lup Wong; Stuart Winter
Economic priority	High

Background

The rapid assessment of a neck lump suspected to be related to cancer of the upper aerodigestive tract cancer [CUAT] is an important part of the patient pathway.

It is important to note that not all neck lumps are malignant and there are a wide variety of potential causes, both benign and malignant. Therefore providing a timely diagnosis is important. Patients who are referred with suspected CUAT but have a benign cause for their neck swelling should be reassured at the earliest opportunity and unnecessary hospital visits reduced. While patients who have cancer can be informed, appropriate investigations planned and organised to avoid delays so that treatment planning can be started.

Current NICE guidance (IOG) states that newly diagnosed lumps suspicious for CUAT are seen in a rapid access clinic. However there is widespread variation around the country in interpretation of this.

It is anticipated that a comprehensive history and examination is part of the assessment of all patients and this can provide very useful information in order to diagnose the cause of the neck swelling. Thereafter there are a wide range of further investigations, available in the clinic setting that are used in some centres.

These include: Flexible nasendoscopy, Flexible transnasal oesophagoscopy, Fine needle aspiration cytology (FNAC) and ultrasound. With regard to FNAC, there are a wide variety of practices, including ultrasound guided or palpation guided aspiration. The cytological aspirate may be obtained by the surgeon and on another day reported by the cytopathologist: or surgeon performed aspiration and same day quality assessment by a lab technician followed by subsequent reporting by the cytopathologist; and finally cytopathologist aspiration and same day reporting.

Ultrasound, if utilised, may be performed by either the surgeon or an ultrasonographer.

FNAC is often the only test required for confirmation of metastatic squamous cell carcinoma. The accuracy of testing is influenced by a number of factors, including sample adequacy, preparation and the experience and expertise of the cytopathologist. Failure to obtain a definite diagnosis with FNAC requires more intrusive tissue sampling, such as core biopsy in which a solid tissue sample is achieved for histological assessment. Core biopsy may be carried out under UG.

In addition to the above range of 'same' day investigations many clinics offer rapid assessment with cross-sectional imaging, MRI or CT,.

The ultimate aim of the clinic is to be able to identify a cause for the swelling in the neck with the highest level of accuracy utilising the least intrusive set of investigations in the timeliest fashion. Thereby

reassuring the patient with the benign neck lump or, in the case of malignancy, diagnosing the disease and facilitating planning at the earliest opportunity. The clinician also needs to be aware that not all patients are prepared for the amount of information suddenly given and the prospect of life-changing treatment.

Currently the assessment of neck lumps is contentious. Firstly, tests vary in their cost, availability and accuracy. Furthermore, the sequence in which tests should be carried out, the length of time between tests and the organisation of neck lump clinics is variable.

The aim of this guidance would be to provide guidance on the set up of a rapid access clinic.

PICO table

Population	Index Test	Reference Standard	Outcomes
Adults initially referred with undiagnosed neck lumps suspected as cancer of the upper aerodigestive tract.	• FNAC (with or without ultrasound guidance; with or without same day confirmation of sample adequacy and same day reporting of diagnosis) • Core biopsy (with or without ultrasound guidance • Flexible nasendoscopy • Flexible transnasal oesophagoscopy • MRI • CT • Ultrasound With or without same-day access to cross-sectional imaging.	Final diagnosis based on cyto/histopathology/clinical imaging and follow up	• Sensitivity • Specificity • Test-related morbidity • Time to diagnosis • Patient reported outcomes (for example patient satisfaction

Additional comments on PICO	

	Details	**Additional Comments**
Type of review	Diagnostic test	
Language	English only	
Study design	Studies of diagnostic test accuracy	
Status	Published studies only	
Other criteria for inclusion / exclusion of	Inclusion criteria: sufficient data reported to calculate the total number of true positives, true negative, false positives, and false	

studies	negatives for the studied test(s). Exclusion criteria: Reference standard is unclear or undefined.	
Search strategies	Search from 1990 onwards. This is the date of the earliest evidence on any test included in the PICO.	
Useful search terms		
Review strategies	The evidence table for studies of diagnostic accuracy will be used (NICE Guidelines Manual Appendix J) to extract and present data from individual studies. Sensitivity and specificity data will be pooled when appropriate. Other outcomes will be presented as risk ratios or hazard ratios. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender.	
Identified papers		
Amendments	Inclusion/exclusion criteria updated to ensure these are consistently applied across all DTA questions in the guideline.	

1

2

Review question	What is the most effective investigative pathway for identifying the occult primary site in patients presenting with metastatic neck disease (squamous cell carcinoma)? (Review question C1)
Subgroup members	**Lead**: Vin Paleri **Subgroup**: Selvam Thavaraj; Wai Lup Wong
Economic priority	Low

Background

A small proportion of patients with head and neck cancer (~5%) present with a neck lump and no clinical evidence of cancer in the upper aerodigestive tract mucosa. This occurs because the primary site is smaller than can be seen on clinical or radiological examination. In these patients it is important to try and identify the source of the primary site. There are two advantages in identifying the primary site: treatment can be directed to the primary site thus avoiding blanket treatment of all probable sites and appropriate site directed examination can be performed during follow up. Current practice when a primary tumour is not evident involves biopsy of several sites in the mouth, nose and throat to confirm the site of the primary. While there is broad consensus to perform radiological investigations prior to the biopsy procedure, there is no agreement on the precise role of these tests or their diagnostic efficacy. In addition, the lack of availability of certain investigative modalities in some parts of the country has led to no uniformity in investigating these patients. There is also disagreement regarding the role of certain investigations. Some tests are expensive, lack quality assurance and necessary expertise and can also cause a delay in the diagnostic process, thus causing breaches of the diagnostic target times. Thus following the review several recommendations could be made:

Which tests are useful?

What is the diagnostic efficacy of these tests

What is the order in which they should be performed?

PICO table

Population	Index Test	Reference Standard	Outcomes
Adults presenting with metastatic neck disease (squamous cell carcinoma) and clinically occult primary presumed to be of upper aerodigestive tract origin	• CT • MRI • PET CT • Examination under anaesthesia, panendoscopy, biopsy, bilateral tonsillectomy • PET • Narrow band imaging • Trans oral robotic surgery • Nasendoscopy • Combinations of the above	Identification of primary tumour site/confirmation of staging based on histopathological diagnosis/imaging/follow up	• Sensitivity • Specificity • Process-related morbidity • HRQoL • Time to diagnosis

Additional comments on PICO	

	Details	Additional Comments
Type of review	Diagnostic test	
Language	English only	
Study design	Studies of diagnostic test accuracy	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Inclusion criteria: sufficient data reported to calculate the total number of true positives, true negative, false positives, and false negatives for the studied test(s). Exclusion criteria: Reference standard is unclear or undefined.	
Search strategies	Searches will be limited to after 1995, as cross sectional imaging (CT, MRI) has been widely available only since the 1990s.	
Useful search terms	cervical lymph node metastases, unknown primary tumor, squamous cell carcinoma, diagnostics, panendoscopy, CT PET scan, CT scan, MRI scan	
Review strategies	The evidence table for studies of diagnostic accuracy will be used (NICE Guidelines Manual Appendix J) to extract and present data from individual studies. Sensitivity and specificity data will be pooled when appropriate. Other outcomes will be presented as risk ratios or hazard ratios. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. In addition to individual tests, where possible, different combinations or sequences of tests will be compared using the outcomes listed in the PICO.	
Identified papers		
Amendments	Inclusion/exclusion criteria updated to ensure these are consistently applied across all DTA questions in the guideline.	

1

Review question	Which patients with cancer of the upper aerodigestive tract require systemic staging? (Review question C2)
Subgroup members	**Lead**: Wai Lup Wong **Subgroup**: Laurence Newman; Selvam Thavaraj
Economic priority	Low

Background

Systemic staging is a key consideration in patients with primary & recurrent squamous cell cancer of the UAT and in patients with metastases in neck nodes and no obvious primary cancer. This is because in patients with UAT cancer the presence of distant metastases is one of the single most important factors which influence plan of treatment. For some patients it can mean the difference between treatment with curative intent and best symptomatic control. However, not all patients require systemic staging, or at least it may not be cost-effective to systemically stage all patients with UAT cancer. There are two main factors that will contribute to whether a patient requires systematic staging. Firstly, likelihood of distant metastases in the individual patient. Also, the ability of imaging to detect metastases. There is established data on the likelihood of distant metastases in the individual patient. However, there is debate as to which of the imaging tests usually used for systemic staging is most accurate for detecting distant metastases. Specifically, FDG PET CT compared with diagnostic CT. This has resulted currently in variation in practice across the UK as to which patients are systematically staged and the observation that for those who are systemically staged the initial preferred imaging test varies. Informing the discussion will potentially contribute to improving results of treatment through more appropriate treatment for more patients and will improve the patient experience – fewer diagnostic tests without compromise on accuracy of diagnosis and sparing of unnecessary treatment that will be of limited benefit. More broadly it will contribute to more appropriate use of health care resources and may result in some financial savings.

Following the evidence review we can imagine firstly recommending no systemic staging for patients with a low risk of distant metastases such as patients with early vocal cord cancer with no nodal spread. Secondly, we can also imagine recommending systemic staging with FDG PET CT and diagnostic CT of the chest with no intravenous contrast as the initial investigation for patients with moderate and high risk of distant metastases such as in nasopharyngeal cancer patients and patients with advanced disease at the primary site and within nodes.

1

PICO table			
Population	**Index Test**	**Reference Standard**	**Outcomes**
Adults with cancer of the upper aerodigestive tract Subgroups: • Newly diagnosed cancer • Recurrent cancer (within 2cm of original primary and within 3 years from primary treatment) • Unknown primary of suspected upper aerodigestive tract origin • Second primary tumour	• TN stage • Smoking status • HPV status • Tumour site	Detection of distant malignant disease and/or detection of synchronous primary	• Sensitivity • Specificity • Positive predictive value • Negative predictive value

Additional comments on PICO	

	Details	**Additional Comments**
Type of review	Diagnostic test	
Language	English only	
Study design	Studies of diagnostic test accuracy	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Inclusion criteria: sufficient data reported to calculate the total number of true positives, true negative, false positives, and false negatives for the studied test(s). Exclusion criteria: • reference standard is unclear or undefined. • studies that exclusively report the detection of malignant disease at the primary tumour site or regional (cervical) lymph nodes.	
Search strategies	None specified	
Useful search terms	MR, CT, whole body MR, FDG, Emission Tomography Positron, PET–CT, staging, restaging, recurrence, occult primary, unknown primary tumour, squamous cell carcinoma	
Review strategies	The evidence table for studies of diagnostic accuracy will be used (NICE Guidelines Manual Appendix J) to extract and present data from	

	individual studies. Sensitivity and specificity data will be pooled when appropriate. Other outcomes will be presented as risk ratios or hazard ratios. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. In addition to individual tests, where possible, different combinations or sequences of tests will be compared using the outcomes listed in the PICO.	
Identified papers		
Amendments	Inclusion/exclusion criteria updated to ensure these are consistently applied across all DTA questions in the guideline.	

1

Review question	What is the most effective systemic imaging strategy for investigating cancer of the upper aerodigestive tract? (Review question C3)
Subgroup members	**Lead**: Tom Roques **Subgroup**: Leah Cox; Wai Lup Wong
Economic priority	Low
Background	

Much of the focus in the initial diagnosis and management of UAT cancers is focussed on the primary tumour site and regional lymph nodes as distant metastases are less common (<10% at diagnosis) then in many other cancers. But the need to identify distant disease is particularly relevant in cancers where initial treatment has very significant morbidity. There is also a documented risk of synchronous primary cancers (most commonly arising in the lung) in UAT cancer patients.

There is therefore a need to exclude metastatic disease (most commonly in the lungs and bones) and to screen for second primary cancers in patients presenting with UAT cancer in a cost-effective manner. Current national guidance and practice is to 'stage the chest' but there are inconsistencies in how this is done.

Common approaches include a chest radiograph (CXR) or contrast enhanced computerised tomography (CT) scan of the thorax. It is not known which subgroups of UAT patients would most benefit from a CXR or a CT nor what the cost-effectiveness of such imaging is. Furthermore PET-CT is now an established technique for evaluating neck nodes without a clear primary site and for evaluating response to radiochemotherapy in oropharyngeal cancer and in each of these settings unexpected metastases can be detected. Would PET-CT scanning at diagnosis in some/all UAT patients be cost-effective?

The harms of each approach are well documented and include exposure to radiation and the discovery of other problems (lung nodules, thyroid nodules etc) which may complicate future care unnecessarily and without clinical benefit. There are significant financial costs to a 'scan all' strategy.

Possible recommendations after the review include:

•One modality being recommended for all UAT patients as cost-effective

•A differing approach – nothing – CXR – CT – PET-CT depending on the primary tumour site and stage of disease and intended treatment plan (and HPV status?)

PICO table

Population	Intervention (Index Test)	Comparator (Reference Standard)	Outcomes
Adults with cancer of the upper aerodigestive tract who require systemic imaging Subgroups: • Tumour site • Disease stage • HPV status	• CT • Chest X-ray • Bone scan • MRI • PET-CT • PET • US • PET-MRI • Combinations of the above	Final diagnosis (based on clinical imaging/follow up/histopathology)	• Sensitivity • Specificity • Process-related morbidity • HRQoL

Additional comments on PICO	

	Details	Additional Comments
Type of review	Diagnostic test.	
Language	English only	
Study design	Diagnostic accuracy studies. Conference abstracts will be excluded.	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	For the purposes of this review, systemic imaging is defined as imaging of sites other than the primary tumour site or regional (cervical) lymph nodes. Inclusion criteria: sufficient data reported to calculate the total number of true positives, true negative, false positives, and false negatives for the studied test(s). Exclusion criteria:Reference standard is unclear or undefined. Studies including non-cancer patients or cancers outside the upper aerodigestive tract will be excluded.	
Search strategies	Limit search to post-1994.	
Useful search		

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terms		
Review strategies	The evidence table for studies of diagnostic accuracy will be used (NICE Guidelines Manual Appendix J) to extract and present data from individual studies. Sensitivity and specificity data will be pooled when appropriate. Other outcomes will be presented as risk ratios or hazard ratios. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender.	
Identified papers		
Amendments	Inclusion/exclusion criteria updated to ensure these are consistently applied across all DTA questions in the guideline.	

1

2

Chapter 3. Treatment of early stage disease

Review question	What is the most effective treatment for newly diagnosed T1 or T2 carcinoma of the larynx? (Review question D1)
Subgroup members	**Lead:** Shreerang Bhide **Subgroup:** Leah Cox, Jane Thornton, Vin Paleri, Stuart Winter, Tony Smith, Tom Roques
Economic priority	Medium

Background

The overall 5-year survival rates for laryngeal cancer are of the order of 66%. Stage wise survival rates vary, with higher 5-year survival for Stage I (90% to 95%) and Stage II (70% to 85%) disease. T1 and T2 tumours are treated either with radical radiotherapy, transoral laser resection, transoral robotic resection or less frequently, open partial laryngectomy. There is lack of evidence in terms of the superiority of either of these techniques over the other in terms of oncologic outcomes, laryngeal function or health economic gains [1]. Therefore further clarity is required on patient selection in terms of patient and tumour related factors in this group of patients.

There is a lack of evidence for quality of voice and/or swallow following the various treatment modalities.

Although there are no randomized trials on the topic, there are several prospective series in the literature, in addition to patient views from qualitative studies. Thus, a systematic assessment and synthesis of evidence based on the three suggested outcomes might be able to make a narrative and objective recommendations on treatment for early stage laryngeal cancer.

Questions to be answered

Patient selection criteria for radical treatment of T1/T2 tumours.

Voice and swallow related function following treatment for various stages.

Health economic gains

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**

Adults diagnosed with new (T1, T2, N0) squamous cell carcinoma of the larynx
 	
Subgroups:
 	
• Glottis
• Supraglottis
• T1a
• T1b
• T2a
• T2b
• Performance status
	• Radiotherapy
	• Larynx preserving surgery:
	  • trans oral
	  • open
		Each other	• Overall survival
			• Disease free survival
			• Tumour recurrence
			• Progression free survival
			• Treatment related mortality
			• Treatment related morbidity
			• Organ preservation rates
			• Length of stay
			• Health related quality of life
			  • Swallow function
			  • Voice quality

Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour site of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10; At least 75% of the included patients meet the	

	population defined in the PICO.	
Search strategies		
Useful search terms	Laryngeal cancer, glottic cancer, supra-glottic cancer, radical radiotherapy, radical chemoradiation, trans-oral laser, open partial laryngectomy, , dysphonia /voice and swallowing disorder/dysphagia/aspiration, transoral robotic surgery, transoral laser microsurgery	
Review strategies	The evidence tables for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. In addition to studies comparing surgery with radiotherapy, the radiotherapy regimen and type of surgery (open or trans oral) used in relevant studies will be important considerations for the review. Comparisons of different radiotherapy regimens/different surgical approaches will also be included, if these exist.	
Identified papers		
Amendments	Inclusion/exclusion criteria for studies not limited to the tumour site of interest added, for consistency with other similar review questions. Some amendments made to the wording of outcomes for consistency with other similar review questions.	

1

Review question	What is the most effective management strategy for the clinically and radiologically N0 neck in patients with early squamous cell carcinoma of the oral cavity? (Review question F1)
Subgroup members	**Lead:** Loz Newman **Subgroup:** Vin Paleri, Sheerang Bride; Michael Fenlon
Economic priority	Medium

Background

The management of early oral cavity squamous cell carcinoma (SCC) – stage T1N0 – remains controversial. In these cases elective neck dissection, which is widely performed, reveals occult metastases only in up to 26% of cases, which means that the majority of neck dissections performed in this patient cohort are probably unnecessary. Debate continues regarding the depth of tumour invasion and how this relates to the risk of metastasis – 4mm/5mm/6mm depth (Spiro/Woolgar). Equally a discohesive invasive front together with lymphovascular and perineural invasion are considered to be poor prognostic indicators. Recent studies suggest that tumour outcome can be predicted on the basis of myofibroblast absence/presence in the resected specimen (Thomas G).

At least 4 randomised trials and a meta analysis (Fasunla 2009) have tried to address this question. The evidence should be considered and the question being asked is the oncologic, functional and health economic benefit of an elective neck dissection in T1 (add T2 as well given that a trial with these cases is in progress?) N0 cases at the time of tumour ablation compared to observation and delayed management of the neck when metastatic disease is detected on follow up. Also to be assessed is the benefit of delaying neck dissection until definitive histology is available following tumour ablation.

Some centres perform sentinel node biopsy in T1N0 cases. Should this be considered to be best practice? If the sentinel node is positive then presumably the surgeon will perform a neck dissection. If the sentinel node is negative should a neck dissection be aborted?

The main options for treatment of the N0 neck include:

Sentinel node biopsy. Generally, this is an intraoperative staging procedure. If frozen section of the sentinel node(s) reveals metastasis/micrometastasis, selective neck dissection would be carried out immediately. The sentinel node would be assessed more thoroughly on routine fixed sections and with immunohistochemistry and if positive on detailed assessment, completion selective neck dissection would be carried out in a second operation.

Removal of primary tumour and assessment of histological features (reconstructed thickness / depth of invasion; cohesion at invasive front, etc). If risk of metastasis is high, then neck could be treated by elective selective neck dissection or elective radiotherapy.

Elective selective neck dissection. Levels I-III or I-IV or II-IV depending on site of primary tumour. SND has low morbidity. It can also be considered a staging ND since if there is more than one positive node or ECS (even microscopic) on routine histological assessment, then post-operative radiotherapy would generally be recommended.

1

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults diagnosed with early (stage T1-2,N0) squamous cell carcinoma of the oral cavity undergoing curative surgery at the primary site Subgroups: • Tumour depth • Tumour sites	• Radiotherapy • Chemotherapy (induction/neo-adjuvant and concomitant) • Elective neck dissection (extent, eg levels 1-3, levels 1-4) • Other systemic therapies • Sentinel node biopsy • Active surveillance (radiology) • No treatment • Combinations of the above	Each other	• Overall survival • Disease free survival • Progression free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Organ preservation rates • Health related quality of life
Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials ~~and~~ or observational studies in the absence of RCTs	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour site of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10; At least 75% of the included patients meet the population defined in the PICO.	
Search strategies	Limit search to 1994 onwards. According to the GDG, this is the date of publication for the earliest evidence on this topic.	
Useful search terms	For neck dissection: Supraomohyoid neck dissection	

	Supra hyoid neck dissection Selective neck dissection Functional neck dissection Function preserving neck dissection Level 1 - 3 neck dissection Level 1-4 neck dissection Level 2-5 neck dissection Modified radical neck dissection/MRND	
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.	
Identified papers	Fasunla et al. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. *Oral Oncol* 2011	
Amendments	Inclusion/exclusion criteria for studies not limited to the tumour site of interest added, for consistency with other similar review questions. Some amendments to the wording of outcomes for consistency with other similar review questions.	

1

2

Review question	What is the optimal management of T1-2, N0 squamous cell carcinoma of the oropharynx? (Review question I1)
Subgroup members	**Lead:** Stuart Winter **Subgroup:** Jane Thornton; Bella Talwar; Tom Rocques; Vin Paleri
Economic priority	High

Background

The incidence of carcinoma of the oropharynx, in particular the tonsil and tongue base has more than doubled over the last decade and may well become the most common site of cancer in the head and neck. While smoking and alcohol remain significant risk factors for developing this disease viral infection with the Human Papilloma Virus (HPV) has become increasingly important and has altered the 'classic' presentation of the patient oropharyngeal cancer.

The rise in incidence of this tumour has seen a change in patients presenting with the disease, so that the average age is decreasing and it is starting to affect younger men and a higher proportion of women.

Currently different protocols are used around the country to manage early oropharyngeal cancer. Furthermore a distinction in some centres between HPV related disease and HPV unrelated tumours are being made when deciding on the treatment.

Single modality treatment with either surgery or radiotherapy to the primary site and at risk neck are recognised treatment approaches. Both claim excellent cure rates but the short and long term morbidity of each approach differs. Approaches to recurrent or second primary disease in the future will also depend on the initial treatment choice. In a disease with a high chance of cure considering salvage options and long term side effects will be paramount. The lack of randomised controlled trials comparing these approaches reflects the developing understanding of the tumour biology and the importance of HPV in disease behaviour as well as rapid technological advances in surgery and radiotherapy and the availability of surgical/radiotherapeutic expertise. The latter include trans-oral laser or trans-oral robotic resections and Intensity Modulated Radiotherapy Therapy (IMRT)

The addition of chemotherapy or biological therapy to radiation for more advanced disease is widely supported. The role for this in early stage disease or being used as a single modality treatment is limited but needs to be discussed. The importance of HPV+ status within this also needs to be considered.

The aim of this guidance would be to offer some clarity on the treatments options to cure the disease with minimal impact on quality of life.. Furthermore it may be possible to advise on whether there is currently sufficient evidence to make a treatment choice based on HPV status of the tumour.

The impact of modifying risk factors and behaviours (tobacco and alcohol use) on the treatment outcome is unclear. This is an added recommendation that could be an outcome of this topic

1

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults diagnosed with new T1-2, N0 squamous cell carcinoma of the oropharynx Subgroups: • HPV status • Smoking status and smoking history	• Radiotherapy • Surgery (laser, robotic) • Chemotherapy • Chemoradiotherapy • Other systemic therapies • Combinations of the above	Each other	• Overall survival • Disease free survival • Progression free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Organ preservation rates • Health related quality of life
Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour site of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10; At least 75% of the included patients meet the population defined in the PICO.	
Search strategies	Search from 1994 onwards.	According to the GDG, this is the date of publication for the earliest evidence on this topic.
Useful search terms		

Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.	
Identified papers		
Amendments	Inclusion/exclusion criteria for studies not limited to the tumour site of interest added, for consistency with other similar review questions. Some amendments to the wording of outcomes for consistency with other similar review questions. PICO population amended during review to explicitly match the review question. “M0” in review question and PICO population amended to “N0” as this was a typographical error.	

1

2

Chapter 4. Treatment of advanced disease

Review question	What is the most effective treatment for newly diagnosed T3 and T4 squamous cell carcinoma of the larynx? (Review question D2)
Subgroup members	**Lead:** Tom Roques **Subgroup:** Margred Capel; Leah Cox; Stuart Winter
Economic priority	High

Background

Treatment for locally advanced (T3-T4a) larynx cancer aims to cure the patient of cancer whilst maintaining an acceptable quality of voice and swallow. A total laryngectomy offers a good chance of cure and a functional swallow but the patient will need to learn alternative ways to form a voice. Cure rates can be increased by post-operative radiotherapy +/- chemotherapy/other systemic therapies but these may also increase late side effects.

An alternative approach is to use primary radiotherapy, usually combined with neo-adjuvant or concomitant chemotherapy (or both). It is often stated that this approach offers equivalent cure rates to primary surgery but with a better chance of laryngeal preservation but questions over this statement remain. Does laryngeal preservation mean having a larynx or having a functioning larynx? Does the equivalent cure rate rely on salvage surgery when necessary? Are the complications of the salvage surgery acceptable when operating in an irradiated neck? How is a non-functioning larynx after radiation but without tumour recurrence best managed? How does primary radio(chemo)therapy affect long term swallowing function. And how can we best explain these trade-offs to the individual patient faced with very different treatment options.

The GDG will be able to appraise current evidence as to the potential benefits and risks of these approaches. There may not be one overall best strategy, but an evidence -based options appraisal will help clinicians guide patients through their treatment options with much greater clarity than exists at present

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**

Adults with locally advanced (T3 to T4a) squamous cell carcinoma of the larynx undergoing curative treatment.
 	
Subgroups:
• Glottis
• Supraglottis
• Subglottic
• Transglottic
• Stage
• Performance status
• N-stage
	• Surgery (non organ sparing and organ sparing, with or without reconstruction)
	• Radiotherapy (altered fractionation)
	• Chemotherapy (induction/neo-adjuvant and concomitant)
	• Other systemic therapies (e.g. lapatinib or other EGFR antagonists)
	• Combinations of the above
		Each other	• Overall survival
			• Disease free survival
			• Progression free survival
			• Tumour recurrence
			• Treatment related mortality
			• Treatment related morbidity
			• Organ preservation rates
			• Length of stay
			• Health related quality of life
			  • swallow function
			  • voice quality

Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour site of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10; At least 75% of the included patients meet the	

	population defined in the PICO.	
Search strategies	Search from 1991 onwards.	This is the date of publication for the earliest evidence on this topic.
Useful search terms		
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Different chemotherapy regimens (eg induction, neo/adjuvant) and radiotherapy regimens (dose and fractionation are of particular importance) will be considered and compared where these comparisons exist.	
Identified papers		
Amendments	Inclusion/exclusion criteria for studies not limited to the tumour site of interest added, for consistency with other similar review questions. Some amendments to the wording of outcomes for consistency with other similar review questions.	

1

2

Review question	What is the most effective treatment for newly diagnosed locally advanced squamous cell carcinoma of the hypopharynx (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)? (Review question E1)
Subgroup members	**Lead:** Vin Paleri **Subgroup:** Stuart Winter; Tom Rocques; Loz Newman; Leah Cox
Economic priority	Low

Background

Hypopharyngeal squamous cell cancers usually present late with metastatic spread to the neck, and have a poorer prognosis compared to other head and neck cancer subsites.

Treatment options include primary non-surgical therapy with the aim of preserving the larynx and hypopharynx, or radical surgery usually followed by adjuvant (chemo)radiation therapy. The latter approach, which involves removal of the voice box and the adjacent swallowing passage (pharynx) with reconstruction, has been considered to be appropriate for this aggressive disease for several years.

However, some trials have investigated and challenged this dogma by offering patients primary radiotherapy with concomitant or induction chemotherapy (or both) with equivalent control rates. Although non-surgical therapy may preserve the larynx, this treatment can be associated with the risk of leaving the patient with a non-functional larynx that impairs speech and swallowing. Salvage surgery if the tumour recurs can also be technically very challenging. Developments in radiotherapy (routine use of IMRT, dose escalation) and in chemotherapy regimes offer the promise of better cure rates with non surgical approaches but there is a lack of high level evidence comparing surgery with non-surgical treatments.

Both approaches have significant treatment related morbidities as well as technical challenges. There is probably a role for both approaches, but greater clarity in patient selection for these treatments is necessary.

1

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults diagnosed with stage 3 or 4a carcinoma of the hypopharynx undergoing curative treatment Subgroups: • Tumour stage	• Surgery (non organ sparing and organ sparing, with or without reconstruction) • Radiotherapy (altered fractionation) • Chemotherapy (induction/neo-adjuvant and concomitant) • Other systemic therapies (e.g. lapatinib, EGFR antagonists) • Combinations of the above	Each other	• Overall survival • Disease free survival • Progression free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Organ preservation rates • Health related quality of life
Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the hypopharynx but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site and subgroup analysis of patients with hypopharynx cancer is possible, and where the number of patients in this category is ≥10; At least 75% of the included patients meet the population defined in the PICO. Evidence on cetuximab will not be considered under the 'other systemic therapies' category of interventions, as cetuximab is covered by NICE TA145 and TA172.	
Search	Search from 1995 onwards. According to the	

strategies	GDG, this is the earliest date of publication for relevant studies of the interventions in the PICO. Any earlier studies that exist would not be relevant to current clinical practice.	
Useful search terms	Hypopharyngeal cancer, pyriform fossa cancer, postcricoid cancer, chemoradiation therapy, total laryngopharyngectomy, hypopharyngeal reconstruction	
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.	
Identified papers		
Amendments	Inclusion/exclusion criteria for studies not limited to the tumour site of interest added, for consistency with other similar review questions. Some amendments to the wording of outcomes for consistency with other similar review questions.	

1

2

Review question	What are the most effective palliative treatments for people with incurable upper aerodigestive tract cancer experiencing breathing difficulties? (Review question N1)
Subgroup members	**Lead:** Margred Capel **Subgroup:** Shreerang Bhide, Vin Paleri, Stuart Winter
Economic priority	Low

Background

Respiratory complications are a significant cause of mortality and morbidity in patients with locally advanced and/or metastatic cancers of the aerodigestive tract.

Patients can experience significantly distressing symptoms including stridor and dyspnoea as a result of partial or complete upper airway obstruction secondary to these tumours.

Strategies to palliate or ameliorate these symptoms can be challenging and will often require one or a combination of surgical interventions; disease modification with chemo-radiotherapy and pharmacological treatments.

Surgical interventions that may be of benefit include surgical debulking, using laser, microdebrider, coblatror or other such device, stenting or tracheostomy insertion. The type of intervention will be dependent on disease type, location and may incur consequences to the individual patient which impact upon their quality of life. Hospital admission may be required for certain procedures and the positives and negatives of each approach must be carefully considered with the patients. Tracheostomy formation may relieve the symptoms of airway obstruction but this may impact on a patient's place of care and their quality of life, resulting in a need for education and training for both patient and carers. Radical or conservative surgical interventions may have a role in select cases as may newer modalities like photodynamic therapy.

Chemotherapy and radiotherapy have significant side-effects which may make this therapy inappropriate or unacceptable to an individual with advanced disease. Patients who receive best supportive care only receive symptom control through manipulation of pharmacology.

The impact on the individual of the different interventions is significant. it is therefore important to identify those patients who would have better outcomes with the different approaches in terms of both survival and quality of life. The different interventions incur different financial implications relating to the procedure itself and ongoing support as a consequence of the interventions.

The use of the above strategies requires significant communication between the MDT and the patients to decide on the best course of management to achieve the optimum symptom control with the minimum impact on an individual's quality of life. It is therefore imperative that professionals in this field have the most up-to-date evidence to advise patients on the positives and negatives of differing approaches.

Recommendations for palliative treatments for patients with breathing difficulties from incurable upper aerodigestive tract cancers are likely to address:

Which patients will have better outcomes from surgical intervention including debulking and which will have better outcomes from trachostomy?

Which patients will have better outcomes from radiotherapy or chemotherapy?

Which patients will have better outcomes from best supportive care alone?

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults with incurable upper aerodigestive tract cancer with: • dyspnoea • stridor	• Tracheostomy • De-bulking surgery • Radiotherapy • Chemoradiotherapy • Chemotherapy • Other systemic therapies • Best supportive care	Each other	• Symptom control • Treatment-related morbidity • Quality of life • Length of stay • Survival • Burden of care
Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.	The focus of the review is studies of patients with incurable cancer of the upper aerodigestive tract. However, studies may exist that include a mixed population of patients with dyspnoea/stridor: either curable/incurable CUADT, or a mixture of CUADT and other conditions. These studies will be included only where either: • >75% of patients included in the study meet the definition of population given in the PICO; • sufficient evidence is presented to determine outcomes specifically in the subgroup of patients relevant to the PICO, and this group of patients comprises at least 10 patients in each treatment arm.

Search strategies		
Useful search terms	End of life, terminal, palliative, incurable, airways obstruction, stridor, breathlessness, against head and neck cancer and the different anatomical sites of head & neck cancer. The following terms with palliative or head and neck cancer or the specific disease sites: laser, microdebrider, coblatror, surgical debulking, tracheostomy, photodynamic therapy	
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, and dose of any palliative treatment will be important considerations for the review.	
Identified papers		
Amendments		

1

2

Chapter 5. HPV-related disease

Review question	What is the most effective test to identify an HPV positive tumour in people with cancer of the upper aerodigestive tract? (Review question K2)
Subgroup members	**Lead**: Selvam Thavaraj **Subgroup**: Vin Paleri
Economic priority	High

Background

A substantial and increasing proportion of oropharyngeal squamous cell cancers (OPSCCs), especially the tonsillar and base of tongue sites, are associated with, and caused by, HPV infection. Studies from the United States, Finland, Sweden, the Netherlands and the United Kingdom have shown an epidemic rise in the number of new cases over the last three decades. Between 1984 and 2004, the number of OPSCCs that were HPV positive rose from 16.9% to 71.9% in the USA, and the population incidence rose by 225%. If current trends continue, it has been estimated that by 2020 the annual incidence of HPV-positive OPSCCs in the USA will surpass the annual number of cervical cancers. In Sweden, where there has been a 7-fold increase in disease incidence over the last 30 years, HPV associated OPSCC is likely to account for almost half of all new cases of Head and Neck Cancer (HNC) cancer in 10 years time. The incidence of oropharyngeal cancer in the UK has more than doubled in the ten years between 1995 and 2006. In Scotland, oropharyngeal cancer is the fastest rising of all cancers The viral strain most commonly involved is HPV-16, the cause of genital Herpes.

Although there are clinical and histological pointers to which OPSCCs are HPV-positive, confirmation requires specific tests. Accurate diagnosis is important because management, counselling and prognosis differs for HPV-16 cytopositive and HPV-16 cytonegative (smoking/alcohol-related) tumours. Immunohistochemical staining for p16 protein is used as a screening test on all OPSCCs. Identification of HPV-16 cytopositive tumours (in which the virus is actively driving the cancer) requires specific, more sophisticated, tests. These specific tests include polymerase chain reaction (PCR), in situ hybridisation (ISH), gene expression profiling, and RNA scope. These specific tests differ in the kind of tissue sample required, specificity, sensitivity, overall accuracy, availability, expertise required, cost and time to issuing the report.

Uncertainty exists over which of the specific tests, or combination of tests, is the "gold standard" and hence, should be recommended for routine clinical use.

PICO table

Population	Intervention (Index Test)	Comparator (Reference Standard)	Outcomes
Adults diagnosed with cancer of the upper aerodigestive tract in whom HPV testing is indicated	• Immunohistochemistry (p16 IHC) • Quantitative polymerase chain reaction (qPCR) for viral E6 RNA (RNA qPCR) and DNA (DNA qPCR) • In situ hybridisation for high-risk HPV (HR HPV ISH) • Gene expression profiling • RNA in situ hybridisation test (RNAscope) • Combinations of the above	Real time DNA and RNA analysis using quantitative PCR on fresh tumour tissue	• Sensitivity • Specificity

Additional comments on PICO	

	Details	Additional Comments
Type of review	Diagnostic test	
Language	English only	
Study design	Studies of diagnostic test accuracy	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Inclusion criteria: sufficient data reported to calculate the total number of true positives, true negative, false positives, and false negatives for the studied test(s). Exclusion criteria: reference standard is unclear or undefined.	
Search strategies	Search from 2000 onwards	According to the GDG, this is the date of publication for the earliest evidence on this topic.
Useful search terms		
Review strategies	The evidence table for studies of diagnostic accuracy will be used (NICE Guidelines Manual Appendix J) to extract and present data from individual studies. Sensitivity and specificity data will be pooled when appropriate. Other outcomes will be presented as risk ratios or hazard ratios. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Different types of tumour tissue preparation (formalin fixed vs. fresh frozen) for individual tests will also be compared, where this evidence is available.	
Identified papers		
Amendments	Inclusion/exclusion criteria updated to ensure these are consistently applied across all DTA questions in the guideline.	

1

2

Review question	Is there a role for de-intensification of treatment in patients with HPV-positive upper aerodigestive tract tumours? (Review question K3)
Subgroup members	**Lead:** Tom Roques **Subgroup:** Bella Talwar; Tony Smith; Leah Cox, Loz Newman
Economic priority	Medium
Background	

Retrospective data analyses looking at HPV status of treated patients have confirmed that HPV+ oropharyngeal cancers have an excellent cure rate with standard therapeutic approaches whether these approaches are based around radiotherapy or surgery.

Radiation with concomitant chemotherapy (and sometimes induction chemotherapy) has been a standard treatment option for HNSCC for many years and predates the recognition of HPV+ disease. Curative surgery can involve trans-oral laser resection or open surgery and reconstruction and is often followed by post-operative radiotherapy with or without chemotherapy.

These treatments have significant acute and long term morbidity with late effects varying from dysphagia to an increased risk of stroke. Now that the majority of HPV+ patients can expect to live for decades after treatment there is interest in reducing the intensity of initial therapy in the interests of improving long term quality of life.

If standard treatment is assumed to be radiotherapy with concomitant cisplatin based chemotherapy, approaches to deintensify treatment could include reducing radiation dose, changing radiation treatment volume (eg not treating some nodal levels), using concomitant biological agents rather than chemotherapy or using radiation alone with no systemic therapy. If surgery is a standard approach, deintensification could include reducing the extent of surgery (or avoiding it altogether) or reducing the amount of adjuvant treatment (lower radiation dose, less chemotherapy)

Any deintensified approach would need to look carefully at acute and long term toxicity to prove that treatment was less intense and to look at survival and local recurrence rates to ensure these were not compromised.

Because HPV+ disease has only recently been recognised, this deintensification approach is a recent idea (within the last 6 years or so). Prospective RCTs are currently being designed and carried out in the UK and worldwide but final results are unlikely to be published by the time the guidleline is written. There may be retrospective data analyses to support the idea of deintensification.

Recommendations could include carrying out further research (including comments on the outcomes to be studied) or to consider reducing treatment in certain subgroups.

1

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults diagnosed with HPV-positive cancer of the upper aerodigestive tract Subgroups: • Site • Stage	• Radiotherapy (altered fractionation) • Chemotherapy (induction/neo-adjuvant and concomitant) • Other systemic therapies (e.g. lapatinib, EGFR antagonists) • Surgery (trans oral or open) • Combinations of above	Standard dose chemoradiotherapy	• Overall survival • Event free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Health related quality of life
Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.	
Search strategies	Searches will be conducted from 2000 onwards	According to the GDG, this is the date of publication for the earliest evidence on this topic.
Useful search terms		
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used.	

	Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.	
Identified papers		
Amendments		

1

2

Chapter 6. Less-common upper aerodigestive tract cancers

Review question	What is the most effective curative treatment for carcinoma of the nasopharynx? (Review question G1)
Subgroup members	**Lead:** Sheerang Bhide **Subgroup:**Wai Lup Wong; Sarah Orr; Margred Capel
Economic priority	Low

Background

Carcinoma of nasopharynx is rare and makes up approximately 2-3% of all head and neck cancers (HNC) diagnosed in the UK. The disease has a much higher prevalence in Southeast Asia. WHO classification is most commonly used for histological classification. The classification is based on differentiation of disease and ranges from type I-III, with type I being well differentiated and type III being undifferentiated. Type III is associated with Ebstein-Barr virus (EBV) in majority of the cases (>90%). Type I &II are associated with classical HNC causative factors like smoking and alcohol ingestion. Type I disease is more common in Caucasians and type III in Southeast Asians. Nasopharyngeal carcinoma is distinct from other head and neck squamous carcinomas in terms of natural history and response to treatment. Stage for stage it carries a better prognosis (type III in particular). This is reflected in a distinct TNM staging system.

Treatment of nasopharyngeal cancer is primarily non-surgical. Surgery may be used for debulking disease prior to or on disease recurrence following radical treatment. Various combinations of induction chemotherapy, radical radiotherapy +/-concomitant chemotherapy are used for non-surgical treatments. This results in a 90% and 85% 5-year survival for Stage I and IIa disease respectively. The 5-year survival for higher stage disease is lower. The benefits of adding chemotherapy to radiation for advanced disease (stage IIb and above) are well proven in systematic reviews and meta-analyses. There is a lack of consensus on the benefits of adding chemotherapy to radiation for early stage (I and IIa) disease.

Given the position of the nasopharynx in close proximity to the visual structures (optic nerve, chiasm, eyeballs and lenses), pituitary gland, brain stem, cochlea and temporal lobe, chemo-radiation carries significant long-term morbidity and altered QOL.

Questions:

1) What is the role of chemotherapy in early stage nasopharyngeal carcinoma?

2) Does surgery have a role in curative treatment of nasopharyngeal carcinoma?

3) Which curative treatment offers the highest probability of cure, with minimal side effects?

Detailed structured review of evidence will enable recommendations to be made on optimum treatment, that carries the lowest morbidity.

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults diagnosed with newly diagnosed non-metastatic carcinoma of the nasopharynx Subgroups: • EBV status (type 3 WHO pathology) • Early stage (stage 1 and 2a) • Advanced stage (stage 2b, 3 and 4)	• Radiotherapy (altered fractionation, brachytherapy) • Chemotherapy (induction/neo-adjuvant and concomitant) • Other systemic therapies (e.g. lapatinib, EGFR antagonists) • Combinations of above) • Surgery	Each other	• Overall survival • Disease free survival • Progression free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Organ preservation rates • Health related quality of life
Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour site of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour site, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10; At least 75% of the included patients meet the population defined in the PICO.	
Search strategies	Search from 1994 onwards.	The GDG are not aware of any relevant evidence published before this date.
Useful search terms		

Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.	
Identified papers		
Amendments	Inclusion/exclusion criteria for studies not limited to the tumour site of interest added, for consistency with other similar review questions. Some amendments to the wording of outcomes for consistency with other similar review questions.	

1

2

Review question	What is the optimal role and timing (in relation to other treatments) of surgery in the management of paranasal sinus carcinoma? (Review question H1)
Subgroup members	**Lead:** Loz Newman **Subgroup:**Leah Cox; Michael Fenlon; Tom Rocques
Economic priority	Low

Background

The management of patients with carcinoma of the nose & paranasal sinuses presents significant surgical challenges, often confering significant patient morbidity. Treatment following low-level maxillectomy (use Brown's classification throughout – this is a Class 2 case) involves either obturation - with essesntially an extended denture – or complex free flap reconstruction with or without the sequential placement of osseointegrated implants to facilitate oral rehabilitation to enable the restoration of form & function. This mitigates the use of a composite free flap i.e. including bone, which is not universally practised in the UK. With Brown level 3 or 4 resections the perceived oncological benefit of eye removal (exenteration or enucleation) requires further analysis as very often in squamous cell carcinoma the eye, although removed, has not been infiltrated by carcinoma. This has significant cost implications plus potential detrimental quality of life issues. Comparisons should be made between the financial costs and quality of life issues between obturation and free flap reconstruction. There is a feeling that the ability to satisfactorily reconstruct a maxillectomy defect allows surgeons to perform a more radical tumour clearance and therefore achieve better survival outcome. This requires quantification.

If maxillary reconstruction is to be performed are there any survival benefits in delaying reconstruction until pathological confirmation of complete tumour removal is available? Such an approach requires a second operation with obvious manpower and cost implications. Additionally in reconstructed cases the primary tumour site can only be visualised with cross sectional imaging whereas obturated cases can have direct visual inspection. Whilst there seems to be little evidence to support one technique over the other there are obvious fiscal considerations re scanning – and how frequently should scans be performed?

Adjuvant radiotherapy is usually recommended after surgery to improve local control rates. But the optimal sequencing of therapy in borderline resectable disease is unclear. Could pre-op chemotherapy, radiotherapy or chemoradiation reduce the morbidity of surgery? If a tumour is inoperable because of local invasion but responds well to (chemo)radiation, is there then a role for surgery to remove residual disease?

1

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults diagnosed with new carcinoma of the paranasal sinuses in whom surgery is indicated. Subgroups: • Stage • Histology	• Radiotherapy (altered fractionation, bracytherapy) • Surgery (+/- obturator; +/- reconstruction; endoscopic or open surgery) (including timing of surgery) • Chemotherapy (induction/neo-adjuvant and concomitant) • Other systemic therapies (e.g. lapatinib, EGFR antagonists) • Combinations of above	Each other	• Overall survival • Disease free survival • Progression free survival • Tumour recurrence • Treatment related mortality • Treatment related morbidity • Eye/organ preservation rates • Health related quality of life
Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Retrospective studies comparing interventions will be included where a minimum of 10 patients received each studied intervention. Prospective studies of any population size will be included. For studies where only some of the population meets the definition in the PICO, studies will be included only if subgroup analysis of the relevant patients alone is possible, or the proportion of patients relevant to the PICO is <75%. Studies of patients with secondary tumours in the nose/paranasal sinuses will be excluded. Studies focussing on curative treatment only will be included; studies of patients receiving	

	palliative care will be excluded. Melanoma and olfactory neuroblastoma will be excluded (see notes in the review strategy on included histopathologies). Inverting papilloma will also be excluded as this is a precancerous condition.	
Search strategies	Limit search to 1994 onwards. According to the GDG, this is the date of publication for the earliest evidence on this topic.	
Useful search terms		
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing of surgery as an intervention will be an important consideration for this review. The timing, dose, duration, and sequence of other interventions will be considered where relevant evidence is available. The histopathology of nasal sinus tumours will be considered. Evidence is expected to focus on the treatment of squamous cell carcinoma, but tumours of other carcinoma histopathologies (adenoid cystic carcinoma, sinonasal undifferentiated carcinoma, adenocarcinoma) will be included in the review, and subgroup analyses carried out by histopathology if possible.	

Identified papers	
Amendments	Inclusion/exclusion criteria for studies not limited to the tumour site of interest added, for consistency with other similar review questions. Addition exclusion criteria added to keep the review manageable in size and include only the better quality evidence. Some amendments to the wording of outcomes for consistency with other similar review questions. Some details added to the definition of the population to remove any ambiguities, following clarifications from the GDG.

1

Review question	What is the most effective treatment for unknown primary of presumed upper airways tract origin (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)? (Review question J1)
Subgroup members	**Lead:** Sheerang Bhide **Subgroup**: Selvam Thavaraj; Stephen Spragget; Stuart Winter
Economic priority	Low

Background

Squamous cell carcinoma of unknown primary site (SCCUP) metastatic to cervical lymph nodes at presentation is a relatively rare entity forming about 2% of all head and neck carcinomas. The reported incidence of these tumours has declined in recent years with improved diagnostic and imaging techniques. The majority of patients present with unilateral lymph node metastases. The commonest sites are the level II and III cervical nodes. Metastases in levels I, IV, and V are less frequent.

Typically patients are treated with ipsilateral modified radical neck dissection (MRND) and post-operative radiotherapy/chemoradiotherapy (PORT/POCRT) or primary chemoradiotherapy (CRT). There is a lack of consensus on the optimal management of SCCUP and a wide variation in practice exists. In addition, with HPV (p16) testing now standard, an increasing proportion of these patients are HPV positive. Given that HPV positive SCC arises in the oropharynx in majority of patients, should HPV positive SCCUP be treated as primary oropharyngeal HPV positive disease?

In addition, there is a lack of consensus on the radiotherapy target volumes that should be treated after neck dissection. The most common radiotherapy techniques are either unilateral cervical lymph node irradiation to achieve local control in the ipsilateral neck or total mucosal irradiation (TMI) of the head and neck region with the aim of eradicating the primary and the microscopic neck disease. The rate of emergence of the primary tumour is approximately 3% per year, which is equivalent to the development of second primary carcinomas in the head and neck, lung, oesophagus or lung. Therefore, the primary aim of treatment is loco-regional control.

Treatment of the ipsilateral hemi-neck alone is of low toxicity and may achieve local control in the cervical nodes. Potential occult primary sites in the head and neck mucosa, and any sub-clinical metastatic disease in the contralateral side of the neck are left untreated. If a primary tumour subsequently becomes apparent in the head and neck region or there is a overt metastatic disease in the contralateral neck, the previous radiotherapy may make further radiotherapy difficult to deliver.

The study reporting on the largest case series (Grau et. al. 2000) with 350 patients showed that the risk of

locoregional recurrence was twice as likely for patients receiving ipsilateral nodal irradiation as compared to TMI. In addition a systemic review of the published literature performed by Neider et al (2001) showed that the median neck relapse rate was 19% for the TMI group versus 51.5% for unilateral neck irradiation. Therefore some groups recommend bilateral neck and total mucosal irradiation in this setting.

Conventional radiotherapy technique leads to significant acute toxicity and chronic morbidity, mainly xerostomia with its associated complications and effects on quality of life (QOL). IMRT has been shown to reduce the dose to salivary gland tissue and consequently may reduce the incidence of xerostomia and improve quality of life (QOL) in head and neck cancer patients and is a standard of care for SCCUP.

Questions:

1) What is the optimal first line treatment (surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies) for SCCUP?

2) What are the optimal radiotherapy fields (ipsilateral versus TMI irradiation)?

3) Should HPV positive SCCUP be treated as oropharyngeal carcinoma?

Detailed structured review of evidence will enable recommendations to be made on optimum treatment, that carries the lowest morbidity.

PICO table

Population	**Intervention**	**Comparison**	**Outcomes**

Adults presenting with metastatic neck disease (squamous cell carcinoma) and clinically occult primary presumed to be of upper aerodigestive tract origin
 	
Subgroups:
• HPV status
• Tests performed
	• Primary site:
	  • active surveillance
	  • radiotherapy (total mucosal radiation or sub site limited)
	• Neck:
	  • surgery (neck dissection)
	  • radiotherapy
	  • chemotherapy
	  • other systemic therapies
	  • combinations of the above
	• Radical surgical clearance plus chemoradiotherapy
	• Radiotherapy
	• Chemoradiotherapy
		Each other	• Overall survival
			• Disease free survival
			• Progression free survival
			• Tumour recurrence in the neck
			• Emergence of primary site
			• Treatment related mortality
			• Organ preservation rates
			• Treatment related morbidity
			• Health related quality of life

Additional comments on PICO			

	Details	Additional Comments
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Studies that are not limited to the tumour type of interest but include broader 'head and neck' patients will only be included where either: Results are reported separately for each tumour type, subgroup analysis is possible, and the number of patients relevant to the review with data available is ≥10; At least 75% of the included patients meet the population defined in the PICO.	
Search strategies	Search from 1994 onwards.	According to the GDG, this is the date of publication for the earliest evidence on this topic.
Useful search terms		
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.	
Identified papers		
Amendments	Inclusion/exclusion criteria for studies not limited to the tumour site of interest added, for consistency with other similar review questions.	

	Some amendments to the wording of outcomes for consistency with other similar review questions.

1

Review question	What is the optimal locoregional treatment for newly diagnosed upper airways tract mucosal melanoma in the absence of systemic metastases? (Review question L1)
Subgroup members	**Lead:** Stuart Winter **Subgroup:** Selvam Thavaraj, Shreerang Bhide
Economic priority	Low
Background	

Upper airways tract mucosal melanoma represents a small but important subset of head and neck tumours and a small subset of cutaneous melanoma tumours. The exact aetiology of these tumours is not known. However it is unlikely that sunlight (UV radiation) is as important as it is for cutaneous melanoma.

While cutaneous melanoma is often seen in the setting of a skin MDT and treated by an appropriate specialist mucosal melanoma of the upper airways is usually treated within a Head and neck MDT. As such there is a wide variety of practice nationally with no agreed protocols.

There is currently no consensus on the optimal treatment for the primary tumour. Currently surgery, radiotherapy, chemo-radiotherapy or chemotherapy alone or in combination is advocated. Each of these modalities has different consequences for the patient both in terms of loco-regional control and quality of life.

The extent of surgery depends on the site and extent of the primary disease and is also dictated by the size of the margin surrounding the tumour that the surgeon is trying to achieve. Surgery may result in considerable functional and quality of life changes for the patient.

Chemo-radiotherapy, either alone or in combination may also result in functional and quality of life changes and without knowing the benefits to the patient in terms of disease control it can be difficult to counsel the patient.

There is also no consensus on the optimal treatment for regional nodes, including which nodal groups to treat or how best to treat them. This is true for proven nodal spread and in the node negative neck. The treatments commonly advocated are again surgery, radiotherapy, chemo-radiotherapy or chemotherapy alone or in combination.

There are an increasing number of new treatments being trialled for cutaneous melanoma. It is not known if these would be effective for upper airways tract mucosal melanoma.

It is a recognised clinical problem that long term loco-regional control can be difficult to achieve and relapse within the head and neck is common. The aim of these guidelines would be to provide a clear guidance on the treatment of this disease.

2

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**

Adults with newly diagnosed upper airways tract mucosal melanoma in the absence of systemic metastases.
 	
Subgroups:
• Primary site
  • Sinonasal
  • Other sites
	• Primary site surgery
	• Primary site surgery plus post operative radiotherapy
	• Primary site radiotherapy
	• Elective Neck dissection
	• Therapeutic neck dissection
	• Elective radiotherapy to the neck
	• Therapeutic radiotherapy to the neck
	• Adjuvant radiotherapy to the neck
	• Adjuvant biological therapies
	• Chemotherapy
	• Chemoradiotherapy
	• Combinations of the above
		Each other	• Overall survival
			• Disease free survival
			• Progression free survival
			• Treatment related mortality
			• Treatment related morbidity
			• Health related quality of life
			• Locoregional control

Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.	
Search strategies		
Useful search terms		
Review strategies	The evidence tables for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using	

	GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Differences in timing or frequency of radiotherapy, and type of surgery, may also be considered within the review.	
Identified papers		
Amendments		

1

2

Chapter 7. Rehabilitation and optimising function

Review question	What criteria should be used at the point of diagnosis to select patients requiring enteral nutritional support during curative treatment? (Review question Q1)
Subgroup members	**Lead:** Bella Talwar **Subgroup:** Margred Capel, Tom Roques
Economic priority	N/A

Background

Why is this topic contentious? Is there disagreement between healthcare professionals or variation in practice across the UK?

There is consensus with recognising the importance of nutrition in the head and neck cancer population, the effects of treatment on a patients ability to eat and drink and the need for dietetic support to meet nutrition support goals. Nutritional plans instigated before, during and after treatment prevent malnutrition. The consequences of malnutrition include risk of infections, poor wound healing, prolonged hospital stay, poor patient experience, reduced tolerance or interruption to treatment, delayed recovery and survival, quality of life and health care cost. Therefore nutritional management should be incorporated into the decision of every patient at the point of diagnosis.

The need for alternative supplementary tube feeding is well accepted but the decision for type of tube is a current controversial area amongst clinicians leading to variation in practice with dietetic intervention along the pathway and methods of nutrition support (nasogastric v gastrostomy tube). Gastrostomy use as a measure of swallowing outcomes and the presence of a feeding tube for quality of life (QOL) have led to the concept of gastrostomy dependency and a perceived association with poorer outcomes. The multidimensional contributors have been inadequately explored leaving this phenomenon poorly defined and misinterpreted. Best practice nutritional care incorporates malnutrition screening and nutritional assessment using validated tools, early referral to the dietitian and ongoing monitoring to optimize nutritional status throughout the patient's entire care pathway.

NICE, Nutrition Support Guideline suggest that a gastrostomy tube should be recommended if alternative feeding is required for greater than 4 weeks over a nasogastric tube which should be used for less than 4 weeks. In the head and neck population the optimal timing and method of tube feeding remains unclear due to challenges with study design, but improved benefits have been demonstrated with prophylactic tube feeding.

Variation with clinical opinion exists with the following areas as a consequence:

- Selection criteria in the decision for tube placement with a short term (Nasogastric) or long term (Gastrostomy) feeding tube and the most appropriate time to have this inserted and intervention to manage
- Defining prophylactic tube feeding and therefore the optimal timing for tube insertion
- Screening and assessment for gastrostomy placement method (Percutanious v Radiological v Surgical) and complications
- Organisational accountability for tube feeding within head and neck services from the point of decision making to counselling the patient and carer, dietetic assessment and monitoring from insertion to removal of feeding tubes, rehabilitation for swallowing as a joint approach with the speech and language therapist. This will help prevent delays with rehabilitation, manage patients

nutritional status, and understand other contributing factors towards 'gastrostomy dependancy' relating to the effects of treatment and organisational management within the nutrition pathway
- Dietetic intervention from the point of diagnosis, during treatment and rehabilitation, long term care
- Resource investment for managing different methods of nutrition support both in the hospital and community

What are the benefits and harms of the alternative treatments or tests?

This will relate to malnutrition related morbidity which includes risk of infections, poor wound healing, prolonged hospital stay, poor patient experience, reduced tolerance or interruption to treatment, delayed recovery / rehabilitation and contribute to overall survival, quality of life and healthcare costs.

What kind of recommendations could you imagine yourself making following the evidence review?

Criteria for selection of relating to the following factors:

- nutrition
- swallowing
- performance status
- patient demographics
- TNM staging and site
- Radiotherapy / chemoradiotherapy treatment volumes and dose
- Surgical procedures
- Screening and assessment for choice of gastrostomy

Organisational structure for head and neck tube feeding services relating to:

- Nutrition and swallowing management pathway
- enteral tube feeding pathway
- integrated service requirements with gastroenterology and radiology

PICO table

Population	**Factors**	**Outcomes**
Adults who are receiving curative treatment for cancer of the upper aerodigestive tract.	• Patient demographics • Nutritional factors • Tumour site & staging • Treatment (all combinations) • Predicted complications of placement • Swallowing factors • Quality of life	• Malnutrition related morbidity
Additional comments on PICO		

	Details	**Additional Comments**
Type of review	Prognostic	
Language	English only	
Study design	No restrictions	

Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.	
Search strategies	1990	According to the GDG, this is the date of publication for the earliest evidence on this topic.
Useful search terms		
Review strategies	The evidence table for prognostic studies will be used (NICE Guidelines Manual Appendix J) to extract and present results from individual studies. The quality checklists for prognostic studies from the NICE Guidelines Manual (appendix I) will be used.	
Identified papers		
Amendments		

1

2

Review question	Which active speech and language therapy interventions are of most benefit to patients with cancer of the upper aerodigestive tract? (Review question Q2)
Subgroup members	**Lead:** Jane Thornton **Subgroup:** Tony Smith, Bella Talwar
Economic priority	Low

Background

Speech and Language therapists are core members of the MDT (IOG 2004) and care pathways developed by Cancer Action Team (1), RCSLT(2) and ENT UK (3) detail how their input is indicated at all stages of the patient pathway. However, the detail of what SLT is carried out is variable across the country. Whilst most services will have contact with a named SLT (peer review validated) some services will have only limited cover with regards to location, stage of pathway or site of cancer. In the main, the reasons for inconsistency tend to be related to staffing resource rather than evidence based practice although there are assumptions that certain surgeries e.g. maxillectomy, certain stages of the pathway e.g. pre radiotherapy do not need to see SLT . Therefore the amount, type and timing of different SLT active interventions needs to be looked at to enable resources to be targeted most appropriately for both the patient and the service. There is also a growing concern from patients and staff that the centralisation of services has resulted in a de-skilled local workforce therefore the links with central teams and ongoing training is seen as an intervention that should be encouraged.

In recent years there has been an increase in patients with head and neck cancer and this together with the changes in treatment regimens has meant that there are more people experiencing different (e.g. increase in effect on voice of IMRT) more severe (e.g. aphagia) and protracted difficulties with swallowing (dysphagia). It would be useful for services to know when and where to target active SLT assessment and management and what particular therapies work instead of taking a more general approach which may have either no impact or a negative impact on the patient both in mood and performance if therapies are introduced too early/late with resulting lack of progress.

The main contentious issues at present are

- Prophylactic pre radiotherapy exercises: what and when. Are swallowing function and trismus reduced by having this or do patients have enough to cope with without taking on any extra activity at this time?
- Which particular diagnostic groups need to be seen. E.g. do SLT need to see all sites?
- Length of continuation of range of movement/swallowing exercises post treatment. Is there any benefit in reducing late effects?
- SLT input during radiotherapy; type and frequency
- Benefits/harm of certain types of HME/filtration and when they're introduced
- Specific versus direct exercise regimes
- How to manage return to oral diet (classic post CRT when swallow is 'safe' but alteration in taste/texture intolerance prevents individuals eating/drinking)

- Joint working with the dietitian for swallowing rehabilitation
- Timing of commencement of oral diet and voice trials in laryngectomy (not sure this is in this section, determined by surgical team)

By looking at the above it is hoped that SLTs will have guidance on when to intervene, with whom and for what duration to maximise patient performance.

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults with a diagnosis of cancer of the upper aerodigestive tract. Subgroups: • Site • Tumour stage • Point on care pathway • Treatment modality	Active speech and language support • FEES (functional endoscopic evaluation of swallowing) • Swallowing exercises • Range of motion exercises	Each other Nothing	• Voice quality • Speech intelligibilty • Oral diet • Good mouth opening • Reduced aspiration rates • Safe swallow • Dysphagia • Quality of life • Enteral feeding
Additional comments on PICO	Different timings, combinations and durations of treatment will also be considered if available.		

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.	
Search strategies	Search from 2000 onwards	According to the GDG, this is the date of publication for the earliest evidence on this topic.
Useful search terms	VF/MBS,FEES,Prophylactic, Range of motion exercises,Dysphagia, Taste, Mendlesohn, Masako,Voice quality/dysphonia ,Speech, intelligibility, Oral diet/intake, trismus, aspiration, Quality of life, HME/filtration • Videofluoroscopy • Modified barium swallow	

Review strategies	The evidence tables for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, and duration of treatment will be important considerations for the review.	
Identified papers		
Amendments		

1

Review question	What are the most effective interventions for shoulder rehabilitation following neck dissection in people with cancer of the upper aerodigestive tract? (Review question O2)
Subgroup members	**Lead:** Loz Newman **Subgroup:** Margred Capel; Loz Newman; Sarah Orr; Jane Thornton
Economic priority	Low
Background	
The spinal accessory nerve (XI cranial nerve) is at risk during neck dissection. In a traditional radical neck dissection this nerve would be sacrificed electively (neurotmesis), but today's surgeons invariably attempt to preserve it in performing either modified radical neck dissections or selective neck dissections. Even if the nerve is preserved shoulder function may be compromised due to nerve injury – neuropraxia or axonotmesis. The shoulder consequently becomes painful with significant restriction in function adversely affecting quality of life. There is no consensus as to the best way of dealing with this issue – shoulder syndrome. There are various ways of grading the injury (e.g. the Oxford Shoulder Score). Equally the ways that this condition in managed is variable. The incidence of this injury should be evaluated. A universal shoulder scoring system should be adopted by head and neck surgeons and best evidence should dictate best practice as to shoulder rehabilitation.	

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults with cancer of the upper aerodigestive tract and shoulder dysfunction following neck dissection.	Therapeutic exercises: • Range of motion exercise • Progressive resistance training • Proprioceptive neuromuscular facilitation exercise Standard physiotherapy/standard care Nerve exploration +/- repair	Each other	• Shoulder function • Shoulder pain • Shoulder disability • Quality of life • Adverse events
Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.	
Search strategies	Search from 1994 onwards.	According to the GDG, this is the date of publication for the earliest evidence on this topic.
Useful search terms		
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Quality checklists for RCTs, observational studies (NICE manual Appendix C) and meta-analysis and systematic reviews (NICE manual Appendix B) will be used	

	Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review	
Identified papers		
Amendments		

1

2

Chapter 8. Follow-up of people with cancer of the upper aerodigestive tract and management of osteoradionecrosis (ORN)

Review question	In people who are clinically disease free and who have undergone treatment for squamous cell cancer of the upper aerodigestive tract with curative intent, what is the optimal method(s), frequency, and duration of follow-up? (Review question M1)
Subgroup members	**Lead:** Bella Talwar **Subgroup:** Tony Smith, Vin Paleri
Economic priority	High

Background

- *Why is this topic contentious? Is there disagreement between healthcare professionals or variation in practice across the UK?*

The principles of care are evaluation of treatment response, identification of recurrence, detection of new primary tumours, monitoring and managing of complications, optimisation of rehabilitation and provision of support to patients and their families.

Controversies exist with organisation and structure of clinics being arbitrary and reflects institutional and clinician led practices with minimal evidence to support one system.

The areas of focus for consideration include follow up length of time, frequency, setting, type of health care professional, clinical assessments, screening investigations. Other considerations include attention to tumour markers and patient education.

- *What are the benefits and harms of the alternative treatments or tests?*

Benefits to standardising care, reducing waste, improved MDT working, patient and clinical outcomes with financial efficiency.

- *What kind of recommendations could you imagine yourself making following the evidence review?*

Evidence based guidance with length of time, frequency, setting, type of health care professional, clinical assessments, and screening investigations.

A triage system of high and low risk patients follow up

Skill mixing and organisational cross working for a seamless pathway of care across a geographical remit.

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**

Adults who have undergone curative treatment for squamous cell cancer of the upper aerodigestive tract.
 	
Subgroups:
 	
• HPV status
• Smokers
• Site
• Staging
• Treatment modality
	• Protocols involving:
	  • MRI
	  • CT
	  • PET/PET-CT
	  • US
	  • chest X-ray
	  • thyroid function testing
	  • oesophagoscopy
	  • clinical examination
	  • with or without narrow band imaging
	• Non-medic led clinic
	• Remote surveillance (e.g. telephone/online/postal consultation)
		Each other	• Stage of disease at recurrence
			• Detection of second primary
			• Overall survival
			• Progression free survival
			• Disease-specific survival
			• Process related complications
			• Health-related quality of life

Additional comments on PICO	Studies using a single technique/protocol but comparing different timings and/or frequencies of follow up would also meet the inclusion criteria for this review.		

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded.	
Search strategies		
Useful search terms		
Review strategies	The evidence tables for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when appropriate and presented as risk ratios for the	

	identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. Additionally, any differences in timing, frequency and duration of follow up protocol will be considered within the review and subgroup analyses conducted where possible.	
Identified papers		
Amendments		

1

2

Review question	What are the most effective methods of managing osteoradionecrosis following treatment of cancer of the upper aerodigestive tract? (Review question O1)
Subgroup members	**Lead:** Michael Fenlon **Subgroup:** Bella Talwar, Loz Newman, Sarah Orr
Economic priority	Medium

Background

Osteoradionecrosis of the jaws (ORN) is a devastating condition that affects the mandible (lower jaw) more frequently than the maxilla (upper jaw). It is a condition where without doubt prevention is better than cure. However access to quality dental care, which is necessary for prevention, is often a problem for head and neck cancer patients who often come from areas of social deprivation.

Once ORN is established the treatment options essentially are medical management and/or surgical management. Marx was the exponent of treating ORN with hyperbaric oxygen HBO – but this is extremely expensive (most PCTs/CCGs baulk at the thought of funding). There is limited access to diving chambers and HBO usage is highly controversial in terms of efficacy (Annane)

Medical therapy with tocopherol and pentoxyphylline was popularised by Delanian but its use is variable and outcomes are inconsistent.

The mainstay of treatment is surgical debridement with or without reconstruction. The success rates of dental osseointegrated implants is debated in patients who are post-radiotherapy.

We should look at HBO alone and in conjunction with surgery. In Marx's group only around 15% of cases had HBO alone – and the potential benefits of HBO + surgery may have been minimised.

HBO is extremely expensive (both financially to the purchaser and also to the patient in terms of time spent usually away from home) especially if used in conjunction with microvascular free tissue transfer. How can this benefit be measured?

1

PICO table			
Population	**Intervention**	**Comparison**	**Outcomes**

Adults who have been treated for cancer of the upper aerodigestive tract and have developed osteoradionecrosis of the jaws	• Hyperbaric oxygen
	• Surgical intervention:
	  • Debridement
	  • Sequestrectomy
	  • Segmental resection
	  • Rim resection
	  • Free flap reconstruction +/- implant rehabilitation
	• Nutritional support:
	  • Oral nutrition
	  • Enteral nutrition
	• Medical management:
	  • Tocopherol
	  • Pentoxyphylline
	• Smoking cessation
	• Observation
	• Combinations of the above
		Each other
		
		Placebo/sham treatment
			• Symptom control
			• Quality of life
			• Treatment related morbidity
			• Jaw preservation rates
			• Mucosal integrity
			• Fistula closure
			• Trismus
			• Oral intake
			• Nutritional status

Additional comments on PICO			

	Details	**Additional Comments**
Type of review	Intervention	
Language	English only	
Study design	Randomised controlled trials and observational studies.	
Status	Published data only	
Other criteria for inclusion / exclusion of studies	Non-comparative case reports and case series will be excluded. Retrospective case series that use more than one intervention will be included only where results are reported for a mimimum of 10 patients per intervention.	
Search strategies	Search from 1981 onwards – this was the date of publication of a key paper which began research in this field (see identified papers).	
Useful search terms		
Review strategies	The evidence table for intervention studies will be used (NICE Guidelines Manual Appendix J and K) to extract and present results from individual studies. Results for each outcome/comparison will be presented using GRADE. RCT data will be pooled when	

	appropriate and presented as risk ratios for the identified outcomes. Quality checklists from the NICE Guidelines Manual (appendices B–E) will be used. Where possible, evidence will be analysed according to the subgroups specified in the PICO, and also by gender. The timing, frequency, dose and duration of treatment will be important considerations for the review.	
Identified papers	J Oral Surg. 1981 Aug;39(8):585-9. Hyperbaric oxygen as an adjunct in the treatment of osteoradionecrosis of the mandible. Mansfield MJ, Sanders DW, Heimbach RD, Marx RE	
Amendments	'Placebo or sham treatment' has been added as a comparison, to allow unambiguous inclusion of trials using this as a comparator. Exclusion criteria added to include only the higher quality evidence available and keep the evidence review to a manageable size. Some detail added to the PICO population to remove ambiguity.	

1

2

11. Excluded Health Economic Papers

Afrogheh CA, Wright SL, Sellars J, Wetter A, Pelser P, Schubert T, Hille J. An evaluation of the Shandon Papspin liquid-based oral test using a novel cytologic scoring system. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 113 (6):799-807, 2012.

Reason for exclusion: Not a cost-utility analysis

Annunziata S, Caldarella C, Treglia G. "Cost-effectiveness of Fluorine-18-Fluorodeoxyglucose positron emission tomography in tumours other than lung cancer: A systematic review." World Journal of Radiology 6.3 (2014): 48-55.

Reason for exclusion: Review of existing studies, not a de novo cost-effectiveness analysis.

Aviv JE, Sataloff RT, Cohen M, Spitzer J, Ma G, Bhayani R, Close LG. Cost-effectiveness of two types of dysphagia care in head and neck cancer: a preliminary report. *Ear, Nose and Throat Journal* 80(8):553-558: 2001. (Abstract).

Reason for exclusion: Not a cost-utility analysis

Bairati I and Meyer F. Health-related quality of life (HRQOL) of patients 3 years after radiation therapy (RT) for early head and neck cancer (HNC). *Journal of Clinical Oncology* 2011; 29(15 SUPPL. 1)

Reason for exclusion: Not cost-effectiveness analysis. Study obtained as potential source of utilities for use in model.

Bonastre MJ. The cost of intensity modulated radiation therapy in head and neck cancers: results of the 2002 STIC study. *Bulletin of Cancer* 2006; 93(10):1026-1032:

Reason for exclusion: Non-English language study. Not cost-utility analysis

Bongers V, Hobbelink MG, Rijk PP, Hordijk GJ. Cost-effectiveness of dual-head F-18-fluorodeoxyglucose PET for the detection of recurrent laryngeal cancer (Structured abstract). *Cancer Biotherapy.and Radiopharmaceuticals.* 17 (3):303-306, 2002.

Reason for exclusion: Not cost-utility analysis

Boughrassa F and Framarin A. Treatment of esophageal cancer: systematic review on surgical techniques (Structured abstract). *Health Technology Assessment Database* 2011;(2)

Reason for exclusion: Not a cost-utility analysis

Breeze J, Poller DN, Gibson D, Tilley EA, Cooke L, Soar E, Repanos C. "Rapid on-site assessment of specimens by biomedical scientists improves the quality of head and neck fine needle aspiration cytology." Cytopathology 25.5 (2014): 316-21.

Reason for exclusion: Not cost-effectiveness analysis. Cost analysis only.

Brentani A, de Castro G Jr., Federico MH. Cost-effectiveness analysis of cisplatin-based chemoradiation to treat patients with unresectable, nonmetastatic head and neck cancer in Brazil. *Head & Neck* 2011; 33(8): 1199-1205.

Reason for exclusion: Not a cost-utilty analysis

Brown B, Diamantopoulos A, Bernier J, Schoffski P, Hieke K, Mantovani L et al. An economic evaluation of cetuximab combined with radiotherapy for patients with locally advanced head and neck cancer in Belgium, France, Italy, Switzerland, and the United Kingdom (Structured abstract). *Value in Health* 2008; 11(5): 791-799.

Reason for exclusion: Not a cost-utility analysis.

Burgess C, Dias L, Maughan E, Moorthy R. "Neck lump clinics: is on-site assessment of fine needle aspirate diagnostic adequacy cost-effective?" Journal of Laryngology & Otology 127.11 (2013): 1122-26.

Reason for exclusion: Not cost-effectiveness analysis. Cost analysis only.

Byrd JK, Smith KJ, de Almeida JR, Albergotti WG, Davis KS, Kim SW, Johnson JT, Ferris RL, Duvvuri U. "Transoral robotic surgery and the unknown primary: A cost-effectiveness analysis." Otolaryngology - Head and Neck Surgery (United States) 150.6 (2014): 976-82.

Reason for exclusion: Not cost-utility analysis

Cappelli, C Pirola I, Gandossi E, Martino E, Agosti B, Castellano M. Fine-needle aspiration cytology of thyroid nodule: does the needle matter? *Southern Medical Journal* 2009; 102(5): 498-501.

Reason for exclusion: Not a cost-utility analysis

Can S. Cost-effectiveness comparison between palpation- and ultrasound-guided thyroid fine-needle aspiration biopsies (Provisional abstract). *BMC Endocrine Disorders* 9:14 (2), 2009.

Reason for exclusion: Not a cost-utility analysis

Carr MM. Communication after laryngectomy: an assessment of quality of life. *Otolaryngol.Head Neck Surg.* 122(1):39-43: 2000. (Abstract):

Reason for exclusion: Not cost-effectiveness analysis. Study obtained as potential source of utilities for use in model.

Chan AL, Leung HW, and Huang SF. Cost effectiveness of cetuximab concurrent with radiotherapy for patients with locally advanced head and neck cancer in Taiwan: a decision-tree analysis. *Clinical Drug Investigation* 2011; 31(10): 717-726.

Reason for exclusion: Not an OECD member country

Chang MY, Kamrava M, Demanes DJ, Leu M, Agazaryan N, Lamb J, et al. Intraoperative ultrasonography-guided positioning of iodine 125 plaque brachytherapy in the treatment of choroidal melanoma. *Ophthalmology* 119 (5):1073-1077, 2012.

Reason for exclusion: Melanoma, not head and neck cancer patient population.

Chiou WY, Lee MS, Ho HC, Hung SK, Lin HY, Su YC, Lee CC. Prognosticators and the relationship of depression and quality of life in head and neck cancer. *Indian J.Cancer* 50 (1):14-20, 2013.

Reason for exclusion: Not cost-effectiveness analysis. Study obtained as potential source of utilities for use in model.

Conway EL, Farmer KC, Lynch WJ, Rees GL, Wain G, Adams J. Quality of life valuations of HPV-associated cancer health states by the general population. *Sexually Transmitted Infections* 2012; 88(7): 517-521.:

Reason for exclusion: Topic not covered in guideline

Coughlan D and Frick KD. Economic impact of human papillomavirus-associated head and neck cancers in the United States. [Review]. *Otolaryngol.Clin.North Am.* 45 (4):899-917, 2012.

Reason for exclusion: Not a cost-utility analysis

de Almeida JR, Villanueva NL, Moskowitz AJ, Miles BA, Teng MS, Sikora A, Gupta V, Posner M, Genden EM. "Preferences and utilities for health states after treatment for oropharyngeal cancer: transoral robotic surgery versus definitive (chemo)radiotherapy." Head & Neck 36.7 (2014): 923-33.

Reason for exclusion: Not cost-effectiveness analysis. Study obtained as potential source of utilities for use in model.

de Leeuw J, Prins JB, Teerenstra S, Merkx MA, Marres HA, van Achterberg T. Nurse-led follow-up care for head and neck cancer patients: a quasi-experimental prospective trial. *Support.Care Cancer* 21 (2):537-547, 2013.

Reason for exclusion: Not a cost-utility analysis

De Oliveira KG, Bissoli NS, De Podesta JRV, Souza ED, Lenzi J, Sena A, et al. The relationships among pain, symptoms, and analgesics in head and neck cancer patients. *Oral Oncol.* 49:S95-S96, 2013.

Reason for exclusion: Conference abstract

DeRose ER, Pleet A, Wang W, Seery VJ, Lee MY, Renzi S, et al. Utility of 3-year torso computed tomography and head imaging in asymptomatic patients with high-risk melanoma. *Melanoma Res.* 21 (4):364-369, 2011.

Reason for exclusion: Melanoma, not head and neck cancer patient population.

De Souza JA, Santana IA, de Castro G Jr, de Lima Lopes G Jr, Tina Shih YC. "Economic analyses in squamous cell carcinoma of the head and neck: A review of the literature from a clinical perspective." International Journal of Radiation Oncology Biology Physics 89.5 (2014): 989-96.

Reason for exclusion: Review of existing studies. Not a de novo cost-effectiveness analysis.

Diaz-de-Cerio P, Preciado J, Santaolalla F, Sanchez-Del-Rey A. "Cost-minimisation and cost-effectiveness analysis comparing transoral CO2 laser cordectomy, laryngofissure cordectomy and radiotherapy for the treatment of T1-2, N0, M0 glottic carcinoma." European Archives of Oto-Rhino-Laryngology 270.4 (2013): 1181-88.

Reason for exclusion: Not a cost-utility analysis

Eskiizmir G and Cingi C. Nonmelanoma skin cancer of the head and neck: current diagnosis and treatment. [Review]. *Facial Plastic Surgery Clinics of North America* 20 (4):415-417, 2012.

Reason for exclusion: Not head and neck cancer covered in guideline.

Fernandes S, Bansal R, Bater M. An audit assessing the post-operative length of stay in head and neck cancer patients managed by the Maxillofacial Department at the Royal Surrey County Hospital. *Br.J.Oral Maxillofac.Surg.* 49:S55-S56, 2011.

Reason for exclusion: Conference abtract

Focht, K Simpson K, Day T, Martin-Harris B. Drs certificate of merit award markov modeling to evaluate pre-treatment swallowing exercises in head and neck cancer. *Dysphagia* 2012; 27(4): 595-596.

Reason for exclusion: Conference Abstract

Fountzilas G, Papakostas P, Dafni U, Makatsoris T, Karina M, Fountzila A, et al. Paclitaxel and gemcitabine vs. paclitaxel and pegylated liposomal doxorubicin in advanced non-nasopharyngeal head and neck cancer: an efficacy and cost analysis randomized study conducted by the Hellenic Cooperative Oncology Group (Structured abstract). *Ann.Oncol.* 17 (10):1560-1567, 2006.

Reason for exclusion: Not cost-utility analysis

Funk GF. Cost analysis in head and neck oncology. *Current Opinion in Otolaryngology & Head and Neck Surgery* 6:106-112: 1998. (Abstract).

Reason for exclusion: Not a cost-utility analysis

Gerke O, Hermansson R, Hess S, Schifter S, Vach W, Høilund-Carlsen PF. "Cost-effectiveness of PET and PET/computed tomography: A systematic review." PET Clinics 10.1 (2015): 105-24.

Reason for exclusion: Review of existing studies. Not a de novo cost-effectiveness analysis.

Goransson H, Rolin E, Wedmark C. Enteral feeding increases the well-being for patients with head and neck cancer undergoing radiation therapy and lower the cost in out-patient care. *Radiother.Oncol.* 98:S38, 2011.

Reason for exclusion: Conference abtract

Hannouf MB, Sehgal C, Cao J, Mocany JD, Winquist E, Zaric GS. Cost-effectiveness of adding cetuximab to platinum-based chemotherapy for first-line treatment of recurrent or metastatic head and neck cancer. *PLoS ONE [Electronic Resource]* 2012; 7(6): e38557:

Reason for exclusion: Decision problem not covered in guideline

Himmel M, Hartmann M, and Guntinas-Lichius O. Cost effectiveness of neoadjuvant chemotherapy in locally advanced operable head and neck cancer followed by surgery and postoperative radiotherapy: a markov model-based decision analysis. *Oncology* 2013; 84(6): 336-341.

Reason for exclusion: Not cost-utility analysis (life years are used in ICER calculations).

Hollenbeak, CS, Lowe, VJ, and Stack, BC. The cost-effectiveness of fluorodeoxyglucose 18-F positron emission tomography in the NO neck (Structured abstract). *Cancer* 2001; 92(9): 2341-2348.

Reason for exclusion: Not a topic covered in the guideline (similar topic in guideline considers clinically and *radiologically* N0 neck)

Hooren AC, Brouwer J, Bree R, Hoekstra OS, Leemans CR, Uyl-De-Groot CA. The cost-effectiveness of 18FDG-PET in selecting patients with suspicion of recurrent laryngeal carcinoma after radiotherapy for direct laryngoscopy. *European Archives of Oto Rhino Laryngology* 2009; 266(9): 1441-1448.

Reason for exclusion: Not a cost-utility analysis

Hopper C, Niziol C, and Sidhu M. The cost-effectiveness of Foscan mediated photodynamic therapy (Foscan-PDT) compared with extensive palliative surgery and palliative chemotherapy for patients with advanced head and neck cancer in the UK (Structured abstract). *European Journal of Cancer Part B Oral Oncology* 40 (4):372-382, 2004.

Reason for exclusion: Photodynamic therapy not covered in scope. Not cost-utility analysis (life years are used in ICER calculations).

Hsieh, CC and Chien, CW. A cost and benefit study of esophagectomy for patients with esophageal cancer (Provisional abstract). *Journal of Gastrointestinal Surgery* 2009; 13(10): 1806-1812.

Reason for exclusion: Oesophageal cancer not covered in guideline

Hyperbaric Oxygen Therapy (HBOT) for the prevention and treatment of osteoradionecrosis following radiotherapy of head and neck cancer (Structured abstract). *Health Technology Assessment Database* 2006;(2)

Reason for exclusion: Not a cost-utility analysis.

Jalisi S, Koch WM, Burkey BB, Couch ME. Economic aspects of head and neck oncologic surgery: Implications for the head and neck surgeon now and in the future. *Otolaryngol.Head Neck Surg.* 145:9, 2011.

Reason for exclusion: Conference abtract

Khalid AN, Quraishi SA, Hollenbeak CS, Stack BC. Fine-needle aspiration biopsy versus ultrasound-guided fine-needle aspiration biopsy: cost-effectiveness as a frontline diagnostic modality for solitary thyroid nodules (Structured abstract). *Head and Neck* 2008; 30(8): 1035-1039.

Reason for exclusion: Not a cost-utility analysis.

Khalid-Raja M and Uppal HAS. The cost effectiveness of running a rapid access neck lump clinic. *Clinical Otolaryngology* 2012; 37: 42

Reason for exclusion: Conference Abstract

Kim K, Amonkar MM, Hogberg D, Kasterig F. Economic burden of resected squamous cell carcinoma of the head and neck in an incident cohort of patients in the UK. *Head & neck oncology* 2011; 3: 47.

Reason for exclusion: Not a cost-utility analysis

Klussmann JP, Schadlich PK, Chen X, Remy V. Annual cost of hospitalization, inpatient rehabilitation, and sick leave for head and neck cancers in Germany. *Clinicoeconomics & Outcomes Research* 5:203-213, 2013.

Reason for exclusion: Not a cost-utility analysis

Kohler RE, Sheets NC, Wheeler SB, Nutting C, Hall E, Chera BS. "Two-year and lifetime cost-effectiveness of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for head-and-neck cancer." International Journal of Radiation Oncology Biology Physics 87.4 (2013): 683-89.

Reason for exclusion: Not directly relevant to topics in guideline as comparison of radiotherapy types was not explicitly considered.

Kurien G, Hu J, Harris J, Seikaly H. Cost-effectiveness of positron emission tomography/computed tomography in the management of advanced head and neck cancer. *Journal of Otolaryngology: Head and Neck Surgery* 2011; 40(6): 468-472.

Reason for exclusion: Not a cost-utility analysis

Lang K. The economic cost of squamous cell cancer of the head and neck: findings from linked SEER-Medicare data. *Archives of Otolaryngology - Head and Neck Surgery* 130(11):1269-1275: 2004. (Abstract)

Reason for exclusion: Not a cost-utility analysis

Laupacis, A, Paszat, L, and Hodgson, D. Health technology assessment of positron emission tomography in oncology - a systematic review (Structured abstract). *Health Technology Assessment Database* 2002;(2): 20

Reason for exclusion: Review of existing literature. Not a de novo cost-utility analysis

Lee TL, Wang LW, Mu-Hsin Chang P, Chu PY. Quality of life for patients with hypopharyngeal cancer after different therapeutic modalities. *Head and Neck* 2013; 35(2): 280-285.

Reason for exclusion: Not cost-effectiveness analysis. Study obtained as potential source of utilities for use in model.

Mui S, Li T, Rasgon BM, Hilsinger RL, Rumore G, Puligandla B, Sawicki J. Efficacy and cost-effectiveness of multihole fine-needle aspiration of head and neck masses (Structured abstract). *Laryngoscope* 107 (6):759-764, 1997.

Reason for exclusion: Not a cost-utility analysis

Naidu H, Noordzi JP, Samim A, Jalisi S, Grillone GA. Comparison of efficacy, safety, and cost-effectiveness of in-office cup forcep biopsies versus operating room biopsies for laryngopharyngeal tumors. *Journal of Voice* 2012; 26(5): 604-606.

Reason for exclusion: Topic not covered in guideline

Naik H, Howell D, Qiu X, Brown C, Vennettilli A, Irwin M, Pat V, Solomon H, Wang T, Hon H, Eng L, Mahler M, Tiessen K, Thai H, Ho V, Pringle D, Xu W, Seung SJ, Mittmann N, Liu G. "Canadian cancer site-specific health utility values: Creating the basis for measuring value and costs of therapy." Journal of Clinical Oncology Conference.var.pagings (2014).

Reason for exclusion: Not cost-effectiveness analysis. Study obtained as potential source of utilities for use in model.

O'Donnell ME, Salem A, Badger SA, Sharif MA, Kamalapurkar D, Lieo T, Spence RA. Fine needle aspiration at a Regional Head and Neck Clinic: A clinically beneficial and cost-effective service. *Cytopathology* 2009; 20:81-86

Reason for exclusion: Not a cost-utility analysis

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12. List of abbreviations

AC	Adjuvant chemotherapy
ACE-27	Adult Co-morbidity Evaluation 27
AJCC	American Joint Committee on Cancer
ANOVA	Analysis of variance
ASSESSA-FCS	American Shoulder and Elbow Surgeons Shoulder Assessment, functional component score
BDI	Beck Depression Inventory
BI	Burden interview
BIS	Body Image Scale
BMI	Body mass index
CAGE	Alcohol Screening Tool
C-C	Case–control
CCRT	Concomitant chemoradiotherapy
CES-D	Centre for Epidemiologic Studies Depression Scale
CHART	Continuous, hyperfractionated, accelerated radiotherapy
CI	Confidence interval
CNQ	Cancer Needs Questionnaire
CNQ-SF	Cancer Needs Questionnaire, short form
CNQ-sf-hn	Cancer Needs Questionnaire Short Form, head and neck
CQOLC	Caregiver Quality of Life Index
CRA	Caregiver Reaction Assessment
CRT	Chemoradiation therapy
CS	Cross-sectional
CSI	Caregiver Strain Index
CT	Computed tomography
CUADT	Cancer of the upper aerodigestive tract
DAS	Dyadic Adjustment Scale
DIC-2	Distress Inventory for Cancer, version 2
DNA	Deoxyribonucleic acid
DSS	Disease-specific survival
ECS	Extracapsular spread
EIA	Enzyme immunoassay
END	Elective neck dissection
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life – Core 30
EORTC QLQ-H&N35	European Organisation for Research and Treatment of Cancer Quality of Life – Head & Neck 35
EPHPP	Effective Public Health Practice Project
EVPI	Expected value of perfect information

F0	Fundamental frequency
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-HN	Functional Assessment of Cancer Therapy - Head and Neck
FAD	Family Assessment Device
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
FIN	Family Inventory of Needs
FNAC	Fine-needle aspiration cytology
FOIS	Functional intake scale
FOR	Fear of recurrence
GARS	Global Assessment of Recent Stress
GC	Guideline committee
GHQ-20	General Health Questionnaire
GRADE	Grading of recommendations, assessment, development and evaluation
G-tube	Gastrostomy tube
HADS	Hospital Depression and Anxiety Scale
HBO	Hyperbaric oxygen
HDI	High-dose interferon
HNC	Head and neck cancer
HNCI	Head and Neck Cancer Inventory
HNCNQ	Head and Neck Specific Cancer Needs Questionnaire
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HR	Hazard ratio
HR-HPV	High-risk human papillomavirus
HRQoL	Health related quality of life
HS-MOS	Health Survey of the Medical Outcomes Study-short form
IC	Induction chemotherapy
ICER	Incremental cost effectiveness ratio
IMRT	Intensity modulated radiotherapy
IQR	Interquartile range
ISH	In-situ hybridisation
ISSB	Inventory of Socially Supportive Behaviors
IV	Inverse variance
KPS	Karnofsky Performance Status
LETR	Linking evidence to recommendations
LOM	Limitation in opening mouth
LRF	Locoregional failure
MAC-Q	Mental Adjustment to Cancer Questionnaire
MASA	Mann assessment of swallowing ability
MAST	Michigan Alcohol Screening Test
MDADI	MD Anderson Dysphagia Inventory
MDT	Multidisciplinary team
M-H	Mantel-Haenszel

MHI	Mental Health Inventory
MIO	Maximum interincisal opening
MM-UADT	Mucosal melanoma of the upper aerodigestive tract
MRI	Magnetic resonance imaging
MSPSS	Multidimensional Scale of Perceived Social Support
MST	Malnutrition screening tool
NBI	Narrow band imaging
ND	Neck dissection
NNT	Number needed to treat
NPC	Nasopharyngeal carcinoma
NPV	Negative predictive value
NR	Not reported
OC	Oral cancer
OPSCC	Oropharyngeal squamous cell carcinoma
OPSE	Oropharyngeal swallowing efficiency
OR	Odds ratio
ORN	Osteoradionecrosis
OS	Overall survival
OSCC	Oral squamous cell carcinoma
PAIS-SR	Psychological Adjustment to Illness Scale-Self Report
PCI	Patient Concerns Inventory
PCR	Polymerase chain reaction
PCS	Prospective cohort study
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PICO	Population, intervention, comparator, outcome
PPV	Positive predictive value
PRT	Progressive resistance training
PSA	Probabilistic sensitivity analysis
PSS	Head and Neck Performance Status Scale
QALY	Quality adjusted life years
QLQ	Quality of life questionnaire
QoL	Quality of life
QUADAS	Quality assessment of diagnostic accuracy studies
RAND-36	Dutch Version of Short Form-36
R-C	Retrospective correlational
RCS	Retrospective cohort study
RCTs	Randomised controlled trials
RNA	Ribonucleic acid
ROC	Receiver-operating characteristic
RR	Risk ratio
RT	Radiotherapy
SCC	Squamous cell carcinoma

SCIP	Satisfaction with Cancer Information Profile
SD	Standard deviation
SDI	Social Difficulties Inventory
SDS-mhn	Symptom Distress Scale Modified for Head and Neck Cancer
SEER	Surveillance Epidemiology and End Results
SF-12 PCS	Medical Outcomes Score Short Form - 12, physical component score
SLNB	Sentinel lymph node biopsy
SND	Selective neck dissection
SRT	Surgery with radiotherapy
SSQ-6	Short Form Social Support Questionnaire
SSS	Symptom Severity Scale
TLM	Transoral laser microsurgery
TLS	Transoral laser surgery
TNM	Tumour, node, metastasis (classification system)
TORS	Transoral robotic surgery
TPF	Docetaxel plus cisplatin and fluorouracil
UADT	Upper aerodigestive tract
UCL	Utrecht Coping List
UICC	Union for International Cancer Control
US	Ultrasound
UW-QoL	University of Washington Quality of Life Scale
VHI	Voice handicap index
WHO	World Health Organization
WHOQoL-BREF	World Health Organisation Quality of Life abbreviated version
WOC	Worry of cancer
WOC-CA	Ways of Coping – Cancer Version

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