National Collaborating Centre for Cancer

Cancer of the upper aerodigestive tract:

assessment and management in people aged 16 and over

Clinical Guideline

Full guideline

September 2015

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence

Funding
Funded to produce guidelines for the NHS by NICE

Contents

Foreword

Cancer of the upper aerodigestive tract presents patients, carers and healthcare professionals with difficult management decisions. Those affected by the disease often undergo complex treatment with wide ranging short and long term effects that require continued support throughout the initial period of care and beyond. We hope that this document will provide helpful and appropriate guidance to both patients and professionals alike on the diagnosis and subsequent management of early and locally advanced cancers.

It has been impossible to cover every aspect of the patient pathway but instead we have concentrated on those areas where it was felt uncertainty or variation in practice currently exists. As such the guideline is not intended as an exhaustive textbook on the management of cancer of the upper aerodigestive tract. The guideline sets out recommendations that will be helpful and informative in decision-making and management of a variety of situations but cannot be a substitute for clinical judgement in a specific case.

We were aided and supported by a diverse and engaged guideline committee (GC) membership and are grateful for all the hard work, commitment and common sense demonstrated by them throughout the two-year process. Their complementary skills and perspectives have inspired this guideline. We would also like to thank the staff at the NCC-C for their considerable support during the development of this guideline.

Dr Martin Robinson, GC Chair

Mr Cyrus Kerawala, GC Lead Clinician

Key research recommendations

- A prospective study should be undertaken to identify what factors determine the risk of a person presenting with CUADT having metastasis or a second primary cancer. Outcomes of interest include prevalence, predictive value and how the abnormalities identified influence patient management. The presence of metastasis and a synchronous second primary cancer at presentation is rare in patients with CUADT. Subgroups of patients have been identified in whom the risk is clearly elevated. However, it is not clear at which level of risk detailed staging investigations are justified and the impact the results of these would have on decision making by the clinicians and the patient. Health economic modelling is needed to inform this process.
- A prospective study should be undertaken to compare the effectiveness of single-step laboratory diagnostic tests to identify human papillomavirus (HPV) against current diagnostic test algorithms and reference standards in people with cancer of the oropharynx. Outcomes of interest are sensitivity, specificity and resource use. HPV testing is currently recommended in cancer of the oropharynx since it has significant prognostic implication. Current methods utilise a two-step procedure which is not widely available in all treatment centres. A single-step test is likely to be more widely adopted and could have significant budgetary implications for the NHS. The study should also consider the prognostic value and the economic benefits of novel tests.

A prospective study should be undertaken in people with CUADT of unknown primary to identify whether radiotherapy target volumes can be selected based on clinical and pathological factors. Outcomes of interest include local control, progression-free survival, overall survival, and treatment-related morbidity and mortality. In a very small percentage of patients with squamous carcinoma involving a cervical lymph-node the primary site remains occult despite intensive investigations. The optimum treatment of these patients is uncertain. Some clinical teams will treat the neck disease alone and others will treat some or all potential primary sites with the radiotherapy with or without chemotherapy. The latter strategy is associated with a high level of side-effects that may have lifelong consequences, for example xerostomia. A better understanding of the clinico-pathological factors associated with treatment outcomes would improve treatment selection with the potential to reduce these side effects.

- A prospective study should be undertaken to identify the specific clinical and non-clinical factors that allow risk stratification when selecting which people with CUADT would benefit from short or long-term enteral nutrition. Outcomes of interest include resource use, morbidity of tube placement and duration of enteral feeding. There are no nationally agreed selection criteria for the type of feeding tube placed at diagnosis for people that need enteral nutrition support during curative treatment. Variation across the UK exists as a result of clinician-led practices and local policy. The systematic review by NICE in 2015 found some evidence but no specific list was identified due to limitations with study design, and inability to stratify clinical and non-clinical factors meaningfully. These factors included restricted populations for tumour staging, patient demographics, treatment plan and intent, definitions of malnutrition, timing and method of tube placement, and duration of enteral nutrition.
- A prospective study should be undertaken to investigate the optimal method, frequency and duration of follow-up for people who are disease free after treatment for CUADT. Outcomes of interest include quality of life, local control and overall survival. What are the optimal methods, frequency, and duration of follow-up in people who are clinically disease free and who have undergone treatment for squamous cell cancer of the upper aerodigestive tract with curative intent? Considerable resources are expended throughout the country on the follow-up of people who have completed potentially curative treatment. Local follow-up protocols are based more on historical practice than evidence and are often disease- rather than patient-centred. Research to investigate how and when follow-

up should optimally be carried out could improve clinical outcomes and the use of resources.

Methodology

What is a clinical guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and onto more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Who is the guideline intended for?

This guideline does not include recommendations covering every detail of the assessment and management of upper aerodigestive tract cancer. Instead, this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing clinical evidence based questions'.

This guideline is relevant to all healthcare professionals who come into contact with people with upper aerodigestive tract cancer, as well as to the people with upper aerodigestive tract cancer themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care to this group of people.

The remit of the guideline

Involvement of Stakeholders

Key to the development of all NICE guidelines are the relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2012). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the upper aerodigestive tract cancer guideline can be found in Appendix G.

The guideline development process – who develops the guideline?

Overview

The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE 2012 and NICE 2014). A team of health professionals, lay representatives and technical experts known as the Guideline Committee (GC) (Appendix G), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline
- forming the GC

- developing clinical questions
- identifying the health economic priorities
- developing the review protocols
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- consultation and validation

The scope

The scope was drafted by the GC Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2012). The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C
- inform professionals and the public about the expected content of the guideline
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the clinical questions and search strategies

Before the guideline development process started, the draft scope was presented and discussed at a stakeholder workshop. The list of key clinical issues were discussed and revised before the formal consultation process. Further details of the discussion at the stakeholder workshop can be found on the NICE website (www.nice.org.uk).

The scope was subject to a four week stakeholder consultation in accordance with NICE processes. The full scope is shown in Appendix F. During the consultation period, the scope was posted on the NICE website. Comments were invited from registered stakeholder organisations and NICE staff. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed and signed off by NICE and posted on the NICE website.

The Guideline Committee (GC)

The upper aerodigestive tract cancer GC was recruited in line with the 'NICE guidelines manual' (NICE 2012). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and shortlisted candidates were interviewed in person prior to being offered the role. The NCC-C Director, GC Chair and Lead Clinician identified a list of specialties that needed to be represented on the GC. Details of the adverts were sent to the main stakeholder organisations, cancer networks and patient organisations/charities (Appendix G). Individual GC members were selected for telephone interview by the NCC-C Director, GC Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GC, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GC members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GC meetings,

members declared new, arising conflicts of interest which were always recorded (see Appendix G).

Guideline Committee meetings

Thirteen GC meetings were held between 16–17 Dec 2013 and 2–3 Nov 2015. During each GC meeting (held over either 1 or 2 days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GC workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GC in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations before presenting it to the GC. These recommendations were then discussed and agreed by the GC as a whole. Each clinical question was led by a GC member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GC subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/carer representatives

Individuals with direct experience of upper aerodigestive tract cancer services gave an important user focus to the GC and the guideline development process. The GC included two patient/carer members. They contributed as full GC members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GC.

Expert advisers

During the development of the guideline the GC identified shoulder rehabilitation following neck dissection as a topic that required additional expert input. One expert was identified by the NCC-C and GC (Appendix G) and invited to advise the GC on drafting their recommendations for that clinical question.

Developing clinical evidence-based questions

Background

Clinical guidelines should be aimed at changing clinical practice and should avoid ending up as ‘evidence-based textbooks’ or making recommendations on topics where there is already agreed clinical practice. Therefore the list of key clinical issues listed in the scope were developed for areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

From each of the key clinical issues identified in the scope, the GC formulated a clinical question. For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: P – the population (the population under study); I – the interventions (what is being done); C – the comparison (other main treatment options); O – the outcomes (the measures of how effective the interventions have been).

Review of Clinical Literature

Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: NHS Evidence, NICE, Cochrane Databases of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA), TRIP, SIGN, NHS Economic Evaluations Database (NHSEED), Health Economic Evaluations Database (HEED), Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Developing the review protocol

For each clinical question, the information specialist and researcher (with input from other technical team and GC members) prepared a review protocol. This protocol explains how the review was to be carried out (Table 1) in order to develop a plan of how to review the evidence, limit the introduction of bias and for the purposes of reproducibility. All review protocols can be found in the evidence review.

Table 1: Components of the review protocol

Component	Description
Clinical question	The clinical question as agreed by the GC
Rationale	An explanation of why the clinical question is important. For example, is the topic contentious? Is there variation in practice across the UK?
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.
How the information will be searched	The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. Searches should not necessarily be restricted to RCTs.
The review strategy	The methods that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.

Searching for the evidence

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GC. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on ‘Incorporating Health Economic Evidence’).

Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when necessary. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1946 onwards
- Excerpta Medica (Embase) 1974 onwards

- Web of Science [specifically Science Citation Index Expanded (SCI-Expanded) 1900 onwards, Social Sciences Citation Index (SSCI) 1900 onwards and Conference Proceedings Citation Index - Science (CPCI-S) 1990-present]

Subject specific databases used for certain topics:

- Cumulative Index to Nursing and Allied Health Literature (CINAHL) 1937 onwards
- PsycINFO 1806 onwards

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6–8 weeks before the guideline was submitted to NICE for stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, June 2015 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review.

Critical Appraisal and Evidence Grading

Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. When papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. If results from a study were published as more than one paper, the most recent or complete publication was used. For each question, data were extracted on the outcomes identified as critical or important by the GC and recorded in evidence tables and an accompanying evidence summary prepared for the GC (see evidence review). All evidence was considered carefully by the GC for accuracy and completeness.

GRADE (Grading of Recommendations, Assessment, Development and Evaluation)

For interventional questions, studies which matched the inclusion criteria were evaluated and presented using GRADE (NICE 2012; http://gradeworkinggroup.org/). Where possible this included meta-analysis and synthesis of data into a GRADE ‘evidence profile’. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (very low, low, moderate or high) as well as an estimate of the size of effect. A narrative summary (evidence statement) was also prepared.

Each outcome was examined for the quality elements defined in Table 2 and subsequently graded using the quality levels listed in Table 3. The reasons for downgrading or upgrading specific outcomes were explained in footnotes.

Table 2: Descriptions of quality elements of GRADE

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect
Inconsistency	Inconsistency refers to unexplained heterogeneity of results
Indirectness	Indirectness refers to differences in study

Quality element	Description
	population, intervention, comparator or outcomes between the available evidence and the clinical question
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2012). In general, evidence was based on published data only. Study authors were contacted only to resolve any ambiguities, such as unclear presentation of data, or where clarification was needed in order to include or exclude a paper in the evidence review.

For non-interventional questions, for example questions regarding diagnostic test accuracy, a narrative summary of the quality of the evidence was provided. The quality of individual diagnostic accuracy studies was assessed using the QUADAS-2 tool (Whiting et al., 2011).

Incorporating health economics evidence

The aim of providing economic input into the development of the guideline was to inform the GC of potential economic issues relating to upper aerodigestive tract cancer. Health economics is about improving the health of the population through the efficient use of resources. In addition to assessing clinical effectiveness, it is important to investigate whether health services are being used in a cost effective manner in order to maximise health gain from available resources.

Prioritising topics for economic analysis

After the clinical questions had been defined, and with the help of the health economist, the GC discussed and agreed which of the clinical questions were potential priorities for economic analysis. These economic priorities were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2012):

- the overall importance of the recommendation, which may be a function of the number of patients affected and the potential impact on costs and health outcomes per patient
- the current extent of uncertainty over cost effectiveness, and the likelihood that economic analysis will reduce this uncertainty

- the feasibility of building an economic model

A review of the economic literature was conducted at scoping. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence.

For systematic searches of published economic evidence, the following databases were included:

- Medline
- Embase
- NHS Economic Evaluation Database (NHS EED)
- Health Technology Assessment (HTA)
- Health Economic Evaluations Database (HEED)

Methods for reviewing and appraising economic evidence

The aim of reviewing and appraising the existing economic literature is to identify relevant economic evaluations that compare both costs and health consequences of alternative interventions and that are applicable to NHS practice. Thus studies that only report costs, non-comparative studies of 'cost of illness' studies are generally excluded from the reviews (NICE 2012).

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE 2012). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the GC for a specific topic within the guideline. There are two parts of the appraisal process; the first step is to assess applicability (i.e. the relevance of the study to the specific guideline topic and the NICE reference case) (Table 4).

Table 4: Applicability criteria

Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e. the methodological quality, Table 5).

Table 5: Methodological quality

Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should

	usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

If high-quality published economic evidence relevant to current NHS practice was identified through the search, the existing literature was reviewed and appraised as described above. However, it is often the case that published economic studies may not be directly relevant to the specific clinical question as defined in the guideline or may not be comprehensive or conclusive enough to inform UK practice. In such cases, for priority topics, consideration was given to undertaking a new economic analysis as part of this guideline.

Economic modelling

Once the need for a new economic analysis for high priority topics had been agreed by the GC, the health economist investigated the feasibility of developing an economic model. In the development of the analysis, the following general principles were adhered to:

- the GC subgroup was consulted during the construction and interpretation of the analysis
- the analysis was based on the best available clinical evidence from the systematic review
- assumptions were reported fully and transparently
- uncertainty was explored through sensitivity analysis
- costs were calculated from a health services perspective
- outcomes were reported in terms of quality-adjusted life years

Agreeing the recommendations

For each clinical question the GC were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. The GC derived their guideline recommendations from this information. The link between the evidence and the view of the GC in making each recommendation is made explicitly in the accompanying LETR statement (see below).

Wording of the recommendations

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made. Some recommendations were made with more certainty than others. Recommendations are based on the trade-off between the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence.

For all recommendations, it is expected that a discussion will take place with the patients about the risks and benefits of the interventions, and their values and preferences. This discussion should help the patient reach a fully informed decision. Terms used within this guideline are:

- ‘Offer’ – for the vast majority of patients, an intervention will do more good than harm
- ‘Do not offer’ – the intervention will not be of benefit for most patients
- ‘Consider’ – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences than for an ‘offer’ recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

LETR (Linking evidence to recommendations) statements

As clinical guidelines were previously formatted, there was limited scope for expressing how and why a GC made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' and will usually cover the following key points:

- the relative value placed on the outcomes considered
- the strength of evidence about benefits and harms for the intervention being considered
- the costs and cost effectiveness of an intervention
- the quality of the evidence (see GRADE)
- the degree of consensus within the GC
- other considerations – for example equalities issues

Where evidence was weak or lacking the GC agreed the final recommendations through informal consensus. Shortly before the consultation period five key research recommendations were selected by the GC for implementation and the patient algorithms were agreed.

Guideline implementation

NICE invited stakeholders to give their responses to the following questions during consultation of the guideline:

1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.
2. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)

NICE will use the feedback received as well as consultation with members of the committee, engagement with relevant key partners and relevant desk research, to write a chapter which aims to help users of the guideline to get started with implementation. It will highlight up to 3 areas for attention, describing the benefits, barriers and enablers as well as signposting to any relevant resources or examples of practice that may help.

Consultation and validation of the guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GC Chair and Lead Clinician. This was then discussed and agreed with the GC and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (Appendix G) had one opportunity to comment on the draft guideline which was posted on the NICE website between 3 September 2015 and 15 October 2015 in line with NICE methodology (NICE 2014).

The pre-publication process

An embargoed pre-publication version of the guideline was released to registered stakeholders who have signed a confidentiality form to allow them to see how their comments have contributed to the development of the guideline and to give them time to prepare for publication (NICE 2014).

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GC and published at the same time.

Other versions of the guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc).

NICE also produces three other versions of the upper aerodigestive tract cancer guideline which are available from the NICE website:

- the short version, containing all recommendations and the key research recommendations.
- NICE pathways, which is an online tool for health and social care professionals that brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.
- 'Information for the Public (IFP)', which summarises the recommendations in the guideline in everyday language for patients, their family and carers, and the wider public.

Updating the guideline

Literature searches were repeated for all of the clinical questions at the end of the guideline development process, allowing any relevant papers published before 1 June 2015 to be considered. Future guideline updates will consider evidence published after this cut-off date.

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

Funding

The National Collaborating Centre for Cancer (NCC-C) was commissioned by NICE to develop this guideline.

Disclaimer

The GC assumes that healthcare professionals will use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

References

National Institute for Health and Clinical Excellence (2012) The guidelines manual. London: National Institute for Health and Clinical Excellence. Available from The guidelines manual

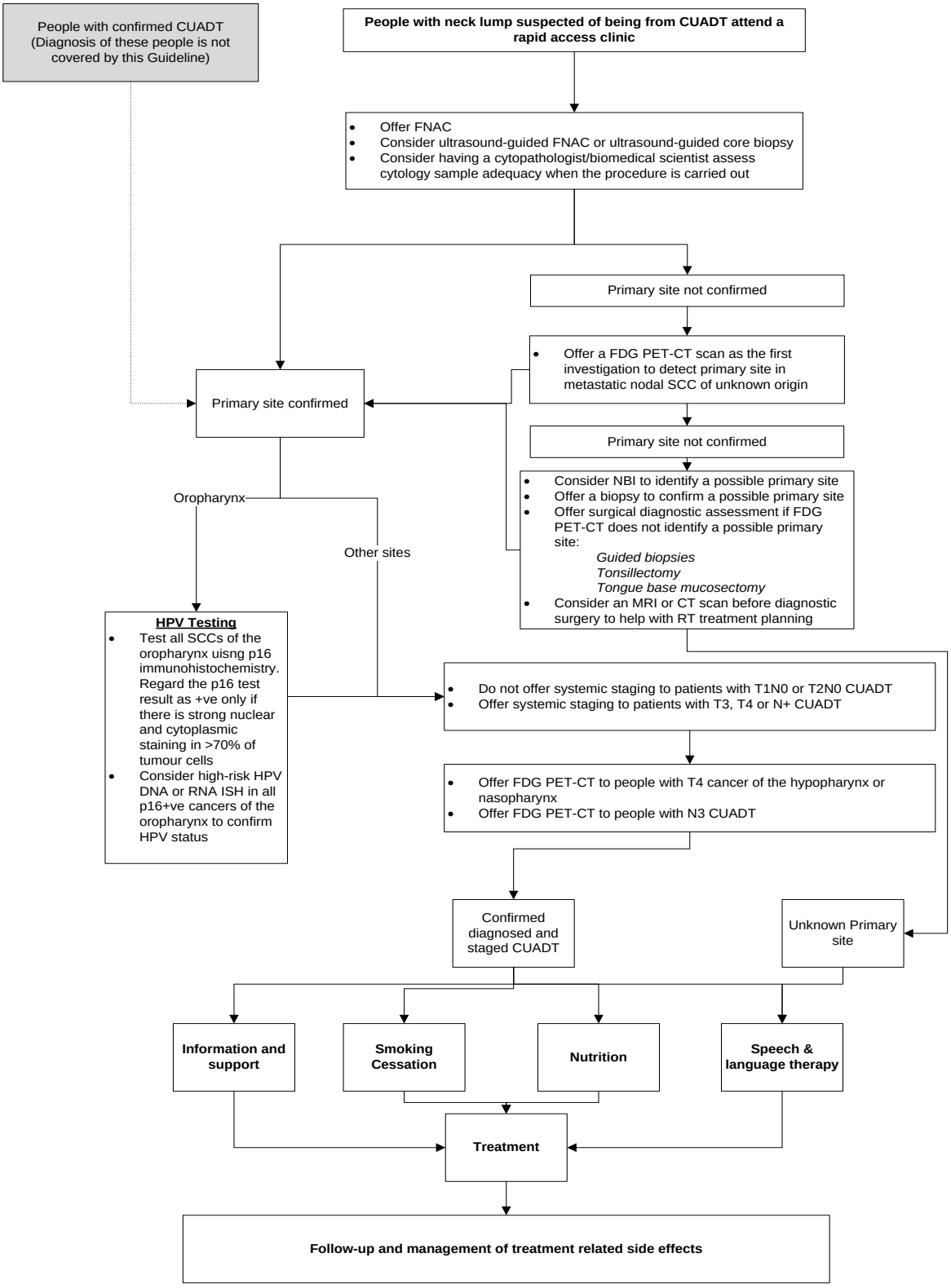
National Institute for Health and Clinical Excellence (2014) Developing NICE guidelines: the manual. London: National Institute for Health and Clinical Excellence. Available from Developing NICE guidelines: the manual

Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM, Group Q-2 (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine, 155: 529-536.

1

Pictorial representation of the diagnostic recommendations

This algorithm is a pictorial representation of the diagnostic recommendations in the guideline. It does not represent a pathway of care.



1 Information and support

1.1 Information needs

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.

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

Clinical evidence (see Appendix H)

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).

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, Ford, & Farah, 2014b). 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 et al. (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, Ridge, Burtness, Galloway, & Fang, 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, Ford, & Farah, 2014a, Moore et al., 2014a; Fang, 2012; Newell, Ziegler, Stafford, & Lewin, 2004; Oskam et al., 2013; Llewellyn, McGurk, & Weinman, 2006; Glavassevich, McKibbon, & Thomas, 1995; Rogers, Hazeldine, O'Brien, Lowe, & Roe, 2015; Nund et al., 2014; Brockbank, Miller, Owen, & Patterson, 2015; Edwards, 1998). 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 et al., 2013) and one cross-sectional questionnaire study (Milbury, Rosenthal, El-Naggar, & Badr, 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, Lai, Liao, Chang, & Lin, 2009; Chen et al., 2010; Chen et al., 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. HNC specific needs remained constant up to six months after treatment.

Patient's 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.

Quality of evidence

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).

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.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**For people with cancer of the upper aerodigestive tract and their carers:** • **offer consistent information and support at diagnosis** • **review their needs throughout the care pathway including at the end of treatment** • **tailor information and support to the person's needs (including the benefits and side effects of treatment, psychosocial and long-term functional issues).** **Give people contact details for their allocated key worker, in line with the NICE service guidance on improving outcomes in head and neck cancer and recommendations of the National Peer Review Programme.** **Give people details of peer support services that can help them throughout their care pathway.** **Offer information about human papillomavirus (HPV) to people with HPV-related cancer of the upper aerodigestive tract.**
Relative value placed on the	The GC considered the information and support needs of patients

outcomes considered	and carers to be the main outcome of this review question. The GC considered that it is important to inform the patient about the complex nature of their treatment and outcomes in both the short and long term. The provision of patient information is also vital for informed consent. All the themes from the PICO were reported in the evidence and were considered to be useful by the GC.
Quality of the evidence	The evidence was assessed as being of moderate quality using the NICE qualitative study checklist. Some limitations with the evidence were noted. Many of the studies, especially the qualitative studies, had small sample sizes. The qualitative studies were generally well conducted and provide rich data about patient's experiences. The cross-sectional questionnaire studies were limited in that they only captured data about patient information and support needs at one point in time. Some studies required patients to retrospectively report their experiences, and so may be subject to participant recall bias. The GC considered that the evidence supported a recommendation to provide patients with tailored, consistent information and support throughout the care pathway and after treatment. This was particularly important for people who have had a laryngectomy as it may be difficult for them to ask questions. Evidence also demonstrated that some patients with HPV-related cancer felt uninformed about the risk of transmission of their disease and were uncertain about HPV as a cause of their cancer. The lack of high quality data about the benefits of peer support for patients reduced the strength of the recommendation that could be made (i.e., the GC made a 'consider' rather than an 'offer' recommendation).
Trade-off between clinical benefits and harms	The GC considered that the potential benefits of the recommendations made include improved patient experience, better informed patients and carers, and the provision of specific information for patients with HPV-related cancers. The latter was thought to be important given the increasing prevalence of HPV-related disease, the impact that its identification has on discussions regarding long-term outcome, preconceptions among patients and carers regarding the transmission of HPV and the relative inconsistency of advice currently available. The recommendations made may potentially lead to information overload for some patients, which may lead to increased anxiety if the information is not tailored to the individual. The GC considered that the majority of patients will benefit from the recommendations and, to minimise the potential harm of information overload, the GC have recommended that the information and support is tailored to the individual.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. There may also be costs from extra appointments and/or longer consultations with clinicians in order to provide sufficient information and support. The GC considered that there may be savings from improved efficiency and reduced litigation costs following better provision of patient information.
Other considerations	A key finding of a systematic review was that patients find that the supportive relationships with their peers are important to them. This support after treatment is sometimes limited, which can contribute to feelings of isolation and anxiety. The GC therefore recommended that this support should be available to all patients. The GC considered that some change in practice may be required

	to implement the recommendation to give information and support after diagnosis as the GC thought that this is often not consistently given across the UK. The recommendations may also require an increase in training patients for peer support. The GC also referred to the NICE service guidance on improving outcomes in head and neck cancers and the National Peer Review Programme as the GC considered that the recommendations on the provision of a key worker were not being consistently implemented.

1.2.1 Smoking cessation

The benefits of smoking cessation are both short and long term. Smokers are at a higher risk of surgical complications which may delay postoperative 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 second 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.

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

Clinical evidence (see Appendix H)

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.

Table 6: GRADE evidence table: former versus active smokers after cancer diagnosis

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Former smokers	Active smokers	Relative (95% CI)	Absolute	Quality
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 to 0.83)	177 fewer per 1000 (from 86 fewer to 248 fewer)	VERY LOW
Tumour recurrence											
3	observational studies	serious[1,2]	no serious inconsistency	serious2	no serious imprecision	none	79/236 (33.5%)	30/80 (37.5%)	RR 0.88 (0.62 to 1.25)	45 fewer per 1000 (from 142 fewer to 94 more)	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 to 0.53)	187 fewer per 1000 (from 140 fewer to 223 fewer)	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 to 1.28)	38 fewer per 1000 (from 197 fewer to 178 more)	VERY LOW
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 to 0.41)	221 fewer per 1000 (from 145	VERY LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Former smokers	Active smokers	Relative (95% CI)	Absolute	Quality
										fewer to 241 fewer)	
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 to 2.40)	115 more per 1000 (from 73 fewer to 445 more)	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 to 1.09)	160 fewer per 1000 (from 320 fewer to 65 more)	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 to 1.28)	70 fewer per 1000 (from 242 fewer to 178 more)	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)	VERY LOW
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 to	205 fewer per 1000	VERY LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Former smokers	Active smokers	Relative (95% CI)	Absolute	Quality
									0.99)	(from 3 fewer to 286 fewer)	
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)	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 to 2.37)	79 fewer per 1000 (from 90 fewer to 125 more)	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 to 1)	178 fewer per 1000 (from 200 fewer to 0 more)	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 to 0.77)	161 fewer per 1000 (from 71 fewer to 217 fewer)	VERY LOW

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

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

3 [3] *Unclear if the treatment by former and active smokers was comparable.*

[4] *Low (<300) number of events; 95% confidence intervals encompass no effect, relative risk increase of 25%, and relative risk decrease of 25%.*

Table 7: GRADE evidence table: Smoking cessation before radiotherapy versus smoking cessation after radiotherapy for improving outcomes in smokers with CUADT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Smoking cessation before RT**	**Smoking cessation after RT**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 3.21)	37 more per 1000 (from 59 fewer to 270 more)	VERY LOW	

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

2 Low (<300) number of events; 95% confidence intervals encompass no effect, relative risk increase of 25%, and relative risk decrease of 25%.

Table 8: GRADE evidence table: Light smoking (<1 cigarette/day) vs heavier smoking during radiotherapy in smokers with CUADT

Quality assessment							No of patients		Effect			
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**	**Quality**	
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 to 1.24)	86 fewer per 1000 (from 213 fewer to 109	VERY LOW	

Quality assessment							No of patients		Effect			
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**	**Quality**	
										more)		

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

2 **Table 9: GRADE evidence table: smoking cessation at or before cancer diagnosis versus continued smoking after cancer diagnosis in**
3 **people with CUADT**

Quality assessment							No of patients		Effect			
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**	**Quality**	
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 to 0.78)	293 fewer per 1000 (from 170 fewer to 394 fewer)	□□□□ 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 to 1.04)	119 fewer per 1000 (from 213 fewer to 17 more)	□□□□ VERY LOW	

Quality assessment							No of patients		Effect			
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**	**Quality**	
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 to 1.70)	19 fewer per 1000 (from 87 fewer to 111 more)	□□□□ 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 to 1.38)	50 more per 1000 (from 78 fewer to 211 more)	□□□□ VERY LOW	
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 to 0.9)	180 fewer per 1000 (from 49 fewer to 272 fewer)	□□□□ VERY LOW	

1 *1 In 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*
2 *before presentation; time of quitting was not known for a further 31%.*

3

Cost effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Inform patients and carers at the point of diagnosis about how continuing to smoke adversely affects outcomes such as:** • **treatment-related side effects** • **risk of recurrence** • **risk of second primary cancers.** **Offer help to people to stop smoking, in line with the NICE guideline on smoking cessation services.**
Relative value placed on the outcomes considered	When drafting the recommendations, the outcomes considered of most importance were survival and the incidence of second primary cancers. Although the evidence for these outcomes was rated as very low quality, the combined results from a number of studies consistently supported the recommendations.
Quality of the evidence	Evidence for all outcomes was assessed as very low quality (using GRADE). In addition to the very low quality of the evidence, the reviewer highlighted to the GC that all of the identified evidence for one of the outcomes (incidence of second primary) was from trials conducted at least 20 years ago. The GC were of the opinion that results from older studies were still applicable to modern clinical practice. No evidence was available on quality of life, and there was uncertainty regarding the effect of smoking on treatment-related morbidity. Based on the evidence of increased risk of second primary cancers as a result of continuing to smoke, the GC agreed to recommend patients and carers should be informed about this. The GC noted that the evidence was uncertain about the impact of continuing to smoke on the risk of recurrence after treatment and the incidence of treatment related side effects. However, their clinical experience was that patients should be informed about this possibility.
Trade-off between clinical benefits and harms	The GC considered the potential benefits of the recommendations to be reduced risk of mortality, treatment related morbidity and of developing a second primary tumour. No potential harms were identified.
Trade-off between net health benefits and resource use	The GC considered that the recommendations would result in a reduction in costs associated with treating treatment-related morbidity, recurrence, second primary tumours, and end of life care. Increased costs may be associated with administering smoking cessation services. No economic model or cost analysis was conducted.

Other considerations	The change in practice required to implement the recommendations would be to make smoking cessation a higher priority on the patient's care pathway and more integration of smoking cessation into the care pathway. When drafting the recommendations, the GC took existing NICE smoking cessation guidance into account. No equalities issues were identified. E-cigarettes were not considered as they did not meet the inclusion criteria for the review.

References

Baxi, S. S., Shuman, A. G., Corner, G. W., Shuk, E., Sherman, E. J., Elkin, E. B., Hay, J. L., and Pfister, D. G. 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., 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

Browman, G. P., Mohide, E. A., Willan, A., Hodson, I., Wong, G., Grimard, L., MacKenzie, R. G., El-Sayed, S., Dunn, E., and Farrell, S. Association between smoking during radiotherapy and prognosis in head and neck cancer: a follow-up study. Head & Neck 2002. 24(12): 1031-1037

Castigliano, S. G. Influence of continued smoking on the incidence of second primary cancers involving mouth, pharynx, and larynx. Journal of the American Dental Association 1968. 77(3): 580-585

Chen, A. M., Chen, L. M., Vaughan, A., Sreeraman, R., Farwell, D. G., Luu, Q., Lau, D. H., Stuart, K., Purdy, J. A., and Vijayakumar, S. Tobacco smoking during radiation therapy for head-and-neck cancer is associated with unfavorable outcome. International Journal of Radiation Oncology, Biology, Physics 2011. 79(2): 414-419

Chen, S. C., Lai, Y. H., Liao, C. T., Chang, J. T., Lin, C. Y., Fan, K. H., and Huang, B. S. Supportive care needs in newly diagnosed oral cavity cancer patients receiving radiation therapy. Psycho-Oncology 2013. 22(6): 1220-1228

Chen, S. C., Yu, W. P., Chu, T. L., Hung, H. C., Tsai, M. C., and Liao, C. T. 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

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

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

Garces, Y. I., Schroeder, D. R., Nirelli, L. M., Croghan, G. A., Croghan, I. T., Foote, R. L., and Hurt, R. D. Second primary tumors following tobacco dependence treatments among head and neck cancer patients. American Journal of Clinical Oncology 2007. 30(5): 531-539

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

Gorsky, M. and Silverman, S. Tobacco Use in Patients with Head and Neck Carcinomas - Habit Changes and 2nd Primary Oral/Oropharyngeal Cancers in Patients from San-Francisco. Cancer Journal 1994. 7(2): 78-80

Kanatas, A., Ghazali, N., Lowe, D., Udberg, M., Heseltine, J., O'Mahony, E., and Rogers, S. N. 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

Lang, H. D., France, E., Williams, B., Humphris, G., and Wells, M. The psychological experience of living with head and neck cancer: a systematic review and meta-synthesis. Psycho-Oncology 2013. 22(12): 2648-2663

Ledeboer, Q. C., Offerman, M. P., van der Velden, L. A., de Boer, M. F., and Pruyn, J. F. 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

Llewellyn, C. D., 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

Llewellyn, Carrie D. 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. [References]. Psychology, Health & Medicine 2005. Vol.10(2): 180-193

Longacre, M. L., Ridge, J. A., Burtness, B. A., Galloway, T. J., and Fang, C. Y. Psychological functioning of caregivers for head and neck cancer patients. Oral Oncology 2012. 48(1): 18-25

Ma, J. L. C. 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

Mayre-Chilton, K. M., Talwar, B. P., and Goff, L. M. 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

Milbury, K., Rosenthal, D. I., El-Naggar, A., and Badr, H. An exploratory study of the informational and psychosocial needs of patients with human papillomavirus-associated oropharyngeal cancer. Oral Oncology 2013. 49(11): 1067-1071

Moore, C. Cigarette smoking and cancer of the mouth, pharynx, and larynx. A continuing study. JAMA : the journal of the American Medical Association 1971. 218(4): 553-558

Moore, K. A., Ford, P. J., and Farah, C. S. I have quality of life but : Exploring support needs important to quality of life in head and neck cancer. European Journal of Oncology Nursing 2014. 18(2): 192-200

Moore, K. A., Ford, P. J., and Farah, C. S. Support needs and quality of life in oral cancer: a systematic review. International Journal of Dental Hygiene 2014. 12(1): 36-47

Newell, R., Ziegler, L., Stafford, N., and Lewin, R. J. 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

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

Oskam, I. M., Verdonck-de Leeuw, I. M., Aaronson, N. K., Witte, B. I., de, Bree R., Doornaert, P., Langendijk, J. A., and Leemans, C. R. 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

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

Rugg, T., Saunders, M. I., and Dische, S. Smoking and mucosal reactions to radiotherapy. British Journal of Radiology 1990. 63(751): 554-556

Sandoval, M., Font, R., Manos, M., Dicenta, M., Quintana, M. J., Bosch, F. X., and Castellsague, X. The role of vegetable and fruit consumption and other habits on survival following the diagnosis of oral cancer: a prospective study in Spain. International Journal of Oral & Maxillofacial Surgery 2009. 38(1): 31-39

Silverman S Jr and Griffith, M. Smoking characteristics of patients with oral carcinoma and the risk for second oral primary carcinoma. Journal of the American Dental Association 1972. 85(3): 637-640

Silverman S Jr, Gorsky, M., and Greenspan, D. Tobacco usage in patients with head and neck carcinomas: a follow-up study on habit changes and second primary oral/oropharyngeal cancers. Journal of the American Dental Association 1983. 106(1): 33-35

van der Voet, J. C., Keus, R. B., Hart, A. A., Hilgers, F. J., and Bartelink, H. The impact of treatment time and smoking on local control and complications in T1 glottic cancer. International Journal of Radiation Oncology, Biology, Physics 1998. 42(2): 247-255

van Imhoff, L. C., Kranenburg, G. G., Macco, S., Nijman, N. L., van Overbeeke, E. J., Wegner, I., Grolman, W., and Pothen, A. J. The prognostic value of continued smoking on survival and recurrence rates in head and neck cancer patients: A systematic review56. Head and Neck 2015.

Zevallos, J. P., Mallen, M. J., Lam, C. Y., Karam-Hage, M., Blalock, J., Wetter, D. W., Garden, A. S., Sturgis, E. M., and Cinciripini, P. M. Complications of radiotherapy in laryngopharyngeal cancer: effects of a prospective smoking cessation program. Cancer 2009. 115(19): 4636-4644

2 Investigation

2.1 Assessment of neck lumps

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, test accuracy and the order in which they are carried out.

Current NICE service guidance (Improving outcomes in head and neck cancers) states that patients with 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 upper aerodigestive tract (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.

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?

Clinical evidence (see Appendix H)

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

Based on the combined results of 13 trials (Akhavan-Moghadam, Afaaghi, Maleki, & Saburi, 2013; Altmann & Clancy, 1998; Draper, Pfleiderer, & Smith, 2003; Fulciniti, Califano, Zupi, & Vetrani, 1997; Howlett et al., 2007; Jandu & Webster, 1999; Khan et al., 2013; Kutluhan, Kisli, Yakut, Yurttas, & Kosem, 2003; Murthy, Laing, & Palmer, 1997; Raab, Sigman, & Hoffman, 1998; Tandon et al., 2008; Veivers & Dent, 2012; Wu et al., 2006; 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 (Lo, 2007, and Robinson 1999; 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 including 80 patients (Pfeiffer, Kayser, Technau-Ihling, Boedeker, & Ridder, 2007) 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 including 97 patients (Shrestha, Ghartimagar, & Ghosh, 2012) 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

All the included studies were retrospective, with the exception of one prospective study (Shrestha et al., 2012). Study quality and applicability was assessed using the QUADAS-2 checklist. 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 range of sites investigated, stating only that patients with head and neck lumps/lesions were included.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer fine-needle aspiration cytology to people with a neck lump that is suspected of being cancer of the upper aerodigestive tract.** **Consider ultrasound-guided fine-needle aspiration cytology or ultrasound-guided core biopsy for people with a neck lump that is suspected of being cancer of the upper aerodigestive tract.** **Consider having a cytopathologist or biomedical scientist assess the cytology sample adequacy when**

	the procedure is carried out.
Relative value placed on the outcomes considered	Sensitivity and specificity were the only outcomes from the PICO for which evidence was available. For this reason, these were the outcomes considered most important by the GC. The evidence suggests a notable non-diagnostic/inadequate sample rate, which the GC inferred would have an important effect on time to diagnosis. For this reason, and in the absence of any direct evidence on time to diagnosis, sample adequacy rates and diagnostic utility (two outcomes not specified in the PICO) were also taken into account when making recommendations.
Quality of the evidence	The quality of the evidence was assessed using QUADAS-2. The reviewer highlighted the following issues: • for many studies, it was unclear whether patients were selected in an unbiased fashion • the definition of neck lumps used by each study varied, most importantly in terms of the sites being investigated • the percentage of adequate samples varied widely from study to study • the sensitivity and specificity values quoted deliberately excluded inadequate samples. Therefore the actual diagnostic accuracy would be lower. Based on the evidence of high sensitivity and specificity the GC agreed to recommend the use of FNAC to diagnose a neck lump suspected of being CUADT. Despite the higher specificity and sensitivity of ultrasound-guided FNAC and core biopsy the GC did not feel that given the potential resource implications its routine use was warranted. Based on the high sample inadequacy rates, the GC recommended the presence of an experienced cytopathologist or biomedical scientist to ensure the sample is adequate at the first attempt and to reduce the potential need to recall the patient.
Trade-off between clinical benefits and harms	The GC consider the potential benefits of the recommendations to be: • more timely and accurate diagnosis in the population of interest if a cytologist or biomedical scientist can assess the adequacy of sampling at the time of the procedure • less need for re-testing • improved patient experience due to lowered anxiety for patients. The GC did not consider there to be any harms associated with making these recommendations.
Trade-off between net health benefits and resource use	There was no economic evidence and no model built. The GC anticipated that the following potential costs and savings will result from the recommendations: • costs of staff (e.g. the requirement for a cytologist/biomedical scientist at clinics) • savings from reduced re-testing • potential savings from earlier diagnosis and treatment of disease. The presence of a cytologist/biomedical scientist at clinics may already reflect current practice in some areas so the GC noted that increased costs are likely to be modest.
Other considerations	The GC noted that the recommendations may reflect current practice in some areas. Recommendations are anticipated to reduce variation in current practice. Since no evidence was available on the most effective configuration of tests the GC were unable to make recommendations on this issue

2.2 Identifying the occult primary

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 uncertainty may result in a delay in the diagnostic process.

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)?

Clinical evidence (see Appendix H)

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, 0.927), 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.

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

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 studies.

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.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer a fluorodeoxyglucose positron emission tomography (FDG PET)-CT scan as the first investigation to detect the primary site in people with metastatic nodal squamous cell carcinoma of unknown origin that is thought to arise from the upper aerodigestive tract.** **Consider using narrow-band imaging endoscopy to identify a possible primary site when it has not been possible to do so using FDG PET-CT.** **Offer a biopsy to confirm a possible primary site.** **Offer surgical diagnostic assessment if FDG PET-CT does not identify a possible primary site. This may include:** • **guided biopsies** • **tonsillectomy** • **tongue base mucosectomy.** **Consider an MRI or CT scan before diagnostic surgery to help with radiotherapy treatment planning.**
Relative value placed on the outcomes considered	When drafting recommendations, the GC considered sensitivity and specificity the most important outcomes. These were the only outcomes in the PICO for which evidence was identified. No evidence on health-related quality of life, time to diagnosis and process-related morbidity was identified.
Quality of the evidence	The evidence was assessed using QUADAS2. The reviewer highlighted patient selection and patient flow as potential sources of bias. The information reported on patient

	characteristics was limited, making it difficult to assess the comparability of different study populations. In several studies the criteria for patient selection (and therefore whether an unbiased sample of patients was chosen) were not clear. In studies of NBI and surgical diagnostic assessment, the reference standard was not always clearly defined. Based on the evidence the GC recommended FDG PET-CT as the first investigation to identify the occult primary as the sensitivity and specificity data demonstrated its superiority over other imaging modalities. The GC also recommended NBI endoscopy be considered as the evidence indicated that this has good sensitivity and specificity but it had only been used in a limited number of centres. The GC acknowledged that in a proportion of patients despite the use of FDG PET-CT and NBI a primary site will not be identified and therefore recommended surgical diagnostic assessment in these instances. Although the GC had recommended FDG PET-CT to identify the occult primary they were aware that this imaging modality does not provide enough anatomical detail to assist with radiotherapy treatment planning. Based on their clinical experience they recommended the use of MRI and CT for this purpose.
Trade-off between clinical benefits and harms	The GC considered the potential benefits of the recommendations to be: • earlier detection of primary tumours, with minimal burden of testing for the patient • detection of a higher proportion of primary tumours • potentially reduced treatment related morbidity as a result of more targeted treatment. The GC considered the potential harms of the recommendations to be additional exposure to low dose radiation in some patients, as a result of cross-sectional imaging. The GC concluded that the risks of low dose radiation exposure were outweighed by the benefits of the recommendations.
Trade-off between net health benefits and resource use	No economic evidence was identified and no model built. The GC envisaged that the recommendations would result in increased costs from more widespread use of FDG PET-CT (and purchasing the equipment and training of NBI), but that there was a potential for cost savings from less unnecessary tests being conducted as a result of the superior accuracy of PET-CT, and reductions in treatment related morbidity. The impact on the resources used by the CUADT service is likely to be small because of the relatively small patient population affected.
Other considerations	The GC envisaged the main changes in practice as a result of implementing the recommendations to be: • greater use of FDG PET-CT • less use of other cross-sectional imaging investigations • greater use of NBI.

2.3 Systemic staging – who and how?

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?

Clinical evidence (see Appendix H)

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 used 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 (Chan 2011, Ng 2008) 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 0.07, 0.10) and 0.06 (95% CI 0.04, 0.09), respectively). All other studies that included these tumour subsites (Chan 2011, Haerle 2011, Kim 2008, Ng 2008, Wax 2002) also reported highest positive predictive values for either nasopharynx or hypopharynx tumours.

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.

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 (HNC) 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.

Cost-effectiveness evidence

Background

The presence of distant metastases is uncommon in cancer of the upper aerodigestive tract (<10% at diagnosis). As such, it may not be necessary or cost-effective to adopt a strategy of systemic imaging to detect distant metastases. It may instead be preferable to perform

staging in a selected higher risk group based upon known risk factors (such as tumour site and stage).

There is also debate over the preferred imaging method with more advanced techniques such as PET CT sometimes advocated over more established approaches such as chest radiographs or computerised tomography (CT) scans. These newer techniques are likely to be diagnostically superior but they come at much greater expense and so may not be cost-effective.

The aim of this analysis was to estimate the cost-effectiveness of systemic imaging in patients with cancer of the upper aerodigestive tract.

Existing Economic Evidence

A systematic literature review was conducted to identify economic evaluations that may be applicable to the current decision problem. However, no relevant studies were identified.

De Novo Economic Model

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness.

Clinical data

Prevalence

An audit dataset of 18,968 patients from DAHNO has been utilised to provide data on the prevalence of distant metastases in patients with cancer of the upper aerodigestive tract. The dataset shows that distant disease was present in 548 patients, equating to an overall prevalence of 3% when considering all patients with cancer of the upper aerodigestive tract.

The detail given in the dataset also allows for the prevalence of distant metastases to be calculated for each tumour site, T stage and N stage. For instance, the risk of distant metastases was found to be much higher in patients with cancer of the hypopharynx (96 of 1,118 patients, equating to a prevalence of 9%).

Diagnostic accuracy

Diagnostic accuracy data (sensitivity and specificity) were obtained from Xu et al. 2012, which was adjusted to be the best available evidence identified in the systematic review. The meta-analysis by Xu et al. 2012 compared the diagnostic accuracy of PET or PET-CT in comparison to conventional imaging (consisting of a chest CT with or without an abdominal CT for most patients and a chest radiography, abdominal ultrasonography, and bone scan in nasopharyngeal cancer patients). It was found that PET or PET-CT was more sensitive than conventional imaging (sensitivity of 83% and 44%, respectively) and equally specific (specificity of 96% with both strategies). In a subgroup analysis, it was found that PET strategies are particularly beneficial in patients with nasopharyngeal cancer where the difference in sensitivity was even more marked (sensitivity of 82% and 30% in the PET and conventional imaging arms, respectively) while the specificity is once again equivalent (97% with both strategies). In patients with non-nasopharyngeal cancer, it was found that the superiority of PET strategies was not as pronounced with a smaller difference in sensitivity (85% and 62% in the PET and conventional imaging arms, respectively) and a slightly improved specificity (95% and 93% in the PET and conventional imaging arms, respectively).

As these differences in diagnostic accuracy were found to be significant, it was decided that, for the purposes of the economic model, the diagnostic accuracy data from the subgroups analysis should be utilised rather than the overall diagnostic accuracy data.

Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2013-14 prices.

The majority of costs were sourced from NHS reference costs 2013/14 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit – accessed 2015) combined with dose information from the British National Formulary (BNF). Other resource use and cost information were sourced from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

It should be noted that due to time constraints, this economic model did not consider an exhaustive list of all the potential costs in each strategy. Instead, a pragmatic approach has been adopted where only the key cost differences between strategies have been captured. Therefore, the model is essentially comparing the upfront costs of imaging strategies (PET or conventional imaging) against the potential cost offsets that may be achieved through detection in terms of avoiding the initial treatment that would have otherwise been received (if unaware of M+ status).

Systemic imaging costs

The costs associated with imaging modalities were obtained from NHS reference costs 2013-14 using the relevant procedure codes in outpatient diagnostic imaging. PET-CT was estimated to cost £651.96 based on procedure code 'RA42Z' which refers to 'Nuclear Medicine, Category 8 (PET-CT)'. Conventional imaging for non-nasopharyngeal sites, consisting of chest CT with abdominal scan, was estimated to cost £120.05 which was based on procedure code 'RA12Z' which refers to 'Computerised Tomography Scan, two areas with contrast'. Conventional imaging for nasopharyngeal sites, consisting of chest radiography, abdominal ultrasound and bone scan, was estimated to cost £285.65 based on the combined cost of these individual elements. A chest radiograph was estimated to cost £29.60 based on of a direct access plain film (DAPF). An abdominal ultrasound was estimated to cost £51.91 based on procedure code 'RA23Z' which refers to 'Ultrasound Scan, less than 20 minutes'. A bone scan (bone scintigraphy) was estimated to cost £204.14 based on procedure code 'RA36Z' which refers to 'Nuclear Medicine, Category 2'.

Biopsy costs

It was assumed that potential sites of distant metastases would be biopsied under ultrasound guidance by a radiologist at an estimated cost of £100.05. The cost for this procedure was sourced from NHS reference costs 2013-14 using codes associated with 'Ultrasound Mobile Scan or Intraoperative Procedures'. A weighted average cost was calculated to account for the differing lengths of time that may be required to perform the procedure (weightings were based on the number of examinations recorded in NHS Reference costs).

Based upon the guideline committee's uncertainty as to whether patients with a positive finding on an imaging scan would always necessarily undergo a biopsy, it was assumed that 10% of patients would not be biopsied.

Initial treatment costs avoided

In patients that are correctly identified as having distant metastases, it is assumed that they would avoid the initial treatment of curative intent that would otherwise have been appropriate in the absence of distant disease.

The cost of the initial treatment that is avoided varies depending on the tumour site, T stage and N stage. Appropriate treatments were identified for each stage and tumour site using the expertise of the GDG who estimated the most likely treatments that patients would receive in current clinical practice. The cost associated with each initial treatment was then estimated primarily using data from NHS reference costs 2013/14 with some additional costs identified

through eMit and the Personal Social Services Research Unit (PSSRU). Estimated treatment costs ranged from £2,960-£7,451 in the early stages of disease (stage I and II) and £7,594-£21,319 in more advanced stages (stage III and IV). Full details of the cost estimations can be found in supplementary tables in the appendices.

It should be noted that there was no consensus in the guideline committee around the likelihood that these curative treatments would be avoided in patients with detected distant disease. While it is likely that the intent of the management strategy will change as a result of distant disease detection (from curative to palliative), it was thought that there will still be cases where treatment of the primary tumour would be required. Therefore, an additional parameter was specified in the model as an estimate of the likelihood that management will change as a result of distant disease detection. In the base case, it was assumed that this figure was 100% but wide variations were explored in sensitivity analyses (including a scenario where the figure was 0%).

Health related quality of life (QoL) values

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state.

As described in previous sections, QALYs were estimated in this analysis based on the assumption that there would be a QoL benefit associated with avoiding 'unnecessary' treatment of curative intent in those patients with distant disease. Thus, treatment related QoL decrements were used to estimate the QALY gain that would be accrued for patients correctly identified with distant disease. In order to estimate QALYs a survival estimate was also required. In the base case, it was assumed that patients with distant disease would live for an average of one year with variations explored in sensitivity analysis.

No suitable QoL studies were identified that estimated the disutility associated with resection, radiotherapy or radiotherapy and concomitant chemotherapy. Therefore, in absence of better data, this value was estimated using two disparate sources. An estimated utility decrement of 0.0412 was calculated by taking the difference between the QoL value for patients with no evidence of disease (0.9130) from a cost-utility analysis by Sher et al. 2010 (based on physician estimated values from Hollenbeak et al. 2001) and the QoL value applied in patients after TLM or radiotherapy (0.8718) from the Higgins et al. 2011 study derived from a sample of 30 Canadian patients using the Health Utilities Index Mark 3.

The disutility associated with an elective neck dissection was identified from a study by Lassig et al. 2008 that reported QoL for patients receiving radiotherapy and concomitant chemotherapy, and radiotherapy and concomitant chemotherapy in addition to neck dissection. The study measured QoL using the Short Form 36 health survey (SF-36). These values have been converted to EQ-5D values (the measure preferred by NICE) using a published and widely used mapping algorithm by Ara et al. 2008. The neck dissection disutility was estimated by taking the difference between oropharyngeal patients receiving radiotherapy and concomitant chemotherapy, and radiotherapy and concomitant chemotherapy in addition to neck dissection.

The QoL decrements associated with more complex surgical procedures such as a partial laryngectomy, laryngectomy, glossectomy or pharyngectomy were estimated using data from a cost-utility analysis by Higgins et al. 2011. Higgins et al. 2011 estimated QoL values for patients alive with their voice box partially intact and patients alive without a voice box, which were applied in their analysis to patients after a partial laryngectomy and total laryngectomy, respectively. Decrements were calculated for this analysis by using the QoL value for patients with their voice box intact as the baseline (also from the Higgins et al. 2011 study) and then calculating the reductions in QoL associated with having a partially intact voice box or no voice box (0.1658 and 0.5068, respectively). Owing to a lack of QoL data, it was

assumed that these values would apply to other complex surgical procedures such as a glossectomy or pharyngectomy.

The table below shows the QoL values that were applied in the model.

Table 10: Quality of life decrements avoided applied in the economic model

Treatment	QoL value	PSA distribution	Source
Health state values			
Pre-treatment (a)	0.9130	Beta (alpha = 7, beta = 1)	Sher et al. 2010 and Hollenbeak et al. 2001
Alive after resection, radiotherapy or chemoradiotherapy (b)	0.8718	Beta (alpha = 26, beta = 4)	Higgins et al. 2011 (value after resection or radiotherapy)
Alive after more complex treatment (c)	0.7060	Beta (alpha = 21, beta = 9)	Higgins et al. 2011 (value after partial laryngectomy)
Alive after very complex treatment (d)	0.3650	Beta (alpha = 11, beta = 19)	Higgins et al. 2011 (value after total laryngectomy)
Estimated decrements			
Resection, radiotherapy or chemoradiotherapy	0.0412		Difference between (a) and (b)
Neck dissection	0.0386	Beta (alpha = 55, beta = 10) - Beta (alpha = 31, beta = 7)	Difference in QoL values for patients treated with and without neck dissection from Lassig et al. 2008 (converted to EQ-5D using Ara et al. 2008†)
More complex treatment	0.1658		Difference between (b) and (c)
Very complex treatment	0.5068		Difference between(b) and (d)
† SF-36 values from Lassig et al 2008 converted to EQ-5D values using mapping algorithm from Ara et al. 2008			

It should be noted that, there was thought to be considerable uncertainty around the validity of the QoL estimates applied in the analysis. As such, the conclusions drawn in scenarios where the quantities of QALY benefits were a crucial determinant of cost-effectiveness were considered carefully.

Base Case Results

The base case results of the analysis for the pooled group of all patients with cancer of the upper aerodigestive tract (n=18,968) are presented in the tables below. In table 11, a common baseline approach is adopted with both imaging strategies compared against no imaging whereas in table 12 a dominance rank approach is used in order to determine the optimal strategy.

It can be seen that both strategies were found to be more effective than a strategy of no imaging (incremental QALYs of 71.75 and 98.83 for conventional imaging and PET-CT, respectively). However, only conventional imaging was found to be cost-effective in comparison to no imaging. Indeed, the conventional imaging strategy was found to be cheaper overall than the no imaging strategy (£1,723,947) because the cost-offsets (through treatments avoided) outweighed the upfront costs of imaging. Therefore, conventional imaging was found to be dominant in comparison to no imaging (i.e. more effective and less expensive). Conversely, the PET-CT strategy was found to be substantially more costly than the no imaging strategy (£6,642,707) and not cost-effective as it's ICER value of £67,212 per QALY is well above the £20,000 per QALY threshold.

Using the dominance rank approach it can be seen that conventional imaging is the optimal strategy. While PET-CT was found to be more effective than conventional imaging (27.08 QALYs), it was also found to be substantially more expensive (£8,366,653). Overall the PET-CT strategy was not found to be cost-effective in comparison to conventional imaging with an ICER value of £308,977 per QALY.

Table 11: Base case cost-effectiveness results against common baseline (no imaging)

Strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
No imaging	£0	-	0.00	-	-
Conventional imaging	-£1,723,947	-£1,723,947	71.75	71.75	**Dominant**
PET-CT	£6,642,707	£6,642,707	98.83	98.83	**£67,212**

Table 12: Base case cost-effectiveness results using dominance rank approach

Strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
No imaging	£0	-	0	-	-
Conventional imaging	-£1,723,947	-£1,723,947	71.75	71.75	**Dominant**
PET-CT	£6,642,707	£8,366,653	98.83	27.08	**£308,977**

One-way sensitivity analysis results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result. The table below shows the results of the one-way sensitivity analysis with the most cost-effective strategy (at a threshold of £20,000 per QALY) detailed in each scenario.

Table 13: One-way sensitivity analysis results

Change made	Optimal strategy
PET-CT – upper sensitivity value	Conventional imaging
PET-CT – lower sensitivity value	Conventional imaging
Conventional imaging – upper sensitivity value	Conventional imaging
Conventional imaging – lower sensitivity value	Conventional imaging
PET-CT – upper specificity value	Conventional imaging
PET-CT – lower specificity value	Conventional imaging
Conventional imaging – upper specificity value	Conventional imaging
Conventional imaging – lower specificity value	Conventional imaging
Proportion of patients that cannot be biopsied = 25%	Conventional imaging
Proportion of patients that cannot be biopsied = 50%	Conventional imaging
Proportion of patients that cannot be biopsied = 75%	No imaging
Proportion of M+ patients with change in management = 75%	Conventional imaging
Proportion of M+ patients with change in management = 50%	Conventional imaging
Proportion of M+ patients with change in management = 25%	No imaging
Biopsy costs + 50%	Conventional imaging
Biopsy costs - 50%	Conventional imaging
Conventional imaging costs + 50%	Conventional imaging
Conventional imaging costs - 50%	Conventional imaging

Change made	Optimal strategy
PET-CT + 50%	Conventional imaging
PET-CT - 50%	Conventional imaging
Cost offsets +50%	Conventional imaging
Cost offsets -50%	Conventional imaging
QoL decrements +50%	Conventional imaging
QoL decrements -50%	Conventional imaging
No resection, RT or chemoRT decrements	Conventional imaging
No QoL decrements	Conventional imaging*
Very complex treatment decrement = 0.1658	Conventional imaging
Complex treatment decrements = 0.0412	Conventional imaging
Average life expectancy for M+ patients =6 months	Conventional imaging
Average life expectancy for M+ patients =6 months	Conventional imaging

It can be seen that the conclusion of the analysis is relatively insensitive to changes in most of the input parameters. However, the notable exceptions are the proportions of patients that cannot be biopsied and the proportion of patients whose management changes as a result of distant disease detection.

Threshold analysis

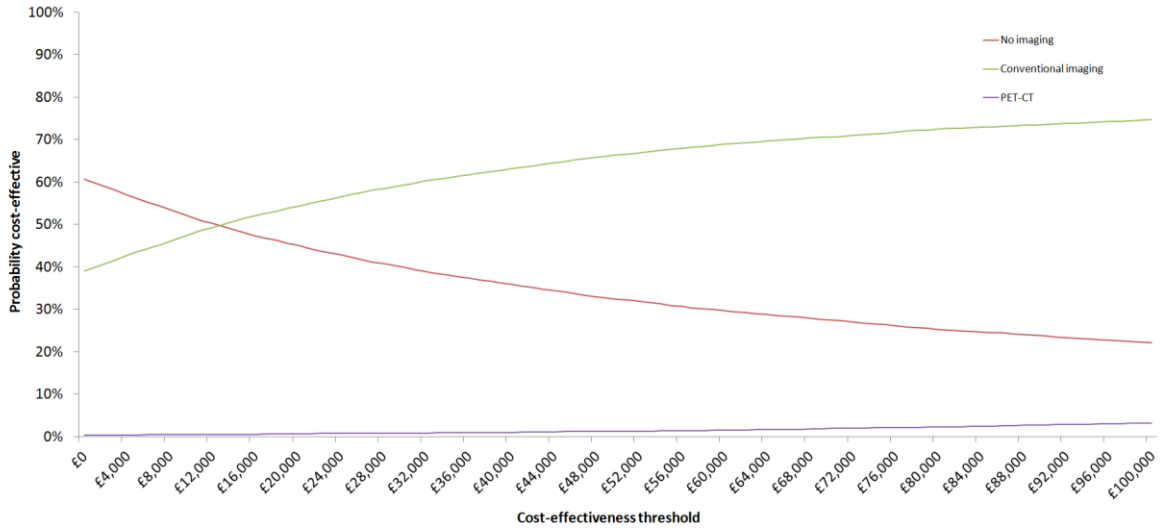
Owing to concerns around the likelihood of management changing as a result of distant disease detection, a threshold analysis was conducted to determine how low this value can be before imaging is no longer cost-effective. It was found that conventional imaging was no longer dominant when the likelihood of management changing as result of distant disease detection fell below 60%. Furthermore, it was found that conventional imaging was no longer cost-effective at a threshold of £20,000 per QALY when the likelihood of management changing as result of distant disease detection fell below 45%.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base case are replaced with values drawn from distributions around the mean values (see input tables detailed in above sections for distribution parameters used in analysis).

The results of 10,000 runs of the probabilistic sensitivity analysis are shown using a cost-effectiveness acceptability curve (CEAC). The CEAC graph shows the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

Figure 1: Cost-effectiveness acceptability curves (CEACs) for imaging strategies for distant disease in a pooled group of all patients with cancer of the upper aerodigestive tract



It can be seen that, at a threshold of £20,000 per QALY, conventional imaging has a 52% probability of being cost-effective, while PET-CT has a 1% probability of being cost-effective and no imaging has a 47% probability of being cost-effective. It should be noted that the key uncertainty in this analysis was the proportion of patients with a change in management, which was varied considerably in the PSA (between 0% and 100%). Running the PSA without including this variable led to conventional imaging having a 98% probability of being cost-effective while no imaging had a 0% probability of being cost-effective and PET-CT had a 2% probability of being cost-effective.

Subgroup analysis results (by disease site, T stage and N stage)

The cost-effectiveness of the imaging strategies in various subgroups of T and N stages was evaluated for each of the disease sites (as well as all sites combined). The full results of this analysis can be found in the full economic report for this topic in the appendix but some trends were observed. In general, the imaging strategies (conventional imaging and PET-CT) were more likely to be cost-effective in the more advanced T and N stages, reflecting both the greater risk of distant metastases in these groups and the larger cost offsets.

Most notably, it could be seen that the optimal strategy differs from the base case analysis in numerous instances. PET-CT was found to be cost-effective in numerous high risk groups, such as in patients with N3 disease or in higher risk groups within nasopharyngeal or hypopharyngeal cancer. It was also found that a strategy of no imaging was cost-effective in the lowest risk groups (T1N0 and T2N0).

Conclusion

The results of the base case analysis suggest that conventional imaging is an effective and cost-effective approach in a pooled group of all HNC patients. One-way and probabilistic sensitivity analysis revealed that the result was particularly sensitive to the proportions of patients whose management changes as a result of distant disease detection. This was of particular interest as there was uncertainty amongst the guideline committee as to what extent management would be altered in many patients.

Despite the better diagnostic accuracy of PET-CT, its use was not found to be a cost-effective strategy to use in the pooled group of all HNC patients. In this group of patients, it

was found that the benefits were too small to justify the substantial additional cost associated with PET-CT.

However, subgroup analysis revealed numerous deviations from the base case result. In particular, PET-CT was found to be cost-effective in numerous higher risk groups, such as in patients with N3 disease or in higher risk groups within nasopharyngeal or hypopharyngeal cancer.

Recommendations	**Do not offer systemic staging to people with T1N0 or T2N0 cancer of the upper aerodigestive tract.** **Offer conventional imaging to people with cancer of the upper aerodigestive tract that is:** • **T1N1-2 (all sites)** • **T2N1-2 (all sites)** • **T3N1-2 (all sites)** • **T4N1-2 (all sites except the nasopharynx and hypopharynx).** **Offer systemic staging to people with T3, T4 or N+ cancer of the upper aerodigestive tract.**
Relative value placed on the outcomes considered	All outcomes within the PICO were reported, but the most value was placed on positive predictive value, as this provides the most useful measure of assessing people's risk of systemic disease.
Quality of the evidence	The included evidence was assessed using QUADAS2; no major issues with bias were identified. Applicability issues included: • some studies reported data for certain tumour subsites only, with a bias towards over-reporting of NPC. • several studies were conducted in South East Asia, where the prevalence of nasopharyngeal cancer is considerably higher than in the UK. The reviewer also highlighted the importance of prevalence and the influence of this on the likelihood of systemic disease. The DAHNO dataset had a lower prevalence than any other identified source of evidence and there was uncertainty around how M1 stage was determined, and whether there was centre-by-centre variation in M-stage workup. Recommendations were based largely on the DAHNO dataset as this was most relevant to the UK population. Although the DAHNO dataset was large, some subgroups of patients were small and contained low numbers of patients with M1 disease, making the results more uncertain in these categories. The GC noted, based on the evidence from the DAHNO dataset, that there was a low level risk of metastatic disease in people with T1-T2N0 CUADT. Given the low incidence, and the additional resource use and risk of false positives associated with systemic staging, the GC agreed to recommend systemic staging should not be recommended to this patient group. The GC also noted from the DAHNO dataset that there was a significant increase in the risk of metastatic disease in people with T3, T4 or N+ CUADT. They therefore recommended systemic staging be offered to these patients. Uncertainty remains about the risk of systemic disease associated with some of the factors investigated factors, and further investigation of risk is needed in these groups. The GC made a

	research recommendation aiming to address this.
Trade-off between clinical benefits and harms	The GC consider the potential benefits of the recommendations to be: • more targeted use of systemic imaging • avoiding unnecessary investigations/radiation exposure in patients who are at very low risk of systemic disease • avoiding over-investigation of incidental and insignificant abnormalities identified by imaging of patients at very low risk of systemic disease. The GC consider the potential harms of the recommendations to be: • patient anxiety from not being tested • in the patient groups who should not routinely receive systemic imaging, a very small proportion will have systemic disease that initially goes undetected. Some patients will therefore require later systemic imaging, after surgery for example. Not detecting systemic disease in a small proportion of low-risk patients is outweighed by the large number of unnecessary investigations avoided, and the false positive tests avoided. Therefore, the GC considered the benefits of the recommendations to outweigh the harms.
Trade-off between net health benefits and resource use	An economic model was developed based on a DAHNO dataset that presented prevalence data by site and stage. The GC used the economic model to determine populations in whom systemic staging with conventional imaging or FDG PET-CT may be cost-effective. It was shown that using conventional imaging as the systemic staging strategy was cost-effective in the majority of patient populations. Notable exceptions were the T1N0 and T2NO patient subgroups, in which no imaging was found to be the optimal strategy because of the low number of patients with systemic disease. However, the GC were unsure about the proportion of patients whose management changes as a result of distant disease detection and the economic model showed that the results were sensitive to changes in this aspect. Therefore, there was some uncertainty over the economic results, which was reflected in the sensitivity analyses. Overall though, the GC felt that the base case results coupled with benefits that could not be captured in the model (such as better patient prognosis and planning) were sufficient to make strong recommendations.
Other considerations	The major change in practice from the recommendations will be the cessation of systemic staging for people with T1N0 and T2N0 disease. The evidence available focussed on newly diagnosed CUADT, not recurrent disease or second primary tumours.

1

Research recommendation	**A prospective study should be undertaken to identify what factors determine the risk of a person presenting with CUADT having metastasis or a second primary cancer. Outcomes of interest include prevalence, predictive value and how the abnormalities identified influence patient management.**
Why this is important	The presence of metastasis and a synchronous second primary cancer at presentation is rare in patients with CUADT. Subgroups

	of patients have been identified in whom the risk is clearly elevated. However, it is not clear at which level of risk detailed staging investigations are justified and the impact the results of these would have on decision making by the clinicians and the patient. Health economic modelling is required to inform this process.

Clinical question: What is the most effective systemic imaging strategy for investigating cancer of the upper aerodigestive tract?

Clinical evidence (see Appendix H)

The evidence summary identified 10 systematic reviews and meta-analyses that were directly relevant to the review question. 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 HNC. 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 HNC. 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)

Head and neck cancer (any site)

Four systematic reviews and meta-analyses (Xu 2011a, Xu 2012a, Xu 2011b, Yi 2013) investigated the diagnostic accuracy of PET/CT in people with HNC. 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 HNC 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 HNC. 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 HNC. 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.

Cost-effectiveness evidence

See cost-effectiveness evidence section on pages 42-48.

1

Recommendations	**Offer FDG PET-CT to people with T4 cancer of the hypopharynx or nasopharynx.** **Offer FDG PET-CT to people with N3 cancer of the upper aerodigestive tract.**
Relative value placed on the outcomes considered	Sensitivity and specificity were considered the most important outcomes in the PICO. Predictive values were not specified in the PICO, but these were also used to assess the usefulness of imaging investigations. This is because the usefulness of a test assessing systemic disease depends on the prevalence of systemic disease as well as on test performance. Process related morbidity and health-related quality of life were other outcomes included in the PICO, but no evidence was identified for these outcomes.
Quality of the evidence	The included evidence was assessed using QUADAS2. The reviewer did not identify and major issues with bias or applicability. There was limited evidence directly comparing the diagnostic accuracy of different tests, most studies only reporting the diagnostic accuracy of a single test. The most useful evidence, and that which most influenced the GC's recommendations, came from studies that included direct comparative evidence. One meta-analysis directly compared FDG PET-CT to conventional imaging. For nasopharyngeal cancers, conventional imaging included chest radiography, abdominal ultrasonography and bone scan. For other sites conventional imaging methods were defined as chest with/without abdominal CT. This was assumed to be representative of conventional imaging in the UK population. The GC noted that the evidence showed higher sensitivity for FDG PET-CT and equivalent specificity compared with conventional imaging,
Trade-off between clinical benefits and harms	The GC consider the potential benefits of the recommendations to be: • better rates of detection of systemic disease • less over treatment (of incurable patients). The GC consider the potential harms of the recommendations to be: • increased radiation exposure for patients as a result of more FDG PET-CT use • more testing burden for patients. The benefits of the recommendations were considered by the GC to outweigh the harms.
Trade-off between net health benefits and resource use	An economic model was developed based on a DAHNO dataset that presented prevalence data by site and stage. The GC used the economic model to determine populations in whom systemic staging with conventional imaging or FDG PET-CT may be cost-effective. FDG PET-CT was found to be more cost-effective than conventional imaging in high risk groups (i.e. groups with high prevalence of distant metastases). This was most evident in patients with N3 disease at any subsite, T4 nasopharynx or T4 hypopharynx cancer, where FDG PET-CT was found to be dominant. Therefore the GC recommended the use of FDG PET-

	CT for systemic staging in these patient groups only. However, the GC were unsure about the proportion of patients whose management changes as a result of distant disease detection and the economic model showed that the results were sensitive to changes in this aspect. Therefore, there was some uncertainty over the economic results, which was reflected in the sensitivity analyses. Overall though, the GC felt that the subgroup results coupled with benefits that could not be captured in the model (such as better patient prognosis and planning) were sufficient to make strong recommendations.
Other considerations	The major changes in practice from the recommendations will be FDG PET-CT imaging for all patients with N3 disease at any subsite, T4 nasopharynx or T4 hypopharynx cancer. There may also be a reduction in the use of other tests, such as chest CT. The available evidence focussed on distant metastases and not synchronous second primary cancer. However, the GC acknowledged that it is not always possible to distinguish between these.

References

Aassar, O. S., Fischbein, N. J., Caputo, G. R., Kaplan, M. J., Price, D. C., Singer, M. I., Dillon, W. P., and Hawkins, R. A. Metastatic head and neck cancer: Role and usefulness of FDG PET in locating occult primary tumors. Radiology 1999. 210(1): 177-181

Akhavan-Moghadam, J., Afaaghi, M., Maleki, A. R., and Saburi, A. Fine needle aspiration: An atraumatic method to diagnose head and neck masses. Trauma Monthly 2013. 18: 117-121

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

Ara, R. and Brazier, J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value in Health 2008. 11(7): 1131-1143

Bohuslavizki, K. H., Klutmann, S., Kroger, S., Sonnemann, U., Buchert, R., Werner, J. A., Mester, J., and Clausen, M. FDG PET detection of unknown primary tumors. Journal of Nuclear Medicine 2000. 41(5): 816-822

Braams, J. W., Pruim, J., Kole, A. C., Nikkels, P. G., Vaalburg, W., Vermey, A., and Roodenburg, J. L. Detection of unknown primary head and neck tumors by positron emission tomography. International Journal of Oral & Maxillofacial Surgery 1997. 26(2): 112-115

Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck. NICE technology appraisal guidance 145. 2008

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. European Journal of Nuclear Medicine and Molecular Imaging 2011. 38(9): 1607-1619

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

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 and Neck 2009. 31(3): 346-354

Cianchetti, M., Mancuso, A. A., Amdur, R. J., Werning, J. W., Kirwan, J., Morris, C. G., and Mendenhall, W. M. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 2009. 119(12): 2348-2354

Curtis, L. Unit Costs of Health and Social Care 2014, Personal Social Services Research Unit (PSSRU), University of Kent, Canterbury

Dangore, S. B., Degwekar, S. S., and Bhowate, R. R. Evaluation of the efficacy of colour Doppler ultrasound in diagnosis of cervical lymphadenopathy. Dentomaxillofac Radiol 2008. 37: 205-212

Draper, M. R., Pfleiderer, A. G., and Smith, W. Assessment of a cytology grading system for head and neck masses. Clinical Otolaryngology and Allied Sciences 2003. 28: 34-38

Drugs and pharmaceutical electronic market information (eMit) [database on the internet]. London: UK Department of Health

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

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

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

Greven, K. M., Keyes, J. W., Jr., Williams, D. W., III, McGuirt, W. F., and Joyce, W. T., III. Occult primary tumors of the head and neck: lack of benefit from positron emission tomography imaging with 2-[F-18]fluoro-2-deoxy-D-glucose. Cancer 1999. 86(1): 114-118

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

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

Higgins, K. M. 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

Hollenbeak, C. S., Lowe, V. J., and Stack, B. C., Jr. The cost-effectiveness of fluorodeoxyglucose 18-F positron emission tomography in the N0 neck. Cancer 2001. 92(9): 2341-2348

Howlett, D. C., Harper, B., Quante, M., Berresford, A., Morley, M., Grant, J., Ramesar, K., and Barnes, S. Diagnostic adequacy and accuracy of fine needle aspiration cytology in neck

lump assessment: Results from a regional cancer network over a one year period. Journal of Laryngology and Otology 2007. 121: 571-579

Jandu, M. and Webster, K. The role of operator experience in fine needle aspiration cytology of head and neck masses. International Journal of Oral and Maxillofacial Surgery 1999. 28: 441-444

Johansen, J., Buus, S., Loft, A., Keiding, S., Overgaard, M., Hansen, H. S., Grau, C., Bundgaard, T., Kirkegaard, J., and Overgaard, J. Prospective study of 18FDG-PET in the detection and management of patients with lymph node metastases to the neck from an unknown primary tumor. Results from the Dahanca-13 study. Head and Neck 2008. 30(4): 471-478

Jungehulsing, M., Scheidhauer, K., Damm, M., Pietrzyk, U., Eckel, H., Schicha, H., and Stennert, E. 2[F]-fluoro-2-deoxy-D-glucose positron emission tomography is a sensitive tool for the detection of occult primary cancer (carcinoma of unknown primary syndrome) with head and neck lymph node manifestation. Otolaryngology - Head & Neck Surgery 2000. 123(3): 294-301

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 2011. 121(6): 1194-1201

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

Khan, N., Afroz, N., Haider, A., Hassan, M. J., Hashmi, S. H., and Hasan, S. A. Role of fine needle aspiration, imprint and scrape cytology in the evaluation of intraoral lesions. Journal of Cytology 2013. 30: 263-269.

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 Oncology 2008. 44(2): 148-152

Kutluhan, A., Kisli, E., Yakut, F., Yurttas, V., and Kosem, M. The role of fine-needle aspiration biopsy in the evaluation of head and neck masses. Oto-Rhino-Laryngologia Nova 2003. 12: 291-294

Lassig, A. A.D., Duffy, S. A., Fowler, K. E., Ronis, D. L., Chepeha, D. B., and Terrell, J. E. The effect of neck dissection on quality of life after chemoradiation. Otolaryngology-Head and Neck Surgery 2008. 139(4): 511-518

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. Journal of Nuclear Medicine 2007. 48(10): 1614-1619

Lo, C. P., Chen, C. Y., Chin, S. C., Lee, K. W., Hsueh, C. J., Juan, C. J., Kao, H. W., and Huang, G. S. Detection of suspicious malignant cervical lymph nodes of unknown origin: Diagnostic accuracy of ultrasound-guided fine-needle aspiration biopsy with nodal size and central necrosis correlate. Canadian Association of Radiologists Journal 2007. 58: 286-291

Masaki, T., Katada, C., Nakayama, M., Takeda, M., Miyamoto, S., Seino, Y., Matsuba, H., Okamoto, T., Koizumi, W., Tanabe, S., Horiguchi, S., Okamoto, M., and Muto, M. Usefulness and pitfall of Narrow band imaging combined with magnifying endoscopy for detecting an unknown head and neck primary site with cervical lymph node metastasis. Auris Nasus Larynx 2012. 39(5): 502-506

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.

Mehta, V., Johnson, P., Tassler, A., Kim, S., Ferris, R. L., Nance, M., Johnson, J. T., and Duvvuri, U. A new paradigm for the diagnosis and management of unknown primary tumors of the head and neck: a role for transoral robotic surgery. Laryngoscope 2013. 123(1): 146-151

Miller, F. R., Karnad, A. B., Eng, T., Hussey, D. H., Stan, McGuff H., and Otto, R. A. Management of the unknown primary carcinoma: long-term follow-up on a negative PET scan and negative panendoscopy. Head and Neck 2008. 30(1): 28-34

Mukherji, S. K., Drane, W. E., Mancuso, A. A., Parsons, J. T., Mendenhall, W. M., and Stringer, S. Occult primary tumors of the head and neck: detection with 2-[F-18] fluoro-2-deoxy-D-glucose SPECT. Radiology 1996. 199(3): 761-766

Murthy, P., Laing, M. R., and Palmer, T. J. Fine needle aspiration cytology of head and neck lesions: an early experience. J R Coll Surg Edinb 1997. 42: 341-346

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.

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

NHS reference costs 2013-14 [internet database]. London: UK Department of Health

Patel, S. A., Magnuson, J. S., Holsinger, F. C., Karni, R. J., Richmon, J. D., Gross, N. D., Bhrany, A. D., Ferrell, J. K., Ford, S. E., Kennedy, A. A., and Mendez, E. Robotic surgery for primary head and neck squamous cell carcinoma of unknown site. JAMA Otolaryngol Head Neck Surg 2013. 139(11): 1203-1211

Pattani, K. M., Goodier, M., Lilien, D., Kupferman, T., Caldito, G., and Nathan, C. O. Utility of panendoscopy for the detection of unknown primary head and neck cancer in patients with a negative PET/CT scan. Ear, Nose, & Throat Journal 2011. 90(8): E16-E20

Pfeiffer, J., Kayser, G., Technau-Ihling, K., Boedeker, C. C., and Ridder, G. J. Ultrasound-guided core-needle biopsy in the diagnosis of head and neck masses: Indications, technique, and results. Head and Neck 2007. 29: 1033-1040

Prowse, S. J., Shaw, R., Ganeshan, D., Prowse, P. M., Hanlon, R., Lewis-Jones, H., and Wieshmann, H. The added value of 18F-fluorodeoxyglucose positron emission tomography

computed tomography in patients with neck lymph node metastases from an unknown primary malignancy. Journal of Laryngology & Otology 2013. 127(8): 780-787

Raab, S. S., Sigman, J. D., and Hoffman, H. T. The utility of parotid gland and level I and II neck fine-needle aspiration. Arch Pathol Lab Med 1998. 122: 823-827

Regelink, G., Brouwer, J., de Bree, R., Pruim, J., van der Laan, B. F. A. M., Vaalburg, W., Hoekstra, O. S., Comans, E. F. I., Vissink, A., Leemans, C. R., and Roodenburg, J. L. N. Detection of unknown primary tumours and distant metastases in patients with cervical metastases: value of FDG-PET versus conventional modalities. European Journal of Nuclear Medicine and Molecular Imaging 2002. 29(8): 1024-1030

Robinson, I. A. and Cozens, N. J. A. Does a joint ultrasound guided cytology clinic optimize the cytological evaluation of head and neck masses? Clinical Radiology 1999. 54: 312-316

Roh, J. L., Kim, J. S., Lee, J. H., Cho, K. J., Choi, S. H., Nam, S. Y., and Kim, S. Y. Utility of combined (18)F-fluorodeoxyglucose-positron emission tomography and computed tomography in patients with cervical metastases from unknown primary tumors. Oral Oncology 2009. 45(3): 218-224

Ryu, I. S., Choi, S. H., Kim, D. H., Han, M. W., Roh, J. L., Kim, S. Y., and Nam, S. Y. Detection of the primary lesion in patients with cervical metastases from unknown primary tumors with narrow band imaging endoscopy: Preliminary report. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck 2013. 35(1): 10-+

Sacco, J. J., Botten, J., Macbeth, F., Bagust, A., and Clark, P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. PLoS One 2010. 5(1): e8933

Safa, A. A., Tran, L. M., Rege, S., Brown, C. V., Mandelkern, M. A., Wang, M. B., Sadeghi, A., and Juillard, G. The role of positron emission tomography in occult primary head and neck cancers. Cancer Journal From Scientific American 1999. 5(4): 214-218

Sakai, A., Okami, K., Ebisumoto, K., Sugimoto, R., Maki, D., and Iida, M. New techniques to detect unknown primaries in cervical lymph node metastasis. Laryngoscope 2010. 120(9): 1779-1783

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

Sher, D. J., Tishler, R. B., Annino, D., and Punglia, R. S. Cost-effectiveness of CT and PET-CT for determining the need for adjuvant neck dissection in locally advanced head and neck cancer. Annals of Oncology 2010. 21(5): 1072-1077

Shinozaki, T., Hayashi, R., Ebihara, M., Miyazaki, M., Daiko, H., Saikawa, M., and Ebihara, S. Narrow band imaging endoscopy for unknown primary tumor sites of the neck. Head and Neck 2012. 34(6): 826-829

Shrestha, M. K., Ghartimagar, D., and Ghosh, A. Diagnostic accuracy of computed tomogram in the evaluation of a neck mass. Journal of the Nepal Medical Association 2012. 51: 164-170

Silva, P., Hulse, P., Sykes, A. J., Carrington, B., Julyan, P. J., Homer, J. J., Hastings, D. L., and Slevin, N. J. Should FDG-PET scanning be routinely used for patients with an unknown head and neck squamous primary? Journal of Laryngology & Otology 2007. 121(2): 149-153

Stoeckli, S. J., Mosna-Firlejczyk, K., and Goerres, G. W. Lymph node metastasis of squamous cell carcinoma from an unknown primary: impact of positron emission

tomography. European Journal of Nuclear Medicine & Molecular Imaging 2003. 30(3): 411-416

Tandon, S., Shahab, R., Benton, J. I., Ghosh, S. K., Sheard, J., and Jones, T. M. Fine-needle aspiration cytology in a regional head and neck cancer center: comparison with a systematic review and meta-analysis. Head and Neck 2008. 30(9): 1246-1252

van Veen, S. A., Balm, A. J., Valdes Olmos, R. A., Hoefnagel, C. A., Hilgers, F. J., Tan, I. B., and Pameijer, F. A. Occult primary tumors of the head and neck: accuracy of thallium 201 single-photon emission computed tomography and computed tomography and/or magnetic resonance imaging. Archives of Otolaryngology -- Head & Neck Surgery 2001. 127(4): 406-411

Veivers, D. and Dent, J. Lateral cervical cysts: An Australian perspective. ANZ Journal of Surgery 2012. 82: 799-802

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

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. Archives of Otolaryngology--Head & Neck Surgery 2002. 128(6): 703-707

Wong, W. L., Sonoda, L. I., Gharpurhy, A., Gollub, F., Wellsted, D., Goodchild, K., Lemon, C., Farrell, R., and Saunders, M. 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the assessment of occult primary head and neck cancers--an audit and review of published studies. . Clinical Oncology (Royal College of Radiologists) 2012. 24(3): 190-195

Wu, E. N. H., Chen, Y. L., Toh, C. H., Ko, S. F., Lin, Y. U. C., and Ng, S. H. CT-guided core needle biopsy of deep suprahyoid head and neck lesions in untreated patients. Interventional Neuroradiology 2013. 19: 365-369.

Wu, M., Burstein, D. E., Yuan, S., Nurse, L. A., Szporn, A. H., Zhang, D., and Genden, E. A comparative study of 200 fine needle aspiration biopsies performed by clinicians and cytopathologists. Laryngoscope 2006. 116(7): 1212-1215

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

Xu, G.-Z. 18FDG-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

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.

Yabuki, K., Tsukuda, M., Horiuchi, C., Taguchi, T., and Nishimura, G. Role of 18F-FDG PET in detecting primary site in the patient with primary unknown carcinoma. Eur Arch Otorhinolaryngol 2010. 267(11): 1785-1792

1 Yi, X., Fan, Min, Liu, Yilin, Zhang, Hongting, and Liu, Shixi. 18 FDG PET and PET-CT for the
2 detection of bone metastases in patients with head and neck cancer. A meta-analysis.
3 Journal of Medical Imaging & Radiation Oncology 2013. 57(6): 674-679.

3 Treatment of early stage disease

3.1 Squamous cell carcinoma of the larynx

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.

Clinical question: What is the most effective treatment for newly diagnosed T1 or T2 carcinoma of the larynx?

Clinical evidence (see Appendix H)

Transoral laser surgery (TLS) versus radiotherapy (RT)

Evidence came from a systematic review of observational studies (Abdurehim et al., 2012) and four observational studies published since the review (Dinapoli et al., 2010; Osborn et al., 2011; Remmelts et al., 2013; van Gogh, Verdonck-de Leeuw, Wedler-Peeters, Langendijk, Mahieu, 2012, & Comert, 2014) 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 to 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 et al., 2014). 5 year overall survival was better with larynx 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 larynx preserving surgery plus neck dissection (versus RT: HR = 0.89; 95% C.I. 0.69 to 1.15; P = 0.36) versus 76% for surgery without neck dissection (versus RT: HR = 0.48; 95% C.I. 0.33 to 0.71; P<0.001). For T2 supraglottic tumours, 5 year overall survival was 45% with radiotherapy versus 49% with larynx preserving surgery plus neck dissection (HR = 0.93; 95% C.I. 0.65 to 1.3; versus RT; P = 0.67) versus 77% for surgery without neck dissection (HR = 0.36; 95% C.I. 0.23 to 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 to 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 to 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 to 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 to 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 to 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, Majumdar, Morton, 2010; van et al., 2012, & Greulich, Parker, Lee, Merati, & Misono, 2015) 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 et al., 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 et al. 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

Overall survival

Very low quality evidence from two observational studies (Mantsopoulos et al., 2012; Puxeddu et al., 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 to 10.99; OR >1 favours TLS).

Disease specific survival

Very low quality evidence from three observational studies (Puxeddu et al., 2000; Karatzanis et al., 2010; Maurizi, Almadori, Plaudetti, De, & Galli, 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 to 9.74; OR >1 favours TLS). In patients with T2 laryngeal carcinoma (Mantsopoulos et al., 2012; Karatzanis et al., 2010) there is uncertainty about which of the treatments is the most effective (OR = 1.89; 95% CI 0.72 to 4.91; OR >1 favours TLS) in terms of disease specific survival.

Local control

Very low quality evidence from observational studies (Puxeddu et al., 2000; Karatzanis et al., 2010; Maurizi et al., 2005; Mantsopoulos et al., 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 to 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 to 1.55; OR >1 favours TLS) in terms of local control.

Laryngeal preservation

Very low quality evidence from four observational studies (Puxeddu et al., 2000; Karatzanis et al., 2010; Maurizi et al., 2005; Mantsopoulos et al., 2012) suggests that laryngeal

preservation is more likely with transoral laser surgery than with open partial laryngectomy (OR = 3.71; 95% CI 1.87 to 7.35; OR >1 favours TLS).

Voice function

A single observational study (Puxeddu et al., 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

Two observational studies (Puxeddu et al., 2000, & Milovanovic et al., 2014) provided very low quality evidence about the mean length of hospital stay: 2.1 to 3.3 days with transoral laser surgery versus 7.5 to 8.4 days with open partial laryngectomy.

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 et al., 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% C.I. 95% to 98%) and a permanent gastrostromy rate of 2% (95% C.I. 0.9% to 3.9%).

Serious complications

Very low quality evidence from 2 observational studies (Karatzanis et al., 2010; Mantsopoulos et al., 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 to 0.90; OR <1 favours TLS).

1 **Table 14: GRADE Profile transoral laser surgery (TLS) versus radiotherapy (RT) for early stage laryngeal cancer.**

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TLS**	**RT**	**Relative (95% CI)**	**Absolute**	**Quality**
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 to 1.60)	27 more per 1000 (from 17 fewer to 64 more)	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 to 3.20)	11 more per 1000 (from 10 fewer to 21 more)	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 to 0.95)	48 fewer per 1000 (from 5 fewer to 102 fewer)	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 to 3.28)	51 fewer per 1000 (from 6 more to 78 more)	LOW
Progression free survival - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Treatment related mortality - not reported											
0	-	-	-	-	-	none	-	-	-	-	

Morbidity - decannulation - not reported												
0	-	-	-	-	-	none	-	-	-	-		
Laryngeal 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 to 2.01)	12 fewer per 1000 (from 129 fewer to 49 more)	LOW	
Laryngeal 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 to 16.71)	100 more per 1000 (from 82 more to 108 more)	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	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 RT.	VERY LOW	
Voice function (measured with: maximum phonation time; Better indicated by higher values)												
4	observationa	no	Serious[2]	no serious	Serious[4]	none	55	57	-	MD 1.41 lower	VER	

	l studies	seriou s risk of bias		indirectness						(3.51 lower to 0.69 higher)	Y LOW	
Voice function (measured with: air flow rate; Better indicated by higher values)												
3	observationa l studies	no seriou s risk of bias	Serious[2]	no serious indirectness	Serious[4]	none	36	39	-	MD 21.46 higher (78.79 lower to 121.72 higher)	VER Y LOW	
Voice function (measured with: Fundamental frequency; Better indicated by higher values)												
7	observationa l studies	no seriou s risk of bias	Serious[2]	no serious indirectness	Serious[4]	none	119	113	-	MD 13.89 higher (9.64 lower to 18.13 higher)	VER Y LOW	
Voice function (measured with: jitter; Better indicated by higher values)												
7	observationa l studies	no seriou s risk of bias	Serious[2]	no serious indirectness	Serious[4]	none	168	136	-	MD 0.13 higher (0.28 lower to 0.53 higher)	VER Y LOW	
Voice function (measured with: shimmer; Better indicated by lower values)												
7	observationa l studies	no seriou s risk of bias	Serious[2]	no serious indirectness	Serious[4]	none	168	143	-	MD 0.08 higher (0.65 lower to 0.81 higher)	VER Y LOW	
Voice function (measured with: Voice Handicap Index; Better indicated by higher values)												
6	observationa l studies	no seriou s risk of bias	Serious[2]	no serious indirectness	Serious[4]	none	194	176	-	MD 5.02 higher (2.14 lower to 12.17 higher)	VER Y LOW	

[1] *T1a tumours only.*

[2] *Considerable heterogeneity*

[3] *Measured patient's perception of swallow function.*

[4] *Low numbers of patients.*

1 **Table 15: GRADE Profile open partial laryngectomy for early stage laryngeal cancer.**

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TLS**	**Open partial laryngectomy**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 10.99)	202 more per 1000 (from 209 fewer to 216 more)	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 to 9.74)	108 more per 1000 (from 53 more to 133 more)	VERY 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 to 4.91)	33 more per 1000 (from 25 fewer to 57 more)	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 to 4.56)	101 more per 1000 (from 24 more to 146 more)	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 to 1.55)	26 fewer per 1000 (from 122 fewer to 26 more)	VERY LOW	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TLS**	**Open partial laryngectomy**	**Relative (95% CI)**	**Absolute**	**Quality**	
Laryngeal 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 to 7.35)	85 more per 1000 (from 52 more to 102 more)	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	VERY LOW	
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)	VERY LOW	
Decannulation												
42	observational studies	Serious[1]	Serious[2]	no serious indirectness	no serious imprecision	none	-	3955	-	96.3% [94.9 – 97.6%]	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%]	VERY LOW	
Permanent gastrostomy												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TLS**	**Open partial laryngectomy**	**Relative (95% CI)**	**Absolute**	**Quality**	
20	observational studies	Serious[1]	serious	no serious indirectness	no serious imprecision	none	-	2000	-	2.0% [0.9 – 3.9%]	VERY LOW	
Health related quality of life (swallow function) - not reported												
0	-	-	-	-	-	none	-	-	-	-		

1 *1 Unclear whether treatment groups are from the same historical period.*
2 *2 Considerable heterogeneity.*

3

Cost-effectiveness evidence

Background

Early carcinomas of the larynx (T1 and T2 tumours) are typically treated with either radical radiotherapy or transoral laser microsurgery (TLM). There is lack of evidence demonstrating the superiority of either of these techniques over the other in terms of oncologic outcomes, laryngeal function or cost-effectiveness.

The aim of this analysis was to estimate the cost-effectiveness of initial treatments for newly diagnosed T1 or T2 carcinoma of the larynx.

Existing Economic Evidence

A systematic literature review identified one paper that was deemed to be partially applicable to the current decision problem. The cost-effectiveness of treatments for early stage glottic carcinoma was assessed in a study by Higgins 2011, in which transoral laser excision was found to dominate radiotherapy with higher QALYs and lower costs. However, as this study considered the Canadian health care system it was not deemed sufficient to address the decision problem in the UK context.

De Novo Economic Model

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel.

Clinical data

Recurrence rates

The recurrence rates for T1a laryngeal cancer patients undergoing radiotherapy or TLM were estimated using data on progression free survival from the clinical evidence review conducted for this guideline. A meta-analysis of 14 observational studies in patients with stage T1a disease treated with TLM and radiotherapy reported an odds ratio (OR) of 0.92 for local control rates suggesting a slight benefit in patients treated with radiotherapy.

For the purposes of the economic model, annual recurrence rates for patients treated with radiotherapy were estimated using the local control rates observed in patients treated with radiotherapy in the studies (89.3% over a follow-up period of 5-139 months). A relative risk of 0.88 was then estimated based on the odds ratio and this was used to estimate local control rates in patients treated with TLM (88.5%). These values were then converted to annual recurrence rates of 2.05% and 2.21% for patients treated with radiotherapy and TLM, respectively (assuming a constant rate of recurrence over the follow-up period).

While differences in recurrence rates have been modelled in the base case, it should be noted that the slight difference in local control rates reported in the clinical evidence (OR=0.92) was not found to be statistically significant (OR 95% CI 0.62 to 1.36). Therefore, there is uncertainty about the modelled difference in local control rates and this uncertainty was explored in sensitivity analysis (both probabilistic and one-way). In particular, the impact of assuming equivalent recurrence rates with radiotherapy and TLM was explored in one-way sensitivity analysis.

In the absence of high quality comparative evidence for the T1b-T2 laryngeal group, observational evidence was used. A systematic review by O'Hara et al. 2013 found that 3-year local control rates were lower in patients treated with TLM (76.8%) rather than radiotherapy (86.2%). These were converted to annual recurrence estimates of 6.56% and 2.99% for the TLM and radiotherapy arms respectively (assuming a constant rate of recurrence over the time period).

It was assumed that there were no recurrences after five years of being recurrence free. This is intended to reflect clinical practice where recurrences after five years are very rare.

Mortality

A meta-analysis of 11 observational studies in patients with stage T1a disease treated with TLM and radiotherapy reported an odds ratio (OR) of 1.55 for disease specific survival, suggesting a slight benefit in patients treated with TLM. However, as above, this difference in survival was not found to be statistically significant (OR 95% CI 0.75 to 3.20). Furthermore, in the opinion of the guideline committee, there was no reason to expect them to differ. It should also be noted that the mortality rates are somewhat contradictory when compared with the recurrence rates (i.e. TLM is favoured when considering survival but radiotherapy is favoured when considering recurrence). Therefore, for the purposes of the economic model, it was assumed that there was no difference in disease specific mortality in the base case. A combined mortality rate was estimated using the disease specific survival observed in T1a patients treated with radiotherapy or TLM in the studies (98.0% over a follow-up period of 5-139 months). This value was then converted to an annual mortality rate of 0.4% (assuming a constant rate of mortality over the follow-up period). Note that, due to a lack of more appropriate data, these values were also applied to T1b-T2 laryngeal cancer patients.

The impact of assuming a difference in mortality rates was explored in one-way sensitivity analysis and the full uncertainty around the estimate was explore in probabilistic sensitivity analysis.

Death from other causes was captured using 2011-2013 life tables for England and Wales from the office of national statistics (ONS).

Treatment proportions following a recurrence

There are numerous treatment options available for patients that experience a recurrence. The treatment proportions for recurrent patients that were initially T1a and treated with radiotherapy were estimated from a survey of current UK practice by Paleri et al. 2012 (personal communication). All other treatment proportions for recurrent patients were estimated by the guideline committee based on their experience in clinical practice.

Costs

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. GP visit). Where possible, all costs were estimated in 2013-14 prices.

The majority of costs were sourced from NHS reference costs 2013/14 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dose and unit cost information from the British National Formulary (BNF), resource use and cost information from the Personal Social Services Research Unit (PSSRU) and the advice of the guideline committee.

Initial treatment costs

The total cost of initial radiotherapy was estimated to be £3,430, based upon preparation (£906.16) and delivery costs (£126.17 per fraction) from NHS reference costs and assuming that 20 fractions of complex conformal radiotherapy would be delivered. The cost of TLM was estimated to be £2,035, based upon the cost of 'intermediate mouth or throat procedures with and without co-morbidities and complications (weighted average using procedure numbers from NHS reference costs).

Salvage treatment costs

Patients that experience a recurrence were assumed to receive salvage treatment with treatment options and proportions estimated by the guideline committee (see appendix for full details). For those patients receiving a TLM or conventional radiotherapy as salvage treatment, the same costs outlined above (for initial treatment) were applied. However, patients with late stage recurrences (T3 or T4) undergoing radiotherapy were assumed to receive more intensive treatment with intensity modulated radiotherapy (IMRT). In the base case, it was assumed that 30% of patients receiving radiotherapy for a recurrence would receive IMRT. The cost of IMRT was estimated to be £5,411, based upon preparation (£1626) and delivery costs (£126.17 per fraction) from NHS reference costs, assuming that 30 fractions of complex conformal radiotherapy would be delivered.

In addition, it was assumed that 50% of patients receiving IMRT would also receive concomitant chemotherapy. It was assumed that cisplatin would be given in two doses of 100mg/m2 at an estimated cost of £658.

The costs of salvage treatment with a partial laryngectomy or total laryngectomy for patients that experience a recurrence were based on the cost of 'Very Complex, Mouth or Throat Procedures' from NHS Reference costs. It was assumed that adjuvant IMRT would be performed for 60% of patients undergoing total laryngectomy if they have not previously been irradiated. It was further assumed that 50% of those patients that receive IMRT would receive concomitant chemotherapy with two doses of cisplatin. The IMRT and chemotherapy costs shown above (for patients with a late stage recurrence receiving IMRT) were also applied in this context.

Follow-up costs

The cost per follow-up consultation was estimated to be £86.92 based upon the average cost of a 'Non-Admitted Face to Face Attendance' (WF01A) from NHS reference costs in ENT and Maxillo-facial surgery. In addition, it was assumed that a nasendoscopy would be performed at each visit which was estimated to cost £115.09 based on the cost of 'Minor Nose Procedures, 19 years and over without CC' (CA24A) from NHS reference costs in ENT and Maxillo-facial surgery. The number of follow-up visits typically required after each treatment was estimated by the guideline committee.

Speech and language therapy (SLT) and dietetics costs

The costs of a dietetics session and speech and language therapy session were estimated to be £80.81 and £120.22, respectively. These costs were estimated based upon the weighted average cost of a 'Non-Admitted Face to Face Attendance - First' (WF01B) and 'Non-Admitted Face to Face Attendance – Follow up' (WF01A) from NHS reference costs in Dietetics and Speech and language therapy, respectively. The number of sessions required after each treatment modality were estimated by the guideline committee.

Valve change costs (after laryngectomy)

Local audits report that the costs associated with the regular valve changes required in patients after a total laryngectomy range from £530-£670 per patient per annum (personal communication with guideline committee member). For the purpose of the base case economic analysis the midpoint of £600 was used (variations were explored in sensitivity analysis).

Systemic chemotherapy and palliative care

A metastatic cancer state was not explicitly modelled as such. However, it was assumed that patients that die from upper aerodigestive tract cancer were likely to have developed metastatic disease. Thus, the costs associated with treating metastatic disease as well as the cost of palliative care were applied to these patients.

It was assumed that 50% of patients would have received systemic chemotherapy with a regimen of cisplatin 80mg/m2 (day 1) and fluorouracil 800mg/m2 (day 1, 2, 3 and 4) assumed to be given for an average of four cycles (patients may receive up to six but many will not receive the maximum). This regimen was selected as it was thought to be the most commonly used. The chemotherapy costs were estimated in the same fashion as above (for concomitant chemotherapy) by combining drug costs from eMit (accessed 2015) with administration costs from NHS reference costs. It was estimated that systemic chemotherapy would cost £889 per cycle (£3,555 for 4 cycles).

The cost of palliative care was estimated using estimates from a costing report by the Nuffield Trust (Georghiou et al. 2014, 'Exploring the cost of care at the end of life'). A cost of £7,287 was applied based on the average resource use of patients with cancer in the last three months of life.

Health related quality of life (QoL) values

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs were estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state. The majority of the QoL values utilised in the analysis were sourced from an existing cost-utility analysis by Higgins et al. 2011. The QoL data were differentiated depending on whether the patient is alive with the voice box entirely intact, partially intact (i.e. after a partial laryngectomy) or without voice box (i.e. after a total laryngectomy).

In addition, a QoL value from the NICE HTA on cetuximab was used as an estimate for patients in a metastatic disease state.

Table 16: Quality of life values applied in the economic model

Health state	Utility	Source
Alive with voice box entirely intact	0.8718	Higgins et al. 2011
Alive with part of voice box intact	0.7060	Higgins et al. 2011
Alive without voice box	0.3650	Higgins et al. 2011
End of life (metastatic disease)	0.6500	NICE HTA on cetuximab

Base Case Results

The model was run over a ten year time horizon with total costs and QALYs estimated for each treatment strategy with future costs and benefits discounted at a rate of 3.5% per year as recommended by NICE.

The deterministic base case results of the analysis are presented in the table below. It can be seen that, in both T1a and T1b-T2 laryngeal cancer, using radiotherapy as the initial treatment strategy was more expensive (£2,654 and £623 in T1a and T1b-T2 laryngeal cancer, respectively) and less effective (reduction of 0. 141 and 0.04 in T1a and T1b-T2 laryngeal cancer, respectively) than transoral laser microsurgery (TLM). Therefore, in cost-effectiveness terms, TLM can be considered the dominant strategy i.e. more effective and less costly.

T1a laryngeal cancer

Table 17: Base case cost-effectiveness results for T1a laryngeal cancer

	Cost		QALYs		ICER (cost per QALY)
Initial treatment	Total	Incremental	Total	Incremental	
Transoral laser microsurgery (TLM)	£8,202	-	6.48	-	-
Radiotherapy	£10,857	£2,654	6.34	-0.14	Dominated

T1b-T2 laryngeal cancer

Table 18: Base case cost-effectiveness results for T1b-T2 laryngeal cancer

Initial treatment	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Transoral laser microsurgery (TLM)	£11,025	-	6.28	-	-
Radiotherapy	£11,648	£623	6.23	-0.04	Dominated

Deterministic sensitivity analysis

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the one-way sensitivity analysis are shown in the tables below.

Table 19: One-way sensitivity analysis results for T1a and T1b-2 laryngeal cancer

Change made	ICER (cost per QALY gained with RT)	
	T1a	T1b-T2
No Damage following RT	RT Dominated	RT Dominated
No difference in local control	RT Dominated	RT Dominated
Lower local control odds ratio (RR = 0.62)	RT Dominated	-
Lower DSS odds ratio (RR = 0.75)	RT Dominated	RT Dominated
Lower recurrence and mortality odds ratio	RT Dominated	-
No difference in recurrence rates	RT Dominated	RT Dominated
No difference in QoL values	RT Dominated	RT Dominated
No discounting	RT Dominated	RT Dominated
Day case costs for TLM	RT Dominated	RT Dominated
TLM cost increased by 50%	RT Dominated	£8,995
TLM cost = radiotherapy cost	RT Dominated	£17,492
Same treatments in TLM and RT after first recurrence	RT Dominated	RT Dominant
Post treatment QoL with RT 0.01 higher than with TLM	RT Dominated	£26,232
Post treatment QoL with RT 0.05 higher than with TLM	£12,134	£2,093
Recurrence rates maintained over 10 years	RT Dominated	RT Dominanted

It can be seen that, in the T1a laryngeal cancer group, the conclusion of the analysis is unchanged in most modelled scenarios i.e. TLM is found to be the dominant strategy in most analyses. The exception to this was when it was assumed that QoL was higher in patients treated with radiotherapy. When assuming radiotherapy was associated with QoL gains of 0.05, radiotherapy became the most cost-effective strategy with an ICER of £12,280.

In the T1b-T2 laryngeal cancer group, the analysis was found to be more sensitive with the conclusion changing in numerous scenarios. In particular, radiotherapy became the most cost-effective intervention when TLM costs were increasedand in scenarios where a QoL gain was assumed for radiotherapy.

The influence of assuming a QoL benefit for patients treated with radiotherapy was further explored in a threshold analysis. The analysis showed that, at a threshold of £20,000 per QALY, radiotherapy would become cost-effective in comparison to TLM when the post treatment QoL with radiotherapy was 0.038 and 0.011 higher than that with TLM in the T1a and T1b-T2 laryngeal cancer groups, respectively.

Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base case are replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using cost-effectiveness acceptability curves (CEACs) in Figure 2 and Figure 3, which show the probability of each strategy being cost-effective at various cost-effectiveness thresholds.

Figure 2: Cost-effectiveness acceptability curve (CEAC) for TLM and radiotherapy in T1a laryngeal cancer patients

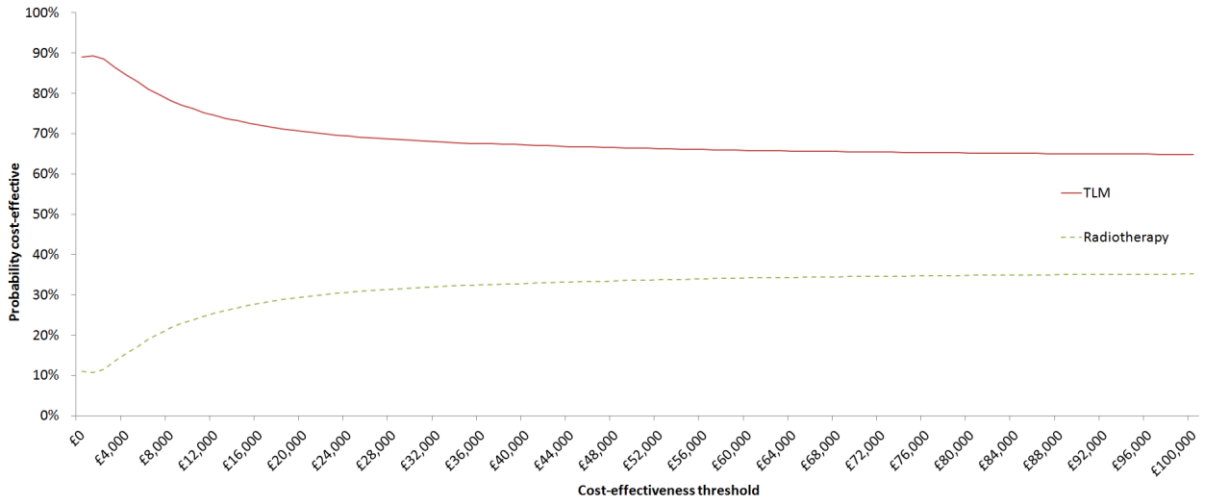
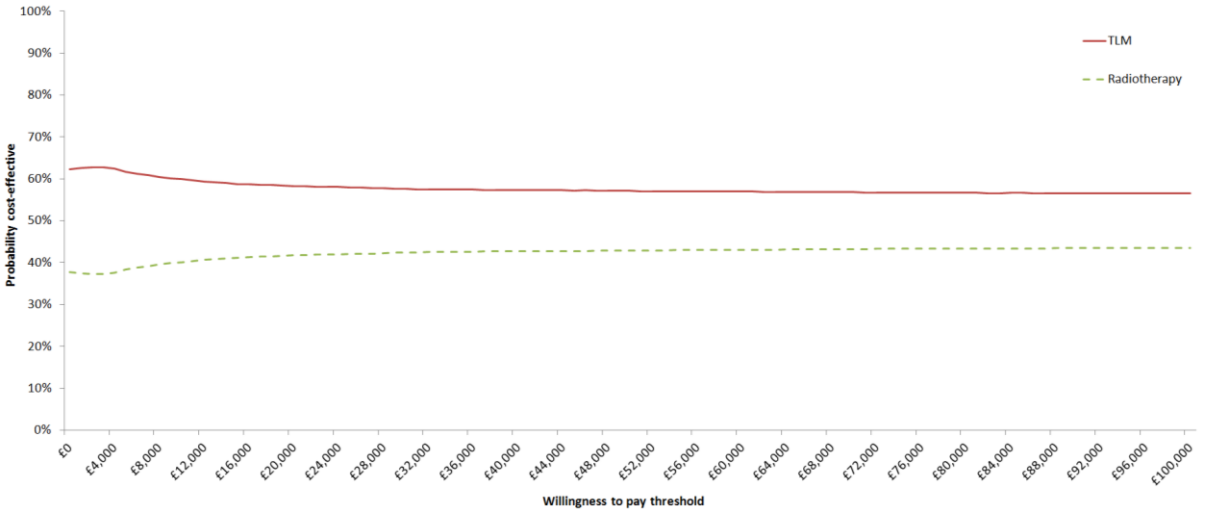


Figure 3: Cost-effectiveness acceptability curve (CEAC) for TLM and radiotherapy in T1b-T2 laryngeal cancer patients



It can be seen that, in the CEAC for the T1a laryngeal cancer group, TLM has a 71% probability of being cost-effective at a threshold of £20,000 per QALY. Whereas in the CEAC

for the T1b-T2 laryngeal cancer group, TLM has a 58% probability of being cost-effective at a threshold of £20,000 per QALY.

Conclusion

The results of the base case analysis suggest that using transoral laser microsurgery as the initial treatment for early stage laryngeal cancer is a cost-effective strategy in T1a and T1b-T2 laryngeal cancer. In T1a laryngeal cancer, this conclusion was further bolstered in sensitivity analysis where the result was found to be insensitive to the majority of changes made in deterministic analysis. Furthermore, in probabilistic sensitivity analysis it showed that TLM had a high probability of being cost-effective.

However, in the case of T1b-T2 laryngeal cancer, the result was found to be very sensitive to the changes made in deterministic sensitivity analysis and in probabilistic sensitivity analysis, the probability of TLM being cost-effective was found to be marginally higher than 50%. Therefore, the optimal strategy, in cost-effectiveness terms, remains uncertain in this patient group.

Recommendations	**Offer transoral laser microsurgery to people with newly-diagnosed T1a squamous cell carcinoma of the glottic larynx.** **Offer a choice of transoral laser microsurgery or radiotherapy to people with newly-diagnosed T1b–T2 squamous cell carcinoma of the glottic larynx.** **Offer a choice of transoral surgery or radiotherapy to people with newly-diagnosed T1–T2 squamous cell carcinoma of the supraglottic larynx.**
Relative value placed on the outcomes considered	Overall, disease-free and progression-free survival were considered important outcomes when comparing the treatment options for early laryngeal cancer. Laryngeal preservation and health related quality of life were also important because swallowing and voice quality can be affected by the treatments causing long-term issues for patients.
Quality of the evidence	The quality of the evidence was low to very low using GRADE. This was because evidence came from non-randomised trials – some of which had small sample sizes. Despite the lack of randomised trials of transoral laser microsurgery (TLM) versus radiotherapy in patients with T1a disease, there was consistent evidence from observational studies which was used to inform the health economic model. However, relatively few studies compared treatments in T1b-T2 patients. Uncertainty existed about both clinical effectiveness and cost effectiveness in the health economic model. The GC noted that there was uncertainty about the relative effectiveness of transoral surgery compared with RT (in terms of overall survival) in patients with T1–T2N0 supraglottic cancer of the larynx. Therefore the GC recommended both these treatments as options.
Trade-off between clinical benefits and harms	The group considered that T1–T2 patients avoiding open partial laryngectomy would benefit from reduced complications. Patients with T1a disease who avoid RT may also have a better chance of laryngeal preservation. A small proportion of patients will require an extra anaesthetic (due to discrepancy between histological and surgical margins) but the group believed the improved clinical outcomes outweigh risk of the additional procedures.

Trade-off between net health benefits and resource use	A de-novo health economic model was developed that considered the cost-effectiveness of TLM and radiotherapy in T1a and T1b-T2 cancer of the glottic larynx. In patients with T1a cancer of the glottic larynx the results of the base case analysis showed that radiotherapy was dominated by TLM i.e. TLM was found to be more effective and less costly. This result was found to be insensitive to changes in the model inputs. On the basis of a probabilistic sensitivity analysis, it was found that TLM had a 99% probability of being cost-effective at a threshold of £20,000 per QALY. As in patients with T1a cancer of the glottic larynx, the base case results for patients with T1b-T2 cancer of the glottic larynx again showed that radiotherapy was dominated by TLM. However, unlike T1a cancer of the glottic larynx, this result was found to be sensitive to changes in the deterministic sensitivity analysis. This uncertainty was also demonstrated in the probabilistic sensitivity analysis where it was found that TLM had a 53% probability of being cost-effective at a threshold of £20,000 per QALY. The GC recommendations reflect the results and uncertainty shown in the analysis. In both T1a and T1b-T2 cancer of the glottic larynx TLM was shown to be the preferred strategy. However, this result was only considered to be robust in the case of T1a cancer of the glottic larynx. In T1b-T2 cancer of the glottic larynx, there was far more uncertainty around the result and radiotherapy could be preferred under plausible alternative assumptions.
Other considerations	To implement this recommendation each MDT would need access to surgeons with appropriate training in TLM. Where this is currently not available locally there may be additional patient travel time or setup costs. Consultation times may increase due to patients being offered a choice of TLM and RT

3.2 Management of the N0 neck in T1–2 squamous cell carcinoma of the oral cavity

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 a quarter of cases. 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.

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?

Clinical evidence (see Appendix H)

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 et al., 2015; Kligerman et al., 1994; Vandenbrouck et al., 1980; Fakih, Rao, Borges,

& Patel, 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 et al., 2015), suggests that elective neck dissection improves overall survival (HR 0.64, 95% CI 0.45 to 0.92). Across all eligible trials, the relative risk of death from any cause ranged from 0.4 to 1.45 (where RR <1 favours elective neck dissection) with a pooled estimate of RR 0.76 (95% CI 0.47 to 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 et al., 2015; Kligerman et al., 1994; Vandenbrouck et al., 1980; Fakih et al., 1989; Yuen et al., 2009; 778 patients included 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 to 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 et al (2009), patients received ultrasound of the neck every three months for three years; in Vandenbrouk et al (1980) patients received clinical follow up for 3 years; and in D'Cruz et al (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 et al, 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 to 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 et al., 2015; Kligerman et al., 1994; Vandenbrouck et al., 1980; Fakih et al., 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 et al., 1998) including 252 patients 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 to 1.83; where HR >1 favours selective neck dissection). The quality of the evidence was downgraded partly for reasons of applicability: the Bier et al (1994) trial included an unspecified number of patients with clinically positive but mobile nodes and 38% of the patients included in Brentani et al (1998) had T3 or T4 disease.

Treatment related morbidity

Very low quality evidence from one randomised trial (Brentani et al., 1998) including 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 to 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 et al., 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 et al (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, Hannink, Merkx, Takes, & Rovers, 2013; Yamauchi et al., 2015) including 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% to 95%) and 91% (95% CI 85% to 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 et al (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% to 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% to 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% to 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 et al., 2014) including 62 patients 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 an individual patient data meta analysis of 87 randomised trials (Blanchard, 2011) including 428 patients with oral cavity carcinoma 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 to 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 to 1.15; HR <1 favours chemotherapy).

Table 20: GRADE evidence profile for chemotherapy plus locoregional treatment vs locoregional treatment alone for T1-2, N0 oral cancer

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chemotherapy plus locoregional treatment**	**Locoregional treatment alone**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 1.24)	-	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 to 1.15)	-	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 21: GRADE evidence profile for elective neck dissection versus therapeutic neck dissection alone for T1-2, N0 oral cancer

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Elective neck dissection**	**Therapeutic neck dissection**	**Relative (95% CI)**	**Absolute**	**Quality**	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Elective neck dissection**	**Therapeutic neck dissection**	**Relative (95% CI)**	**Absolute**	**Quality**	
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	-	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	-	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 to 0.60)	234 fewer per 1000 (from 184 fewer to 280 fewer)	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		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 Yeun 2009.*

Table 22: GRADE evidence profile for radical neck dissection selective neck dissection alone for T1-2, N0 oral cancer

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radical neck dissection**	**Selective neck dissection**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 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 to 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 to 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	serious[1]	Serious[3]	serious[1]	none	2/76 (2.6%)	1/72 (1.4%)	RR 1.89 (0.18 to	12 more per 1000	VERY LOW	

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radical neck dissection	Selective neck dissection	Relative (95% CI)	Absolute	Quality	
		risk of bias							20.45)	(from 11 fewer to 270 more)		

[1] *Unclear blinding, random sequence generation and allocation concealment.*
[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, Brentani 1998.*

Table 23: GRADE evidence profile for surgery plus radiotherapy versus radiotherapy for T1-2, N0 oral cancer

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery plus RT	RT alone	Relative (95% CI)	Absolute	Quality	
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 to 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 to 0.83)	-		

[1] *37 % of patients had N1 disease, 57% had T3-T4 disease.*
[2] *Small sample size.*
[3] *Robertson 1998.*

Table 24: GRADE evidence profile for 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-positive patients 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 25: GRADE evidence profile for 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		VERY LOW	
Local recurrence												
9	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38/296 (12.8%	152/1382	Local recurrence rate ranged from 8% to 17% for surgery+PORT, 7% to 20%		VERY LOW	

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**		
							)	(11%)	for surgery alone			
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		VERY LOW	

1 [1] *The baseline characteristics are not reported – unclear how patients were allocated treatment.*
2 [2] *Low event rates.*
3 [3] *Brown 2012 systematic review.*

4

Cost-effectiveness evidence

Background

The optimal management of patients with a clinically and radiologically N0 neck remains controversial. Elective neck dissection, which is widely performed, reveals occult metastases only in up to 26% of cases, meaning that the majority of neck dissections performed are unnecessary. Alternatively, a strategy of watchful waiting may result in under treatment for those patients with occult metastases and the delay in the treatment for these patients could have severe consequences. Thus, there is a balance between over treatment and under treatment.

Recently, the use of sentinel lymph node biopsy (SLNB) has been introduced as a further option. This could be used to stratify patients into those that require an elective neck dissection and those that can be observed under watchful waiting, which could minimise the potential for over treatment and under treatment.

Aims

To estimate the cost-effectiveness of the following management strategies for the clinically and radiologically N0 neck:

1. Elective neck dissection
2. Watchful waiting
3. Sentinel lymph node biopsy then neck dissection or watchful waiting

Existing Economic Evidence

A systematic literature review identified one paper that was deemed to be partially applicable to the current decision problem. Govers et al. 2013 assessed the cost-effectiveness of management strategies for the N0 neck in early stage oral squamous cell cancer.

The results of the analysis suggested that SLNB followed by neck dissection or watchful waiting was the most effective and cost-effective strategy (with an ICER of €3,356 per QALY below the author's chosen cost-effectiveness threshold of €80,000 per QALY). However, as this study considered the Dutch health care system it was not deemed sufficient to address the decision problem in the UK context.

De Novo Economic Model

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel.

Clinical data

Occult metastases and regional failure rates

The proportion of patients with occult metastases was estimated using data identified in the clinical evidence review conducted for this guideline. In patients undergoing observation, it was found that 46% will eventually require a neck dissection. This value has been used as the estimate for the proportion of patients with occult metastases.

An underlying assumption in the model (and much of the clinical literature) is that all occult metastases will become overt metastases. Therefore, in patients in the observation arm, the regional failure rate is equivalent to the proportion of patients with occult metastases (46%). For patients in the elective neck dissection arm, the results of the clinical evidence review were used, which showed that the risk of locoregional recurrence with elective neck dissection is approximately half that associated with observation (pooled RR estimate of

0.49). Therefore, the regional failure rate in patients undergoing an elective neck dissection was 21.1%.

Neck dissection related morbidity and mortality

Morbidity rates were based on alternative data identified in the clinical evidence review on selective neck dissections in comparison to radical neck dissections. It has been assumed that patients undergoing an elective neck dissection would undergo a selective neck dissection while patients undergoing a therapeutic neck dissection would undergo a more radical procedure. Therefore, patients undergoing an elective neck dissection arm have a morbidity risk of 25.0% and patients undergoing a therapeutic neck dissection have a morbidity risk of 41.3%.

Disease related and other cause mortality

Disease related mortality was captured in the model using data from the studies identified in the clinical evidence review. The annual rate of disease-specific death given recurrence was estimated to be 26.83% using data on the total number of disease related deaths and locoregional recurrences in patients in the watchful waiting arms of studies.

Note that full data was only available for the watchful waiting arm as the D'Cruz paper did not report disease related death in the END arm. In any case, it was considered reasonable to assume that disease related death given recurrence would be equivalent in the two treatment strategies (overall disease-related death would be expected to differ but this would be driven by differences in recurrence).

Death from other causes was captured using 2011-2013 life tables for England and Wales from the office of national statistics (ONS).

Diagnostic accuracy of sentinel lymph node biopsy

The diagnostic accuracy of sentinel lymph node biopsy (SLNB) was derived from data identified in the clinical evidence review conducted for this guideline. According to the systematic review by Govers et al. 2013, the sensitivity of SLNB was found to be 92% in cancers of the oral cavity while specificity was assumed to be 100%. Therefore in patients with occult metastases, 92% would be correctly identified (true positive) and 8% would be missed (false negative). In patients without occult metastases, the evidence suggests that all would be correctly identified as being negative (i.e. there are no false positives).

It was assumed that patients with positive sentinel lymph nodes will undergo an elective neck dissection. Those patients correctly identified as being sentinel node positive (true positives) were assumed to have the same regional recurrence rate as patients found to be node positive in the elective neck dissection arm.

Modelled patients with negative nodes were assumed to be observed in a watchful waiting program. Those patients correctly identified as negative (true negatives) were assumed to have the same regional failure rates as patients without occult metastases. However, patients that are incorrectly identified as negative (false negatives) were assumed to have the same regional recurrence rates as patients with occult metastases in the watchful waiting arm.

Costs

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. GP visit). Where possible, all costs were estimated in 2013-14 prices.

The majority of costs were sourced from NHS reference costs 2013/14 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dose information from the British National Formulary (BNF) and unit costs from the Electronic Market Information Tool (eMit – accessed 2015). Other costs were estimated using resource use and cost information from the Personal Social Services Research Unit (PSSRU) and the advice of the guideline committee.

Neck dissection

The cost of a neck dissection was estimated to be £3,548 based on the inpatient cost associated with Intermediate Maxillofacial Procedures (CA94Z) in NHS reference costs.

It is sometimes postulated that therapeutic neck dissections carry a greater morbidity risk, which could result in therapeutic neck dissections taking longer and thus carrying a greater cost. However, no distinction was made between the procedures in NHS reference costs and as such it has been assumed that there is no difference in the cost of a TND and an END.

Sentinel lymph node biopsy

Obtaining an accurate cost for sentinel lymph node biopsy in the context of head and neck cancer (HNC) proved to be problematic. Procedural codes associated with sentinel lymph node biopsy (T862, T873, T911 and O142) currently map to HRG codes associated with breast cancer – "Intermediate breast procedure" with and without complications. The applicability of this cost in the context of HNC is not completely clear but, in the absence of more appropriate data, it was applied in the base case. Thus, the cost of SLNB was estimated to be £1,427 (based on day case and inpatient procedures proportions from NHS Reference costs).

In addition, patients undergoing a SLNB would receive imaging to identify the sentinel node(s). The cost of imaging before the SLNB was also estimated from NHS Reference Cost using Nuclear Medicine Category 3 (£234).

Given the uncertainty in this area, the cost of SLNB was subjected to wide variations in the sensitivity analysis to estimate the influence of this parameter on the overall result. It should also be noted that the guideline committee thought that the cost of pathology was unlikely to be adequately captured by the cost reported in NHS Reference Costs. The impact of adding such a cost was also assessed in sensitivity analysis.

Post operative radiotherapy

For the purposes of the model it was estimated that 67% of patients undergoing neck dissection will also receive post-operative radiotherapy. This estimate was based on the study by Yuen et al. 2009, in which the 33% of patients with pN1 disease without extracapsular spread did not receive radiotherapy. Reflecting advances in clinical practice, it was assumed that all patients undergoing radiotherapy would receive intensity modulated radiotherapy (IMRT). The cost of IMRT was estimated to be £5,411, based upon preparation (£1626) and delivery costs (£126 per fraction) from NHS reference costs, assuming that 30 fractions of complex conformal radiotherapy would be delivered.

In addition, it was estimated that 46% of patients would receive chemotherapy in conjunction with radiotherapy. This estimate was based on the proportion of patients with extracapsular spread after nodal recurrence from Yuen et al. 2009, under the assumption that all patients with extracapsular spread would receive concomitant chemotherapy. It was assumed that cisplatin would be given in two doses of 100mg/m2 at an estimated cost of £658.

Follow-up costs

The cost per follow-up consultation was estimated to be £86.92 based upon the average cost of a 'Consultant Led Non-Admitted Face to Face Attendance' (WF01A) from NHS reference

costs in ENT and Maxillo-facial surgery. The number of follow-up visits typically required after each treatment was estimated by the guideline committee.

Physiotherapy sessions

It was assumed that 50% of patients undergoing TND and 26% of patients undergoing END would require physiotherapy based on the proportion of patients reporting severe activity disability in a survey by El Ghani et al. 2002. In those patients receiving physiotherapy, it was assumed that the patient would be seen once or twice as an inpatient with a further six sessions as an outpatient. The inpatient visits were assumed to be captured in the reference costs for a neck dissection and so only the additional costs of the outpatient attendances were considered in the model. The cost per consultation was estimated to be £57.94 based on the cost of 'Consultant Led Non-Admitted Face to Face Attendances' from NHS reference costs in Physiotherapy.

Systemic chemotherapy and palliative care

A metastatic cancer state was not explicitly modelled as such. However, it was assumed that patients that die from upper aerodigestive tract cancer were likely to have developed metastatic disease. Thus, the costs associated with treating metastatic disease as well as the cost of palliative care were applied to these patients.

It was assumed that 50% of patients would have received systemic chemotherapy with a regimen of cisplatin 80mg/m2 (day 1) and fluorouracil 800mg/m2 (day 1, 2, 3 and 4) assumed to be given for an average of four cycles (patients may receive up to six but many will not receive the maximum). This regimen was selected as it was thought to be the most commonly used. The chemotherapy costs were estimated in the same fashion as above (for concomitant chemotherapy) by combining drug costs from eMit with administration costs from NHS reference costs. It was estimated that systemic chemotherapy would cost £889 per cycle (£3,555 for 4 cycles).

Palliative care costs

The cost of palliative care was estimated using estimates from a costing report by the Nuffield Trust (Georghiou et al. 2014, 'Exploring the cost of care at the end of life'). A cost of £7,287 was applied based on the average resource use of patients with cancer in the last three months of life.

Health related quality of life (QoL) values

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs were estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state. For the purposes of this economic evaluation, the QoL data shown in table 26 were utilised.

Table 26: Quality of life values applied in the economic model

Health state	Utility	Source
No evidence of disease (N0 patient)	0.9130	Sher et al. 2010 and Hollenbeak et al. 2001
Neck dissection disutility	0.0386	Difference in QoL values for patients treated with and without neck dissection from Lassig et al. 2008 (converted to EQ-5D using Ara et al. 2008†)
End of life (metastatic disease)	0.6500	NICE HTA on Cetuximab
† SF-36 values from Lassig et al 2008 converted to EQ-5D values using mapping algorithm from Ara et al. 2008		

For patients with no evidence of disease (N0), a QoL weight of 0.9130 was assigned. This value has been utilised in a previous economic evaluation by Sher et al. 2010 and was based on assumptions from Hollenbeak et al. 2001.

The key QoL data applied in the model is the disutility associated with an elective neck dissection. This value was estimated by taking the difference between oropharyngeal patients receiving radiotherapy and concomitant chemotherapy, and radiotherapy and concomitant chemotherapy in addition to neck dissection from a QoL study by Lassig et al. 2008. The study measured QoL using the Short Form 36 health survey (SF-36). These values have been converted to EQ-5D values (the measure preferred by NICE) using a published and widely used mapping algorithm by Ara et al. 2008.

In addition, a QoL value from the NICE HTA on cetuximab was used as an estimate for patients in a metastatic disease state.

Base Case Results

The model was run over a ten year time horizon with total costs and QALYs estimated for each treatment strategy with future costs and benefits discounted at a rate of 3.5% per year as recommended by NICE.

The base case results of the analysis for are presented in the table below. It can be seen that, in comparison to watchful waiting, both SLNB and elective neck dissection are cost-effective with ICERS of £2,490 and £1,960 per QALY, respectively. Using dominance rank to ascertain the optimal strategy overall, it can be seen that SLNB is the most cost-effective strategy with elective neck dissection found to be both more costly and less effective than SLNB (i.e. dominated by SLNB).

Table 27: Base case cost-effectiveness results against common baseline (watchful waiting)

	Cost		QALYs		ICER (cost per QALY)
Initial treatment	Total	Incremental	Total	Incremental	
Watchful waiting	£284	-	4.87	-	-
Elective neck dissection	£9,509	£2,225	5.77	0.89	**£2,490**
SLNB	£9,175	£1,891	5.84	0.96	**£1,960**

Table 28: Base case cost-effectiveness results using dominance rank

	Cost		QALYs		ICER (cost per QALY)
Initial treatment	Total	Incremental	Total	Incremental	
Watchful waiting	£7,284	-	4.87	-	-
SLNB	£9,175	£1,891	5.84	0.96	**£1,960**
Elective neck dissection	£9,509	£334	5.77	-0.07	**Dominated**

Deterministic sensitivity analysis

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the one-way sensitivity analysis are shown in the tables below.

Table 29: One-way sensitivity analysis results

Change made	Optimal strategy
Prevalence of occult metastases = 30%	SLNB

Change made	Optimal strategy
Prevalence of occult metastases = 20%	SLNB
Proportion occult metastases that become overt = 75%	SLNB
Proportion occult metastases that become overt = 50%	SLNB
Proportion occult metastases that become overt = 25%	**WW**
Yamauchi SLNB sensitivity = 84%	SLNB
SLNB sensitivity = 80%	**END**
Equivalent morbidity with END and SND	SLNB
No survival benefit with END	**WW**
SLNB costs + 50%	SLNB
SLNB costs - 50%	SLNB
Neck dissection costs + 50%	SLNB
Neck dissection costs - 50%	SLNB
Conventional RT instead of IMRT	SLNB
Neck dissection disutility - 50%	SLNB
No neck dissection disutility	**END**
Disease specific mortality from Fasunla et al. 2011	SLNB
Disease specific mortality from D'Cruz et al. 2015	SLNB
Locoregional recurrence from D'Cruz et al. 2015	SLNB
Recurrence and mortality from D'Cruz et al. 2015	SLNB
WW Scenario - same effectiveness with ultrasound scans	SLNB
WW Scenario – Yuen effectiveness with ultrasound scans	**WW**
WW Scenario – Yuen effectiveness without ultrasound scans	**WW**
100% Elective inpatient SLNB	SLNB
100% Day case SLNB	SLNB
SLNB cost from melanoma model	SLNB
SLNB Best practice day case PbR tariff	SLNB
SLNB Ordinary elective PbR tariff	SLNB
Additional pathology cost = £200	SLNB
Additional pathology cost = £400	SLNB
Radiotherapy QoL decrement	SLNB

It can be seen that the conclusion of the analysis is unchanged in most modelled scenarios. However, there were notable exceptions where watchful waiting or elective neck dissection became the most cost-effective strategy. Watchful waiting was found to be cost-effective in the scenarios where the effectiveness estimates from Yuen et al. were applied or when the proportion of occult metastases that become overt disease was lowered to 25%.

Elective neck dissection was found to be cost-effective when the sensitivity of SLNB was reduced to 80% and when the disutility associated with neck dissections was removed. The former reduces the effectiveness of the SLNB strategy (as more positive nodes would be missed) and the latter removes the negative QoL impact that elective neck dissections can have.

Threshold analysis

The guideline committee were interested in an analysis to ascertain the risk of occult metastases required for each strategy to become cost-effective. The prevalence of occult metastases required for each strategy to become cost-effective is shown below (at a threshold of £20,000 per QALY):

Elective neck dissection versus watchful waiting (SLNB not included)

- WW is the optimal strategy when the prevalence of occult metastases ≤ 18.1%
- END is the optimal strategy when the prevalence of occult metastases > 18.1%

All comparators (SLNB included)

- WW is the optimal strategy when the prevalence of occult metastases ≤ 5.2%
- SLNB is the optimal strategy when the prevalence of occult metastases > 5.2% and <64.5%
- END is the optimal strategy when the prevalence of occult metastases ≥ 60.5%

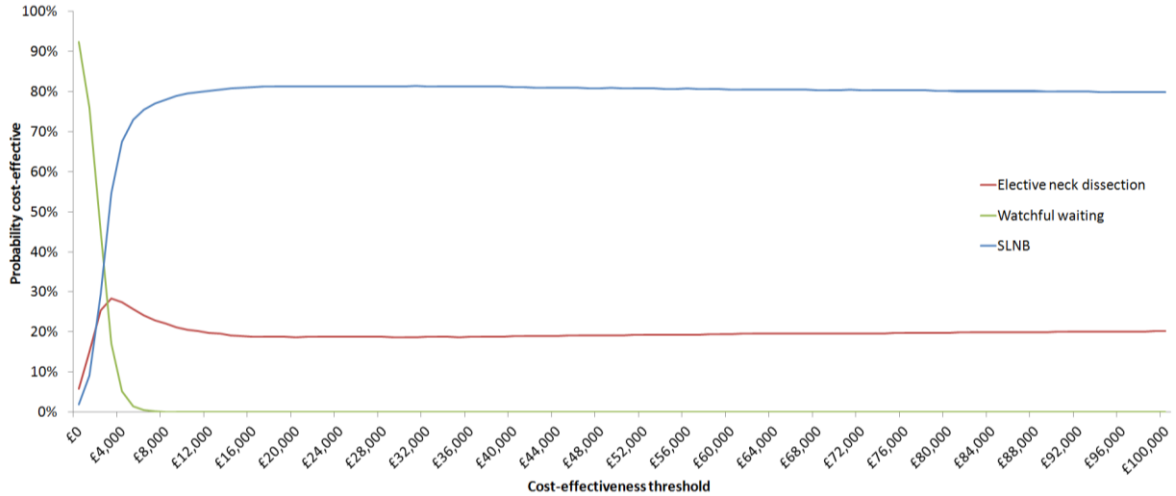
In addition, due to concerns about the reliability of SLNB sensitivity estimates in the clinical literature, a further threshold analysis was conducted on this parameter. It was found that SLNB was no longer cost-effective if its sensitivity ≤ 83.7%, at which point END becomes the preferred strategy.

Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base case are replaced with values drawn from distributions around the mean values.

The results of 10,000 runs of the probabilistic sensitivity analysis are shown using a cost-effectiveness acceptability curve (CEAC). The CEAC graph shows the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds. It can be seen that, at a threshold of £20,000 per QALY, SLNB has an 81% probability of being cost-effective, while END and watchful waiting have a 19% and 0% probability of being cost-effective, respectively.

Figure 4: Cost-effectiveness acceptability curve (CEAC) for management strategies for the clinically and radiologically N0 neck



Conclusion

The results of the base case analysis suggest that the use of SLNB is a cost-effective strategy for the clinically and radiologically N0 neck. This result was strengthened further in the PSA where SLNB was shown to have an 81% probability of being cost-effective at a threshold of £20,000 per QALY. However, one-way sensitivity analysis showed that the conclusion of the analysis was sensitive to changes in many of the input parameters. In particular, the influence of changes in SLNB sensitivity on the results was particularly

noteworthy as END was found to be cost-effective under some plausible assumptions with lower sensitivity.

Recommendations	**Offer surgical management of the neck to all people with early oral cavity cancer (T1–T2, N0).** **Offer sentinel lymph node biopsy instead of elective neck dissection to people with early oral cavity cancer (T1–T2, N0), unless they need cervical access at the same time (for example, free-flap reconstruction).**
Relative value placed on the outcomes considered	The GC considered treatment related morbidity as the key outcome. Although not included the review protocol the GC also considered evidence about the sensitivity of SLNB when making their recommendation. None of the included studies reported quality of life outcomes.
Quality of the evidence	The quality of the evidence was low to moderate using the GRADE system. This was because two out of the four elective ND versus therapeutic ND trials were conducted before 2000 and there was a lack of comparative SLNB vs. elective ND trials randomised.
Trade-off between clinical benefits and harms	The GC considered that 28% of patients with T1 N0 SCC will have neck metastases at presentation, hence approximately 70% of all cases are overtreated for the benefit of approximately 30%. Therefore the GC considered if watchful waiting of the neck in this cohort was acceptable. Evidence of a variable nature existed regarding tumour depth & the risk of nodal metastasis. Most would proceed only in tumours >4mm deep. The GC was convinced by the D'Cruz paper which showed that END in tumour of any thickness, including <3mm, conferred an overall survival benefit. Hence the GC felt that watchful waiting of the neck in early oral cavity SCC was no longer appropriate. The GC felt therefore that the choice for neck management was either END or SNB, that later dominated in the economic model. For patients not needing a neck operation for reconstruction the GC believed that most MDTs would offer SNB, which would reduce the number of ENDs being performed by circa 50%. If a reconstruction was being offered then an END would be offered rather than SNB. The GC therefore believes using SLNB could reduce by half the number of elective neck dissections and any associated morbidity. However a proportion of negative SLNBs would be false negative (approximately 5%). These patients may require therapeutic neck dissection and may have a poorer outcome than if they had received an initial elective neck dissection. The GC believed that the benefit of less treatment significantly outweighs this small risk.
Trade-off between net health benefits and resource use	A cost-utility analysis by Govers et al. (2013) was identified. However, the study was only partially applicable to our decision problem as it did not consider the UK health care setting. Therefore this evidence was not used by the GC when agreeing their recommendations. A health economic model was developed for this topic and the results of the analysis were used to inform the recommendations made on the use of SLNB. The base case results showed that SLNB was the most cost-effective strategy. In comparison to a watchful waiting strategy, SLNB was found to provide an additional QALY at a cost of

	£1960, substantially below the NICE threshold of £20,000 per QALY. In comparison to elective neck dissection, SLNB was found to be dominant: more effective and less expensive. One-way sensitivity analysis showed that the conclusions of the analysis changed in some scenarios where alternative inputs or assumptions were used. In particular, END was found to be cost-effective under some plausible assumptions with lower SLNB sensitivity. The result of the probabilistic sensitivity analysis showed that at, a threshold of £20,000 per QALY, SLNB had an 81% probability of being cost-effective.
Other considerations	Most centres do not use SLNB for HNC patients so more histopathology services will be required to process sentinel lymph nodes. Also the SLNB procedure will require more use of nuclear medicine services. This recommendation applies to patients deemed at sufficiently high risk of cervical metastasis to require neck dissection. The GC was also aware of more recent robust work from several centres that shows that tumour depth may not have as large an impact on the occult metastatic rate as was thought in the past; the GC was thus comfortable in recommending some form of neck management even for the "thin" tumours.

3.31 Squamous cell carcinoma of the oropharynx (T1–T2, N0)

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 transoral 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.

Clinical question: What is the optimal management of T1-2, N0 squamous cell carcinoma of the oropharynx?

Clinical evidence (see Appendix H)

Transoral robotic surgery (TORS) and intensity 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 (Almeida et al., 2014) (including 20 studies and 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 (one study) and ranged from 82% to 90% following IMRT (three studies).

Adverse events

Adverse events reported following TORS included: post-operative bleeding 2.4% (6/247, seven studies); pharyngocutaneous fistula 2.5% (10/395, eight studies); gastrostomy placement at time of surgery 1.4% (2/139, three studies); gastrostomy placement at time of adjuvant therapy 30% (32/107, three studies); tracheostomy 12% (31/258); and hospital readmission 3% (one patient; one study).

Adverse events reported following IMRT included: osteoradionecrosis of the mandible 2.6% (4/151, three studies); oesophageal stenosis 4.8% (4/84, two studies); and hospital readmission 17% (9/52, one study).

Locoregional treatment alone versus locoregional treatment with chemotherapy

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 (Blanchard et al., 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 to 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 (Blanchard et al., 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 to 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 radiotherapy and concomitant chemotherapy. 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., 1994), suggests uncertainty about whether hyperfractionated radiotherapy improves overall survival compared with conventionally fractionated RT. 5-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 HNC within a larger individual patient level meta-analysis (Baujat et al., 2010), suggests altered fractionation does not improve overall survival compared to conventional fractionation (HR for death 0.98; 95% C.I. 0.85 to 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., 1994), 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 radiotherapy and concomitant chemotherapy treatment have significantly fewer problems eating or chewing compared with patients treated with conventional radiotherapy and concomitant chemotherapy.

Table 30: 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			
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)**	**Quality**	
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 to 1.00)	Not estimable	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 to 1.00)	Not estimable	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+chemo RT 66.67 (59.22 to 70.91) Surgery+RT 66.67 (56.85 to 72.95) Surgery alone 75.00 (62.79 to 80.16)	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 31: GRADE evidence profile: transoral robotic surgery (TORS) versus intensity-modulated radiotherapy (IMRT) for oropharyngeal carcinoma

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TORS**	**IMRT**	**Absolute**	**Quality**	
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%	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%	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%	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%	VERY LOW	
Overall survival											
6[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4 studies (patient	2 studies (patient	IMRT: 84%-	VERY LOW	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TORS	IMRT	Absolute	Quality	
							numbers not reported)	numbers not reported)	95.5% TORS: 82%-94%		

[1] *De Almeida et al, 2014. Systematic review of non-comparative, retrospective studies.*
[2] *Analysis based on single-arm observational studies.*

Table 32: GRADE evidence profile: altered fractionation radiotherapy versus conventional radiotherapy for patients with oropharyngeal cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Altered fractionation radiotherapy	Conventional radiotherapy	Relative (95% CI)	Quality	
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).	MODERATE	
Overall Survival											

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)		
	ed trials	serious risk of bias	inconsistency		imprecision				40% with hyperfractionated RT and 30% with conventional RT (p = 0.08)	-	E

[1] *Horiot et al, 1992*
[2] *Population not exclusively T1-T2*

Table 33: 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)		□□□□ VERY LOW

[1] *Allal et al, 2003.*

1 [2] *Population not exclusively T1/T2.*

1 Cost-effectiveness evidence

2 A literature review of published cost-effectiveness analyses did not identify any relevant
3 papers for this topic. Whilst there were potential cost implications of making
4 recommendations in this area, other questions in the guideline were agreed as higher
5 priorities for economic evaluation. Consequently no further economic modelling was
6 undertaken for this question.

7

Recommendations	**Offer people the choice of transoral surgical resection or primary radiotherapy for T1–2 N0 tumours of the oropharynx.** **Consider postoperative radiotherapy, with or without concomitant chemotherapy, for T1–2 N0 tumours of the oropharynx if pathologically adverse risk factors have been identified.**
Relative value placed on the outcomes considered	All outcomes were considered important when drafting the recommendation, although no comparative evidence was found that reported quality of life or adverse events.
Quality of the evidence	The quality of the evidence was very low to moderate using the GRADE system. Some studies included N+ patients. In some the stage was unclear. In the non-randomised studies higher risk patients tended to be more likely to receive adjuvant therapies. The MACH-NC oropharyngeal subgroup analysis contained outdated studies and could have included patients with node-positive disease. The MARCH subgroup analysis also included hypopharyngeal cancer patients. The GC could not recommend between surgery or RT as the best treatment due to the lack of randomised trials comparing the two. Both surgery and RT result in excellent local control and survival in this group of patients. Although there is no evidence supporting the use of one over the other either treatment may be offered to persons with T-2 N0 oropharyngeal cancer with excellent prospect of cure. The recommendation about adjuvant therapy was informed by evidence of benefit in the included studies, and international standards.
Trade-off between clinical benefits and harms	The recommendation of a choice of treatments should enable discussion of adverse event profiles and preferences with patients. Patients could experience anxiety when choosing treatments and some may end up having bimodality or trimodality therapy anyway. However, the evidence published so far suggests similar outcomes and ongoing randomised trials support equipoise.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no model developed. The GC thought that the recommendation did not differ significantly from current practice and would not lead to a change in resource use. At present it is likely that individual centres would favour either surgery or RT for this population, so this recommendation may lead to greater discussion of alternative treatment options. Centres are also already delivering adjuvant therapies to appropriate individuals so this is unlikely to result in a change in resource use.
Other considerations	This is an area where ongoing randomised trials are due to report in the coming years. These include: • PATHOS (comparing different radiotherapy doses, with or without chemotherapy)

	• ADEPT (comparing radiotherapy alone with radiotherapy plus cisplatin in surgically-treated patients) • ECOG 3311 (comparing different total radiotherapy doses) • NIMRAD (comparing nimorazole plus radiotherapy with placebo plus radiotherapy).

References

Abdurehim, Y., Hua, Z., Yasin, Y., Xukurhan, A., Imam, I., and Yuqin, F. Transoral laser surgery versus radiotherapy: systematic review and meta-analysis for treatment options of T1a glottic cancer. [Review]. Head & Neck 2012. 34(1): 23-33.

Allal, A. S., Nicoucar, K., Mach, N., Dulguerov, P., and Allal, Abdelkarim S. 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

Arshad, H., Jayaprakash, V., Gupta, V., Cohan, D. M., Ambujakshan, D., Rigual, N. R., Singh, A. K., and Hicks, W. L., Jr. Survival Differences between Organ Preservation Surgery and Definitive Radiotherapy in Early Supraglottic Squamous Cell Carcinoma. Otolaryngology - Head & Neck Surgery 2014. 150(2): 237-244

Baujat, B., Bourhis, J., Blanchard, P., Overgaard, J., Ang, K. K., Saunders, M., Le Maitre, A., Bernier, J., Horiot, J. C., Maillard, E., Pajak, T. F., Poulsen, M. G., Bourredjem, A., O'Sullivan, B., Dobrowsky, W., Andrzej, H., Skladowski, K., Hay, J. H., Pinto, L. H. J., Fu, K. K., Fallai, C., Sylvester, R., and Pignon, J. P. Hyperfractionated or accelerated radiotherapy for head and neck cancer. Cochrane Database of Systematic Reviews 2010. (12)

Bessell, A., Glenny, A. M., Furness, S., Clarkson, J. E., Oliver, R., Conway, D. I., Macluskey, M., Pavitt, S., Sloan, P., and Worthington, H. V. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database of Systematic Reviews 2011. (9)

Blanchard, P. Baujat. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): A comprehensive analysis by tumour site. Radiotherapy and Oncology 2011. 100(1): 33-40

Brentani, R. R., Kowalski, L. P., Soares, J. F., Torloni, H., Camargo, A. C., Pereira, R. N., Camargo, A. C., Ikeda, M. K., Andrade, R. P., Magrin, J., Miguel, R. E. V., Santos, C. R., Saba, L. M. B., Salvajoli, J. V., Curado, M. P., Oliveira, J. C., Montandon, P. O., Machado, M. M., Denofrio, G. F., Quinta, W. C., Alvarez, R. B., Alencar, R. C. G., Jorge, A., Ferraz, A. R., Brandao, L. G., Cernea, C. R., Santos, L. R. M., Araujo, V., Antonangelo, A., Silva, J. L. F., Della-Molle, R., Feriancic, C. V., Carneiro, P. C., Oliveira, B. V., Ramos, G., Antunes, L. S., Sobrinho, J. A., Rapoport, A., Carvalho, M. B., Fava, A. S., Gois, J. F., Chagas, J. F. S., Kanda, J. L., Gripp, F. M., Ribas, M. H., Castro, I. S., Oliveira, J. M. S., Oliveira, J. A. M., Carvalho, R. C., Araujo, L. B., Pontes, P. A. L., Gregorio, L. C., Abrahao, M., Cervantes, O., Paiva, M. B., Hebbel, W. S., Fujita, R. R., Motta, P. H. H., Segreto, R. A., Herter, N. T., Mota, N. W., Scholl, J. G., Kroef, R. G., and Godoy, P. R. F. 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 1998. 176(5): 422-427

Brown, J. S. S. Systematic review of the current evidence in the use of postoperative radiotherapy for oral squamous cell carcinoma. British Journal of Oral and Maxillofacial Surgery 2012. 50(6): 481-489.

Comert, Ela. Comparison of early oncological results of diode laser surgery with radiotherapy for early glottic carcinoma. Otolaryngology - Head & Neck Surgery 2014. 150(5): 818-823

D'Cruz, A. K., Vaish, R., Kapre, N., Dandekar, M., Gupta, S., Hawaldar, R., Agarwal, J. P., Pantvaidya, G., Chaukar, D., Deshmukh, A., Kane, S., Arya, S., Ghosh-Laskar, S., Chaturvedi, P., Pai, P., Nair, S., Nair, D., and Badwe, R. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. New England Journal of Medicine 2015 (epub ahead of print).

de Almeida, J. R., Byrd, J. K., Wu, R., Stucken, C. L., Duvvuri, U., Goldstein, D. P., Miles, B. A., Teng, M. S., Gupta, V., and Genden, E. M. A systematic review of transoral robotic surgery and radiotherapy for early oropharynx cancer: a systematic review. Laryngoscope 2014. 124(9): 2096-2102

Dinapoli, N., Parrilla, C., Galli, J., Autorino, R., Micciche, F., Bussu, F., Balducci, M., D'Alatri, L., Marchese, R., Rigante, M., Di, Lella G., Liberati, L., Almadori, G., Paludetti, G., and Valentini, V. Multidisciplinary approach in the treatment of T1 glottic cancer. The role of patient preference in a homogenous patient population. Strahlentherapie und Onkologie 2010. 186(11): 607-613

Ebrahimi, A. Clark. Minimum nodal yield in oral squamous cell carcinoma: Defining the standard of care in a multicenter international pooled validation study. Annals of Surgical Oncology 2014. 21(9): 3049-3055

Fakih, A. R., Rao, R. S., Borges, A. M., and Patel, A. R. Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. American Journal of Surgery 1989. 158(4): 309-313

Flach, G. B., Bloemena, E., Klop, W. M., van Es, R. J., Schepman, K. P., Hoekstra, O. S., Castelijns, J. A., Leemans, C. R., and de, Bree R. Sentinel lymph node biopsy in clinically N0 T1-T2 staged oral cancer: the Dutch multicenter trial. Oral Oncology 2014. 50(10): 1020-1024

Govers, T. M., Hannink, G., Merkx, M. A. W., Takes, R. P., and Rovers, M. M. Sentinel node biopsy for squamous cell carcinoma of the oral cavity and oropharynx: A diagnostic meta-analysis. Oral Oncology 2013. 49(8): 726-732

Greulich, M. T., Parker, N. P., Lee, P., Merati, A. L., and Misono, S. Voice outcomes following radiation versus laser microsurgery for T1 glottic carcinoma: systematic review and meta-analysis. Otolaryngology - Head & Neck Surgery 2015. 152(5): 811-819

Horiot, J. C., Le, Fur R., N'Guyen, T., Chenal, C., Schraub, S., Alfonsi, S., Gardani, G., Van Den Bogaert, W., Danczak, S., Bolla, M., and . Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiotherapy and Oncology 1992. 25(4): 231-241

Karatzanis, A. D., Psychogios, G., Zenk, J., Waldfahrer, F., Hornung, J., Velegrakis, G. A., and Iro, H. Evaluation of available surgical management options for early supraglottic cancer. Head & Neck 2010. 32(8): 1048-1055

Kligerman, J., Lima, R. A., Soares, J. R., Prado, L., Dias, F. L., Freitas, E. Q., and Olivatto, L. O. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. American Journal of Surgery 1994. 168(5): 391-394

Lea, J., Bachar, G., Sawka, A. M., Lakra, D. C., Gilbert, R. W., Irish, J. C., Brown, D. H., Gullane, P. J., and Goldstein, D. P. Metastases to Level Iib in Squamous Cell Carcinoma of the Oral Cavity: A Systematic Review and Meta-Analysis. Head and Neck 2010. 32(2): 184-190

Mantsopoulos, K., Psychogios, G., Koch, M., Zenk, J., Waldfahrer, F., and Iro, H. Comparison of different surgical approaches in T2 glottic cancer. Head & Neck 2012. 34(1): 73-77

Maurizi, M., Almadori, G., Plaudetti, G., De, Corso E., and Galli, J. Laser carbon dioxide cordectomy versus open surgery in the treatment of glottic carcinoma: our results. Otolaryngology - Head & Neck Surgery 2005. 132(6): 857-861

Milovanovic, J., Jotic, A., Djukic, V., Pavlovic, B., Trivic, A., Krejovic-Trivic, S., Milovanovic, A., Milovanovic, A., Artiko, V., and Banko, B. Oncological and Functional Outcome after Surgical Treatment of Early Glottic Carcinoma without Anterior Commissure Involvement. Biomed Research International 2014.

O'Hara, J., Markey, A., and Homer, J. J. 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 2013. 127(8): 732-738.

Osborn, H. A., Hu, A., Venkatesan, V., Nichols, A., Franklin, J. H., Yoo, J. H., Ceron, M., Whelan, F., and Fung, K. Comparison of endoscopic laser resection versus radiation therapy for the treatment of early glottic carcinoma. Journal of Otolaryngology: Head and Neck Surgery 2011. 40(3): 200-204

Puxeddu, R., Argiolas, F., Bielamowicz, S., Satta, M., Ledda, G. P., and Puxeddu, P. Surgical therapy of T1 and selected cases of T2 glottic carcinoma: cordectomy, horizontal glottectomy and CO2 laser endoscopic resection. Tumori 2000. 86(4): 277-282

Remmelts, A. J., Hoebers, F. J., Klop, W. M., Balm, A. J., Hamming-Vrieze, O., and van den Brekel, M. W. Evaluation of laser surgery and radiotherapy as treatment modalities in early stage laryngeal carcinoma: tumour outcome and quality of voice. European Archives of Oto-Rhino-Laryngology 2013. 270(7): 2079-2087

Robertson SM, Yeo JC, Sabey, and Robertson, Stuart M. 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

Ryzek, D. F., Mantsopoulos, K., Kunzel, J., Grundtner, P., Zenk, J., Iro, H., and Psychogios, G. Early Stage Oropharyngeal Carcinomas: Comparing Quality of Life for Different Treatment Modalities. BioMed Research International 2014.

Spielmann, P. M., Majumdar, S., and Morton, R. P. 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 2010. 35(5): 373-382.

Tandon, S., Munir, N., Roland, N. J., Lancaster, J., Jackson, S. R., and Jones, T. M. 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 2011. 38(6): 702-709.

Thomas, L., Drinnan, M., Natesh, B., Mehanna, H., Jones, T., and Paleri, V. Open conservation partial laryngectomy for laryngeal cancer: a systematic review of English language literature (DARE structured abstract). Cancer Treatment Reviews 2012. 38: 203-211.

Vandenbrouck, C., Sancho-Garnier, H., Chassagne, D., Saravane, D., Cachin, Y., and Micheau, C. Elective versus therapeutic radical neck dissection in epidermoid carcinoma of the oral cavity: results of a randomized clinical trial. Cancer 1980. 46(2): 386-390

van Gogh, C. D., Verdonck-de Leeuw, I. M., Wedler-Peeters, J., Langendijk, J. A., and Mahieu, H. F. 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 2012. 269(6): 1647-1652

van, Loon Y., Sjogren, E. V., Langeveld, T. P., Baatenburg de Jong, R. J., Schoones, J. W., and van Rossum, M. A. Functional outcomes after radiotherapy or laser surgery in early glottic carcinoma: a systematic review. [Review]. Head & Neck 2012. 34(8): 1179-1189.

Yamauchi, K., Kogashiwa, Y., Nakamura, T., Moro, Y., Nagafuji, H., and Kohno, N. Diagnostic evaluation of sentinel lymph node biopsy in early head and neck squamous cell carcinoma: A meta-analysis. Head and Neck. 37(1): 127-133

Yao, M., Karnell, L. H., Funk, G. F., Lu, H., Dornfeld, K., and Buatti, J. M. Health-related quality-of-life outcomes following IMRT versus conventional radiotherapy for oropharyngeal squamous cell carcinoma. International Journal of Radiation Oncology, Biology, Physics 2007. 69(5): 1354-1360

Yuen, A. P., Ho, C. M., Chow, T. L., Tang, L. C., Cheung, W. Y., Ng, R. W., Wei, W. I., Kong, C. K., Book, K. S., Yuen, W. C., Lam, A. K., Yuen, N. W., Trendell-Smith, N. J., Chan, Y. W., Wong, B. Y., Li, G. K., Ho, A. C., Ho, W. K., Wong, S. Y., and Yao, T. J. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. Head and Neck 2009. 31(6): 765-772

4 Treatment of advanced disease

4.1 Squamous cell carcinoma of the larynx

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 laryngeal preservation approaches may offer equivalent cure rates to primary surgery but with variable functional outcomes.

Clinical question: What is the most effective treatment for newly diagnosed T3 and T4 squamous cell carcinoma of the larynx?

Clinical evidence (see Appendix H)

Addition of chemotherapy to locoregional therapy

Evidence about the addition of chemotherapy to locoregional therapy comes from the MACH-NC (Blanchard et al., 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%C.I. 0.71 to 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 neo-adjuvant chemotherapy on overall survival. (HR 1.00; 95%C.I. 0.81 to 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% C.I. 0.83 to 1.33; HR <1 favours adjuvant chemotherapy).

Laryngeal preservation

Evidence about laryngeal preservation comes from a systematic review (Denaro, Russi, Lefebvre, & Merlano, 2014) including seven trials in patients with laryngeal cancer.

Neo-adjuvant chemotherapy and RT versus initial surgery and RT

Moderate quality from two randomised trials including 200 patients (included in Denaro et al. (2014)), suggests that around 60% of patients treated with neo-adjuvant chemotherapy and RT (instead of initial surgery then RT) had laryngeal preservation. Moderate quality evidence from these trials suggests that disease recurrence, however, is more likely in those treated with neo-adjuvant chemotherapy than those initially treated with surgery (HR 2.08; 95% C.I. 1.33 to 2.89; HR <1 favours neo-adjuvant chemotherapy).

Neoadjuvant chemotherapy and RT versus radiotherapy and concomitant chemotherapy versus RT alone

The RTOG 91-11 trial (Forastiere, Zhang, Weber, & Maor, 2013), including 518 patients with laryngeal cancer, provides high quality evidence about laryngeal preservation rates following neo-adjuvant chemotherapy and radiotherapy versus radiotherapy and concomitant chemotherapy versus radiotherapy alone. This evidence suggests that laryngeal preservation is more likely with radiotherapy and concomitant chemotherapy, than with neo-adjuvant 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 et al., 2010) and one subsequent randomised trial (Zackrisson et al., 2011) suggests uncertainty over whether radiotherapy with altered fractionation improves survival compared with conventionally fractionated radiotherapy (HR 0.92; 95% CI 0.82 to 1.03).

Table 34: GRADE evidence profile for locoregional treatment plus chemo versus locoregional treatment alone (MACH-NC: Blanchard 2011).

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Locoregional treatment plus chemotherapy**	**Locoregional treatment**	**Relative (95% CI)**	**Absolute**	**Quality**	
event free survival[4] (neo-adjuvant chemotherapy)												
17[9]	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 to 1.38)	14 fewer per 1000 (from 96 fewer to 69 more)[5]	HIGH	
event free survival[4] (adjuvant chemotherapy)												
9[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 to 1.32)	10 fewer per 1000 (from 94 fewer to 74 more)[5]	HIGH	
event free survival[4] (concomitant chemotherapy)												
47[9]	randomised trials	no serious risk	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 to	54 more per 1000	HIGH	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Locoregional treatment plus chemotherapy**	**Locoregional treatment**	**Relative (95% CI)**	**Absolute**	**Quality**	
		of bias[1]							0.87)	(from 7 more to 101 more)[5]		
overall survival[8] (adjuvant chemotherapy)												
9[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 to 1.33)	1 more per 1000 (from 85 fewer to 87 more)[6]	MODERATE	
overall survival[8] (neo-adjuvant chemotherapy)												
17[9]	randomised trials	no serious risk of bias1	no serious inconsistency	no serious indirectness[2,3]	serious[7]	none	334/338 (98.8%)	319/275 (116%)	HR 1.00 (0.81 to 1.23)	38 more per 1000 (from 46 fewer to 122 more)[6]	MODERATE	
overall survival[8] (concomitant chemotherapy)												
47[9]	randomised trials	no serious risk	no serious inconsistency	no serious indirectness[2,3]	no serious imprecision	none	591/990 (59.7%)	630/990 (63.6%)	-	636 fewer per 1000	HIGH	

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**		
		of bias[1]								(from 636 fewer to 636 fewer)		

[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.*
[9] *MACH-NC individual patient meta-analysis, Blanchard (2011).*

Table 35: GRADE evidence profile for neo-adjuvant chemotherapy versus surgery, both followed by RT

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**		
Laryngeal preservation												
2[3]	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 to 824.88)	60% of patients treated with neo-adjuvant	MODERATE	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Neoadjuvant chemo then RT**	**Surgery then RT**	**Relative (95% CI)**	**Absolute**	**Quality**	
										chemo retained their larynx.		
Overall survival[2]												
2[3]	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 to 1.43)	59 more per 1000 (from 31 fewer to 110 more)	MODERATE	
Acute toxicity (grade 2 mucositis)												
1[3]	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)	MODERATE	
Treatment related mortality												
1[3]	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 to 3.93)	0 fewer per 1000 (from 18 fewer to 71 more)	MODERATE	
Disease recurrence												
2[3]	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 to 2.89)	145 more per 1000 (from 47 more to 238 more)	MODERATE	

1 [1] *low number of events*

[2] *event is death from any cause*
[3] *Denaro (2014) meta-analysis*

Table 36: GRADE evidence profile for altered fractionation RT versus conventionally fractionated RT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Altered fractionation RT	Conventionally fractionated RT	Relative (95% CI)	Absolute	Quality	
overall survival[3]												
15[4]	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 to 1.03)	28 fewer per 1000 (from 66 fewer to 10 more)	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.*
[4] *MARCH meta-analysis: (Baujat 2010).*

Cost-effectiveness evidence

Two relevant studies were identified in a literature review of published cost-effectiveness analyses on this topic. 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 (HNC) 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 HNCs 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 HNC. However, the use of a general HNC population rather than a laryngeal cancer population limits applicability. Further disease site specific evidence is required to conclusively demonstrate cost-effectiveness.

Table 37: 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 to PF as neo-adjuvant chemotherapy in a patient with locally advanced SCCHN	PF	£28,718	2.04				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.	Partially applicable with minor limitations.
		TPF	£32,440	4.12	£3721	2.09	£1782		
	Comments:								

Recommendations	**Offer people with T3 squamous cell carcinoma of the larynx a choice of:** • **radiotherapy with concomitant chemotherapy, or** • **surgery with adjuvant radiotherapy, with or without concomitant chemotherapy.** **Discuss the following with people with T3 squamous cell carcinoma of the larynx and their carers, to inform their choice of treatment:** • **the potential advantages of laryngeal preservation** • **the risk of needing salvage laryngectomy (and its associated complications)** • **the benefits of primary surgery in people with existing compromised swallowing and airway function** • **likely voice and swallowing function after treatment (including the need for a long-term feeding tube).** **For people with T4a squamous cell carcinoma of the larynx consider surgery with adjuvant radiotherapy, with or without concomitant chemotherapy.**
Relative value placed on the outcomes considered	The effect of the treatments on overall and progression-free survival, laryngeal preservation, voice function, swallow and length of stay were considered the most influential outcomes when making these recommendations, although there were limited data on treatment related morbidity and its impact on function.
Quality of the evidence	The quality of the evidence was judged as moderate to high using GRADE criteria. Patients with small volume T3 were included in some studies and those with locally advanced T4 were excluded in others. There was no direct comparison of radiotherapy and concomitant chemotherapy with surgery and postoperative adjuvant therapies. For these reasons the group made a weaker recommendation for patients with T4a disease (based on their clinical experience) and recommended a choice of radiotherapy and concomitant chemotherapy or surgery with postoperative adjuvant therapies for those with T3 disease. Given that it was not possible to recommend one particular treatment for T3 squamous cell carcinoma of the larynx, based on their clinical experience the GC agreed to include a list of factors that should be discussed to inform the decision on choice of treatment. Such factors thought to be important included in part the potential advantages of maintaining an intact larynx, the likely functioning of the larynx after preservation particularly in those patients where voice or swallowing was compromised prior to treatment and the risks of salvage laryngectomy after failed radiotherapy given its increased complication rate.
Trade-off between clinical benefits and harms	For patients with T3 disease there should be better patient selection for laryngeal preservation protocols, and more informed patient discussions about treatment choices. These discussions, however could lead to anxiety associated with making treatment decisions. The group believed that making a more informed choice outweighed the possible additional anxiety. The group noted the importance of laryngeal preservation varies between individual patients, so it would be vital to establish each patient's

	values and preferences. For patients with T4a disease the group believe the recommendation offers a better cure rate but with a possible reduced chance of laryngeal preservation. The group believed that potential laryngeal preservation rates would be low (and may be overestimated in the studies due to the exclusion of advanced T4 patients in trials) and many may require salvage laryngectomy. The GC agreed that potential for cure outweighed the drawbacks of loss of laryngeal function.
Trade-off between net health benefits and resource use	No health economic model was developed. Two partially relevant studies of cost-effectiveness were identified. The economic evidence compared different chemotherapy regimens (specifically, the addition of docetaxel to 5-fluorouracil and cisplatin) in a pooled group of head and neck cancer patients. However, the GC did not make any recommendations specifying one chemotherapy regimen over another, due to the uncertainty associated with this comparison in the subgroup of laryngeal patients. The GC considered the potential costs and savings of the recommendations. For patients with T3 disease there may be longer consultation time due to discussion about treatment choices and there may be a need to see more healthcare professionals. However, the group believed that the recommendations did not differ greatly from current practice and therefore costs would not change greatly.
Other considerations	

4.2 Squamous cell carcinoma of the hypopharynx

Squamous cell carcinomas of the hypopharynx usually present late with metastatic spread to the neck, and have a poorer prognosis compared to other HNC 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 neo-adjuvant chemotherapy given to preserve structure and function has challenged this approach. Although this technique preserves the larynx it 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.

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)?

Clinical evidence (see Appendix H)

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. 5-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. 5-year overall survival was 19% and 37% for radiotherapy alone and surgery plus radiotherapy, respectively ($p = 0.04$). 5-year local control was 37% and 63% for radiotherapy alone and surgery plus radiotherapy, respectively ($p < 0.01$).

Radiotherapy and concomitant chemotherapy versus radiotherapy alone

Moderate quality evidence from a single randomised controlled trial (Bensadoun 2006; 163 patients, 40 with hypopharynx cancer) suggests uncertainty over whether is beneficial compared to radiotherapy alone in people with stage IV hypopharyngeal cancer. After two years, overall survival was comparable between the two treatments. Radiotherapy and concomitant chemotherapy improved locoregional control (50.7% and 24.3% with radiotherapy and concomitant chemotherapy and radiotherapy alone, respectively) and disease-free survival (38% and 22% with radiotherapy and concomitant chemotherapy 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 hypopharygeal cancer) did not indicate any benefit to overall survival or progression-free survival from the addition of docetaxel (Posner et al., 2009) or vinorelbine (Rivera et al., 2008) to cisplatin-based chemotherapy in patients with advanced hypopharyngeal cancer.

Timing and sequence of radiotherapy and concomitant chemotherapy

Moderate quality evidence from a single randomised trial (Prades et al., 2010) including 71 patients suggests that in people with T3 hypopharyngeal cancer, concomitant treatment with chemotherapy and radiotherapy may improve some outcomes compared with neo-adjuvant 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, Waldfahrer, Fietkau, & Gramatzki, 1997) including 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 chemotherapy and radiotherapy, and radiotherapy and concomitant chemotherapy respectively) in patients with non-resectable stage IV hypopharyngeal cancer.

Table 38: GRADE evidence table: locoregional treatment with chemotherapy vs locoregional treatment alone in hypopharynx SCC (Blanchard, 2011; Pignon, 2009, Pignon, 2000)

Quality assessment							No of patients		Effect			
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**	**Quality**	
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 to 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 to 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 39: GRADE evidence table: altered fractionation radiotherapy vs conventional radiotherapy be used in hypopharynx SCC (Bourhis, 2006; Baujat, 2010)

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 to 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 HNC sites. Seventeen studies in total were included; the number of these studies that included hypopharynx tumours was not specified.*

Table 40: GRADE evidence table: locoregional treatment with radiotherapy vs locoregional treatment with surgery followed by postoperative radiotherapy in advanced hypopharynx 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	no serious inconsistency	no serious indirectness	serious[2]	none	45	45	39% and 63% for radiotherapy alone and radiotherapy + surgery,	□□□□ MODERATE

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**				
		risk of bias							respectively. P <0.01.				
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		**RT**	**S + RT**		MODERATE
									5-year OS	19 %	37 %	P = 0.04	
									Median OS, months	20	40		
OS: overall survival; RT: radiotherapy; S: surgery.													

1 [1] *Beauvillain, 1997.*
2 [2] *Downgraded due to small study population.*

3 **Table 41: GRADE evidence table: radiotherapy and concomitant chemotherapy vs 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**	**Radiotherapy and concomitant chemotherapy**	**Radiotherapy alone**	**Relative (95% CI)**	**Absolute**		
Complete response at treatment end (follow-up median 45 months)												

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy and concomitant chemotherapy**	**Radiotherapy alone**	**Relative (95% CI)**	**Absolute**	
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 to 2.29)	99 more per 1000 (from 158 fewer to 580 more)	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: Chemo RT / RT alone / —		MODERATE
									2-year OS, %: 21.5 / 21.7 / NS		
									Median OS, months: 12 / 9 / NS		
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 radiotherapy and concomitant chemotherapy and radiotherapy alone, respectively		MODERATE
Disease free survival, Kaplan-Meier estimates (follow-up median 45 months)											
1	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	Rate of disease-free survival at 2 years: 38% and 22% with radiotherapy and concomitant chemotherapy and radiotherapy alone, respectively		MODERATE

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy and concomitant chemotherapy**	**Radiotherapy alone**	**Relative (95% CI)**	**Absolute**	**Quality**	
		bias										
CI: confidence interval; NS: not significant; OS: overall survival; RT: radiotherapy.												

1 [1] *Bensadoun 2006.*
2 [2] *Small study population.*

3 **Table 42: GRADE evidence table: chemotherapy vs surgery in stage IV hypopharynx SCC**

Quality assessment							No of patients		Effect					
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy	Surgery	Relative (95% CI)	Absolute			**Quality**	
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 to 1.19)		Surgery (n = 94)	Chemotherapy (n = 100)	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	13.8 (6.1–	13.1 (5.6–20.6)		

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			
										survival, % (95% CI)	21.6)		
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 to 1.12)		Surgery (n = 94)	Chemotherapy (n = 100)	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	no seri	no serious inconsisten	no serious	serious[3]	none	29/94 (30.9%)	33/100	RR 0.93	23 fewer per 1000 (from 125 fewer to 135 more)			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	
	trials	ous risk of bias	cy	indirectness				(33%)	(0.62 to 1.41)		
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.	MODERATE
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 to 2.67)	82 more per 1000 (from 45 fewer to 229 more)	MODERATE
CI: confidence interval; HR: hazard ratio; RR: risk ratio.											

1 *1 Lefebvre 2012.*
2 *2 Lefebvre 2006.*
3 *3 95% CI around the effect includes values corresponding to appreciable benefit and no effect.*
4 *4 95% CI around the effect includes values corresponding to appreciable harm and no effect.*

5 **Table 43: GRADE evidence table: concomitant chemoRT vs neo-adjuvant chemo 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	Neo-adjuvant 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	Neo-adjuvant chemo (	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	Neo-adjuvant chemo	MODERATE	
									Estimated 1-year event free survival, %	68	58		

Quality assessment							No of patients		Effect		Quality	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Concomitant chemoRT**	**Neo-adjuvant chemo followed by RT**	**Relative (95% CI)**	**Absolute**		
									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 to 1.65)	212 more per 1000 (from 21 more to 459 more)	MODERATE	
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 to 1.18)	152 fewer per 1000 (from 194 fewer to 37 more)	MODERATE	
Neutropenia												
1	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	serious[1]	none	12/37 (32.4%)	7/34 (20.6%)	RR 1.58 (0.7 to 3.53)	119 more per 1000 (from 62 fewer to 521 more)	MODERATE	

Quality assessment							No of patients		Effect		Quality	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Concomitant chemoRT**	**Neo-adjuvant chemo followed by RT**	**Relative (95% CI)**	**Absolute**		
		of bias										
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 to 19.36)	25 more per 1000 (from 24 fewer to 540 more)	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 to 1.05)	173 fewer per 1000 (from 338 fewer to 41 more)	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 to 1.58)	11 more per 1000 (from 180 fewer to 307 more)	MODERATE	
Renal toxic effects												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Concomitant chemoRT**	**Neo-adjuvant chemo followed by RT**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 92.63)	Not estimable	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 to 14.12)	2 fewer per 1000 (from 28 fewer to 386 more)	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 44: GRADE evidence table: sequential chemotherapy and radiotherapy vs radiotherapy and concomitant chemotherapy 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 chemotherapy and radiotherapy	Radiotherapy and concomitant chemotherapy	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 chemotherapy and radiotherapy and radiotherapy and concomitant chemotherapy, respectively	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 chemotherapy and radiotherapy and radiotherapy and concomitant chemotherapy, respectively	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 chemotherapy and radiotherapy and radiotherapy and	LOW	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential chemotherapy and radiotherapy	Radiotherapy and concomitant chemotherapy	Absolute	Quality	
									concomitant chemotherapy, respectively		

[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 45: GRADE evidence table: neo-adjuvant chemotherapy (5-FU and cisplatin) with docetaxel (TPF) vs neo-adjuvant 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	Neo-adjuvant chemotherapy (5-FU and cisplatin) with docetaxel	Neo-adjuvant 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 to 1.20)	TPF (n = 43)	PF (n = 34)	MODERATE	

Quality assessment							No of patients		Effect				Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neo-adjuvant chemotherapy (5-FU and cisplatin) with docetaxel	Neo-adjuvant chemotherapy without docetaxel	Relative (95% CI)	Absolute			
										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 to 1.32)		TPF (n = 43)	PF (n = 34)	MODERATE
										Median PFS, months	16	11	
										Estimated 3-year PFS, %	38	32	

Quality assessment							No of patients		Effect		Quality	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neo-adjuvant chemotherapy (5-FU and cisplatin) with docetaxel	Neo-adjuvant chemotherapy without docetaxel	Relative (95% CI)	Absolute		
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 46: GRADE evidence table: comparison of Neo-adjuvant 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	Neo-adjuvant chemotherapy with vinorelbine, cisplatin and uracil-tegafur (UFTVP)	Neo-adjuvant 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.	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 47: GRADE evidence table: accelerated radiotherapy vs 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	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.*

Cost-effectiveness evidence

Two relevant studies were identified in a literature review of published cost-effectiveness analyses on this topic. The base case results of both cost-effectiveness analyses showed that the addition of docetaxel to cisplatin and fluorouracil in patients with unresectable HNC 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 HNCs 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 HNC. However, the use of a general HNC population rather than a hypopharyngeal cancer population limits applicability. Further disease site specific evidence is required to conclusively demonstrate cost-effectiveness.

Table 48: 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 to PF as neo-adjuvant chemotherapy in a patient with locally advanced SCCHN	PF	£28,718	2.04				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.	Partially applicable with minor limitations.
		TPF	£32,440	4.12	£3721	2.09	£1782		
	Comments:								

Recommendations	**Offer larynx-preserving treatment to people with locally advanced squamous cell carcinoma of the hypopharynx if radiation and neo-adjuvant and/or concomitant chemotherapy would be suitable for them and they do not have:** • **tumour-related dysphagia needing a feeding tube** • **a compromised airway** • **recurrent aspiration pneumonias.** **Offer radiotherapy with neo-adjuvant and/or concomitant chemotherapy if larynx-preserving treatment is suitable for the person.** **Offer primary surgery followed by adjuvant radiotherapy to people if chemotherapy is not a suitable treatment for them.** **Offer adjuvant radiotherapy to people having surgery as their primary treatment. Add concomitant chemotherapy if appropriate.**
Relative value placed on the outcomes considered	When drafting recommendations the outcomes considered most important by the GC were overall survival and disease-free survival (when comparing surgery with and without radiotherapy or adjuvant treatment), and laryngeal preservation (for larynx preservation vs immediate surgery). No evidence on treatment-related mortality or health-related quality of life was reported in the evidence. Treatment-related morbidity outcomes were only reported by one study, and the results were associated with uncertainty; this evidence was therefore not considered useful in making recommendations.
Quality of the evidence	The quality of the evidence, as assessed by GRADE, varied from high to low. The reviewer highlighted that many of the comparisons in the included randomised trials involved small numbers of patients. In addition, not all studies were specific to the hypopharynx, and therefore subgroup analyses were heavily relied upon, further reducing the number of relevant patients for some comparisons. The small patient numbers meant that outcomes for several comparisons were associated with uncertainty. The GC noted that there was no evidence of a benefit for surgery over organ-preserving treatment in terms of overall survival or disease-free survival. As organ preservation has the potential to preserve the larynx, they therefore recommended this as the first option. For those people who are suitable for larynx-preserving treatment the GC agreed that pre-treatment dysphagia, airway compromise and recurrent aspiration pneumonia predict poor functional outcome. The GC also noted that subgroup analyses from the MACH-NC meta-analysis had suggested that neo-adjuvant or concomitant chemotherapy gives greater benefits (in terms of disease progression or survival) than adjuvant chemotherapy. It was also acknowledged that Beauvillain et al (1997) had shown where patients are receiving surgery, the combination of surgery and radiotherapy is beneficial. The GC also noted evidence from a subgroup analysis of MACH-NC showing that the addition of chemotherapy to surgery improves overall and disease-free

	survival. Two sources of health economic evidence were identified. Liberato et al is only partially applicable to the review, because it considered an Italian health care system. Parthan et al is also only partially applicable because evidence is presented for HNCs and not specific to hypopharynx cancers alone. The economic evidence compared different chemotherapy regimens (specifically, the addition of docetaxel to 5-fluorouracil and cisplatin). However, the GC did not make any recommendations specifying one chemotherapy regimen over another, due to the uncertainty associated with this comparison in the subgroup of hypopharynx patients.
Trade-off between clinical benefits and harms	The GC considered the potential benefits of the recommendations to be: • improved laryngeal preservation rates • improved patient choice • improved overall survival and progression free survival in patients treated with surgery (from the addition of radiotherapy with or without chemotherapy to primary treatment). Chemotherapy and radiotherapy-associated morbidities were considered to be potential harms of the recommendations that have been made. Treatment-related morbidity is outweighed by improvements in survival and disease control as a result of chemotherapy.
Trade-off between net health benefits and resource use	No health economic model was developed. Two partially relevant studies of cost-effectiveness were identified. The economic evidence compared different chemotherapy regimens (specifically, the addition of docetaxel to 5-fluorouracil and cisplatin). However, the GC did not make any recommendations specifying one chemotherapy regimen over another, due to the uncertainty associated with this comparison in the subgroup of hypopharynx patients. The GC considered the potential costs and savings of the recommendations made to be: • savings from lower rates of progression/recurrence and hence less cost of salvage treatment • increased costs from delivery of additional chemotherapy or RT.
Other considerations	The major change in practice envisaged as a result of the recommendations is greater delivery of larynx preserving radiotherapy combined with chemotherapy and less surgery to this group of patients. There is likely to be an increase in the proportion of patients receiving larynx preservation instead of surgery as a result of the recommendations.

4.3 Palliation of breathing difficulties

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.

Clinical question: What are the most effective palliative treatments for people with incurable upper aerodigestive tract cancer experiencing breathing difficulties?

Clinical evidence (see Appendix H)

The review identified no evidence that met the inclusion criteria of the review.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Identify people at risk of airways obstruction for whom intervention is appropriate. Think about:** • **their performance status** • **treatment side effects and length of hospital stay** • **involving the palliative care team and other specialists when appropriate.** **Consider endoluminal debulking in preference to tracheostomy.** **Establish a management plan if surgical intervention is not appropriate, in conjunction with the person, carers and clinical staff.** **Assess and treat other causes of breathlessness in people with incurable upper aerodigestive tract cancer.**
Relative value placed on the outcomes considered	All the outcomes in the PICO were considered important by the GC, but no evidence was identified for any outcome.
Quality of the evidence	The GC were concerned that there was a small group of patients with breathing difficulties due to impending airway problems in whom no proactive treatment plan was in place which can result in inappropriate management and patient and carer distress particularly in the emergency setting. No evidence was identified. Therefore, the GC agreed to make recommendations based solely on clinical experience. They also recommended what factors people would need to take into consideration when deciding on appropriate interventions. For those patients with impending airways problems debulking is still considered preferable to tracheostomy, in terms of quality of life, shorter inpatient hospital stay, and the patients' ability to return to their usual residence. Debulking however may require multiple procedures. Breathing difficulties in people with incurable cancer can be multifactorial. In patients experiencing dyspnea, the GC agreed that clinical assessment should determine the underlying causes to tailor the

	management appropriately, and any coexisting conditions should be optimised. The GC also agreed that involvement of the palliative care team is appropriate for symptom management of dyspnea and developing an appropriate plan of care with the patient, their carers and health professionals involved in the individuals care. The recommendations aimed to emphasise the importance of considering this when planning and delivering care.
Trade-off between clinical benefits and harms	The anticipated benefits of the recommendations are: • better planning of treatment, development of individualised care plans, and therefore a reduction in emergency unplanned presentations (e.g. to accident and emergency departments) • reduced length of hospital stay and improved quality of life for patients treated with debulking instead of tracheostomy • Earlier implementation of palliative care leading to timely symptom control and better planning for end of life care. Anticipated harms are: • the need for some patients to undergo multiple debulking procedures (as opposed to a single tracheostomy) • in those patients with potential airways obstruction there is the potential increased patient anxiety from discussing planned treatment, which may not subsequently be needed. The benefits of planned management outweigh patients' anxieties from discussing treatment options.
Trade-off between net health benefits and resource use	No economic evidence was identified and no economic model was developed. The GC anticipates that there will be increased costs associated with debulking. The GC also noted that multiple procedures are sometimes required, which would further increase costs. However, this will be offset by a reduction in tracheostomy care costs, both in acute care and the community. As there is often a substantial number of bed days associated with tracheostomies in this setting, it is likely that the use of debulking procedures will be cost neutral. However, even if there were a net increase in costs from the use of debulking, the GC anticipates that it would be cost-effective because of the improved quality of life that it offers.
Other considerations	The GC envisage that the following changes in practice are needed to implement the recommendations: • More palliative treatment will be planned in advance with the patient and multidisciplinary team. This is anticipated to result in less emergency presentations of these patients, and therefore less unplanned interventions being given in the emergency setting. • Individual care plans incorporating end of life care for those patients who do not want to undergo surgical intervention for airways obstruction • Expertise for debulking surgery may vary across centres. For debulking, training may be required in some centres, and/or more surgical and anaesthesia resources may be required.

References

Baujat, B., Bourhis, J., Blanchard, P., Overgaard, J., Ang, K. K., Saunders, M., Le, Maitre A.,
Bernier, J., Horiot, J. C., Maillard, E., Pajak, T. F., Poulsen, M. G., Bourredjem, A.,
O'Sullivan, B., Dobrowsky, W., Andrzej, H., Skladowski, K., Hay, J. H., Pinto, L. H., Fu, K. K.,

Fallai, C., Sylvester, R., and Pignon, J. P. Hyperfractionated or accelerated radiotherapy for head and neck cancer. Cochrane Database of Systematic Reviews 2010. (12): CD002026

Beauvillain, C., Mahe, M., Bourdin, S., Peuvrel, P., Bergerot, P., Riviere, A., Vignoud, J., Deraucourt, D., and Wesoluch, M. Final results of a randomized trial comparing chemotherapy plus radiotherapy with chemotherapy plus surgery plus radiotherapy in locally advanced resectable hypopharyngeal carcinomas. Laryngoscope 1997. 107: 648-653

Bensadoun, R. J., Benezery, K., Dassonville, O., Magne, N., Poissonnet, G., Ramaioli, A., Lemanski, C., Bourdin, S., Tortochaux, J., Peyrade, F., Marcy, P. Y., Chamorey, E., Vallicioni, J., Seng, H., Alzieu, C., Gery, B., Chauvel, P., Schneider, M., Santini, J., Demard, F., and Calais, G. French multicenter phase III randomized study testing concurrent twice-a-day radiotherapy and cisplatin/5-fluorouracil chemotherapy (BiRCF) in unresectable pharyngeal carcinoma: Results at 2 years (FNCLCC-GORTEC). International Journal of Radiation Oncology, Biology, Physics 2006. 64: 983-994

Blanchard, P., Baujat, Bertrand, Holostenco, Victoria, Bourredjem, Abderrahmane, Baey, Charlotte, Bourhis, Jean, Pignon, Jean-Pierre, and MACH-CH Collaborative group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiotherapy & Oncology 2011. 100(1): 33-40.

Bourhis, J., Overgaard, J., Audry, H., Ang, K. K., Saunders, M., Bernier, J., Horiot, J. C., Le, Maitre A., Pajak, T. F., Poulsen, M. G., O'Sullivan, B., Dobrowsky, W., Hliniak, A., Skladowski, K., Hay, J. H., Pinto, L. H., Fallai, C., Fu, K. K., Sylvester, R., and Pignon, J. P. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006. 368(9538): 843-854

Denaro, N., Russi, E. G., Lefebvre, J. L., and Merlano, M. C. A systematic review of current and emerging approaches in the field of larynx preservation. Radiotherapy and Oncology 2014. 110(1): 16-24.

Forastiere, A. A., Zhang, Q., Weber, R. S., Maor, M. H., Goepfert, H., Pajak, T. F., Morrison, W., Glisson, B., Trotti, A., Ridge, J. A., Thorstad, W., Wagner, H., Ensley, J. F., and Cooper, J. S. 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 2013. 31(7): 845-852

Iro, H., Waldfahrer, F., Fietkau, R., and Gramatzki, M. Comparison of sequential and simultaneous chemo-radiotherapy for advanced hypopharyngeal carcinoma. Results of a randomised study. Radiotherapy and Oncology 1997. 31: 188-189

Lefebvre, J. L., Andry, G., Chevalier, D., Luboinski, B., Collette, L., Traissac, L., de Raucourt, D., Langendijk, J. A., Head, Eortc, and Neck Cancer, Group. Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. Annals of Oncology 2012. 23: 2708-2714

Lefebvre, J. L., Chevalier, D., Luboinski, B., Kirkpatrick, A., Collette, L., and Sahmoud, T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. Journal of the National Cancer Institute 1996. 88: 890-899

Liberato, N. L., Rognoni, C., Rubrichi, S., Quaglini, S., Marchetti, M., Gorlia, T., Licitra, L., and Vermorken, J. B. 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

Parthan, A., Posner, M. R., Brammer, C., Beltran, P., and Jansen, J. P. Cost utility of docetaxel as induction chemotherapy followed by chemoradiation in locally advanced squamous cell carcinoma of the head and neck. Head and Neck 2009. 31(10): 1255-1262

Pignon, J. P. and Bourhis, J. 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 2000. 355(9208): 949-955.

Pignon, J. P., Bourhis, J., Domenge, C., and Designe, L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. Lancet 2000. 355: 949-955

Pignon, J. P., Le, Maitre A., Maillard, E., and Bourhis, J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiotherapy and Oncology 2009. 92(1): 4-14

Posner, M. R., Hershock, D. M., Blajman, C. R., Mickiewicz, E., Winquist, E., Gorbounova, V., Tjulandin, S., Shin, D. M., Cullen, K., Ervin, T. J., Murphy, B. A., Raez, L. E., Cohen, R. B., Spaulding, M., Tishler, R. B., Roth, B., Viroglio, Rdel C., Venkatesan, V., Romanov, I., Agarwala, S., Harter, K. W., Dugan, M., Cmelak, A., Markoe, A. M., Read, P. W., Steinbrenner, L., Colevas, A. D., Norris, C. M., Jr., and Haddad, R. I. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. New England Journal of Medicine 2007. 357(17): 1705-1715

Posner, M. R., Norris, C. M., Wirth, L. J., Shin, D. M., Cullen, K. J., Winquist, E. W., Blajman, C. R., Mickiewicz, E. A., Frenette, G. P., Plinar, L. F., Cohen, R. B., Steinbrenner, L. M., Freue, J. M., Gorbunova, V. A., Tjulandin, S. A., Raez, L. E., Adkins, D. R., Tishler, R. B., Roessner, M. R., Haddad, R. I., and Group, T. A. X. S. Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324: survival, surgery, and organ preservation. Annals of Oncology 2009. 20: 921-927

Prades, J. M., Lallemant, B., Garrel, R., Reyt, E., Righini, C., Schmitt, T., Remini, N., Saban-Roche, L., Timoshenko, A. P., Trombert, B., and Guerrier, B. Randomized phase III trial comparing induction chemotherapy followed by radiotherapy to concomitant chemoradiotherapy for laryngeal preservation in T3M0 pyriform sinus carcinoma. Acta Oto-Laryngologica 2010. 130: 150-155

Rivera, F., Vega-Villegas, M. E., Lopez-Brea, M., Isla, D., Mayorga, M., Galdos, P., Rubio, A., Del Valle, A., Garcia-Reija, F., Garcia-Montesinos, B., Rodriguez-Iglesias, J., Mayordomo, J., Rama, J., Saiz-Bustillo, R., and Sanz-Ortiz, J. Randomized phase II study of cisplatin and 5-FU continuous infusion (PF) versus cisplatin, UFT and vinorelbine (UFTVP) as induction chemotherapy in locally advanced squamous cell head and neck cancer (LA-SCHNC). Cancer Chemotherapy and Pharmacology 2008. 62: 253-261

Zackrisson, B., Nilsson, P., Kjellen, E., Johansson, K. A., Modig, H., Brun, E., Nyman, J., Friesland, S., Reizenstein, J., Sjodin, H., Ekberg, L., Loden, B., Mercke, C., Fernberg, J. O., Franzen, L., Ask, A., Persson, E., Wickart-Johansson, G., Lewin, F., Wittgren, L., Bjor, O., and Bjork-Eriksson, T. 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 2011. 100: 41-48

5 HPV-related disease

5.1 HPV testing

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.

Clinical question: What is the most effective test to identify an HPV-positive tumour in people with cancer of the upper aerodigestive tract?

Clinical evidence (see Appendix H)

Two studies were identified that investigated the effectiveness of a range of tests to detect human papillomavirus (HPV) in upper aerodigestive tract tumours.

One study (Schache et al., 2011; Schache et al., 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 et al., 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

Study quality was assessed using the QUADAS2 checklist. Both studies were conducted in Europe (one in the United Kingdom) and published within the last ten years, although one study (Smeets et al., 2007) did not report the time period over which patients were tested. One study (Schache et al., 2011; Schache et al., 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 et al., 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 et al., 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.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Test all squamous cell carcinomas of the oropharynx using p16 immunohistochemistry. Regard the p16 test result as positive only if there is strong nuclear and cytoplasmic staining in more than 70% of tumour cells.** **Consider high-risk HPV DNA or RNA in-situ hybridisation in all p16-positive cancers of the oropharynx to confirm HPV status.**
Relative value placed on the outcomes considered	Sensitivity and specificity were considered important for drafting the recommendations. These were the only outcomes included in the PICO.
Quality of the evidence	The evidence was assessed using QUADAS2. The reviewer highlighted that: • Both studies were conducted in Europe (one in the United Kingdom) and published within the last ten years. • Although both studies were small, each reported the diagnostic accuracy of a range of tests, allowing for direct comparison of test performance in the same studied population. • Patient flow was not clearly reported in either study. • Where the diagnostic accuracy of combinations of tests was reported, the methods by which this was done were not clear. Some assumptions had to be made about how the diagnostic accuracy figures were derived – e.g. whether diagnosis required a positive result on both tests. Based on the evidence the GC agreed to recommend testing for all carcinomas of the oropharynx, suggesting p16 testing as it is readily available, relatively sensitive, specific, and inexpensive. The evidence was of sufficient quality to allow a strong recommendation: diagnostic accuracy of p16 testing was directly compared to other tests, in studies that are directly applicable to UK clinical practice and had no major risks of bias associated with

	them. p16 cut-offs varied in the studies presented. The recommended cut-off of 70% is based partially on clinical experience, but reflects current practice. The GC acknowledged that the evidence had demonstrated HPV DNA or RNA in-situ hybridisation were more sensitive than p16 testing for identifying HPV-related disease. However given that it is more expensive and less readily available it was only recommended to confirm HPV status in p16-positive cancers. RNA ISH is an emerging technique for measuring transcriptionally active HPV, and so is a priority for further research. For these reasons, a research recommendation was made in relation to this test.
Trade-off between clinical benefits and harms	The perceived benefit of the recommendations is improved diagnostic accuracy in testing of HPV status. No potential harms were identified.
Trade-off between net health benefits and resource use	No health economic evidence was presented and no model developed. The GC envisage a potential increase in costs from implementing the recommendations, due to the use of a two-tier testing system.
Other considerations	HPV ISH is not currently a widely used test. To fully implement the recommendations, HPV ISH will need to be made more widely available. The review question considered any patients with cancer of the upper aerodigestive tract. However, the majority of the identified evidence is specific to oropharyngeal cancer, and this group of patients is considered most relevant to HPV testing by the GC. For these reasons, a recommendation specific to oropharyngeal cancer was made.

1

Research recommendation	**A prospective study should be undertaken to compare the effectiveness of single-step laboratory diagnostic tests to identify human papillomavirus (HPV) against current diagnostic test algorithms and reference standards in people with cancer of the oropharynx. Outcomes of interest are sensitivity, specificity and resource use.**
Why this is important	HPV testing is currently recommended in cancer of the oropharynx since it has significant prognostic implication. Current methods utilise a two-step procedure which is not widely available in all treatment centres. A single-step test is likely to be more widely adopted and could have significant budgetary implications for the NHS. The study should also consider the prognostic value and the economic benefits of novel tests.

5.2 2 De-intensification of treatment

3 Retrospective data analyses have suggested that people with HPV-positive oropharyngeal
4 cancers (particularly those who have never smoked) have excellent cure rates with standard
5 therapeutic approaches whether these are based around radiotherapy or surgery.

6 Radiation with chemotherapy has been a standard treatment option for oropharyngeal cancer
7 for many years and predates the recognition of HPV-positive disease. Curative surgery can
8 involve transoral or open techniques and is often followed by post-operative radiotherapy
9 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.

Clinical question: Is there a role for de-intensification of treatment in patients with HPV-positive upper aerodigestive tract tumours?

Clinical evidence (see Appendix H)

A systematic review of de-escalation treatment protocols for human papilloma virus (HPV) associated oropharyngeal squamous cell carcinoma (Masterson & Tanweer, 2013; Masterson et al., 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 et al., 2012) including 126 patients with HPV16 DNA-positive and P16-positive tonsillar 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 to 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 (Lassen et al., 2011). The evidence suggests that locoregional recurrence is less likely with accelerated than with conventionally fractionated radiotherapy, (HR = 0.58, 95% CI 0.35 to 0.99; HR <1 favours accelerated fractionation). 5-year locoregional recurrence free survival was 76% with accelerated radiotherapy and 60% with conventional radiotherapy.

Very low quality evidence from one observational study (Attner et al., 2012) including 126 patients with HPV16 DNA-positive and P16-positive tonsillar 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 to 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-positive larynx, pharynx or oral cavity squamous cell carcinoma, who were part of a larger randomized trial (Lassen et al., 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 radiotherapy and concomitant chemotherapy

Overall mortality

Very low quality evidence from an observational study (Attner et al., 2012) including 113 patients with HPV16DNA-positive and P16-positive tonsillar cancer, suggests uncertainty over whether radiotherapy or radiotherapy and concomitant chemotherapy is the more

effective in terms of overall mortality (HR=1.20; 95% CI 0.50 to 2.90; HR < 1 favours radiotherapy). Four year overall survival was 71% with conventionally fractionated radiotherapy compared with 84% for radiotherapy and concomitant chemotherapy.

Disease recurrence

Very low quality evidence from three observational studies (Attner et al., 2012; Haughey & Sinha, 2012; O'Sullivan et al., 2013) suggests uncertainty over whether radiotherapy and concomitant chemotherapy 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 radiotherapy and concomitant chemotherapy). Although recurrence rates were lower with radiotherapy and concomitant chemotherapy 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 & Sinha, 2012; O'Sullivan et al., 2013) suggests uncertainty over whether radiotherapy and concomitant chemotherapy 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 to 23.46; HR <1 favours radiotherapy). Four-year metastasis-free survival was 89% with radiotherapy and 97% with radiotherapy and concomitant chemotherapy.

O'Sullivan et al (2013) performed subgroup comparisons of distant control with RT and concomitant chemotherapy 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 radiotherapy and concomitant chemotherapy 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 radiotherapy and concomitant chemotherapy than with radiotherapy alone. For patients with N2b disease, 3-year distant control rates were 98% with RT and concomitant chemotherapy and 89% with RT; for those with N2c the rates were 92% with RT and concomitant chemotherapy 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 radiotherapy and concomitant chemotherapy, with 91% choosing radiotherapy in this scenario. If radiotherapy and concomitant chemotherapy had a 5% absolute survival benefit over radiotherapy, however, 69% of patients would choose radiotherapy and concomitant chemotherapy.

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-positive oropharyngeal carcinoma (Cmelak, Li, & Marur, 2014), which used a reduced dose (54 Gy) of intensity modulated radiotherapy (IMRT) plus cetuximab in patients with complete clinical response to neo-adjuvant chemotherapy. This evidence reports 2-year overall survival rates of 95% (90% CI 87% to 98%) with reduced dose IMRT. Patients without complete clinical response to neo-adjuvant 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-positive head and neck cancer (HNC) (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 to 7.97; HR <1 favours lower dose chemotherapy). 3-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-positive HNC (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 to 3.75; HR <1 favours lower dose chemotherapy). 3-year recurrence free survival was 82% with lower dose chemotherapy compared with 84% for standard dose in this study.

Radiotherapy plus EGFR inhibitor versus chemo-radiotherapy

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 radiotherapy and concomitant chemotherapy. This evidence suggests better overall survival with RT plus EGFR inhibitor than with radiotherapy and concomitant chemotherapy. For patients with HPV16-positive tumours, HR = 0.22 [95% CI 0.05 to 0.90]; for patients with P16-positive tumours HR = 0.18 [95% CI 0.04 to 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 radiotherapy and concomitant chemotherapy. For patients with P16-positive tumours, two-year overall survival was 88% with RT plus EGFR inhibitor compared with 60% for radiotherapy and concomitant chemotherapy.

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 radiotherapy and concomitant chemotherapy. For patients with HPV16-positive tumours, HR = 0.19 [95% CI 0.47 to 0.80], for patients with P16-positive tumours HR = 0.20 [95% CI 0.01 to 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 radiotherapy and concomitant chemotherapy. For patients with P16-positive tumours, two-year disease free survival was 75% with RT plus EGFR inhibitor compared with 47% for radiotherapy and concomitant chemotherapy.

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.

1 **Table 49: GRADE evidence profile: accelerated radiotherapy versus standard radiotherapy for HPV+ upper airways cancer**

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Accelerated RT**	**Standard RT**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 1.41)	4 year overall survival 84% for accelerated versus 71% for conventional RT.	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	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 to 0.99)	5 year late locoregional recurrence free survival rate: 76% for accelerated RT versus 60% for conventional	LOW	

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**		
										RT.		
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 to 1.75)	4 year disease free survival 85% for accelerated versus 79% for conventional RT.	VERY LOW	

1 [1] *Attner (2012).*
2 [2] *Low event rate.*
3 [3] *Lassen (2011).*
4 [4] *Unclear allocation concealment, relatively low event rate.*
5 [5] *Number of events not reported.*
6 [6] *Subgroup analysis of a larger trial - unclear whether this was a planned or post-hoc analysis.*

7 **Table 50: GRADE evidence profile: radiotherapy versus Chemo-radiotherapy for HPV+ 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 serio	no serious inconsistenc	no serious indirectnes	serious[2]	none	27/86 (31.4%)	4/27 (14.8%)	HR 1.20 (0.50 to	4 year overall survival 71% for	VERY	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy**	**Chemo-radiotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	
		us risk of bias	y	s					2.90)	conventional RT versus 84% for radiotherapy and concomitant chemotherapy	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 to 8.14)	4 year disease free survival 79% for conventional RT versus 91% for radiotherapy and concomitant chemotherapy (Attner et al 2012)	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 to 23.46)	4 year metastasis free survival 89% for conventional RT versus 97% for radiotherapy and concomitant chemotherapy (Attner et al 2012)	VERY LOW	
Patient choice (if survival were equivalent)[3]												
1	observational studies	no serio	no serious inconsistenc	no serious indirectnes	no serious imprecisio	none	46/51 (90.2%)	5/51 (9.8%)	Not applica	For every 100 patients 90 would	LOW	

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	Chemo-radiotherapy	Relative (95% CI)	Absolute	Quality	
		us risk of bias	y	s	n				ble	choose RT and 10 ChemoRT, if overall survival was equivalent		

[1] *Attner (2012).*
[2] *Low number of events.*
[3] *Brotherson (2013).*

Table 51: GRADE evidence profile: low dose radiotherapy plus EGFR inhibitor versus standard dose radiotherapy plus EGFR inhibitor after chemotherapy for HPV+ upper airways cancer.

Quality assessment							No of patients		Effect			
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	Quality	
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	VERY LOW	

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**		
										dose		
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	VERY LOW	

[1] *Cmelak (2014).*
[2] *Only patients with complete clinical response to neo-adjuvant chemotherapy could receive reduced dose IMRT.*
[3] *Low number of events.*
[4] *Event rates not reported.*

Table 52: GRADE evidence profile: lower dose adjuvant chemotherapy versus standard dose adjuvant chemotherapy after surgery for HPV+ 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 to 7.97)	3 year overall survival 86% for low dose versus 91% for standard dose	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 to 3.75)	3 year recurrence free survival 82% for low dose versus 84% for standard dose	VERY LOW	

[1] *Geiger (2014).*
[2] *Low event rate.*

Table 53: GRADE evidence profile: radiotherapy plus EGFR inhibitor versus radiotherapy plus chemotherapy for HPV16+ 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 to 0.90)	2 year overall survival 83% for RT+EGFR inhibitor versus 33% for RT+Chemo	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 to 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 54: GRADE evidence profile: radiotherapy plus EGFR inhibitor versus radiotherapy plus chemotherapy for P16+ 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 to 0.88)	2 year overall survival 88% for RT+EGFR inhibitor versus 60% for RT+Chemo	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 to 2.4)	2 year disease free survival 75% for RT+EGFR inhibitor versus 47% for RT+Chemo	VERY LOW	

[1] *Pajares (2013).*
[2] *Low event rate.*

Table 55: GRADE evidence profile: chemotherapy plus EGFR inhibitor versus chemotherapy for HPV16+ 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 to 1.83)	Median overall survival 13.2 months for chemo plus EGFR inhibitor versus 7.1 months for chemo alone	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 to 1.21)	Median progression free survival 4.8 months for chemo plus EGFR inhibitor versus 4.3 months for chemo alone	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	19 fewer per 1000	LOW	

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		
									(0.33 to 2.68)	(from 258 fewer to 646 more)		

[1] *Vermorken (2014).*
[2] *Subgroup analysis of larger trial - unclear whether this was a pre-planned analysis.*
[3] *Low event rate.*

Table 56: GRADE evidence profile: chemotherapy plus EGFR inhibitor versus chemotherapy for P16+ 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 to 1.34)	Median overall survival 12.6 months for chemo plus EGFR inhibitor versus 9.6months for chemo alone	LOW	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chemotherapy plus EGFR inhibitor**	**Chemotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 1.47)	Median progression free survival 5.6 months for chemo plus EGFR inhibitor versus 3.6 months for chemo alone	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 to 3.64)	22 more per 1000 (from 382 fewer to 1000 more)	LOW	

[1] *Vermorken (2014).*
[2] *Subgroup analysis of larger randomised trial - unclear if pre-planned analysis.*
[3] *Low event rate.*

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	Do not offer de-intensification of curative treatment to people with HPV-positive cancer of the oropharynx, unless it is part of a clinical trial.
Relative value placed on the outcomes considered	The GC thought that reducing treatment morbidity, whilst maintaining overall survival and locoregional control were the important outcomes of treatment de-intensification in this group.
Quality of the evidence	The quality of the evidence was rated as low to very low using GRADE. Health related quality of life was not reported in the evidence. The evidence was limited to oropharyngeal cancer, which is why recommendations were only made for this subgroup. The GC noted that current treatment is effective in the majority of patients. The available evidence did not demonstrate that using less intensive treatments in people with HPV-positive CUADT achieved similar outcomes. On this basis the GC agreed to recommend that deintensification of treatment should not be offered outside a clinical trial.
Trade-off between clinical benefits and harms	Continuing current practice may result in some patients receiving more intense treatment than they require but will ensure that the high levels of cure are maintained.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no health economic model developed. The GC did not believe that this recommendation would lead to any additional costs or savings since there will be no change in current practice.
Other considerations	The GC noted that there are RCTs either recruiting or in development that will eventually answer the question of de-intensification but these will not publish until around 2020. Therefore they did not recommend any further research in this area.

References

Attner, P., Nasman, A., Du, J., Hammarstedt, L., Ramqvist, T., Lindholm, J., Munck-Wikland, E., Dalianis, T., and Marklund, L. 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 2012. 131(5): 1124-1130

Brotherston, D. C., Poon, I., Le, T., Leung, M., Kiss, A., Ringash, J., Balogh, J., Lee, J., and Wright, J. R. Patient preferences for oropharyngeal cancer treatment de-escalation. Head & Neck 2013. 35(2): 151-159

Cmelak A., Li S., and Marur S. 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., Olsen, K. D., Kasperbauer, J. L., Price, D. L., Garces, Y. I., Ma, D. J., Neben-Wittich, M. A., Molina, J. R., Garcia, J. J., and Price, K. A. 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 2014. 50(4): 311-318

Haughey, B. H. and Sinha, P. Prognostic factors and survival unique to surgically treated p16+ oropharyngeal cancer. Laryngoscope 2012. 122: S13-S33.

Lassen, P., Eriksen, J. G., Krogdahl, A., Therkildsen, M. H., Ulhoi, B. P., Overgaard, M., Specht, L., Andersen, E., Johansen, J., Andersen, L. J., Grau, C., Overgaard, J., and Danish Head and Neck Cancer Group (DAHANCA). 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 2011. 100(1): 49-55

Masterson, L., Masterson, Liam, Moualed, Daniel, Liu, Zi Wei, and Howard, James. De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma: a systematic review and meta-analysis of current clinical trials. [Review]. European Journal of Cancer 2014. 50(15): 2636-2648

Masterson, L., Moualed, D., Masood, A., Dwivedi, R. C., Benson, R., Sterling, J. C., Rhodes, K. M., Sudhoff, H., Jani, P., and Goon, P. De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cochrane Database of Systematic Reviews 2014. 2: CD010271

Masterson, L. and Tanweer, F. The role of sequential chemoradiation for local advanced oropharyngeal carcinoma. International Journal of Clinical Oncology 2013. 18(5): 808-816

O'Sullivan, B., Huang, S. H., Siu, L. L., Waldron, J., Zhao, H., Perez-Ordonez, B., Weinreb, I., Kim, J., Ringash, J., Bayley, A., Dawson, L. A., Hope, A., Cho, J., Irish, J., Gilbert, R., Gullane, P., Hui, A., Liu, F. F., Chen, E., and Xu, W. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. Journal of Clinical Oncology 2013. 31(5): 543-550.

Pajares, B., Trigo, J. M., Toledo, M. D., Alvarez, M., Gonzalez-Hermoso, C., Rueda, A., Medina, J. A., de, Luque, V, Jerez, J. M., and Alba, E. 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 2013. 13: 26

Schache, A. G., Liloglou, T., Risk, J. M., Filia, A., Jones, T. M., Sheard, J., Woolgar, J. A., Helliwell, T. R., Triantafyllou, A., Robinson, M., Sloan, P., Harvey-Woodworth, C., Sisson, D., Shaw, R. J., Schache, Andrew G., Liloglou, Triantafilos, Risk, Janet M., Filia, Anastasia, Jones, Terence M., Sheard, Jon, Woolgar, Julia A., Helliwell, Timothy R., Triantafyllou, Asterios, Robinson, Max, Sloan, Philip, Harvey-Woodworth, Colin, Sisson, Daniel, and Shaw, Richard J. Evaluation of human papilloma virus diagnostic testing in oropharyngeal squamous cell carcinoma: sensitivity, specificity, and prognostic discrimination. Clinical Cancer Research 2011. 17(19): 6262-6271

Schache, A. G., Liloglou, T., Risk, J. M., Jones, T. M., Ma, X. J., Wang, H., Bui, S., Luo, Y., Sloan, P., Shaw, R. J., Robinson, M., Schache, A. G., Liloglou, T., Risk, J. M., Jones, T. M., Ma, X. J., Wang, H., Bui, S., Luo, Y., Sloan, P., Shaw, R. J., and Robinson, M. Validation of a novel diagnostic standard in HPV-positive oropharyngeal squamous cell carcinoma. British Journal of Cancer 2013. 108(6): 1332-1339

Smeets, S. J., Hesselink, A. T., Speel, E. J., Haesevoets, A., Snijders, P. J., Pawlita, M., Meijer, C. J., Braakhuis, B. J., Leemans, C. R., Brakenhoff, R. H., Smeets, Serge J., Hesselink, Albertus T., Speel, Ernst Jan, Haesevoets, Annick, Snijders, Peter J. F., Pawlita, Michael, Meijer, Chris J. L. M., Braakhuis, Boudewijn J. M., Leemans, C. Rene, and

Brakenhoff, Ruud H. A novel algorithm for reliable detection of human papillomavirus in paraffin embedded head and neck cancer specimen. International Journal of Cancer 2007. 121(11): 2465-2472

Vermorken, J. B., Psyrri, A., Mesia, R., Peyrade, F., Beier, F., de, Blas B., Celik, I., and Licitra, L. 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 Oncol

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.

6 Less-common upper aerodigestive tract cancers

6.1 Carcinoma of the nasopharynx

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.

Clinical question: What is the most effective curative treatment for carcinoma of the nasopharynx?

Clinical evidence (see Appendix H)

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 eight randomised trials (Chen, 2015) in 2144 patients with stage II to IV (typically WHO type 2 or 3) nasopharyngeal cancer. Moderate quality evidence suggests concomitant chemotherapy (radiotherapy and concomitant chemotherapy) is more effective than radiotherapy alone in terms of overall survival (HR 0.69; 95% C.I. 0.48 to 0.92; where HR < 1 favours radiotherapy and concomitant chemotherapy) and distant metastasis (HR 0.76; 95% C.I. 0.56 to 0.97; where HR < 1 favours radiotherapy and concomitant chemotherapy). There was uncertainty about whether radiotherapy and concomitant chemotherapy was more effective than radiotherapy alone in terms of locoregional recurrence (HR 0.80; 95% C.I. 0.51 to 1.12; where HR < 1 favours radiotherapy and concomitant chemotherapy).

Moderate quality evidence suggests concomitant chemotherapy plus adjuvant chemo (radiotherapy and concomitant chemotherapy +AC) is more effective than radiotherapy alone in terms of overall survival (HR 0.59; 95% C.I. 0.48 to 0.71; where HR < 1 favours radiotherapy and concomitant chemotherapy +AC), locoregional recurrence (HR 0.56; 95% C.I. 0.36 to 0.81; where HR < 1 favours radiotherapy and concomitant chemotherapy +AC) and distant metastasis (HR 0.64; 95% C.I. 0.50 to 0.81; where HR < 1 favours radiotherapy and concomitant chemotherapy +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 radiotherapy and concomitant chemotherapy than with radiotherapy alone. The rates of treatment related mortality were 1.9% versus 0.3% for radiotherapy and concomitant chemotherapy versus radiotherapy alone (RR = 3.11; 95% C.I. 1.60 to 6.05; where RR > 1 favours RT alone).

In subgroup analyses by timing of chemotherapy, treatment related mortality was more likely with sequential chemotherapy (neo-adjuvant or adjuvant therapy) than with radiotherapy

alone (RR 4.24; 95% C.I. 1.76 to 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% C.I. 0.64 to 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., 2012) suggests that severe adverse events (WHO grade 3 or 4) are more likely with cisplatin based radiotherapy and concomitant chemotherapy than with radiotherapy alone. The rates of anaemia, leucopoenia, thrombocytopenia, mucositis and nausea/vomiting were significantly higher in patients treated with radiotherapy and concomitant chemotherapy than in those receiving radiotherapy alone.

Stage II patients

A single randomised trial in 230 patients with stage II nasopharyngeal cancer (Chen & Wen, 2011) provides moderate quality evidence, that radiotherapy and concomitant chemotherapy 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 radiotherapy and concomitant chemotherapy than with RT, with rates of 64% versus 40% respectively (P <0.001, favours RT).

WHO type 1 patients

Low quality evidence comparing radiotherapy and concomitant chemotherapy with RT in 55 patients with WHO type 1 disease comes from an individual patient meta-analysis of eight randomised trials (Baujat, Audry, Bourhis, & Chan, 2006). In patients with WHO type 1 disease radiotherapy and concomitant chemotherapy was more effective than RT alone (HR 0.30; 95%C.I. 0.15 to 0.59; HR <1 favours radiotherapy and concomitant chemotherapy).

Adding neoadjuvant or adjuvant chemotherapy to radiotherapy and concomitant chemotherapy

Moderate quality evidence, from a network meta-analysis of 8 trials (Chen et al., 2015) including 2144 patients suggests uncertainty over whether adding adjuvant chemotherapy to concomitant chemotherapy improves outcomes in terms of overall survival (HR 0.86; 95% C.I. 0.60 to 1.16; where HR < 1 favours radiotherapy and concomitant chemotherapy +AC), locoregional recurrence (HR 0.72; 95% C.I. 0.43 to 1.15; where HR < 1 favours radiotherapy and concomitant chemotherapy +AC) or distant metastasis (HR 0.86; 95% C.I. 0.62 to 1.16; where HR < 1 favours radiotherapy and concomitant chemotherapy +AC).

Moderate quality evidence from a network meta-analysis of 25 trials (Yan, Kumachev, Siu, & Chan, 2015) including 5576 patients suggests uncertainty about the benefit of adding neo-adjuvant chemotherapy to radiotherapy and concomitant chemotherapy in terms of overall survival (HR 1.03; 95% C.I. 0.69 to 1.47; where HR < 1 favours neo-adjuvant chemotherapy + radiotherapy and concomitant chemotherapy). The estimates of 3-year overall survival from this analysis were 61% for radiotherapy and concomitant chemotherapy +AC, 59% for neo-adjuvant chemotherapy + radiotherapy and concomitant chemotherapy and 60% for radiotherapy and concomitant chemotherapy.

Neoadjuvant chemotherapy versus no neoadjuvant chemotherapy

Evidence about the effectiveness of neoadjuvant chemotherapy came from a meta-analysis of 6 randomised trials in 1418 patients with nasopharyngeal carcinoma (Ouyang & Xie, 2013). Moderate quality evidence suggested that the addition of neo-adjuvant chemotherapy improved overall survival (HR 0.82; 95% C.I. 0.69 to 0.98; HR <1 favours neo-adjuvant chemotherapy) and reduced risk of distant metastasis (HR 0.69; 95% C.I. 0.56 to 0.84; HR

<1 favours neo-adjuvant chemotherapy), with uncertain effect on locoregional recurrence (HR 0.90; 95% C.I. 0.66 to 0.98; HR <1 favours neo-adjuvant chemotherapy).

Low quality evidence from a meta-analysis of four randomised trials including 751 patients (Zhang et al., 2012), suggests treatment related mortality is more likely with cisplatin based neo-adjuvant sequential radiotherapy and concomitant chemotherapy than with radiotherapy alone. The rates of treatment related mortality were 2.9% versus 1.2% for neo-adjuvant + concomitant chemotherapy and radiotherapy respectively (RR = 4.20; 95% C.I. 1.52 to 6.05; where RR > 1 favours RT alone).

IMRT versus conventional/conformal radiotherapy

Evidence comparing IMRT to conventional radiotherapy comes from a systematic review of three randomised trials (Kam MK et al., 2007; Peng et al., 2012; Pow et al., 2006) including 717 patients with stage I to III nasopharyngeal cancer (Marta, 2014) . Moderate quality evidence from 2 randomised trials (Pow et al., 2006; Kam MK 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% C.I. 0.64 to 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) including 616 patients there is moderate quality evidence that IMRT improves overall survival when compared with 2D-RT (HR 0.56; 95% CI 0.39 to 0.80; HR < 1 favours IMRT) but uncertainty about whether IMRT improves local control (HR 0.91; 95% CI 0.78 to 1.06; HR < 1 favours IMRT) when compared with conventional RT.

Low quality evidence from one randomised trial (Pow et al., 2006) including 46 patients suggests Global health scores showed continuous improvement in quality of life after both IMRT and radiotherapy and concomitant chemotherapy but at 12 months after RT, SF-36 subscale scores for role-physical, bodily pain and physical function are significantly better with IMRT.

Table 57: GRADE: Profile for 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[1]**
Overall mortality (Chen et al, 2014)						
CCRT+AC v CCRT	0.77 (0.46 – 1.29)	Moderate[2,3]	NR	-	0.86 (0.60 – 1.16)	Moderate[2,3]
CCRT+AC v RT	0.64 (0.53 – 0.76)	Moderate[2]	NR	-	0.59 (0.48 – 0.71)	Moderate[2]
CCRT v RT	0.66 (0.46 – 1.29)	Moderate[2]	NR	-	0.69 (0.48 – 0.92)	Moderate[2]
Locoregional recurrence (Chen et al, 2014)						
CCRT+AC v CCRT	0.50 (0.21–1.17)	Moderate[2,3]	NR	-	0.72 (0.43 – 1.15)	Moderate[2,3]
CCRT+AC v RT	0.59 (0.40 – 0.89)	Moderate[2]	NR	-	0.56 (0.36 – 0.81)	Moderate[2]
CCRT v RT	0.72 (0.47 – 1.10)	Moderate[2]	NR	-	0.80 (0.51 – 1.12)	Moderate[2]
Distant metastases (Chen et al, 2014)						
CCRT+AC v CCRT	0.71 (0.46– 1.10)	Moderate[2,3]	NR	-	0.86 (0.62 – 1.16)	Moderate[2,3]
CCRT+AC v RT	0.67 (0.52– 0.87)	Moderate[2]	NR	-	0.64 (0.50 – 0.81)	Moderate[2]
CCRT v RT	0.68 (0.50– 0.95)	Moderate[2]	NR	-	0.76 (0.56 – 0.97)	Moderate[2]
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[4]	NR	-	NR	-
CCRT v RT	RR 1.85 (0.64 – 5.33)	Low[4]	NR	-	NR	-
CCRT = radiotherapy and concomitant chemotherapy						

[1] *GRADE quality assessment was applied to pairwise comparisons from the NMA, rather than the network as a whole.*
[2] *Allocation concealment was inadequate in all trials.*
[3] *Imprecise effect estimate: confidence interval crosses both no effect and appreciable benefit or harm.*
[4] *Very low number of events.*

Abbreviations: AC, adjuvant chemotherapy; radiotherapy and concomitant chemotherapy, radiotherapy and concomitant chemotherapy; CI, confidence interval; NR, not reported; RT, radiotherapy

Table 58: GRADE profile for neo-adjuvant chemotherapy versus no neo-adjuvant chemotherapy

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Neo-adjuvant chemo plus RT**	**RT**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 11.63)	24 more per 1000 (from 4 more to 81 more)	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 to 0.98)	-	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 to 1.22)	-	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 to 0.84)	-	MODERATE	

[1] *Very low number of events.*
[2] *Various regimens used - 4/6 used no concomitant chemotherapy.*

1 **Table 59: GRADE profile for IMRT versus conventional/conformal radiotherapy**

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IMRT**	**2D-RT**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 0.87)	-	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 to 1.06)	5-year local control rate 90.5% with IMRT vs. 83.8% with 2D-RT	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 to 0.80)	5-year overall survival 76.9% with IMRT vs. 67.1% with 2D-RT	MODERATE	
Quality of life, 6-12 months post RT (Pow, 2006)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious2	none	24	21	continuous improvement in quality of life after both IMRT and RT and concomitant chemotherapy but at 12 months after RT, SF-36 subscale scores for role-physical, bodily pain and physical function were		LOW	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IMRT**	**2D-RT**	**Relative (95% CI)**	**Absolute**	**Quality**	
									significantly better with IMRT.			

[1] *Studies were at unclear risk of bias using the Cochrane risk of bias criteria.*
[2] *Very low number of patients.*

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer intensity-modulated radiation therapy with concomitant chemotherapy to people with locally advanced (stage II and above) nasopharyngeal cancer.** **Consider adjuvant or neo-adjuvant chemotherapy for people with locally advanced (stage II and above) nasopharyngeal cancer.**
Relative value placed on the outcomes considered	Overall survival, disease recurrence and treatment-related morbidity were considered when making the recommendations.
Quality of the evidence	The evidence was of low to moderate quality, using the GRADE system. There was no evidence about the impact of chemotherapy on quality of life and no health economic studies. The older studies were likely to have used a different WHO classification for nasopharyngeal cancer subtype – although almost all the evidence was from patients WHO types 2 or 3.. Based on the evidence of improved overall survival, reduced toxicity and improved quality of life the GC recommended IMRT for the treatment of nasopharyngeal cancer. Given the limited data available on stage I patients the GC were only able to make recommendations on locally advanced disease (stage II or above). The GC were unable to make a strong recommendation in favour of the addition of either neo-adjuvant or adjuvant chemotherapy to radiotherapy and concomitant chemotherapy due to uncertainty about the effectiveness of these treatments.
Trade-off between clinical benefits and harms	The GC believed that better overall survival is an important benefit of concomitant chemotherapy. Recommending IMRT is likely to reduce radiotherapy-related morbidity (e.g. xerostomia). However, additional chemotherapy is likely to be associated with additional toxicity. On balance the GC that the benefits of overall survival outweighed the additional toxicity which is likely to be manageable.
Trade-off between net health benefits and resource use	Radiotherapy and concomitant chemotherapy is current practice for patients with nasopharyngeal cancer. So these recommendations are unlikely to have a significant impact on treatment costs for this rare cancer.
Other considerations	Although the evidence supports current practice there is still uncertainty about optimal sequential chemotherapy.

6.2 Carcinoma of the paranasal sinuses

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.

Clinical question: What is the optimal role and timing (in relation to other treatments) of surgery in the management of paranasal sinus carcinoma?

Clinical evidence (see Appendix H)

Surgery with radiotherapy versus surgery alone

Very low quality evidence from a meta-analysis of 16 observational studies (Amit et al., 2013) including 356 patients suggests that the addition of radiotherapy or radiotherapy and concomitant chemotherapy to surgery does not improve overall survival in patients treated for adenoid cystic carcinoma of the nasal cavity or paranasal sinuses. 5-year overall survival was estimated to be 63% for patients receiving radiotherapy or radiotherapy and concomitant chemotherapy 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 et al., 2013) including 39 studies and 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 (Agger 2009, Blanch 2004, Choussy 2010, Dulguerov 2001; 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 neo-adjuvant 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 neo-adjuvant chemotherapy and radiotherapy and concomitant chemotherapy 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.

Table 60: GRADE table: surgery + radiotherapy vs surgery alone in SCC of the nasal vestibule

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + radiotherapy (SRT)	Surgery alone (S)	Absolute	Quality	
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%	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%	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%	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 61: GRADE table: surgery + radiotherapy/ radiotherapy and concomitant chemotherapy vs 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/ radiotherapy and concomitant chemotherapy	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%	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 62: GRADE table: surgery + radiotherapy vs surgery alone for treatment of sinonasal malignancies

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery + radiotherapy**	**Surgery alone**	**Absolute**	**Quality**	
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%	VERY LOW	

[1] *(Blanch, Ruiz, Alos, Traserra-Coderch, & Bernal-Sprekelsen, 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 categorised as "nonepithelial forms'.*
[4] *Small study population.*

Table 63: GRADE table: surgery + radiotherapy vs 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 to 1.57)	56 more per 1000 (from 112 fewer to 290 more)	VERY LOW	

[1] *Choussy 2010.*
[2] *Length of follow up is not reported.*
[3] *Small population size.*

Table 64: GRADE table: surgery + radiotherapy vs 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)											

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery + radiotherapy**	**Surgery alone**	**Absolute**	**Quality**	
1[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	113	44	2 year survival : SRT = 82 ± 6%, S = 84 ± 6% 5 year survival: SRT = 66 ± 5%, S = 79% ± 6% 10 year survival: SRT = 60 ± 5%, S = 76 ± 6%	VERY LOW	
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	2 year survival : SRT = 70 ± 4%, S = 74 ± 7% 5 year survival: SRT = 63 ± 4%, S = 70% ± 7% 10 year survival: SRT = 57 ± 8%, S = 70 ± 7%	VERY LOW	

1 [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 65: GRADE table: surgery + radiotherapy vs surgery alone be used for treatment of sinonasal adenoid cystic carcinoma

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + radiotherapy	Surgery alone		Absolute	Quality
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%)	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 66: GRADE table: postoperative IMRT vs postoperative radiotherapy and concomitant chemotherapy for cancer of the paranasal sinuses or nasal cavity

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative IMRT	Postoperative radiotherapy and concomitant chemotherapy	Relative (95% CI)	Absolute	Quality
2-year local control											

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Postoperative IMRT**	**Postoperative radiotherapy and concomitant chemotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	40	41	-	IMRT = 76%; radiotherapy and concomitant chemotherapy = 67%	VERY LOW	
2-year overall survival												
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	40	41	-	IMRT = 89%; radiotherapy and concomitant chemotherapy = 73%	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%; radiotherapy	VERY LOW	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Postoperative IMRT**	**Postoperative radiotherapy and concomitant chemotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	
										and concomitant chemotherapy = 60%		
Disease control												
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	40	41	-	IMRT = 89%; radiotherapy and concomitant chemotherapy = 89%	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 to 0.82)	351 fewer per 1000 (from 176 fewer to 488	VERY LOW	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Postoperative IMRT**	**Postoperative radiotherapy and concomitant chemotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	
										fewer)		
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 to 1.35)	116 fewer per 1000 (from 232 fewer to 120 more)	VERY LOW	
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 to 0.63)	523 fewer per 1000 (from 334 fewer to 650 fewer)	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 to	381 fewer per 1000	VERY LOW	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Postoperative IMRT**	**Postoperative radiotherapy and concomitant chemotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	
									0.79)	(from 174 fewer to 522 fewer)		
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 to 0.74)	430 fewer per 1000 (from 228 fewer to 562 fewer)	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 to 0.96)	204 fewer per 1000 (from 37 fewer to 343 fewer)	VERY LOW	
Incidence of fatigue												
1[1]	observation	seriou	no serious	no serious	serious[3]	none	20/40	32/41	RR	281	VERY	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Postoperative IMRT**	**Postoperative radiotherapy and concomitant chemotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	
	al studies	s[2]	inconsistency	indirectness			(50%)	(78%)	0.64 (0.45 to 0.91)	fewer per 1000 (from 70 fewer to 429 fewer)	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 67: GRADE table: postoperative IMRT vs postoperative radiotherapy and concomitant chemotherapy for ethmoid adenocarcinoma

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Postoperative IMRT**	**Postoperative radiotherapy and concomitant chemotherapy**	**Absolute**	**Quality**	
Overall survival											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative IMRT	Postoperative radiotherapy and concomitant chemotherapy	Absolute	Quality	
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	28	30	2 year survival : IMRT = 65%; conventional RT = 83% 4 year survival: IMRT = 58%; conventional RT = 66%	VERY LOW	
Local control											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	28	30	2 year survival : IMRT = 69%; conventional RT = 70% 4 year survival: IMRT = 63%; conventional RT = 63%	VERY LOW	

[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 68: GRADE table: neo-adjuvant + concurrent chemotherapy vs neo-adjuvant chemotherapy alone for treatment of maxillary sinus carcinoma

Quality assessment	No of patients	Effect	Qualit	

										y	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Neo-adjuvant + concurrent chemotherapy (NA + radiotherapy and concomitant chemotherapy)**	**Neo-adjuvant 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 + radiotherapy and concomitant chemotherapy = 66.7% NA = 54.2%	VERY LOW	
5-year disease free survival											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none			NA + radiotherapy and concomitant chemotherapy = 62.5% NA = 50.0%	VERY LOW	
5-year local control											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none			NA + radiotherapy and	VERY LOW	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neo-adjuvant + concurrent chemotherapy (NA + radiotherapy and concomitant chemotherapy)	Neo-adjuvant chemotherapy alone (NA)	Absolute	Quality	
									concomitant chemotherapy = 87.5% NA = 65.6%		

[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 69: GRADE table: neo-adjuvant + concurrent chemotherapy vs concurrent chemotherapy alone be used for treatment of maxillary sinus carcinoma

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neo-adjuvant + concurrent chemotherapy	Concurrent chemotherapy alone	Absolute	Quality	
5-year overall survival											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	NA + radiotherapy and concomitant	VERY LOW	

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Neo-adjuvant + concurrent chemotherapy**	**Concurrent chemotherapy alone**	**Absolute**	**Quality**	
									chemotherapy = 66.7% radiotherapy and concomitant chemotherapy = 54.2%		
5-year disease free survival											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	NA + radiotherapy and concomitant chemotherapy = 62.5% radiotherapy and concomitant chemotherapy = 44.4%	VERY LOW	
5-year local control											
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	NA + radiotherapy and	VERY LOW	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neo-adjuvant + concurrent chemotherapy	Concurrent chemotherapy alone	Absolute	Quality	
									concomitant chemotherapy = 87.5% radiotherapy and concomitant chemotherapy = 68.8%		

[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 70: GRADE table: 40 Gy radiotherapy vs 50 Gy radiotherapy for maxillary sinus squamous cell carcinoma

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	40 Gy radiotherapy	50 Gy radiotherapy	Absolute	Quality	
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%	VERY LOW	
5-year locoregional control											
1[1]	observational	serious	no serious	no serious	serious[3]	none	18	35	40 Gy =	VERY	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	40 Gy radiotherapy	50 Gy radiotherapy	Absolute	Quality	
	studies	[2]	inconsistency	indirectness					58.9%; 50 Gy = 57.8%	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 71: GRADE table: carboplatin vs cisplatin for maxillary sinus squamous cell carcinoma

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carboplatin	Cisplatin	Absolute	Quality	
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%	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%	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	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 72: GRADE table: conservative maxillectomy vs radical maxillectomy be used for primary advanced maxillary sinus malignancy

Quality assessment							No of patients		Effect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radical maxillectomy	Conservative maxillectomy	Absolute	Quality
Overall survival										
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	27	34	2 year survival: radical = 67.65%; conservative = 66.67% 3 year survival: radical = 58.11%; conservative = 53.68% 5 year survival: radical = 44.97%; conservative = 42.95%	VERY LOW
Health related quality of life, composite score at 6 months (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: 658 ± 103; conservative: 746 ± 104	VERY LOW
Health related quality of life, composite score at 12 months (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: 655 ± 101; conservative: 763 ± 88	VERY LOW
Health related quality of life, composite score at 18 months (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: 637 ± 130; conservative: 759 ± 97	VERY LOW

[1] *Liu 2013.*
[2] *Unclear how patients were assigned to treatment. Limited baseline characteristics reported.*
[3] *Small population size.*

1 **Table 73: GRADE table: complete tumour resection vs partial tumour resection or sinonasal malignancies with skull base involvement**

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Complete tumour resection**	**Partial tumour resection**	**Absolute**	**Quality**	
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%	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%	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%	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%	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	VERY LOW	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Complete tumour resection	Partial tumour resection	Absolute	Quality	
									resection = 69%		

1 *1 Resto 2008.*
2 *2 Higher radiotherapy dose delivered to the partial resection group.*
3 *3 Small population size.*

4 **Table 74: GRADE table: endoscopic surgery vs lateral rhinotomy sinonasal adenocarcinoma**

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopic surgery	Lateral rhinotomy	Relative (95% CI)	Absolute	Quality	
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 to 1.39)	167 fewer per 1000 (from 308 fewer to 163 more)	VERY LOW	
Number of deaths, disease related (follow up: Endoscopic surgery group: mean 38 months; lateral rhinotomy group: mean 89 months) (Copy)												
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 to 2.48)	83 fewer per 1000 (from 150 fewer to 247 more)	VERY LOW	
Incidence of local recurrence (follow up: Endoscopic surgery group: mean 38 months; lateral rhinotomy group: mean 89 months) (Copy) (Copy)												
1[1]	observational studies	very seriou	no serious inconsistency	no serious indirectness	serious[3]	none	3/24 (12.5%)	9/24 (37.5%)	RR 0.33	251 fewer per 1000	VERY LOW	

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**		
		s[2]							(0.10 to 1.08)	(from 338 fewer to 30 more)		
Incidence of distant metastasis (follow up: Endoscopic surgery group: mean 38 months; lateral rhinotomy group: mean 89 months) (Copy) (Copy) (Copy)												
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 to 20.6)	42 more per 1000 (from 34 fewer to 817 more)	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%	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.*

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer surgery as the first treatment for carcinoma of the paranasal sinuses if complete resection is possible.** **Consider radiotherapy with or without concomitant chemotherapy before planned surgical resection of the paranasal sinuses if complete resection is not initially possible.**
Relative value placed on the outcomes considered	Outcomes related to survival were considered most important by the GC when drafting recommendations. Some evidence was reported for all outcomes with the exception of eye preservation rates. However, all of the available evidence was of very low quality and associated with considerable uncertainty and risks of bias. The recommendations of the GC were therefore based largely on clinical experience (see Quality of the evidence).
Quality of the evidence	All evidence was rated as very low quality (using GRADE). Issues with the quality of the evidence included: • all studies were non-randomised and assessed as either at a high risk of bias or as 'bias unknown or unclear' • many studies accrued patients over long periods • population sizes were generally small. These issues severely limited the recommendations that could be made using the available evidence. Based on their clinical experience the GC recommended surgery as the first treatment for carcinoma of the paranasal sinuses because this provides the best potential for cure. Recommendations on the role of radiotherapy with or without concomitant chemotherapy before surgical resection were based solely on clinical experience and were made because they may increase the chance of rendering the tumour resectable. Postoperative radiotherapy is currently widely used in this group of patients but there is uncertainty over whether this delivers any benefits. The GC therefore made a research recommendation in this area.
Trade-off between clinical benefits and harms	The benefits of the recommendations are perceived to be improved patient selection for surgery, leading to improved survival and local control, reduced morbidities and therefore improved quality of life. No potential harms were identified.
Trade-off between net health benefits and resource use	The recommendations made reflect current practice in most centres; no major changes in resource use are therefore expected.
Other considerations	

Research recommendation	**A prospective study should be undertaken to compare the effectiveness of adjuvant therapy (radiotherapy with or without chemotherapy) in people following surgery**

	for paranasal sinus carcinoma. Outcomes of interest include local control, progression-free survival, overall survival and treatment-related morbidity/mortality.
Why this is important	Paranasal sinus carcinomas are a rare group of cancers. Disease progression has the potential to cause major morbidities. Surgery is established as the only potentially curative modality but may be associated with major functional loss for example loss of an eye. Radiotherapy is often used post-operatively in an effort to reduce the risk of local recurrence. It is also associated with significant side-effects and the impact on local disease control has not been proven.

6.3 Unknown primary of presumed upper aerodigestive tract origin

This 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.

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)?

Clinical evidence (see Appendix H)

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 four 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 radiotherapy and concomitant chemotherapy. HPV-positivity was associated with better overall survival (Sivars et al., 2014; Park et al., 2012).

Disease specific survival

Disease specific survival at five 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 five years after treatment was 61-72% for neck dissection plus radiotherapy and 65-85% neck dissection plus radiotherapy and concomitant chemotherapy (Madani et al., 2008; Reddy & Marks, 1997; Park et al., 2012).

Local control

Local control in the neck at five 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 radiotherapy and concomitant chemotherapy (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 six months after surgery plus radiotherapy and concomitant chemotherapy 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 11-12% following IMRT (Chen et al., 2011; Strojan, 1998; Madani et al., 2008; Reddy & Marks, 1997).

Neck fibrosis

Late neck fibrosis following radiotherapy occurred in 19-39% of patients (Strojan, 1998; Reddy & Marks, 1997; Iganej et al., 2002).

Table 75: GRADE profile for neck dissection alone vs radiotherapy (RT) alone for unknown primary metastatic cancer of presumed head and neck origin

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Neck dissection alone**	**RT alone**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 76: GRADE profile for neck dissection plus RT vs Neck dissection, chemotherapy and RT for unknown primary metastatic cancer of presumed head and neck origin

Quality assessment							No of patients		Effect			
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**	**Quality**	
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	VERY LOW	

Quality assessment							No of patients		Effect			
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**	**Quality**	
										dissection + RT + Chemo		
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	observation	seriou	no serious	no serious	no serious	none	-	8/51 (16%)	-	-	VERY	

Quality assessment							No of patients		Effect			
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**	**Quality**	
	al studies	s[1]	inconsistency	indirectness	imprecision						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*

1 Cost-effectiveness evidence

2 A literature review of published cost-effectiveness analyses did not identify any relevant
3 papers for this topic. Whilst there were potential cost implications of making
4 recommendations in this area, other questions in the guideline were agreed as higher
5 priorities for economic evaluation. Consequently no further economic modelling was
6 undertaken for this question.

7

Recommendations	**Offer people with squamous cell carcinoma in the cervical lymph nodes with an unknown primary the choice of:** • **neck dissection and adjuvant radiation with or without chemotherapy, or** • **primary radiation with or without chemotherapy, with surgery for persistent disease.** **Consider no further treatment as an option in people with pN1 disease without extracapsular spread after neck dissection.** **Consider including potential primary tumour sites when selecting the volume to be treated with radiotherapy.**
Relative value placed on the outcomes considered	The GC considered treatment morbidity, overall survival and quality of life as the most important outcomes when drafting the recommendations.
Quality of the evidence	The quality of the evidence assessed using GRADE was very low. This was due to biased treatment allocation, comparisons using historical cohorts and studies pooling the results of different treatments. The group therefore relied on their clinical experience to make these recommendations. The GC noted that either primary surgery or primary RT are the treatments currently offered and have the best potential for cure. Given the lack of evidence to support the use of one treatment over the other the GC recommended both as options. The GC noted that there was morbidity associated with adjuvant treatment in the pN1 setting. Given their knowledge of research evidence base in other forms of CUADT (but not reviewed by this guideline) demonstrating no survival benefit for adjuvant treatment in pN1 disease, the GC considered that no further treatment would be appropriate for this clinical scenario. Since the majority of patients cannot be re-irradiated the GC recommended that consideration may be given to including possible primary sites in the RT target volume. The group also made a research recommendation because there was uncertainty about the benefit of targeting radiotherapy to all potential primary sites versus selected primary sites. No health economic evidence was identified and no health economic model was developed for this topic.
Trade-off between clinical benefits and harms	The group believed that patients with pN1 disease with no extracapsular spread (ECS) would be spared morbidity from adjuvant treatment. This should not result in additional harms in this subgroup of patients.
Trade-off between net health benefits and resource use	Although the recommendations largely reflect current practice, the group believed that there would be a net health benefit and

	potentially reduced costs if patients with pN1 and no ECS disease avoid adjuvant therapy.
Other considerations	The GC considered the increased incidence of HPV-positive CUADT cancers which may require different treatments (see recommendations in sections 2.2 and 5.2)).

Research recommendation	**A prospective study should be undertaken in people with CUADT of unknown primary to identify whether radiotherapy target volumes can be selected based on clinical and pathological factors. Outcomes of interest include local control, progression-free survival, overall survival, and treatment-related morbidity and mortality.**
Why this is important	In a very small percentage of patients with squamous carcinoma involving a cervical lymph-node the primary site remains occult despite intensive investigations. The optimum treatment of these patients is uncertain. Some clinical teams will treat the neck disease alone and others will treat some or all potential primary sites with the radiotherapy with or without chemotherapy. The latter strategy is associated with a high level of side-effects that may have lifelong consequences, for example xerostomia. A better understanding of the clinico-pathological factors associated with treatment outcomes would improve treatment selection with the potential to reduce these side effects.

6.4.2 Mucosal melanoma

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.

Clinical question: What is the optimal locoregional treatment for newly diagnosed upper airways tract mucosal melanoma in the absence of systemic metastases?

Clinical evidence (see Appendix H)

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 three years or five 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 to 1.61) and 1.34 (95% CI 0.97 to 1.85) for three- 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 to 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 respectively) 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 three- 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.

Table 77: GRADE evidence table: surgery alone vs surgery + radiotherapy for newly diagnosed upper aerodigestive tract mucosal melanoma in the absence of systemic metastases

Quality assessment							No of patients			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery alone**	**Surgery + RT**	**Effect**	**Quality**
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 to 1.61) (values <1 favour surgery + RT)	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 to 1.85) (values <1 favour surgery + RT)	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	VERY LOW
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) STUDY: Surgery / SRT / Difference (SRT-surgery) Benlyazid: 26.5 / 29.4 / 2.9	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		
									(n=160)	
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 to 0.60) (values <1 favour surgery + RT)	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 to 1.29)	12 fewer per 1000 (from 152 fewer to 170 more) VERY LOW
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) STUDY: Surgery / SRT / Difference (SRT-surgery) Kingdom (n=13): 8 / 25 / 17	VERY LOW
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) STUDY: Surgery / SRT / Difference (SRT-surgery) Nakashima (n=20): 9 / 45 / 36	VERY LOW
Incidence of local failure (follow-up 2-80 months)										
1[8]	observatio	seriou	no serious	no serious	serious18	none	11/19	5/19	RR 2.2 (0.95 to	316 more per 1000 VER

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery alone**	**Surgery + RT**			
	nal studies	s[3,4]	inconsistency	indirectness			(57.9 %)	(26.3 %)	5.12)	(from 13 fewer to 1000 more)	Y LOW
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 to 1.47)	147 fewer per 1000 (from 235 fewer to 128 more)	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		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		VERY LOW

Abbreviations: RFS: relapse-free survival; RT: radiotherapy; SRT: surgery with radiotherapy.

1 [1] *Kingdom 1995*
2 [2] *Nakashima 2008*
3 [3] *Criteria used to allocate patients to treatment not reported.*
4 [4] *Unclear if different treatment groups were comparable at baseline.*
5 [5] *Benlyazid 2010*
6 [6] *Freedman 1973*

[7] *Gal 2011*
[8] *Meleti 2008*
[9] *Owens 2003*
[10] *Lund 2012*
[11] *Temam 2005*
[12] *Allocation 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 78: GRADE evidence table: surgery vs 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	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)	VERY LOW

Quality assessment							No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	RT				
									Freedman (n=35)	61.3	0	-61.3
									Gal (n=151)	20	9	-11
									Tanaka (n=30)	15.4	35.3	19.9
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 to 1.15)	445 fewer per 1000 (from 519 fewer to 79 more)		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 to 123.43)	Not estimable7		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 to 1.64)	101 more per 1000 (from 152 fewer to 462 more)		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 to 1.88)	123 more per 1000 (from 162 fewer to 569 more)		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 to 5.32)	52 fewer per 1000 (from 106 fewer to 480 more)		VERY LOW

1 [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 79: GRADE evidence table: 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	STUDY: Ahn (n=32); 3-yr overall survival, % (Kaplan-Meier estimates): Adjuvant chemo 59; No adjuvant chemo 10; Difference (no adj chemo-adj chemo) -49	VERY LOW
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)	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					
									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)			VERY LOW
									STUDY	Adjuvant chemo	No adjuvant chemo	Difference (no adj chemo-adj chemo)	
									Ahn (n=32)	23	13	-10	
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)			VERY LOW
									STUDY	Adjuvant chemo	No adjuvant chemo	Difference (no adj chemo-adj chemo)	

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					
									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 80: GRADE evidence table: surgery (with or without RT) vs curative 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)	Curative 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)			VERY LOW
									STUDY	Surgery	Curative RT	Difference (RT-surgery)	
									Douglas (n=55)	46	13	-33	
5 year cancer specific survival (follow-up minimum 15 months)													

Quality assessment							No of patients		Effect				Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery (with or without RT)	Curative RT					
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	25	30	STUDY	Cancer-specific survival, % (Kaplan-Meier estimates) Surgery	Curative RT	Difference (RT-surgery)	VERY LOW
									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 81: GRADE evidence table: immunotherapy after primary treatment vs 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)	VERY LOW

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	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 to 3.61)		215 more per 1000 (from 215 fewer to 1000 more)		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 benefit, significant effect and significant harm.*
[4] *Overall number of measured events is low.*

Table 82: GRADE evidence table: after primary surgery: adjuvant interferon vs 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)										

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**					
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	29	30		Overall survival, months (Kaplan-Meier estimates)			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)			LOW
									STUDY	Interferon	Chemotherapy	Difference (chemo-interferon)	
									Lian (n=59)	19.6	8.8	-10.8	

1 [1] *Lian 2013.*
2 [2] *Methods of randomisation to treatment/concealment of randomisation sequence not reported.*
3 [3] *Overall number of events measured is low.*

Table 83: GRADE evidence table: 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	STUDY: Shiga (n=83); Overall survival, % (Kaplan-Meier estimates): Surgery 38.6, RT 29.9, Difference (RT-surgery) -8.7	VERY LOW

[1] *Shiga 2012.*
[2] *Allocation to groups not reported; unclear if different treatment groups were comparable at baseline.*

Table 84: GRADE evidence table: Surgery vs 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	STUDY; Overall survival, % (Kaplan-Meier estimates): Surgery, Surgery + biotherapy, Difference (biotherapy-no biotherapy)	VERY LOW

Quality assessment							No of patients		Effect				Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery**	**Surgery + 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)			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.*

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	Consider surgery and adjuvant radiotherapy for people with newly-diagnosed upper aerodigestive tract mucosal melanoma without systemic metastases.
Relative value placed on the outcomes considered	When drafting the recommendations, the GC considered locoregional recurrence and quality of life to be the most important outcomes. This was due to the severe impact of recurrence in these patients. For the following outcomes from the PICO, no evidence was available: • treatment-related morbidity • treatment-related mortality • health-related quality of life For the survival outcomes specified in the PICO (overall survival, disease-free survival and progression-free survival), there was very limited evidence available and this was of very low quality and associated with considerable uncertainty. Therefore the GC did not consider the evidence on survival outcomes useful in making recommendations.
Quality of the evidence	The quality of the evidence was low or very low (as assessed by GRADE). Specific issues with the evidence highlighted by the reviewer included: • small sample size • very low quality evidence, the majority from retrospective non-randomised studies • uncertainty associated with many of the outcomes. These issues limited the recommendations that the GC were able to make. Despite these issues controlling local disease was considered an important outcome, and the available evidence favoured the use of radiotherapy in addition to surgery. The GC therefore felt it appropriate to make a recommendation based on the available evidence. The uncertainty in the evidence is largely due to small patient numbers and the rarity of this disease. The GC made a research recommendation to try and address these issues.
Trade-off between clinical benefits and harms	The GC considered the potential benefit of the recommendations to be improvements in local control in this group of patients. Increased treatment-related morbidity from radiotherapy was identified as a potential harm of the recommendations, but the GC were of the opinion that the benefits of improved local control outweigh the harms of radiotherapy treatment.
Trade-off between net health benefits and resource use	The GC identified additional radiotherapy treatment and the management of the side-effects of radiotherapy as potential costs resulting from the recommendations. However, savings from a reduction in the need for later treatment (as a result of lower rates of disease recurrence) were also anticipated. No economic evidence was available and no health economic

	model was developed.
Other considerations	The GC highlighted that current practice in treating this group of patients is variable. Changes in practice required to implement the recommendation would therefore include more consistency in clinical practice across different treatment centres.

Research recommendation	**Develop a prospective, centralised national or international collection of data on upper aerodigestive tract melanoma to facilitate research to improve outcomes. Data collection should include site, treatment, local control, progression-free survival and overall survival.**
Why this is important	Mucosal melanoma of the upper aerodigestive tract is uncommon so randomised clinical trials are unlikely to have enough power to show statistically significant differences between treatment options. There is little consensus on the optimal treatment for either the primary disease or any potential or established nodal disease within regional lymph nodes. Current practice uses varying combinations of surgery, radiotherapy or chemotherapy each of which has attendant morbidity. Recent developments in the management of mucosal melanoma using immunotherapy have introduced a number of potential novel agents that could potentially have an impact on the prognosis of its mucosal counterpart. The first step along that process would be a coordinated approach to prospectively collecting relevant data.

References

Agger, A., von, Buchwald C., Madsen, A. R., Yde, J., Lesnikova, I., Christensen, C. B., Foghsgaard, S., Christensen, T. B., Hansen, H. S., Larsen, S., Bentzen, J., Andersen, E., Andersen, L., and Grau, C. Squamous cell carcinoma of the nasal vestibule 1993-2002: a nationwide retrospective study from DAHANCA. Head & Neck 2009. 31(12): 1593-1599

Ahn, H. J., Na, I. I., Park, Y. H., Cho, S. Y., Lee, B. C., Lee, G. H., Koh, J. S., Lee, Y. S., Shim, Y. S., Kim, Y. K., Kang, H. J., Ryoo, B. Y., and Yang, S. H. Role of adjuvant chemotherapy in malignant mucosal melanoma of the head and neck. Oral Oncology 2010. 46(8): 607-611

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

Baujat, B., Audry, H., Bourhis, J., Chan, A. T., Onat, H., Chua, D. T., Kwong, D. L., Al-Sarraf, M., Chi, K. H., Hareyama, M., Leung, S. F., Thephamongkhol, K., and Pignon, J. P. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. International Journal of Radiation Oncology Biology Physics 2006. 64(1): 47-56

Baujat, B. and Audry, H. Chemotherapy as an adjunct to radiotherapy in locally advanced nasopharyngeal carcinoma. [Review] [36 refs]. Cochrane Database of Systematic Reviews 2006. (4).

Benlyazid, A., Thariat, J., Temam, S., Malard, O., Florescu, C., Choussy, O., Makeieff, M., Poissonnet, G., Penel, N., Righini, C., Toussaint, B., Lacau St, Guily J., Vergez, S., and

Filleron, T. Postoperative radiotherapy in head and neck mucosal melanoma: a GETTEC study. Archives of Otolaryngology -- Head & Neck Surgery 2010. 136(12): 1219-1225

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

Blanchard, P., Lee, A., Marguet, S., Leclercq, J., Ng, W. T., Ma, J., Chan, A. T., Huang, P. Y., Benhamou, E., Zhu, G., Chua, D. T., Chen, Y., Mai, H. Q., Kwong, D. L., Cheah, S. L., Moon, J., Tung, Y., Chi, K. H., Fountzilas, G., Zhang, L., Hui, E. P., Lu, T. X., Bourhis, J., and Pignon, J. P. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. Lancet Oncology 2015. 16(6): 645-655

Chen, A. M., Li, B. Q., Farwell, D. G., Marsano, J., Vijayakumar, S., and Purdy, J. A. 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 2011. 79(3): 756-762.

Chen, Q. Y., Wen, Y. F., Guo, L., Liu, H., Huang, P. Y., Mo, H. Y., Li, N. W., Xiang, Y. Q., Luo, D. H., Qiu, F., Sun, R., Deng, M. Q., Chen, M. Y., Hua, Y. J., Guo, X., Cao, K. J., Hong, M. H., Qian, C. N., and Mai, H. Q. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. Journal of the National Cancer Institute 2011. 103(23): 1761-1770

Chen, Y. P., Wang, Z. X., Chen, L., Liu, X., Tang, L. L., Mao, Y. P., Li, W. F., Lin, A. H., Sun, Y., and Ma, J. 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 2015. 26(1): 205-211.

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

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 2011. 145(1): 51-57

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 1994. 168(5): 395-399

Demiroz, C., Vainshtein, J. M., Koukourakis, G. V., Gutfeld, O., Prince, M. E., Bradford, C. R., Wolf, G. T., McLean, S., Worden, F. P., Chepeha, D. B., Schipper, M. J., Mchugh, J. B., and Eisbruch, A. 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

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

Douglas, C. M., Malik, T., Swindell, R., Lorrigan, P., Slevin, N. J., and Homer, J. J. Mucosal melanoma of the head and neck: radiotherapy or surgery? Journal of Otolaryngology: Head and Neck Surgery 2010. 39(4): 385-392

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

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 alone or in combination with neck dissection. International Journal of Radiation Oncology, Biology, Physics 2001. 50(1): 55-63

Freedman, H. M., DeSanto, L. W., Devine, K. D., and Weiland, L. H. Malignant melanoma of the nasal cavity and paranasal sinuses. Archives of Otolaryngology 1973. 97(4): 322-325

Gal, T. J., Silver, N., and Huang, B. Demographics and treatment trends in sinonasal mucosal melanoma. Laryngoscope 2011. 121(9): 2026-2033

Grau, C., Johansen, L. V., Jakobsen, J., Geertsen, P., Andersen, E., and Jensen, B. B. Cervical lymph node metastases from unknown primary tumours. Results from a national survey by the Danish Society for Head and Neck Oncology. Radiotherapy & Oncology 2000. 55(2): 121-129.

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 2006. 126(5): 536-544

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

Iganej, S., Kagan, R., Anderson, P., Rao, A., Tome, M., Wang, R., Dowlatshahi, M., Cosmatos, H., and Morgan, T. Metastatic squamous cell carcinoma of the neck from an unknown primary: management options and patterns of relapse. Head & Neck 2002. 24(3): 236-246.

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

Kam, M. K., Leung, S. F., Zee, B., Chau, R. M., Suen, J. J., Mo, F., Lai, M., Ho, R., Cheung, K. Y., Yu, B. K., Chiu, S. K., Choi, P. H., Teo, P. M., Kwan, W. H., and Chan, A. T. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. Journal of Clinical Oncology 2007. 25(31): 4873-4879

Kanetaka, S., Tsukuda, M., Takahashi, M., Komatsu, M., Niho, T., Horiuchi, C., and Matsuda, H. Mucosal melanoma of the head and neck. Experimental and Therapeutic Medicine 2011. 2(5): 907-910

Kingdom, T. T. and Kaplan, M. J. Mucosal melanoma of the nasal cavity and paranasal sinuses. Head & Neck 1995. 17(3): 184-189

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

Lian, B., Si, L., Cui, C., Chi, Z., Sheng, X., Mao, L., Li, S., Kong, Y., Tang, B., and Guo, J. Phase II randomized trial comparing high-dose IFN-alpha2b with temozolomide plus cisplatin

as systemic adjuvant therapy for resected mucosal melanoma. Clinical Cancer Research 2013. 19(16): 4488-4498

Liang, Z. G., Zhu, X. D., Tan, A. H., Jiang, Y. M., Qu, S., Su, F., and Xu, G. Z. 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 2013. 14(1): 515-521.

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

Lund, V. J., Chisholm, E. J., Howard, D. J., and Wei, W. I. Sinonasal malignant melanoma: an analysis of 115 cases assessing outcomes of surgery, postoperative radiotherapy and endoscopic resection. Rhinology 2012. 50(2): 203-210

Madani, I., Vakaet, L., Bonte, K., Boterberg, T., and De, Neve W. Intensity-modulated radiotherapy for cervical lymph node metastases from unknown primary cancer. International Journal of Radiation Oncology Biology Physics 2008. 71(4): 1158-1166

Marta, G. N. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiotherapy & Oncology 2014. 110(1): 9-15.

Meleti, M., Leemans, C. R., de, Bree R., Vescovi, P., Sesenna, E., and van, der Waal, I. Head and neck mucosal melanoma: experience with 42 patients, with emphasis on the role of postoperative radiotherapy. Head & Neck 2008. 30(12): 1543-1551

Meng, Xin-Jun. Impact of different surgical and postoperative adjuvant treatment modalities on survival of sinonasal malignant melanoma. BMC Cancer 2014. 14: 608

Mistry, R. C., Qureshi, S. S., Talole, S. D., and 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): 54-58.

Nakashima, J. P., Viegas, C. M., Fassizoli, A. L., Rodrigues, M., Chamon, L. A., Silva, J. H., Dias, F. L., and Araujo, C. M. Postoperative adjuvant radiation therapy in the treatment of primary head and neck mucosal melanomas. Orl; Journal of Oto-Rhino-Laryngology & its Related Specialties 2008. 70(6): 344-351

Oen, A. L. Cervical metastasis from the unknown primary tumor. European Archives of Oto-Rhino-Laryngology 1995. 252(4): 222-228

Ouyang, P. Y. and Xie, C. Significant efficacies of neoadjuvant and adjuvant chemotherapy for nasopharyngeal carcinoma by meta-analysis of published literature-based randomized, controlled trials. Annals of Oncology 2013. 24(8): 2136-2146.

Owens, J. M., Roberts, D. B., and Myers, J. N. The role of postoperative adjuvant radiation therapy in the treatment of mucosal melanomas of the head and neck region. Archives of Otolaryngology -- Head & Neck Surgery 2003. 129(8): 864-868

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 2012. 48(12): 1250-1256

Peng, G., Wang, T., Yang, K. Y., Zhang, S., Zhang, T., Li, Q., Han, J., and Wu, G. 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 2012. 104(3): 286-293

Pow, E. H., Kwong, D. L., McMillan, A. S., Wong, M. C., Sham, J. S., Leung, L. H., and Leung, W. K. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. International Journal of Radiation Oncology Biology Physics 2006. 66(4): 981-991

Reddy, S. P. and Marks, J. E. 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.

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.

Shiga, K., Ogawa, T., Kobayashi, T., Ueda, S., Kondo, A., Nanba, A., Kuwashima, S., Asada, Y., Suzuki, S., Nagahashi, T., Takahashi, M., Suzuki, M., Ishida, A., Watanabe, K., Harabuchi, Y., Himi, T., Sinkawa, H., Sato, H., Saijo, S., Fukuda, S., Tanaka, K., Ishikawa, K., Omori, K., Aoyagi, M., and Hashimoto, S. Malignant melanoma of the head and neck: a multi-institutional retrospective analysis of cases in northern Japan. Head & Neck 2012. 34(11): 1537-1541

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 2014. 3(2): 376-384

Strojan, P. Combined surgery and postoperative radiotherapy for cervical lymph node metastases from an unknown primary tumour. Radiotherapy and Oncology 1998. 49(1): 33-40.

Sun, C. Z., Chen, Y. F., Jiang, Y. E., Hu, Z. D., Yang, A. K., and Song, M. Treatment and prognosis of oral mucosal melanoma. Oral Oncology 2012. 48(7): 647-652

Tanaka, N., Mimura, M., Ogi, K., and Amagasa, T. Primary malignant melanoma of the oral cavity: assessment of outcome from the clinical records of 35 patients. International Journal of Oral & Maxillofacial Surgery 2004. 33(8): 761-765

Temam, S., Mamelle, G., Marandas, P., Wibault, P., Avril, M. F., Janot, F., Julieron, M., Schwaab, G., and Luboinski, B. Postoperative radiotherapy for primary mucosal melanoma of the head and neck. Cancer 2005. 103(2): 313-319

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 1997. 173(3): 163-169.

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

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 2011. 32(4): 286-290

Wang, R. C., Goepfert, H., Barber, A. E., and Wolf, P. Unknown primary squamous cell carcinoma metastatic to the neck. Archives of Otolaryngology-Head & Neck Surgery 1990. 116(12): 1388-1393

Wushou, A., Hou, J., Zhao, Y. J., and Miao, X. C. Postoperative adjuvant radiotherapy improves loco-regional recurrence of head and neck mucosal melanoma. Journal of Craniomaxillofacial Surgery 2015. 43(4): 553-558

Yan, M., Kumachev, A., Siu, L. L., and Chan, K. K. Chemoradiotherapy regimens for locoregionally advanced nasopharyngeal carcinoma: A Bayesian network meta-analysis. European Journal of Cancer 2015. epub ahead of print

Zhang, A. M., Fan, Ye, Wang, Xin-Xin, Xie, Qi-Chao, Sun, Jian-Guo, Chen, Zheng-Tang, and Zhu, Bo. Increased treatment-related mortality with additional cisplatin-based chemotherapy in patients with nasopharyngeal carcinoma treated with standard radiotherapy. Radiotherapy & Oncology 2012. 104(3): 279-285.

Zhang, L., Zhao, Chong, Ghimire, Bijesh, Hong, Ming-Huang, Liu, Qing, Zhang, Yang, Guo, Ying, Huang, Yi-Jun, and Guan, Zhong-Zhen. 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 2010. 10: 558.

7 Optimising function and rehabilitation

7.1 Enteral nutrition support

The importance of nutrition in the CUADT population is well established due to the effects of the disease and its treatment on a person'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.

Clinical question: What criteria should be used at the point of diagnosis to select patients requiring enteral nutritional support during curative treatment?

Clinical evidence (see Appendix H)

Weight loss

Moderate quality evidence from six observational studies (Brown, Ross, Jones, Hughes, & Banks, 2014; Cho et al., 2013; Kubrak et al., 2010; Lescut et al., 2013; Mallick et al., 2013; Silander, Nyman, & Hammerlid, 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., 2014; Ottosson S., 2014) 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 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) or continuous variable (Farhangfar et al., 2014; Kubrak et al., 2013; Nourissat et al., 2010; Ottosson et al., 2014; Ottosson S., 2014). 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% C.I. 0.73 to 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% C.I. 1.7 to 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) including 219 patients evaluated malnutrition screening tool (MST) as a predictor of weight loss in patients with head and neck cancer (HNC). 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) 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 (Langius et al., 2013) of two randomised trials (Salas et al., 2009; Silander et al., 2012) observed no overall differences in the post treatment BMI of patients with advanced HNC 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%C.I. 1.18 to 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 HNC (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%C.I. 2.32 to 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 two observational studies (including 222 patients) suggests that treatment with radiotherapy and concomitant chemotherapy (compared to other treatments) increases the risk of significant weight loss (OR 5.88 [95%C.I. 3.03 to 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%C.I. 2.00 to 7.60] - for significant weight loss; OR 4.39 [95%C.I. 1.82 to 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%C.I. 2.00 to 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 HNC. 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, Slevin, Mais, & Sykes, 2006; Mays, 2014; Sachdev S & Refaat, 2015; Sanguineti, Rao, Gunn, Ricchetti, & Fiorino, 2013; Wermker, Jung, Huppmeier, Joos, & Kleinheinz, 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, 2014; Sachdev S & Refaat, 2015; 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; Mays, 2014; Sachdev S & Refaat, 2015; Wopken et al., 2014).

Tumour site & stage

Tumour stage and nodal stage were independent predictors of enteral nutrition four of the six studies that considered them (Mays, 2014; Sachdev S & Refaat, 2015; Sanguineti et al., 2013; Wermker et al., 2012; Wopken et al., 2014; Jang et al., 2013). 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 oropharynx and neck dissection all independent predictors of needing enteral nutrition.

Wopken et al (2014) found both accelerated fractionation and radiotherapy and concomitant chemotherapy increased the risk of needing 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 needing enteral nutrition.

Study 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.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Assess people's need for enteral nutrition at diagnosis, including prophylactic tube placement. The multidisciplinary team should take into account:** • **performance status and social factors** • **nutritional status (weight loss, high or low BMI, ability to meet estimated nutritional needs)** • **tumour stage** • **tumour site** • **pre-existing dysphagia** • **impact of planned treatment (such as radiation treatment volume and dose-fractionation, concomitant chemotherapy, and extent and site of surgery).** **Follow the recommendations in NICE's guideline on nutrition support in adults for people aged 18 years and**

	over .
Relative value placed on the outcomes considered	The GC considered the risk of weight loss, malnutrition, and needing enteral feeding as the most important outcomes when drafting the recommendations. The GC felt that these outcomes would influence admission during treatment, length of hospital stay and quality of life although the evidence did not report morbidity due to weight loss or malnutrition.
Quality of the evidence	The evidence was of moderate quality, using the NICE prognostic checklist, because some studies included restricted populations or used differing definitions of malnutrition, enteral feeding and prognostic factors. The GC used the available evidence and their clinical experience to recommend which broad criteria should be considered when assessing the need for enteral nutrition. There was not enough detail in the evidence to make the recommendations more specific.
Trade-off between clinical benefits and harms	The GC considered that the clinical benefits of the recommendations would be reduced weight loss and malnutrition, with better quality of life clinical outcomes. Patients may also be more likely to complete their course of treatment without interruption and some patients who do not require enteral nutrition may avoid feeding tube placement. Potential harms of the recommendation would be those associated with enteral feeding such as procedure-related morbidity/mortality, skin excoriation and the psychosocial impact. Screening and assessment of patients by a dietitian from the MDT (for suitability of the type of feeding tube and method of insertion) would help minimise these harms. On balance the group believed that the reduction in malnutrition would outweigh any harms associated with enteral feeding.
Trade-off between net health benefits and resource use	No economic evidence was found and no economic model was developed. The assessment of patients may have extra costs (due to extra personnel, resources and time) but the cost of managing the consequences of malnutrition-related morbidity should be reduced. The GC were uncertain whether there would be a net increase or decrease in resource use. At the moment not all centres carry out systematic assessments for nutrition support, so the recommendations will lead to timely MDT discussion and decision-making to reduce variation.
Other considerations	The GC recognised that following assessment a decision would need to be made between prophylactic feeding versus oral nutritional support versus interventional tube feeding versus reactive tube feeding, however the scope of the question did not cover this decision. The GC did not include thresholds for BMI – these are defined in other NICE guidance CG32. As the NICE guideline for nutrition support applies to adults aged18 and over the GC were unable to make a recommendation for those of 16 or 17 years of age. This very small group of patients should be managed according to local clinical guidelines.

1

Research recommendation	**A prospective study should be undertaken to identify the specific clinical and non-clinical factors that allowed risk stratification when selecting which people with CUADT would benefit from short or long-term enteral nutrition. Outcomes of interest include resource use, morbidity of tube placement and duration of enteral feeding.**
Why this is important	There are no nationally agreed selection criteria for the type of

	feeding tube placed at diagnosis for people that need enteral nutrition support during curative treatment. Variation across the UK exists as a result of clinician-led practices and local policy. The systematic review by NICE in 2015 found some evidence but no specific list was identified due to limitations with study design, and inability to stratify clinical and non-clinical factors meaningfully. These factors included restricted populations for tumour staging, patient demographics, treatment plan and intent, definitions of malnutrition, timing and method of tube placement, and duration of enteral nutrition.

7.2.1 Speech and language therapy interventions

The management of CUADT can have a significant impact on speech, voice and swallowing function particularly with the increasing use of chemotherapy and larynx 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.

Clinical question: Which active speech and language therapy interventions are of most benefit to patients with cancer of the upper aerodigestive tract?

Clinical evidence (see Appendix H)

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 to 10.8, and RR 2.32, 95% CI 0.54 to 9.95, respectively), functional swallowing (RR 3, 95% CI 0.73 to 12.39 and RR 2.79, 95% CI 0.68 to 11.42, respectively), rates of non-oral feeding (RR 0.5, 95% CI 0.15 to 1.61 and RR 0.93, 95% CI 0.23 to 3.81, respectively), and the proportion of patients with greater than 10% weight loss (RR 0.67, 95% CI 0.24 to 1.86 and RR 0.62, 95% CI 0.22 to 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 to 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, 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 to 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 to 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 to 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 radiotherapy and concomitant chemotherapy, those who receive swallowing therapy before their cancer treatment suffer from less long-term dysphagia symptoms than those who receive post-treatment 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 to 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 to 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 to 21.9) or severity (mean difference in maximum interincisal opening 0.83 mm greater, 95% CI −3.64 to 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 interincisor 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 to 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 six months after treatment (mouth opening difficulties absent or minor at 6 months: RR 0.77, 95% CI 0.61 to 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 three 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 six 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 six months after treatment (speech difficulties absent or minor at six months: RR 0.71, 95% CI 0.57 to 0.89).

1 **Table 85: GRADE evidence table: high intensity swallowing therapy during cancer treatment versus usual care**

Quality assessment							No of patients		Effect			
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**	**Quality**	
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 to 10.8)	214 more per 1000 (from 60 fewer to 1000 more)	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 to 12.39)	286 more per 1000 (from 39 fewer to 1000 more)	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 to 1.61)	214 fewer per 1000 (from 364 fewer to 261 more)	MODERATE	
Greater than 10% weight loss at last follow up (6 weeks)												
1[1]	randomised trials	no seriou	no serious inconsistency	no serious indirectness	serious[2]	none	4/14 (28.6%)	6/14 (42.9	RR 0.67	141 fewer per 1000	MODERATE	

Quality assessment							No of patients		Effect			
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**	**Quality**	
		s risk of bias						%)	(0.24 to 1.86)	(from 326 fewer to 369 more)		
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)	MODERATE	

1 [1] *Carnaby-Mann 2012.*
2 [2] *Small study population size.*

3 **Table 86: GRADE evidence table: high intensity swallowing therapy during cancer treatment versus sham therapy**

Quality assessment							No of patients		Effect			
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**	**Quality**	
Normal diet at last follow up (6 weeks)												
1[1]	randomise	no	no serious	no serious	serious[2]	none	5/14	2/13	RR	203 more	MODERAT	

Quality assessment							No of patients		Effect			
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**	**Quality**	
	d trials	serious risk of bias	inconsistency	indirectness			(35.7%)	(15.4 %)	2.32 (0.54 to 9.95)	per 1000 (from 71 fewer to 1000 more)	E	
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 to 11.42)	275 more per 1000 (from 49 fewer to 1000 more)	MODERATE	
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 to 3.81)	16 fewer per 1000 (from 178 fewer to 648 more)	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 to 1.71)	175 fewer per 1000 (from 360 fewer to 328 more)	MODERATE	

Quality assessment							No of patients		Effect			
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**	**Quality**	
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)	MODERATE	

1 [1] *Carnaby-Mann 2012.*
2 [2] *Small study population size.*

3 **Table 87: GRADE evidence table: exercises for trismus and dysphagia vs. control (no exercises)**

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Exercises for trismus and dysphagia**	**Control (no exercises)**	**Relative (95% CI)**	**Absolute**	**Quality**	
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)	LOW	
Swallow function improved (follow-up period unclear)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Exercises for trismus and dysphagia**	**Control (no exercises)**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 3.97)	265 more per 1000 (from 18 more to 743 more)	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 88: GRADE evidence table: therapeutic exercises versus repetitive swallowing

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Therapeutic exercises**	**Repetitive swallowing**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to 1.13)	233 fewer per 1000 (from 385 fewer to 70 more)	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 to 0.82)	345 fewer per 1000 (from 90 fewer to 445 fewer)	VERY LOW	

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	
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		VERY LOW

1 [1] *Virani 2014*
2 [2] *Small study population size*

3 **Table 89: GRADE evidence table: 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 to 2.34)	19 more per 1000 (from 53 fewer to 166 more)	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 to 0.98)	149 fewer per 1000 (from 14 fewer to 263 fewer)	VERY LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early preventative therapy	Control	Relative (95% CI)	Absolute	Quality
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 to 1.17)	44 fewer per 1000 (from 163 fewer to 107 more)	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 to 0.97)	160 fewer per 1000 (from 21 fewer to 271 fewer)	VERY LOW
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 to 0.89)	223 fewer per 1000 (from 85 fewer to 330 fewer)	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)	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)	VERY LOW
Vertical hyoid movement, mm (3 months; better indicated by higher values)											
1[4]	observatio	no	no serious	no serious	serious[3]	none	9	9	-	MD 0.91 higher	VER

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**			
	nal studies	serious risk of bias	inconsistency	indirectness						(5.11 lower to 6.93 higher)		Y LOW	
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	Intervention	Control	LOW	
									Pre-radiotherapy and concomitant chemotherapy	100 (50-100)	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)		
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	Intervention	Control	LOW	
									Pre-radiotherap	7 (6-7)	7 (6-7)		

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		
									y and concomitant chemotherapy			
									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)	

[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 90: GRADE evidence table: 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)											

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre- and post-surgery swallowing therapy**	**Post-surgery swallowing therapy only**	**Absolute**	**Quality**	
1[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	18	25	MD 11.38 lower (8.72 to 14.04 lower)	VERY LOW	

1 [1] *Cavalot 2009.*
2 [2] *Allocation to treatment based on time of recruitment into the study. Limited details of patient characteristics reported.*
3 [3] *Small study population size.*

4 **Table 91: GRADE evidence table: adherence with swallowing exercises versus nonadherence**

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adherence with swallowing exercises**	**Nonadherence**	**Relative (95% CI)**	**Absolute**	**Quality**	
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)	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)	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**		
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 to 1.22)	91 more per 1000 (from 15 more to 167 more)	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 to 5.36)	330 more per 1000 (from 43 more to 934 more)	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 to 0.77)	305 fewer per 1000 (from 123 fewer to 407 fewer)	VERY LOW	
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.		VERY LOW	
Swallowing pain 1 month after end of cancer treatment, scale 1-10, better indicated by lower values (Better indicated by lower values)												

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adherence with swallowing exercises**	**Nonadherence**	**Relative (95% CI)**	**Absolute**	**Quality**
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)	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)	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 92: GRADE evidence table: pre-cancer treatment versus posttreatment swallowing exercises

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre-cancer treatment swallowing exercises**	**Posttreatment swallowing exercises**	**Relative (95% CI)**	**Absolute**	**Quality**

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		Pretreatment group (n = 25)	Posttreatment group (n = 12)	P value	VERY LOW	
									MDADI for Patients with HNC 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 HNC scores, adjusted for age, T stage, site (tongue and tonsil vs. other), follow up time, treatment, race, and gender, mean (95% CI)					
									Global assessm	74.4 (64.5,	32.9 (17.0, 48.7)	0.0002		

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		
									ent	84.3)			
									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 93: GRADE evidence table: 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		

Quality assessment							No of patients		Effect			
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**	
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		Intervention group / Control group OPSE score Baseline: 44.63 ± 16.69 / 59.60 ± 8.85 Post-treatment: 46.50 ± 14.85 / 54.56 ± 20.08	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		Intervention group / Control group Tongue strength, Kpa Baseline: 44.63 ± 13.39 / 49.30 ± 10.53 Post-treatment: 46.50 ± 16.50 / 52.40 ± 10.78	LOW	
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		Intervention group / Control group	VERY 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, 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	

[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 94: GRADE evidence table: jaw exercises versus usual care (randomised trials)

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Jaw exercises**	**Usual care**	**Relative (95% CI)**	**Absolute**	**Quality**
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 to 5.29)	not reported	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 to 2.19)	46 more per 1000 (from 122 fewer to 364 more)	MODERATE

[1] *Hogdal 2015.*
[2] *Small study population size.*

Table 95: GRADE evidence table: jaw exercises versus standard care (control): observational studies

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Jaw exercises**	**Standard care (control)**	**Relative (95% CI)**	**Absolute**	**Quality**

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		VERY LOW	
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	Before study group exercise: Intervention Mean (CI); Control group Mean (CI) 3-month follow-up: Intervention Mean (CI); Control Mean (CI); Intervention Diff Δ; Control Diff Δ		VERY LOW	

Quality assessment							No of patients		Effect									
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jaw exercises	Standard care (control)	Relative (95% CI)					Absolute				Quality	
									Facial pain (FP)										
									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		

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 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.											
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		Before study group exercise			3-month follow-up						VERY LOW	
										Intervention group Mean (CI)	Control group Mean (CI)	p	Intervention group Mean (CI)	Control group Mean (CI)	p	Intervention Diff Δ	Control Diff Δ			

Quality assessment							No of patients		Effect									
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jaw exercises	Standard care (control)	Relative (95% CI)					Absolute				Quality
									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			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jaw exercises	Standard care (control)	Relative (95% CI)		Absolute	Quality
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	Dental gap, cm	Jaw exercises	No jaw exercises	VERY LOW
									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	

[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 96: GRADE evidence table: 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	serious[4]	no serious inconsiste	no serious	serious[3]	none	Outcomes from Tuomi 2014b:	LO

Quality assessment							Effect	Quality	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
	trials		ncy	indirectness				W	

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

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

Quality assessment														
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**						**Quality**	
							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)			
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)			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	5.85 (1.31)	5.65 (1.53)	5.71 (1.30)	5.64 (1.50)			

Quality assessment							Effect					Quality	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations							
							lecture						
							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 97: GRADE evidence table: 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)	VERY LOW	
							Baseline	0	18		
							10 weeks	18	9		

Quality assessment											
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**			**Quality**	
							1 year	9	18		
							2 years	0	9		
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)	VERY LOW	
							Baseline	0	0		
							10 weeks	40	43		
							1 year	7	0		
							2 years	0	0		
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)	VERY LOW	
							Baseline	0	21		
							10 weeks	67	43		
							1 year	13	0		
							2 years	17	14		
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)	VERY LOW	
							Baseline	0	21		
							10	13	7		

Quality assessment							Effect			Quality	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations					
							weeks				
							1 year	0	7		
							2 years	0	14		
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)	VERY LOW	
							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)		

[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 98: GRADE evidence table: postoperative swallowing therapy vs. 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%												

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**		
1[4]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none					VERY LOW	
								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		
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					VERY LOW	
								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		

1 [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.*

Cost-effectiveness evidence

Two relevant studies were identified in a literature review of published cost-effectiveness analyses on this topic. 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.

Table 99: 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 HNC 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:								

1

Recommendations	**Consider swallowing-exercise programmes for people having radiotherapy.** **Consider mouth-opening exercises for people having radiotherapy who are at risk of reduced mouth opening.** **Consider voice therapy for people whose voice has changed because of their treatment.**
Relative value placed on the outcomes considered	All of the outcomes in the PICO were considered important and evidence was reported for all outcomes. However, some outcomes had very only low quality evidence and/or very limited amounts of evidence available. Therefore, for some outcomes the GC did not feel the evidence was of sufficient quality to make recommendations.
Quality of the evidence	Evidence from one study was rated as moderate quality evidence; all other evidence was rated as low or very low quality. Evidence was assessed using GRADE. Issues with the evidence included: • small numbers of patients in most studies; • lack of consistency across studies in terms of the interventions investigated and the methods used to measure outcomes, which prevented pooling of results or direct comparison of different studies; • lack of evidence of rigorous randomisation in the RCTs; • unexplained loss of patients to follow-up and incomplete reporting of results in the observational studies. These issues, and in particular the low numbers of patients available for each comparison/outcome, meant that all the evidence was associated with considerable uncertainty. The low quality of evidence in some areas meant that the GC also used their clinical experience to supplement this evidence when recommending which interventions should be used. The GC made research recommendations in those areas with limited evidence to try and obtain more evidence that could be used to answer this question more comprehensively in future. The majority of the evidence related to people treated with radiotherapy. The limitations in the evidence on surgically treated patients limited the recommendations the GC were able to make on this group of people. Due to the lack of evidence in this area, the GC made a research recommendation on surgically treated patients. An additional research recommendation was made to investigate which interventions influence swallowing and nutrition outcomes since this relationship has not been adequately studied at present. The quality of the economic evidence identified was low. Issues with the evidence included use of non-comparative data, and the assumption of a quality of life benefit with the use of swallowing therapy as a key driver of effectiveness. Due to its low quality and lack of applicability to the UK setting the evidence was disregarded by the GC.
Trade-off between clinical benefits and harms	The GC considered the potential benefits of the recommendations to be better patient outcomes in terms of swallowing, voice quality and mouth opening. No potential harms were identified.
Trade-off between net health	No health economic model was developed.

benefits and resource use	The GC considered the potential costs of the recommendations to be more speech and language therapy. The GC anticipate some savings from less long-term cancer treatment-related morbidity as a result of the recommendations. It is difficult to assess the overall net effect of these costs and savings.
Other considerations	The GC anticipate the main change in practice from the recommendations to be more speech and language therapy.

1

Research recommendation	**A prospective study should be undertaken to investigate which active speech and language therapy interventions are most effective in people with CUADT undergoing surgery and the most effective timings of intervention. Outcomes of interest include measures of speech quality and type/duration of intervention.**
Why this is important	The surgical treatment of patients with CUADT may be associated with a significant impact on speech, voice and swallowing function. The role of speech and language therapy within the head and neck cancer MDT is well-established but the evidence for which interventions should be used and their timing is very poor with small numbers of patients in studies and a lack of consistency in the interventions used. This requires a collaborative approach between speech and language therapy and dietetics to evaluate both swallowing and nutrition outcomes.

2

Research recommendation	**A prospective study should be undertaken to investigate which active speech and language therapy interventions before, during and after treatment for CUADT are the most effective at improving swallowing and nutritional outcomes.**
Why this is important	Treatment of patients with CUADT having surgery and or radiotherapy plus or minus chemotherapy may be associated with a significant impairment in swallowing and consequent nutritional status. The evidence for which interventions may help minimise these problems, when and how they should be delivered is very poor. Studies are required to optimise patient swallowing and nutritional outcomes.

7.3 Shoulder rehabilitation

3

4 The spinal accessory nerve is potentially at risk of damage during neck dissection. Shoulder
5 function may be compromised by nerve injury leading to pain and restriction in movement
6 which adversely affects quality of life.

7 There is no consensus as to the most effective way of managing this complication.

8

Clinical question: What are the most effective interventions for shoulder rehabilitation following neck dissection in people with cancer of the upper aerodigestive tract?

9 **Clinical evidence (see Appendix H)**

10 ***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 HNC patients with treatment-induced shoulder dysfunction (Carvalho, Vital, & Soares, 2012). Compared to HNC 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 et al., 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 et al., 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 et al., 2002).

Nerve exploration/repair

No evidence was identified on the effectiveness of this intervention in the population of interest.

Study characteristics and quality

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 et al., 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 et al., 2004; McNeely et al., 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 100: GRADE evidence table: progressive resistance training (PRT) versus standard care for shoulder dysfunction in patients treated for head and neck cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PRT	Standard care	Relative (95% CI)	Absolute	Quality
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)	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)	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)	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)	MODERATE
Active range of motion (forward flexion) (Better indicated by lower values)											
2[1,3]	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 7.01 higher	MODERATE

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PRT**	**Standard care**	**Relative (95% CI)**	**Absolute**	**Quality**	
		risk of bias								(1.93 lower to 15.95 higher)		
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)	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)	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)	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)	MODERATE	
Passive range of motion (horizontal abduction) (Better indicated by lower values)												
2	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 7.34 higher	MODERATE	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PRT**	**Standard care**	**Relative (95% CI)**	**Absolute**	**Quality**	
		risk of bias								(2.86 to 11.83 higher)		
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)	MODERATE	
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 to 65.38)	Not estimable	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 to 71.90]	Not estimable	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)	MODERATE	
Quality of life measured by FACT-H&N questionnaire (Better indicated by lower values)												
1[3]	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[2]	None	8	9	-	MD 3.9 higher (16.3 lower	MODERATE	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PRT**	**Standard care**	**Relative (95% CI)**	**Absolute**	**Quality**	
		bias								to 24.1 higher)		
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)	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)	MODERATE	
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)	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)	MODERATE	
Strength of scapular muscles (chest press, 1-RM with two arms) (Better indicated by lower values)												
1[1]	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[2]	None	27	25	-	MD 14.4 higher	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	
		risk of bias								(3.05 to 25.75 higher)	
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)	MODERATE

[1] *McNeely 2008.*
[2] *Small sample size.*
[3] *McNeely 2004.*
[4] *Small sample size; very low number of events.*

Table 101: Table 3. GRADE evidence table: 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	MODERATE

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**		
										higher)		
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)	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)	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)	MODERATE	

1 [1] *Lauchlan 2011.*
2 [2] *Small sample size.*

Table 102: GRADE evidence table: physiotherapist-led rehabilitation vs autonomous rehabilitation for shoulder dysfunction after neck dissection

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Physiotherapist-led rehabilitation**	**Autonomous rehabilitation**	**Relative (95% CI)**	**Absolute**	**Quality**	
≥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 to 1.18)	0 fewer per 1000 (from 138 fewer to 166 more)	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 to 2.67)	39 more per 1000 (from 143 fewer to 468 more)	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 to 1.27)	162 fewer per 1000 (from 348 fewer to	VERY LOW	

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		
										162 more)		
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 to 3.03)	0 fewer per 1000 (from 134 fewer to 406 more)	VERY LOW	

1 [1] *Baggi 2014.*
2 [2] *Follow up period may be insufficiently short.*
3 [3] *Small sample size.*

4 **Table 103: GRADE evidence table: 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	Arm abduction test score	Rehabilitation group	No rehabilitation group	P value	VERY LOW	

Quality assessment							No of patients		Effect			Quality	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative rehabilitation	No rehabilitation	Absolute				
									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.				

[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 104: 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.	VERY LO	

Quality assessment							No of patients		Effect			Quality	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outpatient physical therapy	Control	Absolute				
									1 month post-surgery	7.8 ± 1.69	7.53 ± 1.69	W	
									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.	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)													

Quality assessment							No of patients		Effect			Quality	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Outpatient physical therapy**	**Control**	**Absolute**				
1[1]	observational studies	serious2	no serious inconsistency	no serious indirectness	serious[3]	none	30	30		Physical therapy.	No physical therapy.	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.	VERY LOW	
									1 month post-surgery	9.93 ± 3.83	9.97 ± 3.94		

Quality assessment							No of patients		Effect				
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Outpatient physical therapy**	**Control**	**Absolute**			**Quality**	
									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.	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 [1] *Salerno 2002*
2 [2] *The care received by the control group, and whether this was the same for all patients, is not reported.*
3 [3] *Small sample size.*

4

1 Cost-effectiveness evidence

2 A literature review of published cost-effectiveness analyses did not identify any relevant
3 papers for this topic. Whilst there were potential cost implications of making
4 recommendations in this area, other questions in the guideline were agreed as higher
5 priorities for economic evaluation. Consequently no further economic modelling was
6 undertaken for this question.

7

Recommendations	Consider progressive resistance training for people with impaired shoulder function, as soon as possible after neck dissection.
Relative value placed on the outcomes considered	All outcomes in the PICO were considered important and evidence was available for all outcomes, although the quality of this evidence varied.
Quality of the evidence	Issues with the evidence included: • Small population size for each comparison • the outcomes used to assess shoulder function are no longer widely used in the UK and most have not been validated in this setting • high risk of bias in some observational studies • unclear if exact details of intervention (PRT) were comparable across pooled studies. These issues lowered the quality of the evidence for using PRT. In addition the GC noted that most of the evidence on PRT was not specific to shoulder dysfunction following treatment for CUADT. Consequently an expert adviser was consulted. Based on the evidence of effectiveness and input from the expert adviser the GC recommended PRT be considered. Evidence existed for only part of the review question; where there was a lack of evidence a research recommendation was made with the aim of addressing this. Specifically, there is uncertainty over whether early identification of shoulder dysfunction improves outcomes.
Trade-off between clinical benefits and harms	The main perceived benefit of the recommendations is improved shoulder-related outcomes in patients following neck dissection. No harms were identified, providing PRT exercises are followed correctly (exercises performed incorrectly could result in harm).
Trade-off between net health benefits and resource use	More physiotherapy intervention, specifically PRT, is anticipated to result in greater resource use. However, lower costs from treating long term shoulder morbidity (e.g. pain, analgesia, GP visits) are anticipated. The net effect is unknown.
Other considerations	Expert advisor opinion suggested: • standard clinical practice involves four to eight physiotherapy contacts and performing exercises twice daily at home. Typically, physiotherapy interventions last for a total of three to four months • physiotherapy can be performed during radiotherapy • the Oxford Shoulder score is the most widely used system for measuring shoulder function outcomes • there is a high level of pre-existing shoulder dysfunction in the general population, hence the potential need for pre-operative assessment.

8

Research	A prospective, randomised study should be undertaken

recommendation	to compare the effectiveness of different routine assessments and interventions for shoulder impairment in people undergoing neck dissection for the management of CUADT. Outcomes of interest include type and duration of intervention, quality of life and short-and long-term shoulder function.
Why this is important	The spinal accessory nerve is potentially at risk of damage during many types of neck dissection. Even if the nerve is preserved its function can be compromised resulting in pain and restricted shoulder movement, both of which can have a significant detrimental impact on a person's quality of life both in the short and long term after surgery. In the main shoulder function is not proactively measured and treatment tends to be employed on a reactive basis only once problems have been identified. There is some evidence in the orthopaedic literature that early identification and treatment of shoulder dysfunction improves outcomes but to date no similar data is available for people undergoing neck surgery for the management of upper aerodigestive tract cancer.

References

Ahlberg, A., Engstrom, T., Nikolaidis, P., Gunnarsson, K., Johansson, H., Sharp, L., and Laurell, G. Early self-care rehabilitation of head and neck cancer patients. Acta Oto-Laryngologica 2011. 131(5): 552-561

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

Brown, T., Ross, L., Jones, L., Hughes, B., and Banks, M. Nutrition outcomes following implementation of validated swallowing and nutrition guidelines for patients with head and neck cancer. Supportive Care in Cancer 2014. 22(9): 2381-2391.

Carnaby-Mann, G., Crary, M. A., Schmalfuss, I., and Amdur, R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. International Journal of Radiation Oncology, Biology, Physics 2012. 83(1): 210-219

Carroll, W. R., Locher, J. L., Canon, C. L., Bohannon, I. A., McColloch, N. L., and Magnuson, J. S. Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope 2008. 118(1): 39-43

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

Cavalot, A. L., Ricci, E., Schindler, A., Roggero, N., Albera, R., Utari, C., and Cortesina, G. The importance of preoperative swallowing therapy in subtotal laryngectomies. Otolaryngology - Head & Neck Surgery 2009. 140(6): 822-825

Cho, Y. W., Roh, J. L., Jung, J. H., Kim, S. B., Lee, S. W., Choi, S. H., Nam, S. Y., Kim, S. Y., and Kim, S. Y. Prediction of posttreament significant body weight loss and its correlation with disease-free survival in patients with oral squamous cell carcinomas. Nutrition & Cancer 2013. 65(3): 417-423

Duarte, V. M., Chhetri, D. K., Liu, Y. F., Erman, A. A., and Wang, M. B. Swallow preservation exercises during chemoradiation therapy maintains swallow function. Otolaryngology - Head & Neck Surgery 2013. 149(6): 878-884

Farhangfar, A., Makarewicz, M., Ghosh, S., Jha, N., Scrimger, R., Gramlich, L., and Baracos, V. 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 2014. 50(9): 877-883.

Gourin, C. G., Couch, M. E., and Johnson, J. T. Effect of Weight Loss on Short-Term Outcomes and Costs of Care After Head and Neck Cancer Surgery. Annals of Otology Rhinology and Laryngology 2014. 123(2): 101-110.

Hogdal N, Juhl C, Aadahl M, and Gluud C. Early preventive exercises versus usual care does not seem to reduce trismus in patients treated with radiotherapy for cancer in the oral cavity or oropharynx: A randomised clinical trial. Acta Oncologica 2015; 54(1):80-87.

Hutcheson, K. A., Bhayani, M. K., Beadle, B. M., Gold, K. A., Shinn, E. H., Lai, S. Y., and Lewin, J. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngology-- Head & Neck Surgery 2013. 139(11): 1127-1134

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.

Jang, J. W., Parambi, R. J., McBride, S. M., Goldsmith, T. A., Holman, A. S., and Chan, A. W. Clinical factors predicting for prolonged enteral supplementation in patients with oropharyngeal cancer treated with chemoradiation. Oral Oncology 2013. 49(5): 438-442.

Kotz, T., Federman, A. D., Kao, J., Milman, L., Packer, S., Lopez-Prieto, C., Forsythe, K., and Genden, E. M. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Archives of Otolaryngology -- Head & Neck Surgery 2012. 138(4): 376-382

Kubrak, C., Olson, K., Jha, N., Jensen, L., McCargar, L., Seikaly, H., Harris, J., Scrimger, R., Parliament, M., and Baracos, V. E. 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 2010. 32(3): 290-300

Kubrak, C., Olson, K., Jha, N., Scrimger, R., Parliament, M., McCargar, L., Koski, S., and Baracos, V. E. Clinical determinants of weight loss in patients receiving radiation and chemoirradiation for head and neck cancer: A prospective longitudinal view. Head & Neck 2013. 35(5): 695-703

Kulbersh, B. D., Rosenthal, E. L., McGrew, B. M., Duncan, R. D., McColloch, N. L., Carroll, W. R., and Magnuson, J. S. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope 2006. 116(6): 883-886

Langius, J. A., Zandbergen, M. C., Eerenstein, S. E., van Tulder, M. W., Leemans, C. R., Kramer, M. H., and Weijs, P. J. 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. Clinical Nutrition 2013. 32(5): 671-678.

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.

Lazarus, C. L., Husaini, H., Falciglia, D., DeLacure, M., Branski, R. C., Kraus, D., Lee, N., Ho, M., Ganz, C., Smith, B., and Sanfilippo, N. Effects of exercise on swallowing and tongue strength in patients with oral and oropharyngeal cancer treated with primary radiotherapy

with or without chemotherapy. International Journal of Oral & Maxillofacial Surgery 2014. 43(5): 523-530

Lescut, N., Personeni, E., Desmarets, M., Puyraveau, M., Hamlaoui, R., Servagi-Vernat, S., Bosset, J. F., and Nguyen, F. [Evaluation of a predictive score for malnutrition in patients treated by irradiation for head and neck cancer: a retrospective study in 127 patients]. Cancer/Radiothérapie 2013. 17(7): 649-655

Mallick, I., Gupta, S. K., Ray, R., Sinha, T., Sinha, S., Achari, R., and Chatterjee, S. Predictors of Weight Loss during Conformal Radiotherapy for Head and Neck Cancers - How Important are Planning Target Volumes? Clinical Oncology 2013. 25(9): 557-563

Mangar, S., Slevin, N., Mais, K., and Sykes, A. Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer: a retrospective review. Radiotherapy & Oncology 2006. 78(2): 152-158.

Mays, A. C. A model for predicting gastrostomy tube placement in patients undergoing surgery for upper aerodigestive tract lesions. JAMA Otolaryngology-- Head & Neck Surgery 2014. 140(12): 1198-1206

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.

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.

Munshi, A., Pandey, M. B., Durga, T., Pandey, K. C., Bahadur, S., and Mohanti, B. K. Weight loss during radiotherapy for head and neck malignancies: what factors impact it? Nutrition & Cancer 2003. 47(2): 136-140

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

Nourissat, A., Bairati, I., Samson, E., Fortin, A., Gelinas, M., Nabid, A., Brochet, F., Tetu, B., and Meyer, F. Predictors of Weight Loss During Radiotherapy in Patients With Stage I or II Head and Neck Cancer. Cancer 2010. 116(9): 2275-2283.

Ottosson S., Lindblom. 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 2014. 22(9): 2361-2369.

Ottosson, S., Soderstrom, K., Kjellen, E., Nilsson, P., Zackrisson, B., and Laurell, G. 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 2014. 9.

Ottosson, S., Zackrisson, B., Kjellen, E., Nilsson, P., and Laurell, G. Weight loss in patients with head and neck cancer during and after conventional and accelerated radiotherapy. Acta Oncologica 2013. 52(4): 711-718.

Pauli, N. Exercise intervention for the treatment of trismus in head and neck cancer. Acta Oncologica 2014. 53(4): 502-509

Righini, C. A., Timi, N., Junet, P., Bertolo, A., Reyt, E., and Atallah, I. Assessment of nutritional status at the time of diagnosis in patients treated for head and neck cancer. European annals of otorhinolaryngology, head & neck diseases 2013. 130(1): 8-14

Rose, T., Leco, P., and Wilson, J. The Development of Simple Daily Jaw Exercises for Patients Receiving Radical Head and Neck Radiotherapy. Journal of Medical Imaging and Radiation Sciences 2009. 40(1): 32-37

Sachdev S and Refaat. Age most significant predictor of requiring enteral feeding in head-and-neck cancer patients. Radiation Oncology 2015. 10(1): 93

Salas, S., Baumstarck-Barrau, K., Alfonsi, M., Digue, L., Bagarry, D., Feham, N., Bensadoun, R. J., Pignon, T., Loundon, A., Deville, J. L., Zanaret, M., Favre, R., Duffaud, F., and Auquier, P. 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 2009. 93(3): 503-509

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

Sanguineti, G., Rao, N., Gunn, B., Ricchetti, F., and Fiorino, C. Predictors of PEG dependence after IMRT+chemotherapy for oropharyngeal cancer. Radiotherapy & Oncology 2013. 107(3): 300-304.

Silander, E., Nyman, J., Bove, M., Johansson, L., Larsson, S., and Hammerlid, E. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer: a randomized study. Head Neck 2012. 34(1): 1-9

Silander, E., Nyman, J., and Hammerlid, E. An exploration of factors predicting malnutrition in patients with advanced head and neck cancer. Laryngoscope 2013. 123(10): 2428-2434

Tang, Y., Shen, Q., Wang, Y., Lu, K., Wang, Y., and Peng, Y. A randomized prospective study of rehabilitation therapy in the treatment of radiation-induced dysphagia and trismus. Strahlentherapie und Onkologie 2011. 187(1): 39-44

Tuomi, L., Andrell, P., and Finizia, C. Effects of voice rehabilitation after radiation therapy for laryngeal cancer: a randomized controlled study. International Journal of Radiation Oncology, Biology, Physics 2014(b). 89(5): 964-972

Tuomi, L., Bjorkner, E., and Finizia, C. Voice outcome in patients treated for laryngeal cancer: efficacy of voice rehabilitation. Journal of Voice 2014(a). 28(1): 62-68

Van Den Berg, M. G. A. A prospective study on weight loss and energy intake in patients with head and neck cancer, during diagnosis, treatment and revalidation. Clinical Nutrition 2006. 25(5): 765-772

van der Molen, L., Rossum, M. A., Rasch, C. R. N., Smeele, L. E., and Hilgers, F. J. M. 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: 1257-1270

van Gogh, C. D., Verdonck-de Leeuw, I. M., Boon-Kamma, B. A., Rinkel, R. N., de Bruin, M. D., Langendijk, J. A., Kuik, D. J., and Mahieu, H. F. The efficacy of voice therapy in patients after treatment for early glottic carcinoma. Cancer 2006. 106(1): 95-105

Virani A. Effects of 2 different swallowing exercise regimens during organ-preservation therapies for head and neck cancers on swallowing function. Head and Neck 2015; 37(2):162-170.

Wermker, K., Jung, S., Huppmeier, L., Joos, U., and Kleinheinz, J. Prediction model for early percutaneous endoscopic gastrostomy (PEG) in head and neck cancer treatment. Oral Oncology 2012. 48(4): 355-360.

Wopken, K., Bijl, H. P., van der Schaaf, A., Christianen, M. E., Chouvalova, O., Oosting, S. F., van der Laan, B. F., Roodenburg, J. L., Leemans, C. R., Slotman, B. J., Doornaert, P., Steenbakkers, R. J., Verdonck-de Leeuw, I. M., and Langendijk, J. A. Development and validation of a prediction model for tube feeding dependence after curative (chemo-) radiation in head and neck cancer. PLoS ONE [Electronic Resource] 2014. 9(4): e94879.

Zhen, Y., Wang, J. G., Tao, D., Wang, H. J., and Chen, W. L. Efficacy survey of swallowing function and quality of life in response to therapeutic intervention following rehabilitation treatment in dysphagic tongue cancer patients. European Journal of Oncology Nursing 2012. 16(1): 54-58

8 Follow-up of people with cancer of the upper aerodigestive tract and the management of osteoradionecrosis (ORN)

8.1 Follow-up

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.

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?

Clinical evidence (see Appendix H)

Very low quality evidence from one observational study including 247 patients (Chu, Tsai, Tai, & Chang, 2012)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 from one observational study including 286 patients (Lucev, Rogic, Licul, Bekafigo, & Hadzisejdic, 2012) 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 from one observational study including 913 patients (Francis, Yueh, Weymuller, Jr., & Merati, 2009) 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 from one observational study including 160 patients (Leeuw et al., 2013) suggests 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 and 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 were the detail of patient's baseline characteristics, and therefore whether these were comparable across groups receiving different interventions. For one study (Leeuw et al., 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 105: 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		
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	Quality
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 to 3.9)	89 more per 1000 (from 3 more to 258 more)	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 to 2.64)	55 more per 1000 (from 26 fewer to 202 more)	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	VERY LOW
									Precancer	13 (50%)	0 (0%)	
									Tis + T1 + T2	12 (46%)	10 (63%)	
									T3 + T4	1 (4%)	6 (38%)	

[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 106: GRADE evidence profile: outcomes for surgeon + nurse-led consultation versus surgeon-led consultation alone

Quality assessment							No of patients		Effect3			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 1	Comparison group significantly better 0	No significant difference between groups 0	VERY LOW
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 2	Comparison group significantly better 0	No significant difference between groups 3	VERY LOW
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 imprecisio	none	80	80	Intervention group significantl	Comparison group significantl	No significant	VERY LOW

Quality assessment							No of patients		Effect3			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgeon + nurse-led consultation	Surgeon-led consultation				
					n				y better	y better	difference between groups	
									10	0	8	
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	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	VERY LOW

Quality assessment							No of patients		Effect3			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgeon + nurse-led consultation	Surgeon-led consultation				Quality
									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 107: 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)			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	VERY LOW
									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)	

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			
									Stage 4, n (%)	25 (23.8)	20 (21.7)	
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 108: 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)			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		+US	−US	VERY LOW
									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)	

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			
									(%)			
									Stage 4, n (%)	25 (23.8)	20 (21.7)	
+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 109: 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	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	

Quality assessment							No of patients 4	Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)			
								≥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	
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	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	

Quality assessment							No of patients 4	Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)			
								≥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 110: 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	VERY LOW

Quality assessment							No of patients 4	Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Absolute			
								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	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.*

1 Cost-effectiveness evidence

2 A literature review of published cost-effectiveness analyses did not identify any relevant
3 papers for this topic. Whilst there were potential cost implications of making
4 recommendations in this area, other questions in the guideline were agreed as higher
5 priorities for economic evaluation. Consequently no further economic modelling was
6 undertaken for this question.

7

Recommendations	**Ensure people with cancer of the upper aerodigestive tract and their carers have tailored information about the symptoms of recurrence and late effects of treatment at the end of curative therapy.** **Consider structured, risk-adapted follow-up using locally-agreed protocols for people who have had curative treatment for cancer of the upper aerodigestive tract. Use the follow-up protocols to:** • **help improve quality of life, including discussing psychosocial issues** • **detect disease recurrence or second primary cancer, possibly including narrow-band imaging to improve detection.**
Relative value placed on the outcomes considered	Of the outcomes listed in the PICO, evidence was available for stage of disease at recurrence, detection of second primary tumour, quality of life and overall survival. However, the evidence presented for the latter outcome was of very low quality and associated with considerable uncertainty. The GC therefore chose not to take the evidence on overall survival into account. No evidence was available for progression free survival, disease specific survival, or process related complications.
Quality of the evidence	All evidence was assessed by GRADE and rated as very low quality evidence. The reviewer highlighted that 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. The limited evidence available, and its very low quality, limited the recommendations the GC were able to make. As a result they were unable to recommend a protocol for follow-up, and agreed that local protocols should be used instead. Based on clinical experience the GC agreed early identification of recurrence and late effects of treatment would improve outcomes and recommended tailored information be provided about these. More evidence is required on the optimal methods, frequency, and duration of follow-up in order to make more detailed recommendations; for this reason, the GC made a research recommendation.
Trade-off between clinical benefits and harms	The GC perceived the potential benefits of the recommendations to be earlier detection of recurrence and second primary tumours. The main perceived harm was a greater burden for patients due to more frequent appointments, and therefore more travel, more

	anxiety associated with appointments and awaiting test results, and from any false positive test results.
Trade-off between net health benefits and resource use	There was no economic evidence and no model built. The GC anticipate that there may be a net increase in costs. This is due to costs from potentially more frequent follow-up and investigations (such as narrow band imaging). However, earlier detection of disease has the potential for cost savings due to the avoidance of potentially more harmful treatment in late stage disease.
Other considerations	The main change in practice anticipated by the GC as a result of these recommendations is wider use of narrow band imaging during follow-up. MDTs will review and update their local policies for follow-up.

1

Research recommendation	**A prospective study should be undertaken to investigate the optimal method, frequency and duration of follow-up for people who are disease free after treatment for CUADT. Outcomes of interest include quality of life, local control and overall survival.**
Why this is important	What are the optimal methods, frequency, and duration of follow-up in people who are clinically disease free and who have undergone treatment for squamous cell cancer of the upper aerodigestive tract with curative intent? Considerable resources are expended throughout the country on the follow-up of people who have completed potentially curative treatment. Local follow-up protocols are based more on historical practice than evidence and are often disease- rather than patient-centred. Research to investigate how and when follow-up should optimally be carried out could improve clinical outcomes and the use of resources.

8.2 Management of ORN

2

3 Osteoradionecrosis most commonly affects the mandible and can have significant
4 consequences for the patient. Treatment options include surgery, hyperbaric oxygen therapy
5 (HBO), and drugs such as tocopherol and pentoxyphylline. These interventions have costs
6 and potential side effects, and have uncertain efficacy.

7

Clinical question: What are the most effective methods of managing osteoradionecrosis following treatment of cancer of the upper aerodigestive tract?

8 **Clinical evidence (see Appendix H)**

9 ***Hyperbaric oxygen (HBO) therapy***

10 Very low quality evidence from a systematic review (Bennett, Feldmeier, Hampson, Smee, &
11 Milross, 2012) of three randomised controlled trials including a total of 246 patients suggests
12 that in people who have or at risk of osteoradionecrosis (ORN) of the jaws, treatment with
13 HBO improves the likelihood of complete mucosal cover in the affected area (risk ratio [RR]
14 1.30, 95% confidence interval [CI] 1.09, 1.55; RR >1 favours HBO). However, this analysis
15 included some patients receiving HBO for the prevention or ORN, rather than as an ORN
16 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 et al., 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 et al., 2006) including 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, Wood, & McLean, 1997) including 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, Sandor, Evans, & Brown, 2001) including 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.

Table 111: GRADE profile: HBO vs 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 to 1.55)	195 more per 1000 (from 59 more to 358 more)	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 to 1.76)	138 more per 1000 (from 94 fewer to 478 more)	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 112: GRADE profile: HBO vs 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]	randomise	no	no serious	serious[3]	serious[2]	none	6/31	12/37	RR 0.6	130 fewer per	LOW

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**		
	d trials	serious risk of bias	inconsistency				(19.4 %)	(32.4%)	(0.25 to 1.4)	1000 (from 243 fewer to 130 more)		
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 to 1.47)	77 more per 1000 (from 139 fewer to 363 more)	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 to 1.17)	55 fewer per 1000 (from 227 fewer to 155 more)	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 113: GRADE profile: Surgery and postoperative HBO vs 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)												

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**		
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 to 0.95)	305 fewer per 1000 (from 48 fewer to 486 fewer)	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 114: GRADE profile: Localized sequestrectomy vs 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 to 2.55)	372 more per 1000 (from 50 more to 861	VERY LOW	

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Localized sequestrectomy	Conservative therapy	Relative (95% CI)	Absolute	Quality	
										more)		

[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 115: GRADE profile: Conservative management, with or without sequestrectomy, for treatment of ORN of the jaws

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conservative management + sequestrectomy	Conservative management w/out sequestrectomy	Relative (95% CI)	Absolute	Quality	
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 to 5.2)	255 more per 1000 (from 102 fewer to 1000 more)	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 to 6.05)	366 more per 1000 (from 54 fewer to	VERY LOW	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Conservative management + sequestrectomy**	**Conservative management w/out sequestrectomy**	**Relative (95% CI)**	**Absolute**	**Quality**	
										1000 more)		
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 to 0.88)	432 fewer per 1000 (from 72 fewer to 546 fewer)	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 116: GRADE profile: HBO plus sequestrectomy vs HBO alone for treatment of ORN of the jaws

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HBO + sequestrectomy**	**HBO alone**	**Relative (95% CI)**	**Absolute**	**Quality**	
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 to	531 more per 1000 (from 122	VERY LOW	

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**		
									4.48)	more to 1000 more)		
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 to 1.16)	0 fewer per 1000 (from 123 fewer to 152 more)	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 117: GRADE profile: HBO plus resection vs 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 to 4.59)	549 more per 1000 (from 129 more to 1000 more)	VERY LOW	
Treatment success or improvement (follow-up mean 1.8 years)												
1[1]	observationa	very	no serious	no serious	serious[3]	none	11/12	18/19	RR 0.97	28 fewer per	VERY	

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HBO + resection**	**HBO alone**	**Relative (95% CI)**	**Absolute**	**Quality**	
	l studies	serious[2]	inconsistency	indirectness			(91.7%)	(94.7 %)	(0.79 to 1.18)	1000 (from 199 fewer to 171 more)	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 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider surgery to remove necrotic bone and to establish soft tissue coverage in people with osteoradionecrosis.** **Only consider hyperbaric oxygen therapy or medical management for treating osteoradionecrosis as part of a clinical trial.**
Relative value placed on the outcomes considered	The only outcomes reported in the evidence review were symptom control and mucosal integrity. These were therefore the only outcomes used by the GC when drafting recommendations. No evidence was reported on any of the following outcomes: • quality of life • treatment related morbidity • fistula closure • trismus • oral intake • nutritional status • jaw preservation rates
Quality of the evidence	The quality of the evidence was assessed using GRADE and rated as low to very low. All observational trials used a small sample size and were rated as having a high risk of bias. In the randomised trials the population included and methods of measuring outcomes were not entirely relevant to the review question. All the evidence identified concerned the effectiveness of hyperbaric oxygen or surgical interventions; no suitable evidence was identified on the effectiveness of nutritional support, medical management (with tocopherol or pentoxyphylline) or smoking cessation. As a consequence of the absence of evidence on some interventions, and the uncertainty of the evidence that was available, the GC were only able to make limited recommendations. The GC recommended use of surgery to remove necrotic bone based on evidence demonstrating its effectiveness. The GC noted that the evidence demonstrated that HBO was not effective for treating ORN. However, it was acknowledged that this evidence was low quality, so given the uncertainty in the results the GC were only able to recommend its use within the setting of a clinical trial. The quality of evidence for the use of medical management was so poor that the GC were only able to recommend use within a clinical trial. Key interventions where little or no relevant evidence was available were the focus of research recommendations. Smoking cessation is covered by another topic in this guideline and, in the absence of any more specific evidence here, no recommendations were made on smoking cessation here.

Trade-off between clinical benefits and harms	The GC consider the potential benefits of the recommendations to be: • reduced treatment-related morbidity from HBO and medical management due to reduction in use of these interventions; • potentially more resolution of ORN due to patients receiving more timely surgery. No potential harms were identified.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no model developed. As a result of the recommendations, the GC anticipate that there will be some savings from less patients receiving hyperbaric oxygen or medical management. No new costs were anticipated.
Other considerations	The main changes in practice envisaged are less use of HBO and medical management in addition to more patients receiving timely surgery.

1

Research recommendation	**A prospective, randomised study should be undertaken to compare the effectiveness of hyperbaric oxygen against standard care for the treatment of established osteoradionecrosis in people with CUADT. Outcomes of interest include quality of life, duration of symptoms and time to clinical resolution of osteoradionecrosis.**
Why this is important	The delivery of radical radiotherapy in the management of upper airways tract cancers has a number of potential long-term side effects which include ORN. This late complication can produce significant morbidity which itself can produce not insignificant symptoms and hence impact detrimentally on a person's quality of life. Some variation in practice exists within the UK with the sporadic use of hyperbaric oxygen in the management of established ORN. The length of a course of treatment compounded by the relatively small number of facilities where it takes place means that for many people hyperbaric oxygen therapy can be a considerable treatment burden. Whilst some clinicians are currently investigating the use of hyperbaric oxygen in the prophylaxis of ORN no well designed trial has yet been undertaken to consider its use in established cases.

2

Research recommendation	**A prospective, randomised study should be undertaken to compare the effectiveness of medical management against standard care for the treatment of established osteoradionecrosis in people with CUADT. Outcomes of interest include quality of life, duration of symptoms and time to clinical resolution of osteoradionecrosis.**
Why this is important	Given the problems in obtaining hyperbaric oxygen therapy the use of pharmacological agents has been suggested as an alternative mode of managing people with established ORN. Whilst drug treatment has theoretical efficacy based on the modern understanding of the pathogenesis of ORN the efficacy of the proposed medications has not been robustly tested. These drugs also have potential side effects and interactions, and not inconsiderable costs.

References

Annane, D., Depondt, J., Aubert, P., Villart, M., Gehanno, P., Gajdos, P., and Chevret, S. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. Journal of Clinical Oncology 2004. 22(24): 4893-4900

Bennett, M. H., Feldmeier, J., Hampson, N., Smee, R., and Milross, C. Hyperbaric oxygen therapy for late radiation tissue injury. [Review][Update of Cochrane Database Syst Rev. 2005;(3):CD005005; PMID: 16034961]. Cochrane Database of Systematic Reviews 2012. 5: CD005005

Cheng, S. J., Lee, J. J., Ting, L. L., Tseng, I. Y., Chang, H. H., Chen, H. M., Kuo, Y. S., Hahn, L. J., and Kok, S. H. A clinical staging system and treatment guidelines for maxillary osteoradionecrosis in irradiated nasopharyngeal carcinoma patients. International Journal of Radiation Oncology, Biology, Physics 2006. 64(1): 90-97

Chu, P. Y., Tsai, T. L., Tai, S. K., and Chang, S. Y. Effectiveness of narrow band imaging in patients with oral squamous cell carcinoma after treatment. Head and Neck 2012. 34(2): 155-161

David, L. A., Sandor, G. K., Evans, A. W., and Brown, D. H. Hyperbaric oxygen therapy and mandibular osteoradionecrosis: a retrospective study and analysis of treatment outcomes. Journal (Canadian Dental Association) 2001. 67(7): 384-Aug

Hsu, Y. B., Chang, S. Y., Lan, M. C., Huang, J. L., Tai, S. K., and Chu, P. Y. Second primary malignancies in squamous cell carcinomas of the tongue and larynx: an analysis of incidence, pattern, and outcome. J Chin Med Assoc 2008. 71(2): 86-91

Francis, D. O., Yueh, B., Weymuller, E. A., Jr., and Merati, A. L. Impact of surveillance on survival after laryngeal cancer in the medicare population. Laryngoscope 2009. 119(12): 2337-2344

Leeuw, J., Prins, J. B., Teerenstra, S., Merkx, M. A. W., Marres, H. A. M., and Achterberg, T. Nurse-led follow-up care for head and neck cancer patients: a quasi-experimental prospective trial. Supportive Care in Cancer 2013. 21(2): 537-547

Lucev, A., Rogic, M., Licul, V., Bekafigo, I. S., and Hadzisejdic, I. Comparison of three postoperative follow-up methods in patients with oral cancer. Collegium Antropologicum 2012. 36(3): 761-765

Maier, A., Gaggl, A., Klemen, H., Santler, G., Anegg, U., Fell, B., Karcher, H., Smolle-Juttner, F. M., and Friehs, G. B. Review of severe osteoradionecrosis treated by surgery alone or surgery with postoperative hyperbaric oxygenation. British Journal of Oral & Maxillofacial Surgery 2000. 38(3): 173-176

Schwartz, D. L., Barker, J., Jr., Chansky, K., Yueh, B., Raminfar, L., Drago, P., Cha, C., Austin-Seymour, M., Laramore, G. E., Hillel, A. D., Weymuller, E. A., and Wallner, K. E. Postradiotherapy surveillance practice for head and neck squamous cell carcinoma--too much for too little? Head and Neck 2003. 25(12): 990-999

Wong, J. K., Wood, R. E., and McLean, M. Conservative management of osteoradionecrosis. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics 1997. 84(1): 16-21