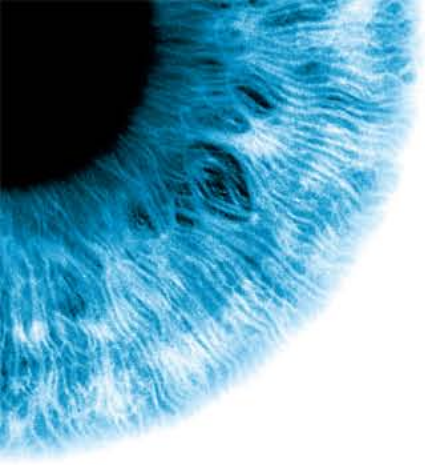

Improving outcomes in head and neck cancers:
Evidence Update May 2012

A summary of selected new evidence relevant to NICE cancer services guidance 'Improving outcomes in head and neck cancers' (2004)

Evidence Update 17

Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might reinforce or generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE guidance development centres. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.evidence.nhs.uk/topic/head-and-neck-cancers). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

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Contents

Introduction

This Evidence Update identifies new evidence that might reinforce or generate future change to the practice laid out in the following reference guidance:

[1]**Improving outcomes in head and neck cancers. NICE cancer services guidance (2004). Available from www.nice.org.uk/guidance/CSGHN**

[1]**Diagnosis and management of head and neck cancer. Scottish Intercollegiate Guidelines Network 90 (2006). Available from www.sign.ac.uk/guidelines/fulltext/90/index.html**

NICE cancer service guidance is a focused programme of work that provides advice to those who develop and deliver cancer services on the planning, commissioning and configuration of those services.

Cancer service guidance has differences in methodology and makes different but complementary recommendations to clinical guidelines. In the absence of a NICE clinical guideline on head and neck cancer, this Evidence Update refers to the NICE cancer service guidance on head and neck cancer (NICE CSGHN) and the Scottish Intercollegiate Guidelines Network (SIGN) guidance on head and neck cancer (SIGN 90).

A search was conducted for new evidence published between 1 July 2010 and 12 December 2011. Just under 2200 pieces of evidence were identified and assessed, of which 32 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of subject experts, reviewed the prioritised evidence and provided a commentary.

Other relevant accredited guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other accredited guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

[2] Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck. NICE technology appraisal 172 (2009). Available from www.nice.org.uk/guidance/TA172

[2] Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck. NICE technology appraisal 145 (2008). Available from www.nice.org.uk/guidance/TA145

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

[1] Guidance published prior to NHS Evidence accreditation

[2] NICE-accredited guidance is denoted by the Accreditation Mark

Key messages

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key messages for this Evidence Update. It also indicates the EUAG's opinion on whether new evidence identified by the Evidence Update reinforces or has potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence, which will be considered in future guidance. For further details of the evidence behind these key messages and the specific guidance that may be affected, please see the full commentaries.

	Effect on guidance	
Key message	**Potential change**	**No change**
Epidemiology		
Lifestyle factors		
• Epidemiological associations with head and neck cancer have been identified for high dietary intake of red meat and low intake of fruit and vegetables, and low or no exercise.		✓
Risk factors		
• Research may be needed to determine whether MUC1 and MUC2 expression is increased in laryngeal carcinoma.		✓
• Human papillomavirus might be associated with oral cancer and dysplasia.		✓
• Plasma testing for Epstein-Barr virus may be a useful marker for nasopharyngeal cancer.		✓
Diagnosis		
Early detection		
• Screening for oral cancer showed no difference in mortality but increased 5-year survival compared with control groups, but this may have been due to lead-time bias.		✓
• Fine-needle aspiration cytology may be effective for histological diagnosis of salivary gland tumours.		✓
Factors indicating prognosis		
• Facial palsy may indicate a more advanced case of cancer than conventional staging would recognise.	✓	
• Carbonic anhydrase-9 expression may indicate a worse prognosis in people with head and neck cancer.		✓
• Uptake of ^{18}F-fluorodeoxyglucose detected by positron emission tomography (^{18}FDG-PET) may help to determine prognosis for people with head and neck cancer.		✓
Imaging		
• ^{18}FDG-PET may be a useful method of assessing distant metastases of head and neck cancer.	✓	
• Auto-fluorescence endoscopy may have better sensitivity and specificity than white-light endoscopy for detecting laryngeal cancer or dysplasia.	✓	

Key message	Effect on guidance	
	Potential change	No change
Treatment		
Radiotherapy		
• Altered fractionated radiotherapy may be associated with better patient outcomes than conventional radiotherapy.	✓	
• Swallowing outcomes do not appear to be reported consistently in clinical trials of intensity-modulated radiation therapy.		✓
Surgery		
• Current evidence seems insufficient to guide the choice of elective or therapeutic neck dissection for people with oral and pharyngeal cancers. However, elective neck dissection for node-negative disease may be associated with a lower risk of disease-specific death than therapeutic neck dissection.		✓
• Placing dental implants at the same time as radical surgery in head and neck cancer may be effective but current evidence is not consistent.		✓
• Open partial laryngectomy might be an effective, organ-sparing treatment alternative to total laryngectomy in people with early laryngeal carcinoma that recurs after radiotherapy.	✓	
Surgery versus radiotherapy		
• CO_2 endolaryngeal laser excision may be more cost effective than standard-fractionation radiotherapy for the treatment of early-stage glottic cancer.	✓	
• Current evidence suggests no difference between radiotherapy and transoral laser surgery for early glottic cancer.		✓
Mixed treatment comparisons		
• Altered fractionated radiotherapy with concurrent chemotherapy is possibly associated with better outcomes than other strategies for treating head and neck cancer.	✓	
Biological treatments		
• Cetuximab in combination with platinum-based chemotherapy seems to be associated with an increase in response over platinum-based chemotherapy plus placebo.		✓
• Hypomagnesaemia may be seen in around a third of people treated with cetuximab.		✓
Alternative therapies		
• Acupuncture does not appear to have any objective benefit for patients with radiation-induced xerostomia.		✓
Nutritional support		
• Evidence is insufficient to guide the choice of nasogastric feeding or percutaneous endoscopic gastrostomy for nutrition support in people with head and neck cancer undergoing radiotherapy or chemotherapy.		✓

Key message	Effect on guidance	
	Potential change	No change
Psychological therapies • Limited evidence exists for psychological interventions in people with head and neck cancer.		✓
Follow-up ***Dental care*** • Limited evidence exists for the use of hyperbaric oxygen for prevention or treatment of osteoradionecrosis of the jaw after tooth extraction in people who have undergone radiotherapy for head and neck cancer.	✓	
Early discharge • Early discharge from follow-up may not be advisable for people with laryngeal dysplasia.	✓	

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided.

1.1 Epidemiology

Lifestyle factors

The International Head and Neck Cancer Epidemiology (INHANCE) Consortium was established in 2004 to pool large molecular epidemiology case-control studies in head and neck cancer (Conway et al. 2009). This dataset contains data from 26 studies with over 26,000 cases and 34,000 controls from around the world. Analyses were undertaken on a range of lifestyle and genetic factors.

Chuang et al. (2012) reported on dietary factors associated with head and neck cancer in 14,520 cases and 22,737 controls. Higher overall vegetable intake was associated with lower rates of head and neck cancer (4th vs 1st quartile odds ratio [OR] = 0.66, 95% confidence intervals [CI] 0.49 to 0.90, p = 0.01). Higher overall fruit intake was also associated with lower rates of head and neck cancer (4th vs 1st quartile OR = 0.52, 95% CI 0.43 to 0.62, p < 0.01). Higher intake of processed meats was associated with higher incidence of head and neck cancer (4th vs 1st quartile OR = 1.37, 95% CI 1.14 to 1.65, p < 0.01), whereas higher intake of white meat (poultry, fish and shellfish) was associated with lower rates of head and neck cancer (4th vs 1st quartile OR = 0.68, 95% CI 0.55 to 0.84, p < 0.01).

The study adjusted for tobacco and alcohol use to minimise confounding factors, however the authors acknowledged that some confounding factors may remain. These factors included: geographical differences in diet that may have affected the results, total energy intake not being available for all participants, and difficulty standardising questionnaires across populations.

Nicolotti et al. (2011) investigated recreational physical activity in four studies of 2289 cases and 5580 controls. Results were adjusted for age, gender, study, ethnicity, education level, occupational physical activity, duration and number of cigarettes smoked and duration and amount of alcohol consumed. Moderate physical activity was associated with reduced rates of head and neck cancer compared with no or low levels of physical activity (OR = 0.78, 95% CI 0.66 to 0.91); however there was no association with high physical activity (OR = 0.72, 95% CI 0.46 to 1.16).

When stratified by type of cancer, both moderate and high physical activity were associated with lower oral cancer (moderate physical activity OR = 0.74, 95% CI 0.56 to 0.97, high physical activity OR = 0.53, 95% CI 0.32 to 0.88) and pharyngeal cancer rates (moderate physical activity OR = 0.67, 95% CI 0.53 to 0.85, high physical activity OR = 0.58, 95% CI 0.38 to 0.89). For laryngeal cancer however no definitive association between moderate physical activity and head and neck cancer was seen (OR = 0.81, 95% CI 0.60 to 1.11).

Limitations recognised by the authors included the fact that the studies involved different populations, with differing sources of controls and data collection. Questionnaires recording physical activity also differed, and information bias may have resulted because the original datasets were not designed to measure the effect of physical activity on cancer.

The results from these papers add to the growing number of publications from the INHANCE consortium (see supporting references). Collectively, associations with increased rates of head and neck cancer have been identified for: family history of head and neck cancer in first degree relatives, especially for people who use tobacco and alcohol (Negri et al. 2009); long duration of passive smoking, especially for pharyngeal and laryngeal cancers (Lee et al.

2008); increased use of alcohol and tobacco, especially used together, but with differences seen for gender, geography, and cancer subtype (Lubin et al. 2009, Hashibe et al. 2009, Purdue et al. 2009); lower body-mass index (Gaudet et al. 2010); and increased number of sexual partners (Heck et al. 2010).

Head and neck cancer was not associated with marijuana smoking (Berthiller et al. 2009) and tea intake (Galeone et al. 2010). Lower rates of head and neck cancer were associated with higher body mass index (Gaudet et al. 2010) and higher coffee intake (Galeone et al. 2010).

The results from the INHANCE studies are unlikely to affect updates to guidance, because this type of evidence does not directly guide clinical practice, but may be useful in preventive public health advice or may influence future research. SIGN 90 includes some population-level recommendations about smoking, alcohol, and dietary risk factors that broadly concur with the results seen in the INHANCE studies. NICE CSGHN did not cover risk factors.

Key references

Chuang SC, Jenab M, Heck JE, et al. (2012) Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. Cancer Causes & Control 23: 69–88
Abstract: www.springerlink.com/content/mt60823818833gx2/

Nicolotti N, Chuang SC, Cadoni G, et al. (2011) Recreational physical activity and risk of head and neck cancer: a pooled analysis within the international head and neck cancer epidemiology (INHANCE) consortium. European Journal of Epidemiology 26: 619–28
Abstract: www.springerlink.com/content/h842p5r14284j004/

Supporting references

Berthiller J, Lee YC, Boffetta P et al. (2009) Marijuana smoking and the risk of head and neck cancer: pooled analysis in the INHANCE consortium. Cancer Epidemiology, Biomarkers & Prevention 18: 1544–51
Full text: www.ncbi.nlm.nih.gov/pmc/articles/PMC3046921/pdf/nihms270553.pdf

Conway DI, Hashibe M, Boffetta P et al. (2009) Enhancing epidemiologic research on head and neck cancer: INHANCE – the international head and neck cancer epidemiology consortium. Oral Oncology 45: 743–6
Available from: www.sciencedirect.com/science/article/pii/S1368837509000463

Galeone C, Tavani A, Pelucchi C, et al. (2010) Coffee and tea intake and risk of head and neck cancer: pooled analysis in the international head and neck cancer epidemiology consortium. Cancer Epidemiology, Biomarkers & Prevention 19: 1723–36
Full text: www.ncbi.nlm.nih.gov/pmc/articles/PMC3047460/pdf/nihms206689.pdf

Gaudet MM, Olshan AF, Chuang SC et al. (2010) Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the international head and neck cancer epidemiology (INHANCE) consortium. International Journal of Epidemiology 39: 1091–102
Full text: www.ncbi.nlm.nih.gov/pmc/articles/PMC2929351/

Heck JE, Berthiller J, Vaccarella S, et al. (2010) Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the international head and neck cancer epidemiology (INHANCE) consortium. International Journal of Epidemiology 39: 166–81
Full text: www.ije.oxfordjournals.org/content/39/1/166.full

Hashibe M, Brennan P, Chuang SC et al. (2009) Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the INHANCE consortium. Cancer Epidemiology, Biomarkers & Prevention 18: 541–50.
Full text: www.ncbi.nlm.nih.gov/pmc/articles/PMC3051410/pdf/nihms270552.pdf

Lee YC, Boffetta P, Sturgis EM et al. (2008) Involuntary smoking and head and neck cancer risk: pooled analysis in the international head and neck cancer epidemiology consortium. Cancer Epidemiology, Biomarkers & Prevention 17: 1974–81
Full text: http://cebp.aacrjournals.org/content/17/8/1974.full

Lubin JH, Purdue M, Kelsey K et al. (2009) Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. American Journal of Epidemiology 170: 937–47
Abstract: www.aje.oxfordjournals.org/content/170/8/937.short

Negri E, Boffetta P, Berthiller J et al. (2009) Family history of cancer: pooled analysis in the International Head and Neck Cancer Epidemiology consortium. International Journal of Cancer 124: 394–401
Full text: www.onlinelibrary.wiley.com/doi/10.1002/ijc.23848/full

Purdue MP, Hashibe M, Berthiller J et al. (2009) Type of alcoholic beverage and risk of head and neck cancer – a pooled analysis within the INHANCE consortium. American Journal of Epidemiology 169: 132–42
Full text: www.aje.oxfordjournals.org/content/169/2/132.full

Risk factors

MUC1 and MUC2 expression

In a systematic review without meta-analysis, **Sipaul et al (2011)** assessed published research evidence regarding the existence and potential roles of mucins in normal larynx and in laryngeal squamous cell carcinoma. MUC1 expression was measured in five studies in a total of 161 carcinoma and 70 normal cell samples, but results were not consistent, ranging from no increased expression in carcinoma cells to substantial expression in carcinoma cells compared with normal cells (no data given). MUC2 was studied in only two of the five studies, which again showed conflicting results. The results of this study alone are not likely to affect a future update to guidance, but further research in this area may be useful. NICE CSGHN and SIGN 90 did not cover this topic.

Key reference

Sipaul F, Birchall M, Corfield A (2011). What role do mucins have in the development of laryngeal squamous cell carcinoma? A systematic review. European Archives of Oto-rhino-laryngology 268: 1109–17
Abstract: www.springerlink.com/content/vm39u182v95x705r/

Human papillomavirus detection in oral cancers

Syrjänen et al. (2011) undertook a systematic review of human papillomavirus (HPV) detection in oral cancers (squamous cell carcinoma) and oral precancerous disorders (that is, oral lichen planus, leukoplakia, erythroplakia, and oral proliferative verrucous leukoplakia [OPVL]). The authors included 39 case-control studies, none of which were defined as having a 'low risk of bias' in their critical appraisal. Overall, 1885 cases of oral cancer with 2248 controls and 956 cases of oral precancerous disorders with 675 controls were included. No randomised controlled trials (RCTs) or cohort studies were identified.

For oral cancer, the pooled OR across studies was 3.98 (95% CI 2.62 to 6.02) and for oral precancerous disorders the pooled OR was 3.87 (95% CI 2.87 to 5.21). However, when individual precancerous disorders were analysed separately, the confidence intervals of the OR for OPVL and carcinoma in situ crossed 1, indicating non-significant results for these indications. These indications had the lowest number of trials included in the review (one and two trials respectively) in very few patients (20 and 31 people respectively), thus not enough data exist to draw any conclusion about HPV in OPVL or carcinoma in situ. For HPV16, the pooled OR for oral cancer was 3.86 (95% CI 2.16 to 6.87), but no pooled OR was reported for oral precancerous disorders.

The authors noted that the data for an association between HPV and oropharyngeal cancer are increasingly compelling, but that evidence for such an association in oral cancer is conflicting. A possible reason for the lack of evidence in this area may be the difficulty in delineating the precise difference between oral tissue and pharyngeal tissue. In this systematic review, the authors stated that they excluded any studies that included patients with cancers other than of the mouth. However, this method relies on accurate reporting of

site of origin of tumours in the included studies. Further research may help to determine the role of HPV testing in oral cancer or oral precancerous disorders.

NICE CSGHN did not cover HPV other than stating that it is 'implicated in the development of some cancers of the oral cavity, pharynx and larynx'. SIGN 90 discussed possible subtyping of HPV in people with head and neck cancer, but recognised that this is 'outwith the remit of most pathology departments at present'. However, in the time since publication of this guidance in 2006, the availability of HPV subtyping has increased, and is now recommended as standard by The Royal College of Pathologists for oropharyngeal tumours (Helliwell and Woolgar 2011). The data reported by Syrjänen et al. (2011) are unlikely to have an effect on future guidance because the results do not have direct clinical implications for the diagnosis or treatment of oral cancers. Additionally, the results might not be directly relevant to the UK population because studies have shown geographical differences in the prevalence of HPV in people with oropharyngeal cancer. For example, a lower prevalence of HPV has been seen in European populations than in US populations (D'Souza et al. 2007, Ribeiro et al. 2011).

Key reference

Syrjänen S, Lodi G, von Bültzingslöwen I et al. (2011) Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. Oral Diseases 17: 58–72
Abstract: http://onlinelibrary.wiley.com/doi/10.1111/j.1601-0825.2011.01792.x/abstract

Supporting references

D'Souza G, Kreimer AR, Viscidi R et al. (2007) Case-control study of human papillomavirus and oropharyngeal cancer. New England Journal of Medicine 356: 1944–56
Full text: www.nejm.org/doi/full/10.1056/NEJMoa065497

Helliwell T Woolgar J (2011) Standards and datasets for reporting cancers: dataset for histopathology reporting of mucosal malignancies of the pharynx. The Royal College of Pathologists: 1–35
www.rcpath.org/publications-media/publications/datasets/mucosal-malignancies-of-the-pharynx.htm

Ribeiro KB, Levi JE, Pawlita M et al. (2011) Low human papillomavirus prevalence in head and neck cancer: results from two large case-control studies in high-incidence regions. International Journal of Epidemiology 40: 489–502
Abstract: www.ije.oxfordjournals.org/content/40/2/489.abstract

Epstein–Barr virus detection in nasopharyngeal cancer

Liu et al. (2011) conducted a meta-analysis of prospective and retrospective patient series and case-control studies that measured the accuracy of detecting Epstein–Barr virus DNA as a marker for nasopharyngeal cancer. Overall, 15 studies in 2393 people were included, with 1140 cases and 1253 controls. Sensitivity was defined as the proportion of patients who tested positive for Epstein–Barr virus DNA and had biopsy-confirmed nasopharyngeal cancer. Specificity was defined as the proportion of patients who tested negative for Epstein–Barr virus DNA and whose biopsy results showed no nasopharyngeal cancer.

The pooled sensitivity was 89.1% (95% CI 87.0% to 90.9%), and pooled specificity was 85.0% (95% CI 83.0% to 86.9%). The positive likelihood ratio was 7.12 (95% CI 3.85 to 13.17) and the negative likelihood ratio was 0.12 (95% CI 0.08 to 0.20). One cause of heterogeneity across studies was use of serum or plasma for testing. For plasma testing, the sensitivity was 91.4% (95% CI 89.0% to 93.4%), specificity was 93.2% (95% CI 91.2% to 95.0%), positive likelihood ratio was 11.00 (95% CI 5.00 to 24.19), and negative likelihood ratio was 0.09 (95% CI 0.05 to 0.16). For serum testing the sensitivity was 84.4% (95% CI 79.9% to 88.3%), specificity was 76.0% (95% CI 72.1% to 79.6%), positive likelihood ratio was 4.30 (95% CI 2.31 to 8.03), and negative likelihood ratio was 0.19 (95% CI 0.09 to 0.39).

The authors concluded that plasma samples appear to have higher sensitivity and specificity for nasopharyngeal cancer than serum samples, although the significance of the difference between the serum and plasma results was not reported. They acknowledged that limitations of their meta-analysis included the small number of included studies, and that the individual

studies had quality issues such as lack of blinding, case-control design, and lack of random or consecutive patient sampling methodology.

Most of the studies were conducted in Asian populations known to have a much higher incidence of nasopharyngeal cancer than is seen in the UK, so the results may not be generalisable to the UK. This evidence alone is unlikely to affect a future update to guidance; neither NICE CSGHN nor SIGN 90 mentions Epstein–Barr virus.

Key reference

Liu Y, Fang Z, Liu L et al. (2011) Detection of Epstein-Barr virus DNA in serum or plasma for nasopharyngeal cancer: a meta-analysis. Genetic Testing and Molecular Biomarkers 15: 495–502 Abstract:http://online.liebertpub.com/doi/abs/10.1089/gtmb.2011.0012

1.2 Diagnosis

Early detection

Population screening for oral cancer

In a Cochrane review, **Brocklehurst et al. (2010)** assessed the evidence from randomised studies of screening for oral cancer. Only one cluster randomised study conducted in India was eligible for inclusion (n = 191,873). No significant difference in oral cancer mortality rate was seen between the screened (16.4 per 100,000 person-years) and control groups (20.7 per 100,000 person-years). However, a significantly higher 5-year survival rate was reported in the intervention group (50%) than in the control group (34%) (p = 0.009).

The authors recognised that the observed increase in survival may have been caused by lead-time bias, that is increasing the time a condition is known about, but not increasing the actual time a person lives with a condition. Other limitations of the study included lack of blinding, little information given on methods of randomisation, and treatment after follow-up was unclear and may not have been standardised.

The authors concluded that current evidence is insufficient and that further studies are needed. Oral cancer is more common in India than in the UK, so the results of this study alone are unlikely to have direct application to UK clinical practice and are not likely to affect a future update to guidance. Screening is not covered by NICE CSGHN or SIGN 90.

Key reference

Brocklehurst P, Kujan O, Glenny AM et al. (2010) Screening programmes for the early detection and prevention of oral cancer. Cochrane Database of Systematic Reviews: CD004150
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD004150.pub3/full

Fine-needle aspiration cytology of salivary glands

Colella et al. (2010) systematically reviewed studies of histological diagnosis in salivary gland tumours that reported the correlation between fine-needle aspiration cytology and histological results. The report included 16 studies with 2018 participants. The primary outcome was concordance between the results of fine-needle cytology and histology in lumps that were confirmed to be malignant.

Overall, 93.25% of cases identified as malignant on fine-needle aspiration were confirmed as such histologically, and 95.46% of cases identified as benign on fine-needle aspiration were confirmed as such histologically.

SIGN 90 specifically excluded salivary tumours. However, NICE CSGHN states that people with suspected salivary gland tumours should be referred to a specialist lump clinic for investigation, with initial flexible endoscopy then fine-needle aspiration cytology to determine the nature of the lump. The results from Colella et al. (2010) support this strategy.

Key reference

Colella G, Cannavale R, Flamminio F et al. (2010) Fine-needle aspiration cytology of salivary gland lesions: a systematic review. Journal of Oral and Maxillofacial Surgery 68: 2146–53
Abstract: www.sciencedirect.com/science/article/pii/S0278239109017686

Factors indicating prognosis

Presence of facial palsy

Higgins and Moody Antonio (2010) undertook a comparative survival analysis of 21 case-series studies in 348 patients with squamous cell carcinomas of the temporal bone or auditory canal. Survival in the presence or absence of facial palsy was compared with three staging systems (Stell, original Pittsburgh [1990], and modified Pittsburgh [2000]).

The presence of facial palsy irrespective of the stage of cancer was associated with a significantly lower 5-year overall survival than no facial palsy (19% vs 59% respectively, p = 0.006). The Pittsburgh 2000 staging system showed a significant difference in 5-year overall survival between T3 and T4 (58% vs 23% respectively, p = 0.017), but no significant difference in 5-year overall survival was seen either between T3 and T4 in Pittsburgh 1990 staging (28% vs 44% respectively, p = 0.862), or between T2 and T3 in Stell staging (47% vs 45% respectively, p = 0.259). The authors suggested that these results may be due to better differentiation between T3 and T4 disease in the Pittsburgh 2000 system than in the others. In Cox regression survival analyses people with facial palsy and cancer of any stage had survival similar to that of people with Pittsburgh 2000 T4 disease (p = 0.897).

The authors noted that their review was limited by the inclusion of only case-series, but that systematic reviews of case-series have been advocated for rare conditions in which conducting higher quality studies is not practical or possible.

Neither NICE CSGHN or SIGN 90 have specific recommendations for temporal bone or auditory canal tumours, and this evidence may be a consideration in a future update to guidance.

Key reference

Higgins TS, Moody Antonio SA (2010) The role of facial palsy in staging squamous cell carcinoma of the temporal bone and external auditory canal: a comparative survival analysis. Otology & Neurotology 31: 1473–9
Abstract: http://journals.lww.com/otology-neurotology/Abstract/2010/12000/The_Role_of_Facial_Palsy_in_Staging_Squamous_Cell.22.aspx

Expression of carbonic anhydrase-9

Peridis et al. (2011) conducted a meta-analysis of 16 papers (1 RCT, 1 prospective, and 14 retrospective studies, n = 1470) that reported carbonic anhydrase-9 (CA-9) expression in squamous cell carcinomas of the head and neck or nasopharyngeal cancers. A significant proportion of head and neck tumours expressed CA-9 (OR = 0.40, 95% CI 0.16 to 0.96, p = 0.04). However, no significant differences were seen in levels of CA-9 expression assessed as high or low by the authors.

Overall survival was significantly higher in people who were CA-9 negative (OR = 1.93, 95% CI 1.41 to 2.64, p < 0.0001), as was disease-free survival (OR = 1.77, 95% CI 1.27 to 2.48, p = 0.0008). Disease-free survival was also significantly higher in people who expressed low levels of CA-9, compared with those expressing high levels (OR = 1.84, 95% CI 1.17 to 2.90, p = 0.009).

The authors noted that their meta-analysis was limited because 14 of the 16 included studies were retrospective, but that use of meta-analysis on these data allowed a larger sample size than could reasonably be achieved in an RCT in head and neck cancer. Furthermore, variability in how CA-9 was designated as high or low expression in different studies may

have affected the results. Finally, the meta-analysis included a wide range of tumours, and CA-9 expression may have a stronger association with some tumour types than others.

This evidence is not likely to affect guidance in the near future because it is early research with no direct clinical application. Further research is needed to assess the association in specific tumour sites and to determine whether CA-9 expression has any use in predicting response to treatment. This topic was not covered by NICE CSGHN or SIGN 90.

Key reference

Peridis S, Pilgrim G, Athanasopoulos I et al. (2011) Carbonic anhydrase-9 expression in head and neck cancer: a meta-analysis. European Archives of Otorhinolaryngology 268: 661–70
Abstract: www.springerlink.com/content/j16p0m75n04u3j57/

^{18}F-fluorodeoxyglucose uptake in tumours

In a meta-analysis, **Zhang et al. (2010)** included eight studies with a total of 495 people with head and neck cancer who had undergone ^{18}F-fluorodeoxyglucose (^{18}FDG) positron emission tomography (^{18}FDG-PET) to assess whether the uptake of ^{18}FDG in tumours correlated with outcome. Increased uptake of ^{18}FDG was associated with lower rates of local control (relative risk [RR] = 0.71, 95% CI 0.63 to 0.81, $p < 0.00001$), disease-free survival (RR) = 0.63, 95% CI 0.54 to 0.73, $p < 0.00001$), and overall survival (RR = 0.57, 95% CI 0.44 to 0.74, $p < 0.0001$).

The authors noted that many factors could affect the rate of uptake including patient factors such as total or lean body weight. Additionally, differences in measurements between centres (for example, using mean or maximum values), or in tumour site (some patients had lymph node measurements rather than primary tumour) would affect the results. As is common with many studies in head and neck cancer, prospective data were lacking.

NICE CSGHN and SIGN 90 have no recommendations on use of PET as an indicator of prognosis. At present there is no evidence for changing treatment strategies for patients whose ^{18}FDG uptake status is known, and no standardised method of measuring uptake is available, therefore this evidence is not likely to affect an update to guidance.

Key reference

Zhang B, Li X, Lu X (2010) Standardized uptake value is of prognostic value for outcome in head and neck squamous cell carcinoma. Acta Oto-Laryngologica 130: 756–62
Abstract: www.informahealthcare.com/doi/abs/10.3109/00016480903402981

Imaging

^{18}F-fluorodeoxyglucose positron emission tomography

In a meta-analysis (**Xu et al. 2011**) of ^{18}FDG-PET for detection of distant metastases and second primary cancers, 12 articles including 1276 patients were evaluated. Histopathological analysis or clinical and imaging follow up, or both, were used as the reference standard. The pooled sensitivity of ^{18}FDG-PET was 0.89 (95% CI 0.83 to 0.93), the specificity was 0.95 (95% CI 0.94 to 0.96), and the diagnostic OR was 120.29 (95% CI 59.19 to 244.49).

The authors stated that chest CT is the most common imaging modality for detecting metastasis from head and neck cancer, but has a sensitivity of 73% and specificity of 80%. They recognised that most metastases from head and neck cancer were found in the lung, except for nasopharyngeal cancer, which most commonly metastasises to skeletal sites. Guidance about indications for the use of PET was developed for the Intercollegiate Standing Committee on Nuclear Medicine (Barrington and Scarsbrook 2012). It recommended PET for staging or restaging in people with a high risk of disseminated disease, because of either advanced locoregional disease or with primary sites with a high propensity for disseminated disease, such as nasopharyngeal cancer.

NICE CSGHN recommended PET only for distinguishing between benign and malignant lung nodules, but noted that the use of PET was expected to increase in the decade after publication of the guidance. SIGN 90 includes recommendations on using PET if diagnosis is difficult, but not as first-line imaging. This evidence might be considered in a future update to guidance, especially for imaging in people with nasopharyngeal cancer.

Key reference

Xu G-Z, Guan D-J, He Z-Y (2011) ^{18}FDG-PET/CT for detecting distant metastases and second primary cancers in patients with head and neck cancer. A meta-analysis. Oral Oncology 47: 560–5
Abstract: www.sciencedirect.com/science/article/pii/S1368837511001618

Supporting reference

Barrington S, Scarsbrook A (2012) Evidence-based indications for the use of PET-CT in the United Kingdom 2012. Royal College of Physicians and The Royal College of Radiologists.
Full text: http://www.rcr.ac.uk/docs/radiology/pdf/BFCR(12)3_PETCT.pdf

Endoscopy

A meta-analysis of 16 articles including 1000 laryngeal lesions by **Kraft et al. (2011)** evaluated the value of fluorescence endoscopy for early diagnosis of laryngeal cancer or dysplastic lesions. The three main methods assessed were auto-fluorescence endoscopy (AFE), induced-fluorescence endoscopy (IFE), and white light endoscopy (WLE).

AFE had higher sensitivity (91% vs 73%, $p < 0.0001$) and specificity (84% vs 79%, $p = 0.039$) than WLE. IFE had higher sensitivity (95% vs 73%, $p < 0.0001$) but lower specificity (62% vs 79%, $p < 0.0001$) than WLE. AFE had no significant difference in sensitivity (91% vs 95%, $p = 0.093$) but higher specificity (84% vs 62%, $p < 0.0001$) compared with IFE.

The evidence suggests that AFE and IFE may have a role in delineating laryngeal lesions from normal tissue, however these modalities cannot distinguish between grades of dysplasia or differentiate between carcinoma in situ or invasive tumour. NICE CSGHN recognises that endoscopy is essential for inspecting inaccessible areas in initial investigations, but does not mention fluorescence. SIGN 90 suggests that AFE is complementary to, not a replacement for WLE (or microlaryngoscopy). This evidence may have potential to affect future updates to guidance in head and neck cancer.

Key reference

Kraft M, Betz CS, Leunig A et al. (2011) Value of fluorescence endoscopy for the early diagnosis of laryngeal cancer and its precursor lesions. Head & Neck 33: 941–8
Abstract: http://onlinelibrary.wiley.com/doi/10.1002/hed.21565/abstract

1.3 Treatment

Radiotherapy

Radiation dosing regimens

Baujat et al. (2010) updated a Cochrane review of overall survival with radiotherapy in head and neck cancer. This review, conducted by the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) collaborative group, included individual data from 6515 patients who participated in 15 trials of conventional radiotherapy versus accelerated radiotherapy or hyperfractionated radiotherapy. Most tumours were of the oropharynx (44%) or larynx (34%). Follow-up ranged from 4 years to 10 years (median 6 years).

Overall, altered fractionated radiotherapy was significantly better than conventional therapy, with an absolute benefit of 3.4% at 5 years (hazard ratio [HR] = 0.92, 95% CI 0.86 to 0.97, $p = 0.003$). Hyperfractionated radiotherapy was associated with the greatest absolute benefit of 8%, compared with accelerated fractionation at 2% without total dose reduction and 1.7% with total dose reduction at 5 years ($p = 0.02$). A significant association with age of patients

was also seen, with those under 50 years gaining the greatest survival benefit (HR = 0.78, 95% CI 0.64 to 0.94, p = 0.007); no other age group showed significant survival benefit.

The trials included in this Cochrane review completed recruitment from 1969 to 1998. To address the age of the trials, the authors explained that meta-analysis of individual patient data was a time-consuming process, and that a new meta-analysis (MARCH 2) of more recent trials is underway.

Use of hyperfractionated and accelerated radiotherapy was mentioned in NICE CSGHN. However, the evidence at that time was limited, thus no specific recommendations were made, and the potential benefit was contrasted with reports of severe acute adverse effects. SIGN 90 recommends accelerated or hyperfractionated radiotherapy for some patients with head and neck cancer who cannot have concurrent chemotherapy or cetuximab. Future guidance could consider the evidence for altered-dose radiotherapy in all patients with head and neck cancer.

Glenny et al. (2010) reported a Cochrane review of 30 trials of radiotherapy in 6535 people with cancer of the oral cavity or oropharynx. Overall, altered fractionation radiotherapy was associated with a reduction in total mortality at 5 years (HR = 0.86, 95% CI 0.76 to 0.98) compared with conventional radiotherapy. Locoregional control was also better with altered fractionation radiotherapy (HR = 0.79, 95% CI 0.70 to 0.89), but no significant difference was seen in disease-free survival.

The authors noted that reporting of adverse events in trials of different radiotherapy regimens needs to be more accurate to allow full evaluation of their clinical performance. This study adds to the evidence for benefit of altered fractionation radiotherapy, and may be considered in an update to guidance. Radiation dosing regimens were covered in both NICE CSGHN and SIGN 90.

Key references

Baujat B, Bourhis J, Blanchard P et al. (2010) Hyperfractionated or accelerated radiotherapy for head and neck cancer. Cochrane Database of Systematic Reviews: CD002062
Full text: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002026.pub2/full

Glenny AM, Furness S, Worthington HV et al. (2010) Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. Cochrane Database of Systematic Reviews: CD006387
Full text: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006387.pub2/full

Swallowing outcomes after radiotherapy

In a systematic review without meta-analysis, **Roe et al. (2010)** included 16 papers (with 1012 participants) relating to swallowing outcomes after intensity-modulated radiation therapy for head and neck cancer. Only one prospective study consistently reported outcomes measured with instruments as well as patient-reported outcomes and toxicity scores. Five further studies used various measures that could be attributed to all three domains of the WHO International Classification of Functioning, Disability and Health Categories, which the authors suggested would give a multidimensional assessment of swallowing.

This review also assessed the evidence for identification of dysphagia and aspiration-related structures. Several studies attempted to reduce the radiation dose delivered to anatomical sites that may have increased risk of dysphagia or aspiration as adverse events of radiation treatment. However, studies differed in the anatomical structures assessed, thus no conclusions were reached in this subject.

The lack of useful data on this clinically important outcome suggests that more research or increased reporting of dysphagia as an adverse event in radiotherapy studies would be useful. A review of guidance is unlikely to be affected by the currently available evidence in this area. NICE CSGHN and SIGN 90 do not cover dysphagia as a consequence of intensity-modulated radiotherapy.

Key reference

Roe JWG, Carding PN, Dwivedi RC et al. (2010) Swallowing outcomes following intensity-modulated radiation therapy (IMRT) for head & neck cancer – a systematic review. Oral Oncology 46: 727–33 Abstract: www.sciencedirect.com/science/article/pii/S1368837510002289

Surgery

Elective versus therapeutic neck dissection

Tandon et al. (2011) conducted a systematic review of 23 studies of head and neck cancer (1611 patients) to determine whether elective treatment for the node-negative neck is necessary and whether selective neck dissection is necessary in people with clinically node-positive disease.

The main results of the analysis were given as the number needed to treat, which was defined as the number of times a specified lymph node level would need to be treated, by surgery or radiotherapy, to cure one positive lymph node. However, these results were presented separately by positive or negative node status, node level and tumour type (around 50 number needed to treat values).

The authors proposed a system to use the number needed to treat in clinical decision-making, suggesting that if the risk of occult metastasis was 20% or more (a number needed to treat of 5), then the patient should have treatment of the neck.

Limitations identified by the authors included the wide timescale of included studies, some of which dated back to 1965, when treatment and imaging standards differed from current practice. Furthermore, the stage of the primary tumour was not taken into account. Therefore, this evidence is unlikely to affect an update guidance. This topic was not covered by NICE CSGHN; however SIGN 90 includes advice to offer prophylactic treatment for patients with node-negative neck if the chance of occult nodal metastases is 20% or more.

In a Cochrane review, **Bessel et al. (2011)** assessed any correlation between surgical treatments for oral and pharyngeal cancers and increased overall survival, disease-free survival, and locoregional control, and reduced recurrence. A total of seven trials were included in the review, with 570 people included in the outcome evaluations.

Limited evidence from four trials suggested that elective neck resection reduces locoregional recurrence rates compared with therapeutic delayed neck dissection, but the data were not suitable for meta-analysis due to the differences between studies in the type of surgery and the duration of follow-up.

Data from two trials (n = 252) suggested no difference in overall survival between elective radical neck dissection and selective neck dissection. One of these trials reported disease-free survival and recurrence, both of which showed no difference in the two treatments.

One study compared radiotherapy plus surgery with radiotherapy alone. This trial was stopped early because of high death rates in the radiotherapy only group. Only 35 patients were available for analysis, and more than half of the participants did not receive their planned radiotherapy due to machine malfunction. Given the limited nature of this evidence it is unlikely to affect an update to guidance.

Fasunla et al. (2011) conducted a meta-analysis to assess outcomes of elective or therapeutic neck dissection in people with oral cavity cancers and node-negative neck. Four trials of 283 patients were included, with recruitment periods from 1966 to 2004. The results showed elective surgery to be associated with a lower risk of disease-specific death (fixed-effects RR = 0.57, 95% CI 0.36 to 0.89, p = 0.014).

However, three of the trials included were around 20 or more years old, and contributed most to the measured benefit. The most recent trial found no benefit of elective surgery (RR = 0.97, 95% CI 0.26 to 3.59).

A randomised trial of elective neck dissection (SEND trial, NCT00571883) is underway in the UK and should provide additional evidence to guide the choice of treatment. The available evidence is not likely to change current practice.

Key references

Bessell A, Glenny AM, Furness S et al. (2011). Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database of Systematic Reviews: CD006205
Full text: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006205.pub3/abstract

Fasunla AJ, Greene BH, Timmesfeld N et al. (2011) A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. Oral Oncology 47: 320–4
Abstract: www.sciencedirect.com/science/article/pii/S1368837511001059

Tandon S, Munir N, Roland NJ et al. (2011) A systematic review and number needed to treat analysis to guide the management of the neck in patients with squamous cell carcinoma of the head and neck. Auris Nasus Larynx 38: 702–9
Abstract: www.sciencedirect.com/science/article/pii/S0385814611000216

Supporting reference

SEND Trial. The role of selective neck dissection used electively in patients with early oral squamous cell carcinoma (1–3 cm primary size) and no clinical evidence of lymph node metastases in the neck. Available from: http://www.ukctg.nihr.ac.uk/trialdetails/NCT00571883?view=healthprofessional

Timing of dental implant surgery

Barber et al. (2010) conducted a systematic review to evaluate the placement of primary osseointegrated dental implants at the same time as radical surgery for head and neck cancer. The authors included 41 papers: 3 were case reports, 13 were reviews, and 25 were clinical studies. No pooling or meta-analysis was attempted. The authors gave a simple description of the ranges of results seen in clinical studies, but drew no firm conclusions for any type of study. This may be due to the apparent lack of consistency between studies.

Data were incomplete regarding the number of implants, implants used for reasons other than restoration, failure of implants, and survival of implants. From studies reporting on survival of implants, 96–100% were reported as surviving with a follow-up range of 15–96 months.

NICE CSGHN and SIGN 90 make no specific recommendations about the timing of placing dental implants, so this evidence is unlikely to affect a future update to guidance.

Key reference

Barber AJ, Butterworth CJ, Rogers SN (2011) Systematic review of primary osseointegrated dental implants in head and neck oncology. British Journal of Oral and Maxillofacial Surgery 49: 29–36
Abstract: www.sciencedirect.com/science/article/pii/S026643560900669X

Open partial laryngectomy

Paleri et al. (2011) conducted a systematic review and meta-analysis of open partial laryngectomy for the treatment of early laryngeal carcinoma that had recurred after initial radiotherapy. The review included only studies that reported local control with at least 24 months of follow-up and from centres reporting at least ten procedures. A total of 26 articles covering 560 patients were included.

The pooled local control at 24 months for all 560 patients was 86.9% (95% CI 84% to 89.5%). Overall survival was reported for 360 people as 83.1% (95% CI 79.1% to 86.7%). Excluding studies on supraglottic tumours (which have high rates of salvage total laryngectomy), the pooled mean rate of salvage surgery for residual tumour or non-functioning larynx was 9.2% (95% CI 7.4% to 11.1%; n = 253).

These results suggest that open partial laryngectomy is clinically effective, which could change clinical practice in the UK from total laryngectomy to this organ-sparing procedure, and thus could be a consideration in future updates to guidance. SIGN 90 recommends

partial laryngectomy rather than total laryngectomy, which is supported by this evidence; NICE CSGHN did not address this topic.

Key reference

Paleri V, Thomas L, Basaviah N, et al. (2011). Oncologic outcomes of open conservation laryngectomy for radiorecurrent laryngeal carcinoma. A systematic review and meta-analysis of English-language literature. Cancer 117: 2668–76
Abstract: http://onlinelibrary.wiley.com/doi/10.1002/cncr.25831/abstract

Surgery versus radiotherapy

Higgins (2011) conducted a cost-utility analysis to compare CO_2 endolaryngeal laser excision with standard-fractionated radiation therapy in early-stage glottic cancer. The cost-analysis was from a Canadian Ministry of Health perspective, and included hospital delivery costs and outpatient community nursing costs. CO_2 endolaryngeal laser excision dominated (that is, was cheaper and more effective than) standard-fractionated radiation therapy, mainly because of lower costs of salvage treatment after laser excision. The cost of CO_2 endolaryngeal laser excision was CAN$ 2476 per case, with a gain of 1.663 quality-adjusted life years (QALYs), and the cost of standard-fractionated radiation therapy was CAN$ 4966 per case, with a gain of 1.506 QALYs.

Although differences between the healthcare systems in Canada and in the UK preclude direct application of these findings to the UK, this information may be useful in guiding treatment choice. In NICE CSGHN, a systematic review of RCTs comparing radiotherapy with surgery in early glottic cancer was identified, but overall, reliable evidence for choosing between these treatments was lacking. SIGN 90 recommends either of these treatments for early glottic cancer. This evidence may be a consideration in a future update to guidance.

Spielmann et al. (2010) conducted a systematic review without meta-analysis of radiotherapy or transoral laser microsurgery for the treatment of early (T1 or T2) glottic cancer. Overall, 21 studies of 880 patients were included, but none were RCTs.

Of the 15 studies reporting vocal outcomes, 11 showed no significant difference between radiotherapy and transoral laser surgery; four reported better vocal outcomes for radiotherapy. However, the small number of participants and associated underpowering of studies, as well as methodological heterogeneity, meant that the authors were unable to rule out the possibility that a difference exists.

Nine of the studies reported quality of life outcomes, which showed no significant differences between radiotherapy and transoral laser surgery. However, instruments used for measuring global and head and neck cancer-specific outcomes were not consistent between studies.

The authors also noted that no study clearly described how the primary histopathological diagnosis was obtained, which could affect the accuracy of the reported staging. They concluded that the evidence does not show a difference between radiotherapy and transoral laser surgery in early glottic cancer, but that carefully designed RCTs with clearly defined outcome variables are needed.

This evidence is unlikely to affect future updates to guidance. NICE CSGHN referred to a review of surgery versus radiotherapy for early glottic cancer including only one study that showed little difference between treatments and made no recommendations about treatment choice. Similarly, SIGN 90 recommends either radiotherapy or surgery for early glottic cancer.

Key references

Higgins KM (2011) What treatment for early-stage glottic carcinoma among adult patients: CO_2 endolaryngeal laser excision versus standard fractionated external beam radiation is superior in terms of cost utility? The Laryngoscope 121: 116–34
Abstract http://onlinelibrary.wiley.com/doi/10.1002/lary.21226/abstract

Spielmann PM, Majumdar S, Morton RP (2010) Quality of life and functional outcomes in the management of early glottic carcinoma: a systematic review of studies comparing radiotherapy and transoral laser microsurgery. Clinical Otolaryngology 35: 373–82
Abstract: http://onlinelibrary.wiley.com/doi/10.1111/j.1749-4486.2010.02191.x/abstract

Mixed treatment comparisons

Results from a meta-analysis of individual patient data were reported by **Blanchard et al. (2011a)**. In this review (Meta-Analysis of Chemotherapy in Head and Neck Cancer, MACH-NC), 87 studies in 16,485 patients with squamous cell carcinoma of the head and neck were included. Because of the design of some trials with three-arm or two-by-two design, some trial arms were included twice, giving a total of 105 comparisons in 17,493 patients. Median follow-up was for 5.6 years and the primary outcome was overall survival.

Overall, locoregional treatment plus chemotherapy was better than locoregional treatment alone (HR for death at 5 years = 0.87, 95% CI 0.84 to 0.91, $p < 0.0001$). When data were stratified by tumour type and timing of chemotherapy, chemotherapy concomitant with locoregional treatment significantly improved 5-year survival with tumours of the oropharynx (HR = 0.78, 95% CI 0.72 to 0.85, $p < 0.0001$) and larynx (HR = 0.80, 95% CI 0.71 to 0.90, $p = 0.05$); there was no significant improvement in survival with adjuvant and neoadjuvant therapy, and no impact of chemotherapy timing for tumours of the oral cavity or hypopharynx.

This analysis included studies with enrolment completed between 1965 and 2000. It therefore does not include analysis of the neoadjuvant chemotherapy regimen of a taxane, cisplatin and 5-fluorouracil, which is currently used in clinical practice.

Blanchard et al (2011b) conducted a mixed treatment comparison network meta-analysis of individual patient data from both MACH-NC and MARCH (Baujat et al. 2010, discussed above in 'Radiotherapy'). A network meta-analysis combines direct comparisons between two treatments with indirect comparisons (two treatments are compared based on their relative efficacy against a common comparator) to identify the best of several treatments. In total, 102 trials in around 23,000 people with non-metastatic squamous cell carcinomas of the head and neck were included. All trials completed recruitment between 1965 and 2000 and the primary outcome of the meta-analysis was overall survival.

Six general treatment strategies were analysed: locoregional treatment alone (surgery or radiotherapy or both); locoregional treatment plus concomitant chemotherapy; induction chemotherapy then locoregional treatment; locoregional treatment then adjuvant chemotherapy; altered fractionated radiotherapy; and altered fractionated radiotherapy with concomitant chemotherapy. Overall survival with each treatment strategy was analysed using a fixed-effects model and four different random effects models.

Compared with locoregional therapy alone, the risk of death at 5 years was reduced by 30% (95% CI 0.61 to 0.80; fixed-effects model) for altered fractionated radiotherapy with concomitant chemotherapy. Altered fractionated radiotherapy with concomitant chemotherapy was most likely to be the best of the six treatment options (probability of 98% with the fixed-effects model and 84–94% with the random effects models).

This meta-analysis did not include any trials of taxane-based chemotherapy regimens because individual patient data were not available for these studies. NICE CSGHN discussed the use of chemotherapy in head and neck cancer but did not make specific recommendations about timing or regimens of chemotherapy. In SIGN 90, recommendations were made by anatomical location of cancer, several of which recommended surgery then either chemotherapy or chemoradiotherapy. The evidence from both Blanchard et al. (2011) studies could be a consideration in a future update to guidance.

Key references

Blanchard P, Baujat B, Holostenco V et al. (2011a) Meta-analysis of chemotherapy in head and neck

cancer (MACH-NC): a comprehensive analysis by tumour site. Radiotherapy and Oncology 100: 33–40
Abstract: www.sciencedirect.com/science/article/pii/S0167814011002295

Blanchard P, Hill C, Guihenneuc-Jouyaux C et al. (2011b) Mixed treatment comparison meta-analysis of altered fractionated radiotherapy and chemotherapy in head and neck cancer. Journal of Clinical Epidemiology 64: 985–92
Abstract: www.sciencedirect.com/science/article/pii/S0895435610004269

Biological treatments

Cao et al. (2010) undertook a meta-analysis of incidence and risk of hypomagnesaemia in patients with advanced cancer treated with cetuximab. A total of 19 studies were included, with 4559 patients, 3081 of whom were treated with cetuximab. The studies included a range of cancers; 629 participants had head and neck cancer.

The pooled analysis looked at incidence of all hypomagnesaemia (< 0.3 mmol/l to 0.5 mmol/l) and grade 3 and 4 hypomagnesaemia (< 0.3 mmol/l to 0.4 mmol/l). The pooled incidence of all hypomagnesaemia was 36.7% (95% CI 22.0 to 54.4) and of grade 3 and 4 hypomagnesaemia was 5.6% (95% CI 3.0 to 10.2).

The authors recognised limitations of their meta-analysis that included the differences between studies in patient populations, concurrent chemotherapy regimens, duration of follow-up, and length of treatment. Additionally, not all trials reported incidence of hypomagnesaemia.

Hypomagnesaemia is a recognised side-effect of treatment with cetuximab and is detailed in the summary of product characteristics for cetuximab, so this study is not likely to affect future updates to guidance.

In a systematic review, **Reeves et al. (2011)** analysed 14 trials of cetuximab in head and neck cancer in 1528 people. Results were separated by phase of trial. Phase I and II trials (394 patients with recurrent or metastatic cancer) showed a partial response as defined in each separate study of 15.7% (95% CI 9.2% to 22.2%), 2% showed complete response (no 95% CI stated), and the overall response was 18.7% (95% CI 10.4% to 27.0%).

In phase III trials (n = 1118) there was an overall response of 17.0% (95% CI 12.6% to 21.4%) for platinum-based regimens plus placebo, and 34.2% for platinum based regimens plus cetuximab (95% CI 28.6% to 39.7%). Median survival increased by 2.2 months in people treated with cetuximab (7.5 months for platinum regimens plus placebo and 9.9 months for platinum-based regimens plus cetuximab).

The authors concluded that cetuximab has a role in treating head and neck cancer but cannot replace existing therapies. However, the heterogeneity of patient populations and concurrent chemotherapy regimens means that gaining a clear impression of the benefits of cetuximab in head and neck cancer is difficult. The results of this meta-analysis are unlikely to affect future updates to guidance. NICE CSGHN does not cover use of cetuximab. SIGN 90 contains advice on using cetuximab in locally advanced head and neck cancer.
NICE has published two technology appraisals about use of cetuximab in head and neck cancer (TA172 and TA145). The new evidence concurs with the evidence used to develop these technology appraisals.

Key references

Cao Y, Liao C, Tan A, et al. (2010) Meta-analysis of incidence and risk of hypomagnesaemia with cetuximab for advanced cancer. Chemotherapy 56: 459–65
Full text: http://content.karger.com/produktedb/produkte.asp?DOI=000321011&typ=pdf

Reeves TD, Hill EG, Armeson KE et al. (2011) Cetuximab therapy for head and neck squamous cell carcinoma: a systematic review of the data. Otolaryngology – Head and Neck Surgery 144: 676–84
Abstract: http://oto.sagepub.com/content/144/5/676.abstract

Supporting references

Summary of product characteristics – cetuximab.
Available from: www.medicines.org.uk/emc/medicine/19595/SPC/erbitux

Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck. NICE technology appraisal 172 (2009).
Available from www.nice.org.uk/guidance/TA172

Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck. NICE technology appraisal 145 (2008).
Available from www.nice.org.uk/guidance/TA145

Alternative therapies

O'Sullivan and Higginson (2010) undertook a systematic review without meta-analysis of three studies (n = 108) of acupuncture in the treatment of radiation-induced xerostomia. No evidence was found to support any objective benefit of acupuncture. Further studies are needed with standardised treatment and development of a valid comparator. The results from this review are not likely to affect future updates to guidance. Neither NICE CSGHN nor SIGN 90 cover use of acupuncture.

Key reference

O'Sullivan EM, Higginson IJ (2010) Clinical effectiveness and safety of acupuncture in the treatment of irradiation-induced xerostomia in patients with head and neck cancer: a systematic review. Acupuncture in Medicine 28: 191–9
Abstract: http://aim.bmj.com/content/28/4/191.abstract

Nutritional support

In a Cochrane review, **Nugent et al. (2010)** looked at the evidence comparing different enteral feeding methods in people with head and neck cancer undergoing radiotherapy or chemotherapy. Only one study of 33 patients was identified, which found greater weight loss 6 weeks after treatment in patients on nasogastric feeding compared with percutaneous endoscopic gastrostomy (PEG; p = 0.001). PEG feeding lasted significantly longer than nasogastric feeding (p = 0.0006) and cost around 10 times more.

The authors concluded that there was not enough evidence to determine the optimum feeding method, and that further research is needed. This evidence is therefore unlikely to affect a future update to guidance. NICE CSGHN and SIGN 90 both contain advice on nutritional support.

Key reference

Nugent B, Lewis S, O'Sullivan JM. (2010) Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy. Cochrane Database of Systematic Reviews: CD007904
Full text: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007904.pub2/full

Psychological therapies

A systematic review by **Luckett et al. (2011)** examined evidence for psychological interventions in people with head and neck cancer. Nine studies in a total of 627 people were identified. Meta-analysis was not possible because of significant heterogeneity between studies. Interventions included cognitive behavioural therapy, communication skills training, supportive expressive therapy, psychoeducation, support groups and stress management.

The authors looked at the results of the individual studies and noted that none of the intervention types studied was supported by a level of evidence defined by the US Preventive Services Task Force Agency for Healthcare Research and Quality.

The authors noted that the evidence for psychological interventions was limited by the small number of studies, methodological issues and poor comparability between interventions. They

suggested that future studies might be guided by recommendations from general psycho-oncology.

NICE CSGHN recognised that psychological interventions can be important in the management of patients with head and neck cancer. SIGN 90 recommends provision of emotional support, with referral to a clinical psychologist for some patients. This evidence is not likely to affect a future update to guidance.

Key reference

Luckett T, Britton B, Clover K et al. (2011) Evidence for interventions to improve psychological outcomes in people with head and neck cancer: a systematic review of the literature. Supportive Care in Cancer 19: 871–81

Abstract: www.springerlink.com/content/7x366122033q1375/

1.4 Follow-up

Dental care

Nabil and Samman (2011) did a systematic review to establish the incidence and factors influencing the development of osteoradionecrosis of the jaw after tooth extraction in people who had undergone radiation treatment for head and neck cancer. The review included 19 articles, covering 57 cases of osteoradionecrosis after post-radiation tooth extractions in 828 patients, which is a total occurrence of 7%. In people who received prophylactic hyperbaric oxygen therapy before extraction, the overall occurrence was 4% (595 teeth extracted with osteoradionecrosis in 10 sockets; incidence of 2% per tooth).

Extractions outside the field of radiation treatment or with doses of radiation less than 60 Gy showed almost no risk of developing osteoradionecrosis. However, the authors noted that the limited sample size means that this finding should be interpreted cautiously. The authors also stated that although the systematic review was performed according to strict standards, the overall quality of the data collected could have introduced bias, especially in the lack of prospective studies and RCTs.

This new evidence is unlikely to affect future updates to guidance because of the limited quality of the included data.

Peterson et al. (2010) reviewed 43 articles of prevention or treatment of osteoradionecrosis of the jaw after radiotherapy or brachytherapy with or without chemotherapy in people with head and neck cancer (n = 1537). The weighted prevalence of osteoradionecrosis was 7.4% for people who had conventional radiotherapy, 5.2% for intensity-modulated radiotherapy, 6.8% for radiotherapy plus chemotherapy and 5.3% for brachytherapy.

The main strategy for prevention noted in the review was use of hyperbaric oxygen therapy, which was associated with an occurrence of osteoradionecrosis of 0–3.4%. Hyperbaric oxygen therapy was also the most studied treatment method, with reported response to treatment ranging from 19% to 93%.

The authors recognised the limitations of the evidence base available to estimate the prevalence of osteoradionecrosis, including the lack of RCTs, the changing methods and dosing of radiotherapy and chemotherapy, differences between studies in grading of osteoradionecrosis, variations in follow-up, and reporting of patient factors (such as local dose and distribution of radiation or other systemic disease) that might affect the likelihood of osteoradionecrosis.

NICE CSGHN, which does not deal with osteoradionecrosis directly, but recommends that a consultant with experience in maxillofacial prosthetics and implantology should liaise with primary care dental practitioners to co-ordinate the dental care of patients after treatment. The

current evidence concurs with SIGN 90, which recommends hyperbaric oxygen for selected patients. This evidence may be a consideration in future updates to guidance.

Key references

Nabil S, Samman N (2011) Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. International Journal of Oral & Maxillofacial Surgery 40: 229–43
Abstract: www.sciencedirect.com/science/article/pii/S0901502710004327

Peterson DE, Doerr W, Hovan A et al. (2010) Osteoradionecrosis in cancer patients: the evidence base for treatment-dependent frequency, current management strategies, and future studies. Supportive Care in Cancer 18: 1089–98
Abstract: www.springerlink.com/content/h4j201q042281882/

Early discharge in laryngeal dysplasia

In a systematic review and meta-analysis of case series, **Weller et al. (2010)** analysed 940 cases of laryngeal dysplasia from nine studies to determine the rate of transformation to cancer and the time to transformation. The overall transformation rate was 14% (95% CI 8 to 22) and the mean time interval was 5.8 years (range 1.8 to 14.4. years).

A significant association between histological grade and rate of transformation was seen, with 11% (95% CI 5 to 21%) of those with mild or moderate dysplasia and 30% (95% CI 16 to 50%) of those with severe dysplasia developing cancer ($p < 0.0002$). However, no significant association between grade of dysplasia and time to transformation was noted: mean time to transformation for mild dysplasia was 4.9 years (range 2.4 to 14.4 years), for moderate dysplasia was 3.4 years (range 1.8 to 4.7 years), and for severe dysplasia was 4.1 years (range 2.1 to 11.0 years, no p value stated).

The authors concluded that no evidence supports the common practice of early discharge from follow-up for people with mild or moderate laryngeal dysplasia. They stated that limitations of their meta-analysis included the small number of heterogeneous studies and patients, which was due to generally poor quality studies and few prospective studies of this topic. Additionally, the presence of risk factors such as smoking was poorly reported across studies, which could have affected the transformation rates.

NICE CSGHN and SIGN 90 both recommend discharge from follow-up after 5 years for people with cancer, but neither guideline mentions follow-up for dysplasia. Future guidance on head and neck cancer could possibly consider evidence for the optimum follow-up for patients with dysplasia. A group of 80 ear nose and throat surgeons and pathologists from the

UK attended a workshop on the diagnosis and management of laryngeal dysplasia and subsequently published a consensus statement detailing their findings (Mehanna et al. 2010). The consensus statement recommended a 5-year follow up for high-risk laryngeal dysplasia.

Key reference

Weller MD, Nankivell PC, McConkey C et al. (2010) The risk and interval to malignancy of patients with laryngeal dysplasia; a systematic review of case-series and meta-analysis. Clinical Otolaryngology 35: 364–72
Abstract: http://onlinelibrary.wiley.com/doi/10.1111/j.1749-4486.2010.02181.x/abstract

Supporting reference

Mehanna H, Paleri V, Robson A et al. (2010) Consensus statement by otorhinolaryngologists and pathologists on the diagnosis and management of laryngeal dysplasia. Clinical Otolaryngology 35: 170–6
Available from:http://onlinelibrary.wiley.com/doi/10.1111/j.1749-4486.2010.02119.x/abstract

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs).

Treatment

Radiotherapy

- Hyperfractionated or accelerated radiotherapy for head and neck cancer www.library.nhs.uk/duets/ViewResource.aspx?resID=410827
- Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy www.library.nhs.uk/DUETs/viewResource.aspx?resid=412301

Surgery

- Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment www.library.nhs.uk/duets/ViewResource.aspx?resID=303285

Alternative therapies

- The effectiveness of acupuncture for treating irradiation-induced xerostomia in patients with head and neck cancer www.library.nhs.uk/DUETs/viewResource.aspx?resid=411900

Nutritional support

- Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy www.library.nhs.uk/DUETs/viewResource.aspx?resid=347087

Further evidence uncertainties for head and neck cancer can be found at www.library.nhs.uk/duets/ and in the NICE research recommendations database at www.nice.org.uk/research/index.jsp?action=rr.

DUETs has been established in the UK to publish uncertainties about the effects of treatment that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Diagnosis and management of head and neck cancer (2006). Scottish Intercollegiate Guidelines Network (SIGN) 90. Available from www.sign.ac.uk/guidelines/fulltext/90/index.html

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 July 2010 (the end of the search period of the most recent Annual Evidence Update) to 12 December 2011:

- AMED
- CINAHL
- Cochrane Library: Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects
- Embase
- MEDLINE
- NHS EED
- PsycINFO

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was adapted from that in the SIGN 90 guideline, because this was used as a base for the 2010 Annual Evidence Update. The search strategy was used in conjunction with validated SIGN search filters for RCTs, systematic reviews and diagnostic test accuracy studies (www.sign.ac.uk/methodology/filters.html).

Two other studies: Chuang et al (2012) and Nicolotti et al. (2011) were identified outside of the literature search. Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Update Adviser (the chair of the EUAG), and the full search strategies, are available on request from contactus@evidence.nhs.uk

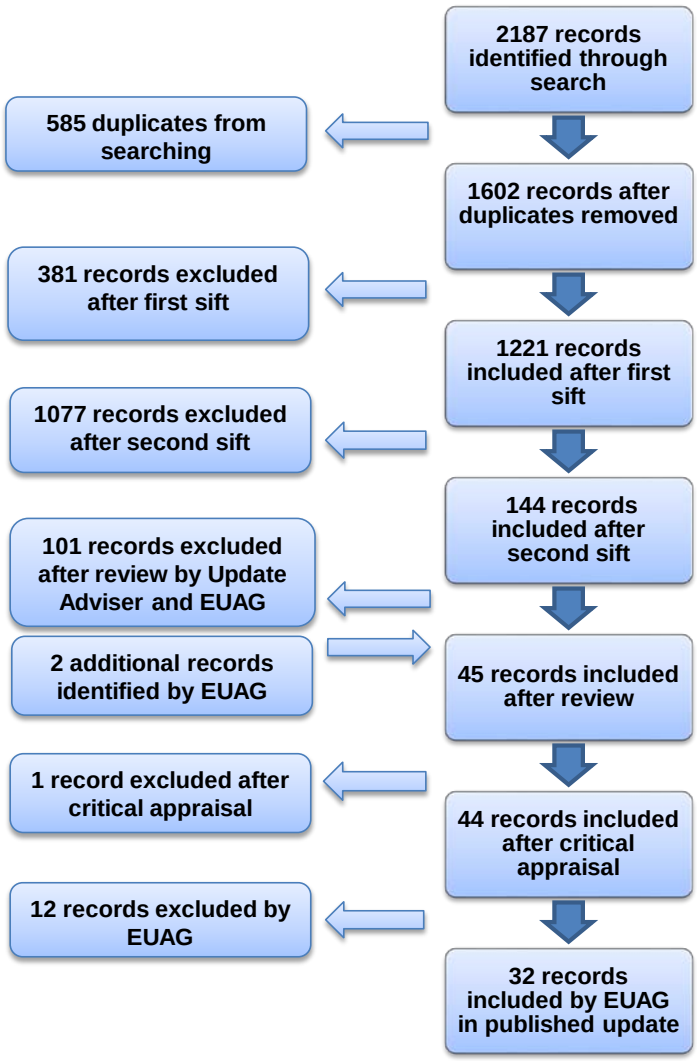
Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp "Head and Neck Neoplasms"/
2	Carcinoma, Mucoepidermoid/
3	Mucoepidermoid Tumor/
4	Esthesioneuroblastoma, Olfactory/
5	or/1-4
6	(cancer$ or tumor$ or tumour$ or carcinoma$ or sarcoma$ or neoplasm$ or adenocarcinoma$ or metastasis or metastases or polyp$).ti
7	(palate or palatal).ti
8	("base of tongue" or (base adj3 tongue)).ti
9	Mouth Mucosa/
10	((oral or buccal or mouth or cheek$) adj (mucous or (mucosa adj membrane$))).ti
11	Mouth Floor/
12	(mouth adj3 (bottom or floor)).ti
13	Retromolar.ti
14	((nose or nasal) adj cavity).ti
15	"post cricoid".ti
16	head.ti
17	neck.ti

18	ear.ti
19	(mouth or "oral cavity").ti
20	lip$.ti
21	Parotid.ti
22	"salivary gland$".ti
23	tongue.ti
24	(nose or nasal or paranasal).ti
25	(larynx$ or larynges or laryngeal or "vocal cord$" or "vocal fold$").ti
26	((pyriform or piriform) adj fossa$).ti
27	(pharyngeal or pharynx$ or pharynges or throat).ti

28	(hypopharyngeal or laryngopharyngeal or "laryngea pharyngis" or hypopharynx$ or larnygopharynx$ or hypopharynges or laryngopharynges).ti
29	(nasopharyngeal or nasopharynx$ or nasopharynges).ti
30	(oropharyngeal or oropharynx$ or oropharynges).ti
31	(tonsillar or tonsil$1).ti
32	(gingival or gum$).ti
33	or/7-32
34	6 and 33
35	5 or 34

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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