# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# **Centre for Clinical Practice – Surveillance Programme**

Surveillance review consultation document

10-year surveillance review of CSGHN: Improving outcomes in Head and Neck Cancer

#### **Background information**

Guideline issue date: November 2004 10 year review: 2015

#### Surveillance review recommendation

#### Surveillance review proposal for consultation:

The CSGHN: Improving outcomes in Head and Neck Cancer guideline should not be considered for an update at this time.

The guideline should be transferred to the static guidance list because it fulfils the following criteria:

• No evidence was identified that would impact on the current guidance and no quality standard has been commissioned

#### Main findings of the current 10 year surveillance review

An <u>Evidence Update</u> was produced for the guideline in 2012 and was used as a source of evidence for the 10 year surveillance review. The Evidence Update considered new evidence from 1st July 2010 to 12th December 2011. New evidence that may impact on the guideline recommendations was identified in nine areas of the Evidence Update. This was in relation to the following:

- Facial palsy may indicate a more advanced case of cancer than conventional staging
- FDG-PET may be useful for assessing distant metastases of the head and neck

- Auto-fluorescence endoscopy may have better sensitivity and specificity than white-light endoscopy for detecting laryngeal cancer or dysplasia
- Altered fractionated radiotherapy may be associated with better outcomes compared to conventional radiotherapy
- Open partial laryngectomy may be an effective organ sparing treatment alternative to total laryngectomy in those with early laryngeal carcinoma that recurs after radiotherapy
- CO<sub>2</sub> endolaryngeal laser excision may be more cost effective than standard fractionation radiotherapy for early stage glottic cancer
- Altered fractionated radiotherapy with concurrent chemotherapy may be associated with better outcomes compared to other treatment strategies
- Limited evidence exists for the use of hyperbaric oxygen for the prevention or treatment of osteoradionecrosis of the jaw after tooth extraction in those who have undergone radiotherapy for head and neck cancer
- Early discharge from follow-up may not be advisable for people with laryngeal dysplasia.

The literature included in the Evidence Update specifically focused on methods for diagnosis and treatment whereas CSGHN provides guidance on services for adult patients with cancers of the head and neck and is intended to inform commissioning and provision of cancer services by people from both clinical and non-clinical communities. As such, recommendations in the head and neck cancer service guidance focus on which healthcare professionals should be involved in treatment and care, and the types of hospital or cancer centre that are best suited to provide that healthcare rather than specific treatments. Furthermore, NICE is currently developing a clinical guideline on <u>Upper</u> airways tract cancers: assessment and management of upper airways tract cancers (including cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and nasal sinuses) which is likely to cover the majority of areas identified through the Evidence Update process. The anticipated publication date for this guideline is February 2016.

For this 10 year surveillance review, a focused literature search was conducted to identify new evidence published between 12th December 2011 (the end of the Evidence Update search period) and 21st January 2015 and relevant abstracts were assessed. The focus of the search was to identify studies evaluating the impact of surgeon and hospital volumes on quality of decision making and outcomes. Due to the nature of the potential evidence sought, the search strategy included observational studies in addition to randomised controlled trials (RCTs) and systematic reviews.

Clinical feedback on the head and neck cancer service guidance was obtained from five members of the GDG of the in-development upper aerodigestive tract mucosal cancers clinical guideline through a questionnaire.

Clinical feedback highlighted evidence and ongoing trials relating to different head and neck cancer treatments. All five GDG members thought that the guideline needed to be updated to reflect these new developments. NICE is currently developing a clinical guideline on assessment and management of upper airways tract cancers (including cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and nasal sinuses) which is likely to cover the majority of areas related to the evidence identified through the questionnaire. Clinical feedback also indicated that there was new evidence regarding the structure and working of head and neck teams, local support teams, neck lump clinic

organisation and the impact of the demise of the Network Site Specific Groups and centralisation. However, no references or study details were provided. Furthermore, it was also highlighted by a GDG member that there were new roles for PET CT. Again, no study details were provided.

New evidence was identified for the current 10 year surveillance review relating to the following areas within the head and neck cancer service guidance.

Clinical area: Referral		
Q: In head and neck cancer does earlier detection of malignancy lead to improved outcomes?		
Evidence summary	GDG/clinical perspective	Impact
Evidence Update (2012)	No GDG feedback was provided by the	The Evidence Update found new evidence about
	GDG questionnaire.	the presence of facial palsy. However, CSGHN
Prognosis		does not currently make any specific recommendations about temporal bone or
Presence of facial palsy		auditory canal tumours.
A comparative survival analysis <sup>1</sup> was conducted		The evidence provided in the Evidence Update on
of 21 case-series in 348 patients with squamous		the presence of facial palsy is unlikely to impact
cell carcinomas of the temporal bone or auditory		on this guidance. This is because CSGHN
canal. Results showed that the presence of facial palsy, irrespective of the stage of cancer, was		provides guidance on services for head and neck cancer patients and does not specifically focus on
associated with significantly lower 5 year overall		diagnosis and treatment options. Nonetheless,
survival compared to no facial palsy. Furthermore,		this evidence may be more relevant to the in-
the Pittsburgh 2000 staging system showed a		development guideline on Upper airways tract
significant difference in 5 year overall survival		cancer.
between T3 and T4 but no significant difference in		
this outcome were found between T3 and T4 in		New evidence on the expression of carbonic
Pittsburgh 1990 staging, or between T2 and T3 in Stell staging. In the Cox regression survival		anhydrase-9 was identified by the Evidence Update. However, it was concluded that this
analysis those with facial palsy and any stage		evidence was unlikely to affect guidance since it
cancer had a survival similar to those with		has no direct clinical application. The Evidence
Pittsburgh 2000 T4 disease.		Update suggested that further research to assess
5		the association in specific tumour sites and to
The Evidence Update stated that no specific		determine if CA-9 expression has any use in
recommendations for temporal bone or auditory		predicting response to treatment was required.

canal tumours were included in CSGHN and this area may be a consideration in a future update of the guidance.

#### **Expression of carbonic anhydrase-9**

A meta-analysis<sup>2</sup> of 16 studies found that a significant proportion of head and neck tumours expressed CA-9. In addition, overall survival and disease free survival were found to be significantly higher in those who were CA-9 negative. Disease free survival was also significantly higher in people who expressed low levels of CA-9 compared to those expressing high levels.

The Evidence Update concluded that this study is unlikely to affect guidance since it has no direct clinical application. It was suggested that further research is required to assess the association in specific tumour sites and to determine if CA-9 expression has any use in predicting response to treatment. CSGHN does not currently cover this topic.

# F-fluorodeoxyglucose (FDG) uptake in tumours

A meta-analysis<sup>3</sup> of eight studies (n=495) assessed if the uptake of FDG in tumours correlated with outcome. It was found that increased uptake of FDG was associated with lower rates of local control, disease free survival and overall survival.

The Evidence Update also identified new evidence regarding FDG uptake in tumours. The Evidence Update concluded that there was no evidence for changing treatment strategies for patients whose FDG uptake status was known. Furthermore, it was stated that there is no standardised method of measuring uptake. As such, it was suggested that this evidence was unlikely to impact on CSGHN.

The Evidence Update concluded that there was no evidence for changing treatment strategies for patients whose FDG uptake status was known. Furthermore, it was stated that there is no standardised method of measuring uptake. As such, it was suggested that this evidence was unlikely to impact on CSGHN. <u>10-Year Surveillance Review (2015)</u> No new evidence in this area was considered.		
Clinical area: Referral		
Q: In groups at a higher risk of developing head and cancers, the risk factors and the features of possible		ng awareness of the existence of head and neck
Evidence summary	GDG/clinical perspective	Impact
	• •	-
Evidence Update (2012) Lifestyle factors A study based on data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium reported on the dietary factors associated with head and neck cancer in 14,520	No GDG feedback was provided by the GDG questionnaire.	New evidence was identified by the Evidence Update relating to lifestyle factors. The Evidence Update concluded that the evidence was unlikely to impact on the guidance since this type of evidence did not directly guide clinical practice. Furthermore, risk factors are not currently covered in CSGHN.
cases and 22,737 controls. Overall, higher vegetable intake and fruit intake were associated with lower head and neck cancer rates whilst higher intakes of processed meats were found to be associated with higher incidents of these cancers. A high intake of white meat was found to be associated with lower head and neck cancer rates. <sup>4</sup>		The Evidence Update also found new evidence about MUC1 and MUC2 expression. However, it was concluded that further research in this area would be required before consideration for inclusion in the guideline. This topic is not currently covered in CSGHN. In addition, the Evidence Update identified new evidence about HPV detection. Nonetheless, the
Another study investigated recreational physical		Evidence Update concluded that the study identified was unlikely to impact on future

activity in four studies (2289 cases, 5580 controls). <sup>5</sup> . Results showed that moderate physical activity was associated with reduced head and neck cancer rates when compared to no or low levels of physical activity. No association was found with high physical activity. Stratification by cancer type showed that moderate and high physical activity were associated with lower oral cancer and pharyngeal cancers. No definitive association was found between laryngeal cancer and moderate physical activity. The Evidence Update concluded that these studies were unlikely to impact on the guidance since this type of evidence does not directly guide clinical practice. Furthermore, risk factors are not currently covered in CSGHN.	guidance because the findings did not have direct clinical implications for the diagnosis or treatment of oral cancers. Furthermore, it was suggested that the results might not be generalisable to the UK since studies have shown geographical differences in the prevalence of HPV in people with oropharyngeal cancer. The Evidence Update also found new evidence on Epstein-Barr virus detection in nasopharyngeal cancer. The Evidence Update concluded that this study may not be generalisable to the UK since most of the included studies were conducted in Asian populations who are known to have higher incidences of nasopharyngeal cancer. Furthermore, it stated that this evidence alone was unlikely to affect any future update of this guidance.
MUC1 and MUC2 expression A systematic review <sup>6</sup> was identified which investigated the existence and potential roles of mucins in the normal larynx and laryngeal squamous cell carcinoma. In the studies which looked at MUCI expression (5 studies with 161 carcinoma and 70 normal cell samples) the results were inconsistent. This was also the case in the two studies examining MUC2. The Evidence Update concluded that further research in this area may be useful. However, it was suggested that the results of this study alone were unlikely to impact on guidance. This topic is not currently covered in CSGHN.	

Human Papillomavirus (HPV) detection	
A systematic review <sup>7</sup> was conducted to investigate the association between HPV in oral carcinoma and potentially malignant disorders (OPMD). It included 39 cross-sectional studies. Results showed significant associations between HPV-DNA detection and oral carcinoma and for HPV16 only. HPV was also found to be associated with OPMD. In the subgroup analysis of OPMD, HPV was found to be associated with oral leukoplakia, oral lichen planus and epithelial dysplasia.	
The Evidence Update concluded that CSGHN does not cover HPV other than stating that it is "implicated in the development of some cancers of the oral cavity, pharynx and larynx". The Evidence Update stated that this study was unlikely to impact on future guidance because the findings do not have direct clinical implications for the diagnosis or treatment of oral cancers. Furthermore, it was suggested that the results might not be generalisable to the UK since studies have shown geographical differences in the prevalence of HPV in people with oropharyngeal cancer.	
Epstein-Barr virus detection in nasopharyngeal cancer	
A meta-analysis <sup>8</sup> of 15 observational studies in 2393 people investigated the accuracy of detecting Epstein-Barr virus DNA as a marker for	

<ul> <li>nasopharyngeal cancer. The pooled sensitivity was found to be 89.1% and the pooled specificity 85%. Furthermore, plasma samples were found to have the highest sensitivity and specificity for this type of cancer compared to serum samples.</li> <li>The Evidence Update concluded that this study may not be generalisable to the UK since most of the included studies were conducted in Asian populations who are known to have higher incidences of nasopharyngeal cancer.</li> <li>Furthermore, it stated that this evidence alone was unlikely to affect any future update of this guidance.</li> <li><u>10-Year Surveillance Review (2015)</u></li> <li>No new evidence in this area was considered.</li> </ul>		
Clinical area: Referral		
Q: Does opportunistic screening for head and neck outcomes for head and neck cancer patients?	cancers, including assessments of the salivary	/ glands and neck nodes, result in improved
Evidence summary	GDG/clinical perspective	Impact
Evidence Update (2012)	No GDG feedback was provided by the	The Evidence Update found new evidence on
Population screening A Cochrane review <sup>9</sup> investigated RCTs of screening for oral cancer. One cluster randomised study was included (n=191,873). This showed no significant difference in oral cancer mortality rate between those screened and the control group. However, the 5 year survival rate was significantly higher in the intervention group compared to the	GDG questionnaire.	population screening for oral cancer. However, it was concluded that this new evidence was unlikely to impact on current guideline recommendations. This is because the study was conducted in India and so its findings are unlikely to have direct application to UK clinical practice because oral cancer is more common in India than in the UK. Furthermore, screening is not covered in CSGHN.

control. The Evidence Update concluded that as this	The Evidence Update also identified new evidence about the sensitivity and specificity of FDG-PET. The Evidence Update concluded that
study was conducted in India its findings are	the evidence found was consistent with CSGHN
unlikely to have direct application to UK clinical	which recommends the use of PET for
practice because oral cancer is more common in	distinguishing between benign and malignant lung
India than in the UK. Furthermore, screening is not covered in CSGHN.	nodules. CSGHN also states that the use of PET is expected to increase. The Evidence Update
not covered in CSGIIN.	stated this area may be a consideration in a future
Imaging	update of the guidance.
magng	apadie of the galdaries.
F-fluorodeoxyglucose positron emission	However, the evidence provided in the Evidence
tomography (FDG-PET)	Update on FDG-PET is unlikely to impact on this
	guidance. This is because CSGHN provides
FDG-PET for the detection of distant metastases	guidance on services for head and neck cancer
and secondary primary cancers was investigated in a meta-analysis of 12 studies (n=1276). <sup>10</sup> The	patients and does not specifically focus on diagnosis and treatment options. Nonetheless,
pooled sensitivity of FDG-PET was 0.89 and the	this evidence may be more relevant to the in-
specificity was 0.95.	development guideline on Upper airways tract
	cancer.
The Evidence Update stated that CSGHN	
recommends PET only for distinguishing between	Lastly, the Evidence Update found new evidence
benign and malignant lung nodules but does state	on fluorescence endoscopy. It was concluded that
that the use of PET is expected to increase. The	CSGHN does recognise that endoscopy is
Evidence Update suggested that this evidence might be considered in a future update to	essential for inspecting inaccessible areas during initial investigations but it does not mention
guidance, especially for imaging in people with	fluorescence. Due to this, the Evidence Update
nasopharyngeal cancer.	concluded that this area may be a consideration in
	a future update of the guidance.
Endoscopy	
	The evidence provided in the Evidence Update on
A meta-analysis <sup>11</sup> was identified which looked at	fluorescence endoscopy is unlikely to impact on
fluorescence endoscopy for early diagnosis of	this guidance. This is because CSGHN provides
laryngeal cancer or dysplastic lesions. Sixteen studies were included. Results showed that auto-	guidance on services for head and neck cancer patients and does not specifically focus on

fluorescence endoscopy (AFE) had higher sensitivity and specificity than white light endoscopy (WLE). Induced –fluorescence endoscopy (IFE) had higher sensitivity but lower specificity than WLE. In addition, there was no significant difference in sensitivity between AFE and IFE but AFE had higher specificity. The Evidence Update concluded that CSGHN recognises that endoscopy is essential for inspecting inaccessible areas during initial investigations but it does not mention fluorescence. As such, this area may be a consideration in a future update of the guidance. <u>10-Year Surveillance Review (2015)</u> No new evidence in this area was considered.		diagnosis and treatment options. Nonetheless, this evidence may be more relevant to the in- development guideline on Upper airways tract cancer.
Clinical area: Structure of Services	•	
Q: Does the volume of head and neck-cancer relate		outcomes?
Evidence summary	GDG/clinical perspective	Impact
Evidence Update (2012) None identified. <u>10-Year Surveillance Review (2015)</u> Physician volume	No GDG feedback was provided by the GDG questionnaire.	The new evidence on surgeon volume indicates that high-volume surgeons and oncologists have better survival rates and lead to a decrease in complication rates. This evidence is consistent with that included in CSGHN and so is unlikely to impact on this guidance at this time.
A retrospective cohort study <sup>12</sup> investigated the association between case volume of radiation oncologists and survival in patients with nasopharyngeal carcinoma. Results showed that		

<ul> <li>those treated by high-volume radiation oncologists had better overall survival compared to those treated by low-volume radiation oncologists.</li> <li>A population based survey<sup>13</sup> was identified which examined the association between physician case volume and survival rates in 1225 Taiwanese patients with nasopharyngeal carcinoma. It was found that patients treated by high-volume physicians had better 10 year survival rates to those treated by low/medium-volume physicians.</li> </ul>		
A retrospective survey <sup>14</sup> looked at surgeon preference for perioperative management of transoral robotic surgery and postoperative complications. It showed that the complication rate decreased significantly with higher surgeon case volume.		
Clinical area: Structure of Services		
Q: Does the volume of head and neck cancer-relate	· · · · · · · · · · · · · · · · · · ·	putcomes?
Evidence summary	GDG/clinical perspective	Impact
Evidence Update (2012) None identified.	No GDG feedback was provided by the GDG questionnaire.	The new evidence on hospital volume suggests that high hospital volume may lead to better survival rates and lower complication rates in
10-Year Surveillance Review (2015)		head and neck cancer patients. This is consistent with the evidence already included in CSGHN.
A cross-sectional ecological study <sup>15</sup> was identified which investigated 11,573 cases of head and neck oncologic surgery and the impact of case volume. It was found that high volume hospitals had a lower complication rate compared to low		The new evidence looking at both surgeon and hospital volume suggests that high surgeon and hospital volume are beneficial for survival in head and neck cancer. This is consistent with the evidence provided in CSGHN.

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volume hospitals.	
In another study <sup>16</sup> , data from the Surveillance,	
Epidemiology and End Results (SEER) –	
Medicare database was used to investigate the	
association between high volume hospitals,	
National Comprehensive Cancer Network	
(NCCN) guideline therapy and survival. Overall,	
1195 patients were included. Results showed that	
head and neck squamous cell carcinoma patients	
treated at high volume hospitals were not more	
likely to receive therapy as per NCCN guidelines	
but had better survival rates than those treated at low volume hospitals.	
A retrospective cross-sectional analysis <sup>17</sup> of 2370	
elderly patients with laryngeal squamous cell	
cancer (SCCA) was identified. This found that	
high volume care was not associated with survival	
for non-operative treatment but was associated	
with improved survival in those receiving surgery.	
Furthermore, high-volume care was found to be	
associated with significantly lower costs of care	
for surgical patients but was not associated with	
differences in costs for patients with non- operative treatment.	
The impact of hospital volume on surgical	
outcomes was examined in a retrospective cohort	
study of 3850 cases of sinonasal malignancy <sup>18</sup> .	
Results indicated that complicated surgeries were	
more likely to occur at high volume hospitals	
without significant changes in surgical	
complication rates. High-volume centres had an	
increased rate of cardiopulmonary and electrolyte	

complications but these were not found to be	
associated with higher mortality.	
Another retrospective cohort study <sup>19</sup> investigated	
variation in bronchoscopy and esophagostomy	
use in 9218 patients with head and neck cancer	
undergoing diagnostic laryngoscopy. It was found	
that patients were more likely to undergo	
concurrent bronchoscopy and esophagoscopy at	
low and medium volume hospitals than in high	
volume hospitals.	
Surgeon and hospital volume	
A retrospective cross-sectional study <sup>20</sup>	
investigated the impact of surgical care on short	
term outcomes in 29,030 cases of oropharyngeal	
cancer. Results showed that high-volume	
hospitals were associated with an increased use	
of oropharyngeal surgery from 2001 to 2008	
compared to 1993 to 2000. Furthermore, high	
volume hospitals were significantly associated	
with pharyngectomy whilst high-volume surgeons	
were found to be associated with flap	
reconstruction and prior radiation. A significant	
interaction was also found between high-volume	
surgeons and high-volume hospitals as reduced	
hospital costs for surgery were found when	
surgery was performed by high-volume surgeons	
at high volume hospitals.	
A retrospective cohort study <sup>21</sup> investigated the	
impact of surgeon and hospital volume on long-	
term survival in 5720 head and neck cancer	
patients. It was found that both high surgeon and	

<ul> <li>hospital volume were predictors of better overall survival. However, this effect was largely explained by hospital volume.</li> <li>A systematic review<sup>22</sup> examined the volume-outcome relationship in the treatment of patients with head and neck cancer. Seventeen studies were included. Results showed that high volume hospitals and high volume surgeons had better overall survival compared to their low volume counterparts.</li> </ul>		
Clinical area: Initial investigation and diagnosis		
Q: In patients with symptoms suggestive of thyroid cytology to confirm or exclude malignancy have on number of patients receiving unnecessary or inappr	stage of tumours identified at referral, diagnos opriate surgery?	effect does performing fine needle aspiration (FNA) tic indices and patient outcomes including the
Evidence summary	GDG/clinical perspective	Impact
<ul> <li>Evidence Update (2012)</li> <li>Fine needle aspiration cytology of salivary glands</li> <li>A systematic review<sup>23</sup> was identified which examined studies of histological diagnoses of salivary gland tumours that reported the correlation between fine needle aspiration cytology and histological results. Sixteen studies of 2018 patients were included. Results showed that 93.2% of cases identified as malignant on fine needle aspiration were confirmed as such histologically. Furthermore, 95.46% of cases identified as benign on fine needle aspiration</li> </ul>	No GDG feedback was provided by the GDG questionnaire.	The Evidence Update found new evidence on fine needle aspiration cytology of the salivary glands. The Evidence update concluded that the new evidence was supportive of the recommendations already included in CSGHN.

The Evidence Update concluded that this study supported the recommendations already included in CSGHN.	
10- Year Surveillance Review (2015)	
No new evidence in this area was considered.	

#### **Clinical area: Primary treatment**

Q: In patients with head and neck cancer (primary disease) what are the relative efficacies of brachytherapy, normal fractionation external beam radiotherapy, accelerated fractionation external bean radiotherapy, altered fractionation external beam radiotherapy, chemoradiotherapy, surgery, chemotherapy and endoscopic/laser excision, alone or in combination, in terms of long term survival, peri-treatment mortality, recurrence rates, incidence and severity of morbidity, voice outcomes, facial nerve damage, xerostomia, complication rates, quality of life, anxiety, patient satisfaction or other patient outcomes?

Evidence summary	GDG/clinical perspective	Impact
Evidence Update (2012)	Feedback from the GDG members indicated	The Evidence Update found new evidence about
<u>Radiotherapy</u>	that there were new chemotherapy regimens and IMRT/different oncological interventions available. Furthermore, it was	radiation dosing regimens. It concluded that this evidence adds to that already included in CSGHN but suggested that it may be considered in an
Radiation dosing regimens	noted that there are new surgical treatments and that robotic/transoral laser was	update to guidance.
An updated Cochrane review <sup>24</sup> investigated	becoming more common. However, no	However, this evidence may be more relevant to
overall survival with radiotherapy in head and	references were provided for these	the in-development guideline on Upper airways
neck cancer patients. Fifteen trials were included.	comments.	tract cancer.
It was found that altered fractionated radiotherapy		
was significantly better than conventional therapy	The GDG also suggested that results of the	New evidence on swallowing outcomes after
whilst hyperfractionated radiotherapy was	PET neck study may produce new guidance	radiotherapy was also found. However, the
associated with the greatest absolute benefit	and stated that there was new evidence on	Evidence Update concluded that this evidence
compared with accelerated fractionation.	the use of preventative therapy. However,	was unlikely to impact on CSGHN. This was
	no references to the evidence were	because the evidence was limited. It was
Another Cochrane review <sup>25</sup> looked at 30 trials of	provided for these comments.	suggested that further research in this area is
radiotherapy in cancer of the oral cavity or		needed along with an increased reporting of
oropharynx. It found that altered fractionation radiotherapy was associated with a reduction in	The following references were also provided by the GDG:	dysphagia as an adverse event in radiotherapy studies.
Taulouterapy was associated with a reduction in		รเนนเธร.

mortality at 5 years when compared to conventional radiotherapy. Furthermore, locoregional control was found to be better with altered fractionation radiotherapy but no difference was seen between the two forms of radiotherapy in disease free survival.

The Evidence Updated concluded that this evidence adds to that on radiation dosing regimens which CSGHN covers and suggested that this evidence may be considered in an update to the guidance. Furthermore, CSGHN does mention the use of hyperfractionated and accelerated radiotherapy but the evidence was limited.

#### Swallowing outcomes after radiotherapy

A systematic review<sup>26</sup> of 16 studies (n=1012) investigated swallowing outcomes after intensity modulated radiation therapy for head and neck cancer. The included studies suggested that limiting the radiation dose to some structures may be beneficial for some swallowing outcomes. However, the authors stated that the included studies were limited in study design and outcome data and suggested that further well-designed studies were needed.

The Evidence Update concluded that this evidence is unlikely to impact on guidance and suggested that further studies in this area are needed.

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Use of stents in head & neck surgery. Carrau RL Curr Opin Otolaryngol head & neck surgery 2005 13(2): 105-6

Laser dubulking in malignant upper airways obstruction. Paleri V, Stafford FW, Sammut MS Head Neck 2005; 27(4): 296-301

Impact of surgical resection on survival in patients with advanced head & neck cancer involving the carotid artery. Manzoor NF et al JAMA Otolaryngol head & neck surg 2013;139(11):1219-25

Carotid blowout. Dixon L & Warriner D Br J Hosp Med 2012;73(7): 98-100

Acute life threatening haemorrhage in patients with head & neck cancer presenting with carotid blowout syndrome: follow up results after initial haemostasis with carotid stent placement. Shah H, Gemmete JJ Chaudhury et al American J of Neuroradiology 2011 32(4): 743-7

Transarterial embolization for control of bleeding. Chen YF et al Otolaryngol Head & neck surgery 2010;142(1):90-4

Acute haemorrhage in patients with advanced head & neck cancer value of endovascular treatment in palliative The Evidence Update also identified new evidence on elective and therapeutic neck dissection. However, the Evidence Update suggested that this evidence was unlikely to impact on the guideline. This was because the included study did not take into account the stage of the primary tumour and included studies which were outdated in terms of treatment and imaging standards. Furthermore, this topic is not covered by CSGHN. The remaining two studies on neck surgery were also considered not to impact upon CSGHN. This was because the evidence was limited and was considered unlikely to change current practice.

New evidence was also found by the Evidence Update on the timing of dental implant surgery. The Evidence Update concluded that this study was unlikely to affect a future update of the guideline since CSGHN does not make specific recommendations about the timing of placing dental implants. Furthermore, new evidence was found on open partial laryngectomy. The Evidence Update concluded that the 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.

In addition, the Evidence Update provided new evidence on surgery versus radiotherapy. As CSGHN does not make recommendations about treatment choice it was concluded that this

Elective versus therapeutic neck dissection	treatment option. Sesterhenn AM, Iwinska-zelder J J laryngol otol 2006 ; 120(2)	evidence may be a consideration in a future update to guidance.
A systematic review <sup>27</sup> of 23 studies (n=1611) was identified. In it the authors proposed that the number needed to treat was a clinically intuitive parameter that could be used to guide the level of treatment in patients with squamous cell carcinoma of the head and neck. They suggested that if the risk of occult metastasis was 20% or more then the patient should have treatment of the neck. The Evidence Update stated that as this study did not take into account the stage of the primary tumour and since some of the included studies dated back to a time when treatment and imaging standards differed from current practice, the evidence was unlikely to impact on guidance. Furthermore, this topic was not covered by CSGHN.	Carotid stenting for impending carotid blowout: suitable supportive care for head & neck cancer patients? Desuter G et al Palliat Med 2005;19(5): 427-9 Clinical applications of palifermin – amelioration of oral mucositis & other potential implications. Vadhan-Roy S, et al. J Cell Mol Med 2013; 17(11) 1371-84 New developments in management of oral musositis in patients with head & neck cancer receiving targeted anticancer therapies. Am J Health Syst Pharm 2012; 69(12):1031-7 However, these references are unlikely to	The Evidence Update also found new evidence which looked at mixed treatment comparisons. Currently, CSGHN does not make specific recommendations about the timing or regimens of chemotherapy. The Evidence Update concluded that the evidence in this area could be a consideration in a future update to guidance. However, The evidence provided in the Evidence Update on mixed treatment comparisons, open partial laryngectomy and surgery versus radiotherapy is unlikely to impact on this guideline. This is because CSGHN provides guidance on services for head and neck cancer patients and does not specifically focus on diagnosis and treatment options. Nonetheless, this evidence may be more relevant to the in-development guideline on Upper airways tract cancer.
A Cochrane review <sup>28</sup> investigated surgical treatments for oral and pharyngeal cancers. Seven trials were included (n=570). The findings from four trials suggested that elective neck resection reduced locoregional recurrence rates when compared to therapeutic delayed neck dissection. However, meta-analysis could not be performed due to differences in types of surgery and the duration of follow-up. Two trials showed no difference in overall survival between elective radical neck dissection and selective neck dissection and one study showed no difference between these two treatments in disease free	impact on CSGHN since it specifically provides guidance on services for adult patients with cancers of the head and neck. However, it is anticipated that they may be relevant to the new Upper airways tract cancer guideline which is currently in development and will include recommendations on assessment and management of upper airways tract cancers.	For biological treatments, the evidence identified by the Evidence Update was unlikely to impact on CSGHN. This was because hypomagnesaemia is already a recognised side effect of cetuximab. Furthermore, in one study, the heterogeneity of the patient populations and concurrent chemotherapy regimens meant that a clear impression of the benefits of cetuximab in head and neck cancer could not be gained. The Evidence Update also found new evidence relating to alternative therapies, nutritional support and psychological therapies. For all three areas

survival and recurrence.	the evidence was found not to impact on CSGHN.
	This was due to a lack of evidence provided for
The Evidence Update concluded that due to the	nutritional support, the importance of
limited evidence provided by this study it was	psychological therapies already being recognised
unlikely to affect an update of CSGHN.	by the guideline and because CSGHN does not cover acupuncture.
A meta-analysis <sup>29</sup> examined the outcomes of	cover acupuncture.
elective or therapeutic neck dissection in people	Clinical feedback highlighted new chemotherapy
with oral cavity cancers and node-negative neck.	regimens, oncological interventions, surgical
It included four trials (n=283). Results showed	treatments and robotic/transoral laser for head
that elective surgery was associated with a lower	and neck cancers. However, no study details were
risk of disease-specific death. However, the three	provided and no additional evidence beyond those
trials showing the most benefit were 20 or more	studies included in the Evidence Update in this
years old whilst the recent study found no benefit	area were identified through this surveillance
of elective surgery.	review.
The Evidence Update concluded that this	The references that were provided by the GDG
evidence was unlikely to change current practice.	are unlikely to currently impact on CSGHN. This is
, , , , , , , , , , , , , , , , , , , ,	because this guidance is concerned with service
Timing of dental implant surgery	use and not specific treatment interventions.
20	However, it is anticipated that they may be
A systematic review <sup>30</sup> evaluated the placement of	relevant to the new Upper airways tract cancer
primary osseointegrated dental implants at the	guideline which is currently in development and
same time as radical surgery. Forty one papers	will include recommendations on assessment and
were included but meta-analysis was not	management of upper airways tract cancers.
attempted. For the number of implants, implants used for reasons other than restoration, failure of	
implants and survival of implants the data were	
incomplete. However, from the studies which	
reported on the survival of implants, 96-100%	
were reported as surviving with a follow-up range	
of 15-96 months.	
The Evidence Update concluded that this study	
was unlikely to affect a future update of the	

guideline since CSGHN does not make specific	
recommendations about the timing of placing	
dental implants.	
Open partial laryngectomy	
A meta-analysis <sup>31</sup> investigated open partial	
laryngectomy for the treatment of early laryngeal	
carcinoma that had recurred after initial	
radiotherapy. It included 26 papers (n=560). The	
results showed that open partial laryngectomy	
was effective.	
Currently, CSGHN does not address this topic.	
The Evidence Update concluded that the 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.	
Surgery versus radiotherapy	
A cost-utility analysis <sup>32</sup> compared CO <sub>2</sub>	
endolaryngeal laser excision with standard	
fractionated radiation therapy in early stage glottic	
cancer. The study was conducted in Canada. It	
was found that CO <sub>2</sub> endolaryngeal laser excision	
was cheaper and more effective than its	
counterpart.	
The Evidence Update concluded that the direct	
application of this study's findings to the UK is	
precluded by the differences between the	
Canadian and UK healthcare systems however,	

the information may be useful in guiding treatment	
choice. It was concluded that this evidence may be a consideration in a future update to guidance.	
A systematic review <sup>33</sup> examined radiotherapy and transoral laser microsurgery for the treatment of early glottic cancer. Twenty one studies of 880 patients were included. The review concluded that the evidence found did not show a difference between radiotherapy and transoral laser surgery in this type of cancer.	
The Evidence Update concluded that this evidence was unlikely to impact on CSGHN as this guideline does not make any recommendations about treatment choice. The Evidence Update stated that CSGHN already contains a systematic review comparing radiotherapy with surgery for this type of cancer. However, it showed little difference between the two treatments.	
Mixed treatment comparisons	
An individual patient data meta-analysis <sup>34</sup> was identified. This included 87 studies of 16,485 patients with squamous cell carcinoma of the head and neck. Results showed that locoregional treatment plus chemotherapy was better than locoregional treatment alone. When stratified by tumour type and timing of chemotherapy, it was found that the chemotherapy concomitant with locoregional treatment significantly improved survival in tumours of the oropharynx and larynx. No significant improvement in survival with	

adjuvant and neoadjuvant therapy and no impact	
of chemotherapy timing was found for tumours of	
the oral cavity or hypopharynx.	
The Evidence Update stated that due to the	
enrolment period for this study, it was unlikely to	
have included some of the neoadjuvant	
chemotherapy regimens which are currently used	
in clinical practice therefore limiting its likely	
impact on the guideline.	
A network meta-analysis <sup>35</sup> was also identified	
which included 102 trials of 23,000 patients with	
non-metastatic squamous cell carcinoma of the	
head and neck. Overall, results showed that	
altered fractionated radiotherapy with concomitant	
chemotherapy was most likely to be the best	
treatment option.	
Currently, CSGHN does not make specific	
recommendations about the timing or regimens of	
chemotherapy. The Evidence Update concluded	
that the evidence in this area could be a	
consideration in a future update to guidance.	
Biological Treatments	
Hypomagnesaemia in patients with advanced	
cancer treated with cetuximab was investigated in	
a meta-analysis <sup>36</sup> . This included 19 studies	
(n=4559) but only 629 patients had head and	
neck cancer. Results showed that the incidence	
of hypomagnesaemia was 36.7% and the	
incidence of grade 3 and 4 hypomagnesaemia	
was 5.6%.	

Hypomagnesaemia is a recognised side effect of cetuximab treatment and so the Evidence Update concluded that this evidence was unlikely to affect future updates to the guideline.	
A systematic review <sup>37</sup> of 14 trials examined cetuximab in head and neck cancer patients with results being separated by trial phase. In phase I and II trials 18.7% of patients showed an overall response to cetuximab. For phase III trials the overall response was 17% for platinum-based regimens plus placebo but 34.2% for platinum based regimens plus cetuximab. Furthermore, survival increased in those in the cetuximab group.	
The Evidence Update concluded that this study was unlikely to influence an update of the guidance. This was because a clear impression of the benefits of cetuximab in head and neck cancer could not be identified due to the heterogeneity of the patient population and concurrent chemotherapy regimens in the included study. Furthermore, CSGHN does not cover the use of cetuximab.	
Alternative therapies	
A systematic review <sup>38</sup> investigated acupuncture for the treatment of radiation-induced xerostomia. It included three studies. No evidence for the benefit of acupuncture was found.	
As CSGHN does not cover acupuncture the	

Evidence Update concluded that this study was unlikely to impact on the guideline. It was stated that further studies with standardised treatments and a valid comparator are needed.	
Nutritional Support	
A Cochrane review <sup>39</sup> evaluated different enteral feeding methods in head and neck cancer patients undergoing radiotherapy or chemotherapy. Only one study (n=33) was included. This found that nasogastric feeding led to greater weight loss compared to percutaneous endoscopic gastrostomy (PEG). Furthermore, PEG feeding lasted significantly longer and cost more than nasogastric feeding. The authors concluded that more research is needed so that the optimum feeding method can be determined. The Evidence Update concluded that this study was unlikely to affect an update of CSGHN due to the lack of evidence it provided.	
Psychological therapies	
Psychological interventions for head and neck cancer patients were examined in a systematic review <sup>40</sup> . Nine studies of 627 patients were included. The authors concluded that the evidence for psychological interventions was limited by a small number of studies, methodological issues and poor comparability between interventions. They noted that none of the included interventions were supported by the necessary level of evidence.	

The Evidence Update stated that this evidence was unlikely to impact on future guidance since CSGHN already recognises the importance of psychological interventions in the management of head and neck cancer patients. <u>10-Year Surveillance Review (2015)</u> No new evidence in this area was considered.		
Clinical area: After-care and rehabilitation		
Q: In patients who have been treated for head and after treatment care period, improve outcomes?	neck cancer, does involvement in the manager	nent of the patient by a restorative dentist, in the
Evidence summary	GDG/clinical perspective	Impact
Evidence Update (2012)         Dental care         A systematic review <sup>41</sup> investigated the factors that influenced the development of osteoradionecrosis of the jaw after tooth extraction in patients with head and neck cancer who had undergone radiation treatment. Nineteen papers were included. It was found that the overall occurrence in those who received prophylactic hyperbaric oxygen therapy before extraction was 4%. Extractions outside the field of radiation treatment or with doses of radiation less than 60 GY showed almost no risk of developing osteoradionecrosis.         The Evidence update concluded that due to the limited quality of this evidence it would not impact	No GDG feedback was provided by the GDG questionnaire.	The Evidence Update identified new evidence relating to the development of osteoradionecrosis of the jaw after tooth extraction in patients with head and neck cancer who had undergone radiation treatment. However, it concluded that this evidence would not impact on CSGHN due to its limited quality. New evidence on the prevention and treatment of osteoradionecrosis of the jaw after radiotherapy or brachytherapy with or without chemotherapy was also provided in the Evidence Update. The Evidence Update concluded that NICE CSGHN does not deal with osteoradionecrosis directly but instead 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.

on future updates of the guidance. A review <sup>42</sup> was identified which included 43 articles on the prevention and treatment of osteoradionecrosis of the jaw after radiotherapy or brachytherapy with or without chemotherapy for head and neck cancer (n=1537). The main strategy for prevention was the use of hyperbaric oxygen therapy which was also the most studied treatment method. Reported response to treatment ranged from 19% to 93%. The Evidence Update concluded that NICE CSGHN does not deal with osteoradionecrosis directly but instead 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. <u>10-Year Surveillance Review (2015)</u> No new evidence in this area was considered.		
Clinical area: Follow-up and recurrent disease		
Q: For patients who have been treated for head and	d neck cancer, what is the effect of routine follo	w-up on outcomes including timelines of detection
of local recurrence or second primary tumour? Evidence summary	GDG/clinical perspective	Impact
-	• •	•
Evidence Update (2012)	No GDG feedback was provided by the GDG questionnaire.	New evidence on early discharge in laryngeal dysplasia was provided in the Evidence Update.
Early discharge in laryngeal dysplasia		The Evidence Update concluded that CSGHN
A meta-analysis <sup>43</sup> of case series was identified		recommends discharge from follow-up after 5 years for those with cancer but does not mention

<ul> <li>which aimed to determine the rate of transformation to cancer and the time to transformation in 940 cases (9 studies) of laryngeal dysplasia. A significant association between histological grade and rate of transformation was found but no significant association was identified between grade of dysplasia and time to transformation.</li> <li>The Evidence Update concluded that CSGHN recommends discharge from follow-up after 5 years for those with cancer but does not mention follow-up for dysplasia. As such, the Evidence Update concluded that this evidence could be considered in future guidance.</li> <li><u>10-Year Surveillance Review (2015)</u> No new evidence in this area was considered.</li> </ul>	follow-up for dysplasia. The Evidence Update concluded that this evidence could be considered in future guidance. The evidence provided in the Evidence Update on early discharge in laryngeal dysplasia is unlikely to impact on this guidance. This is because CSGHN provides guidance on services for head and neck cancer patients and does not specifically focus on diagnosis and treatment options. Nonetheless, this evidence may be more relevant to the in- development guideline on Upper airways tract cancer.
Clinical area: Follow-up and recurrent disease	
detection of recurrence?	at are the relative efficacies of PET, MRI, CT and ultrasound scanning in the

Evidence summary	GDG/clinical perspective	Impact
Evidence Update (2012)	Clinical feedback indicated that there are new roles for PET CT in people with UAT	The clinical feedback is unlikely to impact on CSGHN. This is because no study details were
None identified.	cancers. However, no references for the new evidence were provided.	provided and no evidence in this area was identified through the surveillance review.
10- Year Surveillance Review (2015)		
No new evidence in this area was considered.		

For the following areas of the guideline no new evidence was considered:

- Pre-treatment assessment and management
- Palliative interventions and care

# **Ongoing research**

The following ongoing studies were highlighted by the GDG:

- DeEscalate trial (<u>ISRCTN33522080</u>) A multi-centre RCT determining the optimum treatment for patients with Human Papillomavirus positive oropharyngeal squamous cell carcinoma. The end date for this trial is 28/2/17.
- ART DECO trial (<u>ISRCTN01483375</u>) A multi-centre RCT of dose escalated intensity modulated radiotherapy versus standard dose intensity modulated radiotherapy in 246 patients with laryngeal and hypopharyngeal cancers in the UK. The end date for this trial is 07/03/2020.
- Head and Neck 5000 Trial <u>A cohort study</u> of 5000 head and neck cancer patients to evaluate the outcome of centralisation in head and neck cancer. No end date was found for this study.
- NIMRAD study (<u>NCT01950689</u>) An RCT of Nimorazole versus radiotherapy in patients with head and neck squamous cell carcinoma who are not suitable for synchronous chemotherapy or cetuximab. The end date for this study is June 2020.

### Anti-discrimination and equalities considerations

None identified.

# Conclusion

Through the 10 year surveillance review of CSGHN no new evidence which may potentially change the direction of guidance recommendations was identified. The proposal is not to update the guidance at this time and to move this guidance onto the static list because it fulfils the following criteria:

o No evidence was identified that would impact on the current guidance and no quality standard has been commissioned.

# References

- 1. Higgins TS and 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. [Review]. Otology & Neurotology 31:1473-1479.
- 2. Peridis S, Pilgrim G, Athanasopoulos I et al. (2011) Carbonic anhydrase-9 expression in head and neck cancer: a metaanalysis. European Archives of Oto-Rhino-Laryngology 268:661-670.
- 3. Zhang B, Li X, and Lu X. (2010) Standardized uptake value is of prognostic value for outcome in head and neck squamous cell carcinoma. [Review]. Acta Oto-Laryngologica 130:756-762.
- 4. Chuang S, Jenab M, Heck J 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.
- 5. Nicolotti N, Chuang S, 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. Eur J Epidemiol 26:619-628.
- 6. Sipaul F, Birchall M, and 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 268:1109-1117.
- 7. Syrjanen S, Lodi G, von B, I et al. (2011) Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. [Review]. Oral Diseases 17:Suppl-72.
- 8. Liu Y, Fang Z, Liu L et al. (2011) Detection of Epstein-Barr virus DNA in serum or plasma for nasopharyngeal cancer: a metaanalysis. Genetic Testing & Molecular Biomarkers 15:495-502.
- Brocklehurst P, Kujan O, Glenny AM et al. (10-11-2010) Screening programmes for the early detection and prevention of oral cancer. [Review][Update of Cochrane Database Syst Rev. 2006;3:CD004150; PMID: 16856035]. Cochrane Database of Systematic Reviews 11:CD004150.
- 10. Xu GZ, Guan DJ, and He ZY. (2011) (18)FDG-PET/CT for detecting distant metastases and second primary cancers in patients with head and neck cancer. A meta-analysis. [Review]. Oral Oncology 47:560-565.

- 11. 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 33:941-948.
- 12. Chien CR, Lin HW, Yang CH et al. (2011) High case volume of radiation oncologists is associated with better survival of nasopharyngeal carcinoma patients treated with radiotherapy: a multifactorial cohort analysis. Clinical Otolaryngology 36:558-565.
- 13. Lee CC, Huang TT, Lee MS et al. (2011) Survival rate in nasopharyngeal carcinoma improved by high caseload volume: a nationwide population-based study in Taiwan. Radiation Oncology 6:92.
- 14. Chia SH, Gross ND, and Richmon JD. (2013) Surgeon experience and complications with Transoral Robotic Surgery (TORS). Otolaryngology Head & Neck Surgery 149:885-892.
- 15. Jalisi S, Bearelly S, Abdillahi A et al. (2013) Outcomes in head and neck oncologic surgery at academic medical centers in the United States. Laryngoscope 123:689-698.
- 16. Sharma A, Schwartz SM, and Mendez E. (15-5-2013) Hospital volume is associated with survival but not multimodality therapy in Medicare patients with advanced head and neck cancer. Cancer 119:1845-1852.
- 17. Gourin CG, Dy SM, Herbert RJ et al. (2014) Treatment, survival, and costs of laryngeal cancer care in the elderly. Laryngoscope 124:1827-1835.
- 18. Ouyang D, El-Sayed IH, and Yom SS. (2014) National trends in surgery for sinonasal malignancy and the effect of hospital volume on short-term outcomes. Laryngoscope 124:1609-1614.
- 19. Sun GH, Aliu O, Moloci NM et al. (1-1-2014) Association between hospital case volume and the use of bronchoscopy and esophagoscopy during head and neck cancer diagnostic evaluation. Cancer 120:61-67.
- 20. Gourin CG and Frick KD. (2012) National trends in oropharyngeal cancer surgery and the effect of surgeon and hospital volume on short-term outcomes and cost of care. Laryngoscope 122:543-551.
- 21. Eskander A, Irish J, Groome PA et al. (2014) Volume-outcome relationships for head and neck cancer surgery in a universal health care system. Laryngoscope 124:2081-2088.

- 22. Eskander A, Merdad M, Irish JC et al. (2014) Volume-outcome associations in head and neck cancer treatment: A systematic review and meta-analysis. Head and Neck 36:1820-1834.
- 23. Colella G, Cannavale R, Flamminio F et al. (2010) Fine-needle aspiration cytology of salivary gland lesions: a systematic review. [Review] [19 refs]. Journal of Oral & Maxillofacial Surgery 68:2146-2153.
- 24. Baujat B, Bourhis J, Blanchard P et al. (2010) Hyperfractionated or accelerated radiotherapy for head and neck cancer. [Review]. Cochrane Database of Systematic Reviews 12:CD002026.
- 25. Glenny AM, Furness S, Worthington HV et al. (8-12-2010) Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. [Review]. Cochrane Database of Systematic Reviews 12:CD006387.
- 26. Roe JW, Carding PN, Dwivedi RC et al. (2010) Swallowing outcomes following Intensity Modulated Radiation Therapy (IMRT) for head & neck cancer a systematic review. [Review]. Oral Oncology 46:727-733.
- 27. 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 38:702-709.
- Bessell A, Glenny AM, Furness S et al. (2011) Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. [Review][Update of Cochrane Database Syst Rev. 2007;(4):CD006205; PMID: 17943894]. Cochrane Database of Systematic Reviews 9:CD006205.
- 29. 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. [Review]. Oral Oncology 47:320-324.
- 30. Barber AJ, Butterworth CJ, and Rogers SN. (2011) Systematic review of primary osseointegrated dental implants in head and neck oncology. [Review]. British Journal of Oral & Maxillofacial Surgery 49:29-36.
- 31. Paleri V, Thomas L, Basavaiah N et al. (15-6-2011) Oncologic outcomes of open conservation laryngectomy for radiorecurrent laryngeal carcinoma: a systematic review and meta-analysis of English-language literature. [Review]. Cancer 117:2668-2676.

- 32. Higgins KM. (2011) 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 121:116-134.
- 33. Spielmann PM, Majumdar S, and 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. [Review]. Clinical Otolaryngology 35:373-382.
- 34. Blanchard P, Baujat B, Holostenco V et al. (2011) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiotherapy & Oncology 100:33-40.
- 35. Blanchard P, Hill C, Guihenneuc-Jouyaux C et al. (2011) Mixed treatment comparison meta-analysis of altered fractionated radiotherapy and chemotherapy in head and neck cancer. Journal of Clinical Epidemiology 64:985-992.
- 36. Cao Y, Liao C, Tan A et al. (2010) Meta-analysis of incidence and risk of hypomagnesemia with cetuximab for advanced cancer. Chemotherapy 56:459-465.
- 37. Reeves TD, Hill EG, Armeson KE et al. (2011) Cetuximab therapy for head and neck squamous cell carcinoma: a systematic review of the data. [Review]. Otolaryngology Head & Neck Surgery 144:676-684.
- 38. O'Sullivan EM and 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. [Review]. Acupuncture in Medicine 28:191-199.
- 39. Nugent B, Lewis S, and O'Sullivan JM. (17-3-2010) Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy. [Review] [42 refs]. Cochrane Database of Systematic Reviews.(3):CD007904, 2010. CD007904.
- 40. 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. [Review]. Supportive Care in Cancer 19:871-881.
- 41. Nabil S and Samman N. (2011) Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. [Review]. International Journal of Oral & Maxillofacial Surgery 40:229-243.

- 42. Peterson DE, Doerr W, Hovan A et al. (2010) Osteoradionecrosis in cancer patients: the evidence base for treatmentdependent frequency, current management strategies, and future studies. [Review]. Supportive Care in Cancer 18:1089-1098.
- 43. 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. [Review]. Clinical Otolaryngology 35:364-372.