National Collaborating Centre for Cancer

Cancer of the upper aerodigestive tract

assessment and management in people aged 16 and over

NICE Guideline 36

Appendices A-G

February 2016

Final version

Commissioned by the National Institute for Health and Care Excellence

Funding
Funded to produce guidelines for the NHS by NICE

Contents

Appendix A: The cost-effectiveness of systemic imaging for distant metastases in patients with cancer of the upper aerodigestive tract?

A.1 Background

The presence of distant metastases is one of the most important factors influencing the plan of treatment in patients with cancer of the upper aerodigestive tract. Failing to identify distant metastases can mean that patients may unnecessarily receive treatment of curative intent that they would otherwise avoid. Therefore, a strategy of systemic imaging to detect distant metastases is often advocated.

However, in comparison to other cancers, distant metastases are less common in cancer of the upper aerodigestive tract (<10% at diagnosis). As such, it may not be necessary or cost-effective to systemically stage all patients. It may instead be preferable to perform staging in a selected higher risk group based upon known risk factors (such as tumour site and stage).

As well as uncertainty around which patients should receive systemic imaging, there is also debate over the preferred imaging method. Established approaches such as chest radiographs or contrast enhanced computerised tomography (CT) scans may be replaced by more advanced techniques such as PET CT. These newer techniques are likely to be diagnostically superior but they come at much greater expense and so may not be cost-effective. Furthermore, the cost-effectiveness of such techniques is intrinsically linked to the populations selected for imaging and so it's possible that such techniques may be cost-effective in high risk populations but not in others.

A.2 Aims

To estimate the cost-effectiveness of systemic imaging in patients with cancer of the upper aerodigestive tract.

A.3 Existing Economic Evidence

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

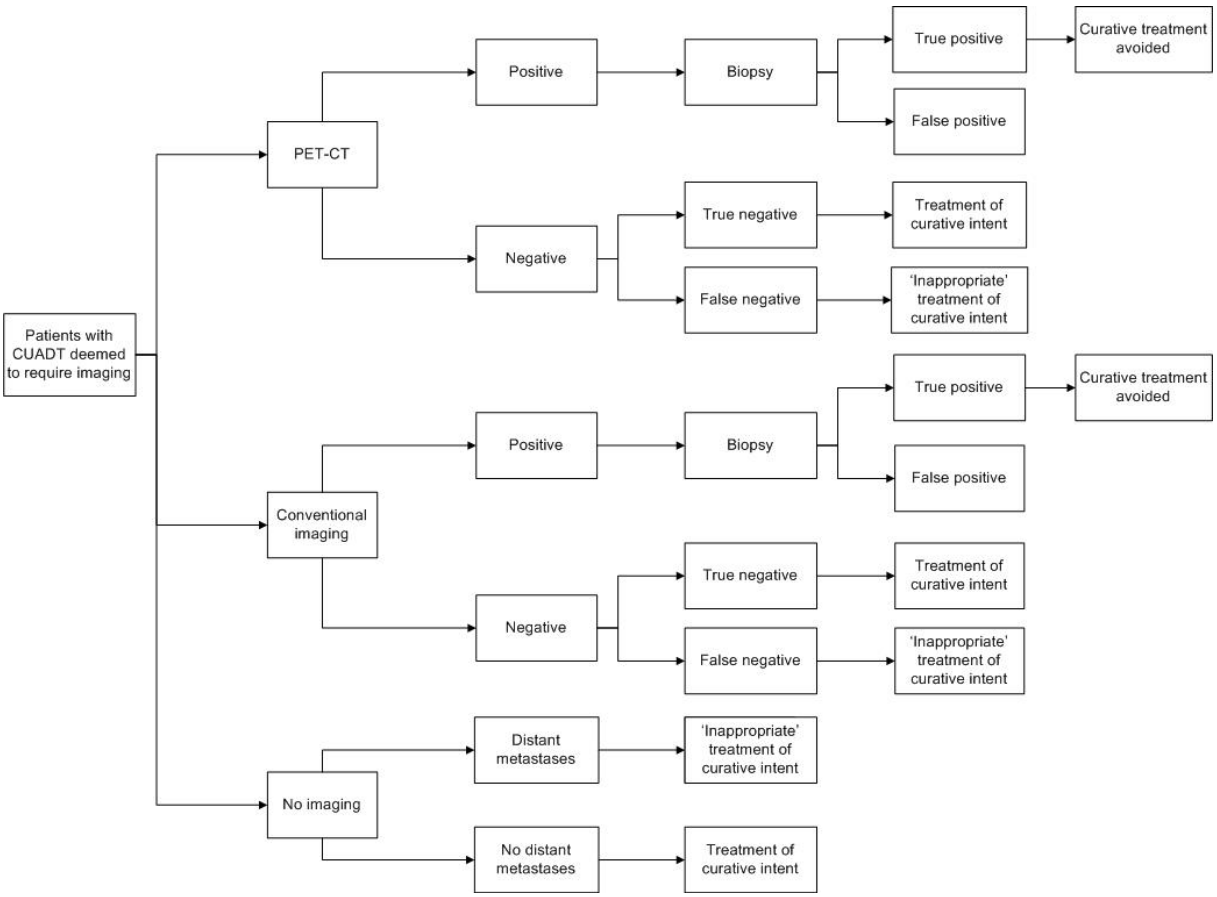
A.4 De Novo Economic Model

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

Patients with CUADT enter the model and may or may not undergo imaging depending upon the systemic staging strategy. Patients in one of the imaging strategies ("PET-CT" or "Conventional imaging") will undergo imaging where a suspected site of distant disease may or may not be detected. Patients with a suspected site of distant disease (i.e. positives) will undergo a biopsy for confirmation of the result. If the positive result is confirmed (true positive) then the patient may no longer undergo treatment for their primary tumour (depending upon the proportion of patients with a change in management described later). If the positive result is not confirmed at biopsy (false positive) then no further action is required and the patient can proceed with treatment of the primary tumour. Patients without suspected

distant disease detected with imaging (negatives) will not undergo a biopsy and will proceed to treatment for their primary tumour. However, some of these negatives will be false and this will be found out subsequently. In these cases, it could be said that the patient has undergone 'unnecessary' treatment of the primary tumour. Patients in the "no imaging" strategy do not undergo imaging and therefore all patients will undergo treatment for their primary tumour. If it is subsequently found that the patient has distant disease then this treatment could be deemed to have been inadequate and inappropriate for the needs of the patient.

Figure 1: Systemic imaging pathway for the detection of distant metastases



A.5 Clinical data

A.5.1 Prevalence

An audit dataset of 18,968 patients from The National head and Neck Cancer Audit (2011-14) has been utilised to provide data on the prevalence of distant metastases in patients with cancer of the upper aerodigestive tract. The dataset shows that distant disease was present in 548 patients, equating to an overall prevalence of 3% when considering all patients with cancer of the upper aerodigestive tract.

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

A.5.2 Diagnostic accuracy

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

As these differences in diagnostic accuracy were found to be significant, it was decided that, for the purposes of the economic model, the diagnostic accuracy data from the subgroups analysis should be utilised rather than the overall diagnostic accuracy data. The implications of this should be noted though as the overall diagnostic accuracy is likely to be far better in the model than it was in the study by Xu et al. 2012. This is a reflection of the vastly differing proportion of patients with nasopharyngeal cancer. In Xu et al. some 70% of patients had nasopharyngeal cancer, whereas only 2% have nasopharyngeal cancer in the National Head and Neck Cancer Audit dataset.

The sensitivity and specificity of the two imaging strategies, as utilised in the model, are given in the table below.

Table 1: Diagnostic accuracy data applied in the model

Test strategy and cancer type	Value	PSA distribution‡	Source
Nasopharyngeal cancer			
PET/CT or PET – Sensitivity	0.82	Beta (alpha =107, beta =23)	Xu et al. 2012
PET/CT or PET – Specificity	0.97	Beta (alpha =620, beta =19)	Xu et al. 2012
Conventional imaging* – Sensitivity	0.30	Beta (alpha =39, beta =91)	Xu et al. 2012
Conventional imaging* – Specificity	0.97	Beta (alpha =620, beta =19)	Xu et al. 2012
Non-nasopharyngeal cancers (Xu 2012)			
PET/CT or PET – Sensitivity	0.85	Beta (alpha =54, beta =10)	Xu et al. 2012
PET/CT or PET – Specificity	0.95	Beta (alpha =298, beta =16)	Xu et al. 2012
Conventional imaging† – Sensitivity	0.62	Beta (alpha =39, beta =24)	Xu et al. 2012
Conventional imaging† – Specificity	0.93	Beta (alpha =292, beta =22)	Xu et al. 2012

*Conventional anatomic imaging methods for nasopharyngeal cancer included chest radiography, abdominal ultrasonography, and bone scan.
†For other sites, conventional imaging methods were defined as chest with/without abdominal CT.
‡Alpha and beta values estimated using patient numbers from Xu et al. 2012

A.6 Costs

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

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

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

A.6.1 Systemic imaging costs

The costs associated with imaging modalities were obtained from NHS reference costs 2013-14 using the relevant procedure codes. Imaging costs applied in the model are shown in the table below.

Table 2: Systemic imaging costs

Test	Cost	PSA distribution‡	Source
PET-CT	£651.96	Gamma (SE =245.89, alpha =7, beta =93)	NHS Reference costs 2013/14 - RA42Z - Nuclear Medicine, Category 8 (PET-CT) in outpatient diagnostic imaging
Conventional imaging for non-nasopharyngeal sites			
Chest CT with abdominal scan	£120.05	Gamma (SE =33.63, alpha =13, beta =9)	NHS Reference costs 2013/14 - RA12Z - Computerised Tomography Scan, two areas with contrast in outpatient diagnostic imaging
Conventional imaging for nasopharyngeal sites			
Chest radiography	£29.60	Gamma (SE =6.89, alpha =18, beta =2)	NHS Reference costs 2013/14 - DAPF - Direct Access Plain Film
Abdominal ultrasound	£51.91	Gamma (SE =18.09, alpha =8, beta =6)	NHS Reference costs 2013/14 - RA23Z - Ultrasound Scan, less than 20 minutes in outpatient diagnostic imaging
Bone scan	£204.14	Gamma (SE =52.49, alpha =15, beta =13)	NHS Reference costs 2013/14 - RA36Z - Nuclear Medicine, Category 2 in outpatient diagnostic imaging
Total for nasopharyngeal conventional imaging	£285.65		
‡ Alpha and beta values estimated using upper and lower cost estimates from NHS Reference costs 2013/14			

A.6.2 Biopsy costs

It was assumed that potential sites of distant metastases would be biopsied under imaging guidance by a radiologist at an estimated cost of £100.05. The cost for this procedure was sourced from NHS reference costs 2013-14 using codes associated with ‘Ultrasound Mobile

Scan or Intraoperative Procedures'. A weighted average cost was calculated to account for the differing lengths of time that may be required to perform the procedure (weightings were based on the number of examinations recorded in NHS Reference costs).

Note that it was thought that a CT scan would be the most likely imaging modality used to guide biopsies in clinical practice. However, in the absence of a code that specifically relates to a CT guided biopsy, the 'Ultrasound Mobile Scan or Intraoperative Procedures' code was thought to be the closest approximation. Alternative biopsy costs, including one based on the guideline committee's estimate of the cost of a CT guided biopsy cost (£150), were explored in sensitivity analysis.

The biopsy costs applied in the model are shown in the table below.

Table 3: Biopsy costs applied in the model

Biopsy type	Value	PSA distribution‡	Source
Image guided biopsy less than 20 minutes - proportion	19%*	Dirichlet (alpha =20)	NHS Reference costs 2013/14 - RA25Z† in outpatient diagnostic imaging
Image guided biopsy 20 to 40 minutes - proportion	76%*	Dirichlet (alpha =77)	NHS Reference costs 2013/14 - RA26Z† in outpatient diagnostic imaging
Image guided biopsy more than 40 minutes - proportion	5%*	Dirichlet (alpha =6)	NHS Reference costs 2013/14 - RA27Z† in outpatient diagnostic imaging
Image guided biopsy less than 20 minutes - cost	£75.99	Gamma (SE =14.34, alpha =28, beta =3)	NHS Reference costs 2013/14 - RA25Z† in outpatient diagnostic imaging
Image guided biopsy 20 to 40 minutes - cost	£107.94	Gamma (SE =38.15, alpha =8, beta =13)	NHS Reference costs 2013/14 - RA26Z† in outpatient diagnostic imaging
Image guided biopsy more than 40 minutes - cost	£74.91	Gamma (SE =27.07, alpha =8, beta =10)	NHS Reference costs 2013/14 - RA27Z† in outpatient diagnostic imaging
Weighted average cost	**£100.05**		

†Ultrasound Mobile Scan or Intraoperative Procedures

*Weightings based on number of examinations recorded in NHS Reference costs 2103/14

‡ Alpha and beta values estimated using upper and lower cost estimates from NHS Reference costs 2013/14

It should be noted that the guideline committee were uncertain as to whether patients with a positive finding on an imaging scan would always necessarily undergo a biopsy. In some cases, it may not be possible to obtain a biopsy sample because of the location of the metastases. In such cases, the clinician would most likely proceed with the planned treatment of the primary tumour and use follow-up appointments to check upon the potential metastases. Thus, these patients would not be spared potentially unnecessary treatment and the only 'benefits' of distant disease detection would be aspects that cannot be readily captured in a cost-effectiveness analysis (such as an accurate prognosis).

In an attempt to capture this aspect in the analysis, we assumed that there would be a proportion of patients that could not be biopsied. However, attempts to obtain a reliable

estimate for this parameter proved unsuccessful and as such an assumed value of 10% was applied based upon advice from the guideline committee.

A.6.3 Initial treatment costs avoided

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

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

The table below shows a summary of the initial treatments avoided for each tumour site and stage together with its associated cost estimate. Full details of the cost estimations are provided in supplementary tables at the end of Appendix A.

Table 4: Summary of costs of treatments avoided by site and stage

Site and stage	Proportion	PSA distribution‡	Source
Hypopharynx			
Stage I – Proportion	0%	Dirichlet (alpha =1)	National Head and Neck Cancer Audit dataset
Stage II – Proportion	1%	Dirichlet (alpha =4)	National Head and Neck Cancer Audit dataset
Stage III – Proportion	1%	Dirichlet (alpha =9)	National Head and Neck Cancer Audit dataset
Stage IV – Proportion	16%	Dirichlet (alpha =86)	National Head and Neck Cancer Audit dataset
Stage I – Cost	£3,689.36	Gamma (SE =1275.66, alpha =8, beta =441)	NHS reference costs 2013/14
Stage II – Cost	£3,559.46	Gamma (SE =1133.38, alpha =10, beta =361)	NHS reference costs 2013/14
Stage III – Cost	£12,421.16	Gamma (SE =4577.60, alpha =7, beta =1687)	NHS reference costs 2013/14 and eMit
Stage IV – Cost	£18,832.17	Gamma (SE =7081.30, alpha =7, beta =2663)	NHS reference costs 2013/14 and eMit
Larynx			
Stage I – Proportion	1%	Dirichlet (alpha =4)	National Head and Neck Cancer Audit dataset
Stage II – Proportion	1%	Dirichlet (alpha =8)	National Head and Neck Cancer Audit dataset
Stage III – Proportion	3%	Dirichlet (alpha =15)	National Head and Neck Cancer Audit dataset

Site and stage	Proportion	PSA distribution‡	Source
Stage IV – Proportion	15%	Dirichlet (alpha =81)	National Head and Neck Cancer Audit dataset
Stage I – Cost	£2,960.32	Gamma (SE =1239.90, alpha =6, beta =519)	NHS reference costs 2013/14
Stage II – Cost	£3,312.25	Gamma (SE =1053.30, alpha =10, beta =335)	NHS reference costs 2013/14
Stage III – Cost	£11,543.70	Gamma (SE =4283.14, alpha =7, beta =1589)	NHS reference costs 2013/14 and eMit
Stage IV – Cost	£18,536.00	Gamma (SE =6908.97, alpha =7, beta =2575)	NHS reference costs 2013/14 and eMit
Nasal cavity and sinus			
Stage I – Proportion	0%	Dirichlet (alpha =2)	National Head and Neck Cancer Audit dataset
Stage II – Proportion	0%	Dirichlet (alpha =1)	National Head and Neck Cancer Audit dataset
Stage III – Proportion	1%	Dirichlet (alpha =4)	National Head and Neck Cancer Audit dataset
Stage IV – Proportion	4%	Dirichlet (alpha =21)	National Head and Neck Cancer Audit dataset
Stage I – Cost	£5,096.75	Gamma (SE =1545.59, alpha =11, beta =469)	NHS reference costs 2013/14
Stage II – Cost	£5,096.75	Gamma (SE =1545.59, alpha =11, beta =469)	NHS reference costs 2013/14
Stage III – Cost	£17,363.19	Gamma (SE =7422.48, alpha =5, beta =3173)	NHS reference costs 2013/14
Stage IV – Cost	£17,363.19	Gamma (SE =7422.48, alpha =5, beta =3173)	NHS reference costs 2013/14
Oral cavity			
Stage I – Proportion	1%	Dirichlet (alpha =5)	National Head and Neck Cancer Audit dataset
Stage II – Proportion	1%	Dirichlet (alpha =7)	National Head and Neck Cancer Audit dataset
Stage III – Proportion	1%	Dirichlet (alpha =8)	National Head and Neck Cancer Audit dataset
Stage IV – Proportion	18%	Dirichlet (alpha =97)	National Head and Neck Cancer Audit dataset
Stage I – Cost	£4,761.44	Gamma (SE =1851.63, alpha =7, beta =720)	NHS reference costs 2013/14
Stage II – Cost	£7,451.39	Gamma (SE =2839.69, alpha =7, beta =1082)	NHS reference costs 2013/14
Stage III – Cost	£20,989.94	Gamma (SE =9074.62,	NHS reference

Site and stage	Proportion	PSA distribution‡	Source
		alpha =5, beta =3923)	costs 2013/14
Stage IV – Cost	£21,319.02	Gamma (SE =9266.10, alpha =5, beta =4027)	NHS reference costs 2013/14 and eMit
Oropharynx			
Stage I – Proportion	0%	Dirichlet (alpha =3)	National Head and Neck Cancer Audit dataset
Stage II – Proportion	1%	Dirichlet (alpha =8)	National Head and Neck Cancer Audit dataset
Stage III – Proportion	2%	Dirichlet (alpha =14)	National Head and Neck Cancer Audit dataset
Stage IV – Proportion	30%	Dirichlet (alpha =165)	National Head and Neck Cancer Audit dataset
Stage I – Cost	£3,969.24	Gamma (SE =1291.76, alpha =9, beta =420)	NHS reference costs 2013/14
Stage II – Cost	£3,849.31	Gamma (SE =1224.94, alpha =10, beta =390)	NHS reference costs 2013/14
Stage III – Cost	£7,868.40	Gamma (SE =2925.42, alpha = 7, beta =1088)	NHS reference costs 2013/14 and eMit
Stage IV – Cost	£7,594.10	Gamma (SE =2808.27, alpha =7, beta =1038)	NHS reference costs 2013/14 and eMit
Nasopharynx			
Stage I – Proportion	0%	Dirichlet (alpha =1)	National Head and Neck Cancer Audit dataset
Stage II – Proportion	0%	Dirichlet (alpha =1)	National Head and Neck Cancer Audit dataset
Stage III – Proportion	1%	Dirichlet (alpha =4)	National Head and Neck Cancer Audit dataset
Stage IV – Proportion	4%	Dirichlet (alpha =20)	National Head and Neck Cancer Audit dataset
Stage I – Cost	£3,429.56	Gamma (SE =991.10, alpha =12, beta =286)	NHS reference costs 2013/14
Stage II – Cost	£6,869.01	Gamma (SE =2504.78, alpha =8, beta =913)	NHS reference costs 2013/14 and eMit
Stage III – Cost	£8,111.95	Gamma (SE =3076.42, alpha =7, beta =1167)	NHS reference costs 2013/14 and eMit
Stage IV – Cost	£9,000.05	Gamma (SE =3500.26, alpha =7, beta =1361)	NHS reference costs 2013/14 and eMit
Weighted average	**£13,856.90**		
‡Alpha and beta values estimated using aggregated upper and lower estimates from NHS reference			

Site and stage	Proportion	PSA distribution‡	Source
costs and eMit			

It should be noted that there was no consensus in the guideline committee around the likelihood that these curative treatments would be avoided in patients with detected distant disease. While it is likely that the intent of the management strategy will change as a result of distant disease detection (from curative to palliative), it was thought that there will still be cases where treatment of the primary tumour would be required.

Therefore, an additional parameter was specified in the model as an estimate of the likelihood that management will change as a result of distant disease detection. In the base case, it was assumed that this figure was 100% but wide variations were explored in sensitivity analyses (including a scenario where the figure was 0%).

A.7 Health related quality of life (QoL) values

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

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

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

There are limitations with combining data across studies in this manner (such as heterogeneity in populations) but, given the absence of better data, this was considered to be the best option in the base case analysis. Furthermore, the estimated value was thought to have face validity by the guideline committee. However, variations are explored in sensitivity analysis (including an analysis where there is no decrement for these procedures).

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

The QoL decrements associated with more complex surgical procedures such as a partial laryngectomy, laryngectomy, glossectomy or pharyngectomy were estimated using data from a cost-utility analysis by Higgins et al. 2011. Higgins et al. 2011 estimated QoL values for patients alive with their voice box partially intact and patients alive without a voice box, which were applied in their analysis to patients after a partial laryngectomy and total laryngectomy,

respectively. Decrements were calculated for this analysis by using the QoL value for patients with their voice box intact as the baseline (also from the Higgins et al. 2011 study) and then calculating the reductions in QoL associated with having a partially intact voice box or no voice box (0.1658 and 0.5068, respectively). Owing to a lack of QoL data, it was assumed that these values would apply to other complex surgical procedures such as a glossectomy or pharyngectomy.

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

Table 5: Quality of life decrements avoided applied in the economic model

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

† SF-36 values from Lassig et al 2008 converted to EQ-5D values using mapping algorithm from Ara et al. 2008

‡ Alpha and beta values estimated using patient numbers from QoL studies

It should be noted that, in addition to the reservations around individual QoL estimates mentioned above, there is a wider limitation regarding the applicability of the data to the modelled population. Most of the treatment related decrements were estimated in patients undergoing treatments of curative intent and it is uncertain to what extent these values would apply to patients with distant disease.

Due to the shortened life expectancy in such patients, there is usually an even greater imperative to maintain QoL. Indeed, it is possible that treatment related decrements may be amplified in such patients as treatment related morbidity that may be considered worth enduring for survival benefits in less advanced patients would no longer be considered acceptable. Therefore, the QoL values shown in the table may underestimate the QoL burden in such patients. However, it is conversely possible that the presented QoL decrements may represent an overestimate for such patients as the worsened Qol caused by the increased severity of the disease may vastly outweigh any treatment related morbidity.

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

A.8 Base Case Results

The base case results of the analysis for the pooled group of all patients with cancer of the upper aerodigestive tract (n=18,968) are presented in the tables below. In table 6, a common baseline approach is adopted with both imaging strategies compared against no imaging whereas in table 7 a dominance rank approach is used in order to determine the optimal strategy.

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

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

Table 6: Base case cost-effectiveness results against common baseline (no imaging)

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

Table 7: Base case cost-effectiveness results using dominance rank approach

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

In addition to the deterministic results above, the base case results were also generated probabilistically. In this analysis the mean total costs and QALYs were recorded after 10,000 probabilistic runs of the analysis (sufficient for stability in the ICER). The probabilistic base case results are presented in tables 8 and 9 below for the comparison against a common baseline and the dominance rank approach.

It can be seen the results are very different even though the conclusion of the analysis remains unchanged. In comparison to no imaging, conventional imaging is now found to be

more costly (£427,260) but still more effective (34.91 QALYs) and cost-effective with an ICER of £12,239 below the NICE threshold of £20,000 per QALY.

The PET-CT strategy was found to be even more costly and less effective than in the base case analysis with an incremental cost of £9,666,909 and incremental QALYs of 48.04 in comparison to the no imaging strategy. Thus, it was again found that PET-CT was not cost-effective with an increased ICER value of £201,226 per QALY well above the £20,000 per QALY threshold. Using the dominance rank approach, it can again be seen that conventional imaging is the optimal strategy (although no longer dominant).

The reason for the large variance in results is explored and explained in a later section showing the probabilistic sensitivity analysis results.

Table 8: Probabilistic base case cost-effectiveness results against common baseline

	Cost		QALYs		
Initial treatment	Total	Incremental	Total	Incremental	ICER (cost per QALY)
No imaging	£0	-	0.00	-	-
Conventional imaging	£427,260	£427,260	34.91	34.91	**£12,239**
PET-CT	£9,666,909	£9,666,909	48.04	48.04	**£201,226**

Table 9: Deterministic Base case cost-effectiveness results using dominance rank

	Cost		QALYs		
Initial treatment	Total	Incremental	Total	Incremental	ICER (cost per QALY)
No imaging	£0	-	0.00	-	-
Conventional imaging	£427,260	£427,260	34.91	34.91	**£12,239**
PET-CT	£9,666,909	£9,239,649	48.04	13.13	**£703,704**

A.9 One-way sensitivity analysis results

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

Table 10: One-way sensitivity analysis results

Change made	Optimal strategy
PET-CT – upper sensitivity value	Conventional imaging
PET-CT – lower sensitivity value	Conventional imaging
Conventional imaging – upper sensitivity value	Conventional imaging
Conventional imaging – lower sensitivity value	Conventional imaging
PET-CT – upper specificity value	Conventional imaging
PET-CT – lower specificity value	Conventional imaging
Conventional imaging – upper specificity value	Conventional imaging
Conventional imaging – lower specificity value	Conventional imaging
Proportion of patients that cannot be biopsied = 25%	Conventional imaging

Change made	Optimal strategy
Proportion of patients that cannot be biopsied = 50%	Conventional imaging
Proportion of patients that cannot be biopsied = 75%	No imaging
Proportion of M+ patients with change in management = 75%	Conventional imaging
Proportion of M+ patients with change in management = 50%	Conventional imaging
Proportion of M+ patients with change in management = 25%	No imaging
Biopsy costs = £150	Conventional imaging
Biopsy costs = £300	Conventional imaging
Conventional imaging costs + 50%	Conventional imaging
Conventional imaging costs - 50%	Conventional imaging
PET-CT + 50%	Conventional imaging
PET-CT - 50%	Conventional imaging
Cost offsets +50%	Conventional imaging
Cost offsets -50%	Conventional imaging
QoL decrements +50%	Conventional imaging
QoL decrements -50%	Conventional imaging
No resection, RT or chemoRT decrements	Conventional imaging
No QoL decrements	Conventional imaging*
Very complex treatment decrement = 0.1658	Conventional imaging
Complex treatment decrements = 0.0412	Conventional imaging
Average life expectancy for M+ patients =6 months	Conventional imaging
Average life expectancy for M+ patients =6 months	Conventional imaging

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

A.10 Threshold analysis

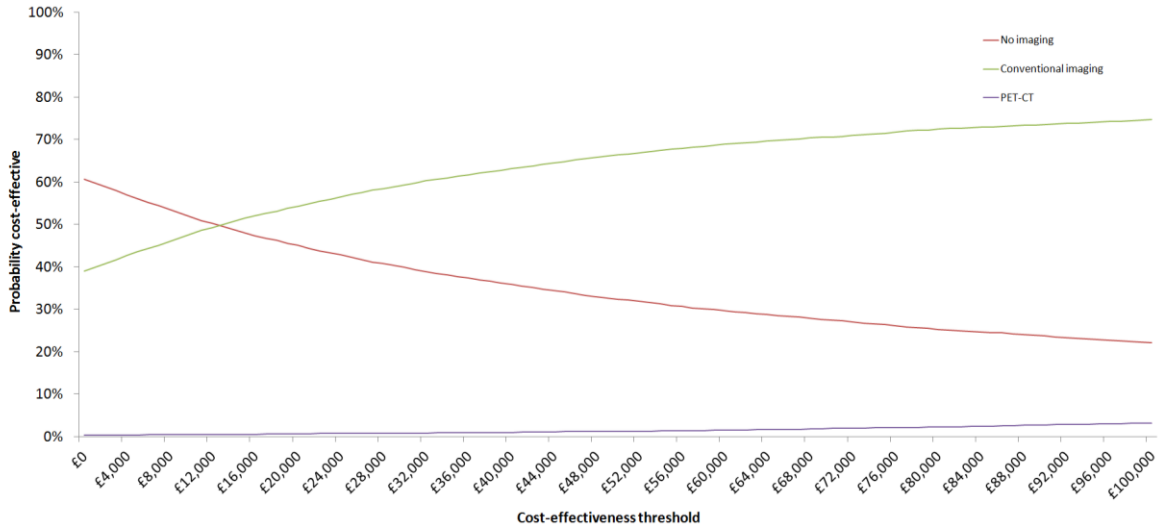
Owing to concerns around the likelihood of management changing as a result of distant disease detection, a threshold analysis was conducted to determine how low this value can be before imaging is no longer cost-effective. It was found that conventional imaging was no longer dominant when the likelihood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

A.11 Probabilistic sensitivity analysis

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

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

Figure 2: Cost-effectiveness acceptability curves (CEACs) for imaging strategies for distant disease in a pooled group of all patients with cancer of the upper aerodigestive tract



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

A.12 Subgroup analysis results (by disease site, T stage and N stage)

The tables below show the optimal strategy (at a cost-effectiveness threshold of £20,000 per QALY) for various subgroups of T and N stages for each disease site.

A.12.1 All sites (n=18,968)

Table 11: Most cost-effective strategies for T and N subgroups in all CUADT sites

	N stage						
T stage	**N0**	**N1**	**N2**	**N3**	**N1+**	**N2+**	**All N stages**
T1	NI	CI	**CI***	PET-CT	**CI***	**CI***	NI
T2	NI	**CI***	**CI***	PET-CT	**CI***	**CI***	CI
T3	NI	CI	**CI***	PET-CT	**CI***	**CI***	**CI***
T4	**CI***	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T2+	CI	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T3+	**CI***	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
All T stages	NI	**CI***	**CI***	PET-CT	CI*	**CI***	**CI***
Key: NI= No imaging CI = conventional imaging							

	N stage						
T stage	**N0**	**N1**	**N2**	**N3**	**N1+**	**N2+**	**All N stages**
Strategies marked in bold with an asterisk were found to be dominant (more effective and less expensive)							

A.12.2 Hypopharyngeal cancer (n=1,118)

Table 12: Most cost-effective strategies for T and N subgroups in hypopharyngeal cancer sites

	N stage						
T stage	**N0**	**N1**	**N2**	**N3**	**N1+**	**N2+**	**All N stages**
T1	NI	NI	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T2	NI	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T3	**CI***	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T4	**CI***	**CI***	**PET-CT***	**PET-CT***	**PET-CT***	**PET-CT***	PET-CT
T2+	**CI***	**CI***	PET-CT	**PET-CT***	PET-CT	PET-CT	**CI***
T3+	**CI***	**CI***	PET-CT	**PET-CT***	PET-CT	**PET-CT***	**CI***
All T stages	**CI***	**CI***	PET-CT	**PET-CT***	PET-CT	PET-CT	**CI***
Key: NI= No imaging CI = conventional imaging							
Strategies marked in bold with an asterisk were found to be dominant							

A.12.3 Laryngeal cancer (n=4,530)

Table 13: Most cost-effective strategies for T and N subgroups in laryngeal cancer sites

	N stage						
T stage	**N0**	**N1**	**N2**	**N3**	**N1+**	**N2+**	**All N stages**
T1	NI	NI	**CI***	**PET-CT***	PET-CT	**PET-CT***	NI
T2	NI	**CI***	**CI***	**PET-CT***	**CI***	**CI***	NI
T3	NI	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T4	**CI***	**CI***	PET-CT	**CI***	PET-CT	PET-CT	**CI***
T2+	CI	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T3+	**CI***	**CI***	**CI***	**PET-CT***	**CI***	PET-CT	**CI***
All T stages	NI	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
Key: NI= No imaging CI = conventional imaging							
Strategies marked in bold with an asterisk were found to be dominant							

A.12.4 Nasal cavity and sinus cancer (n=668)

Table 14: Most cost-effective strategies for T and N subgroups in nasal cavity and sinus cancer sites

	N stage						
T stage	**N0**	**N1**	**N2**	**N3**	**N1+**	**N2+**	**All N stages**
T1	NI	NI	NI	No data	NI	NI	NI
T2	NI	PET-CT	NI	No data	**CI***	NI	NI
T3	**CI***	NI	NI	NI	NI	NI	**CI***

	N stage						
T stage	**N0**	**N1**	**N2**	**N3**	**N1+**	**N2+**	**All N stages**
T4	**CI***	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T2+	**CI***	**CI***	**CI***	PET-CT	**CI***	**CI***	**CI***
T3+	**CI***	**CI***	**CI***	PET-CT	**CI***	**CI***	**CI***
All T stages	**CI***	**CI***	**CI***	PET-CT	**CI***	**CI***	**CI***
Key: NI= No imaging CI = conventional imaging							
Strategies marked in bold with an asterisk were found to be dominant							

A.12.5 Oral cavity cancer (n=6,439)

Table 15: Most cost-effective strategies for T and N subgroups in oral cavity cancer sites

	N stage						
T stage	**N0**	**N1**	**N2**	**N3**	**N1+**	**N2+**	**All N stages**
T1	NI	**CI***	**CI***	**PET-CT***	**CI***	**CI***	NI
T2	NI	**CI***	**CI***	**PET-CT***	**CI***	**CI***	NI
T3	NI	NI	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T4	**CI***	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T2+	NI	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
T3+	**CI***	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
All T stages	NI	**CI***	**CI***	**PET-CT***	**CI***	**CI***	**CI***
Key: NI= No imaging CI = conventional imaging							
Strategies marked in bold with an asterisk were found to be dominant							

A.12.6 Oropharyngeal cancer (n=5,834)

Table 16: Most cost-effective strategies for T and N subgroups in oropharyngeal cancer sites

	N stage						
T stage	**N0**	**N1**	**N2**	**N3**	**N1+**	**N2+**	**All N stages**
T1	NI	NI	NI	**CI***	NI	NI	NI
T2	NI	CI	NI	**CI***	NI	NI	NI
T3	NI	NI	**CI***	**CI***	**CI***	**CI***	**CI***
T4	**CI***	**CI***	**CI***	**CI***	**CI***	**CI***	**CI***
T2+	NI	**CI***	**CI***	**CI***	**CI***	**CI***	**CI***
T3+	NI	**CI***	**CI***	**CI***	**CI***	**CI***	**CI***
All T stages	NI	**CI***	**CI***	**CI***	**CI***	**CI***	**CI***
Key: NI= No imaging CI = conventional imaging							
Strategies marked in bold with an asterisk were found to be dominant							

A.12.7 Nasopharyngeal cancer (n=379)

Table 17: Most cost-effective strategies for T and N subgroups in nasopharyngeal cancer sites

	N stage						
T stage	**N0**	**N1**	**N2**	**N3**	**N1+**	**N2+**	**All N stages**
T1	NI	NI	NI	NI	NI	NI	NI
T2	NI	NI	NI	**PET-CT***	NI	NI	NI
T3	**PET-CT***	NI	NI	NI	NI	NI	NI
T4	NI	NI	**PET-CT***	PET-CT	**PET-CT***	**PET-CT***	**PET-CT***
T2+	NI	NI	PET-CT	**PET-CT***	NI	**PET-CT***	NI
T3+	NI	NI	**PET-CT***	NI	**PET-CT***	**PET-CT***	**PET-CT***
All T stages	NI	NI	NI	**PET-CT***	NI	**PET-CT***	NI
Key: NI= No imaging CI = conventional imaging							
Strategies marked in bold with an asterisk were found to be dominant							

Some trends can be observed from the subgroup analyses. Most notably, it can be seen that the optimal strategy differs from the base case analysis in numerous instances. In general, the imaging strategies (conventional imaging and PET-CT) were more likely to be cost-effective in the more advanced T and N stages, reflecting both the greater risk of distant metastases in these groups and the larger cost offsets.

A.13 Discussion

This analysis aimed to estimate the cost-effectiveness of systemic imaging in patients with cancer of the upper aerodigestive tract. To our knowledge, this is the first model that has investigated the cost-effectiveness of these staging approaches in this setting.

The results of the base case analysis suggest that conventional imaging was the most cost-effective strategy in the pooled group of all head and neck cancer patients. In comparison to a no imaging strategy, conventional imaging was found to be dominant (i.e. more effective and less effective) while in comparison to PET-CT it was found to be less effective but substantially cheaper with an ICER of £308,977 showing that PET-CT is not cost-effective in comparison to conventional imaging.

One-way sensitivity analysis showed that the result was relatively robust with the conclusion of the analysis remaining unchanged in most modelled scenarios. However the notable exception was the proportion of patients whose management changes as a result of distant disease detection, which was of particular interest as there was uncertainty amongst the guideline committee as to what extent management would be altered in many patients. This uncertainty was also reflected in the probabilistic sensitivity analysis. When varying the proportion of patients with a change in management in the PSA (between 0% and 100%), conventional imaging was found to have a 52% probability of being cost-effective at a threshold of £20,000 per QALY. However, when running the PSA without varying this parameter, conventional imaging was found to have a 98% probability of being cost-effective.

Subgroup analysis revealed numerous deviations from the base case result. Notably, PET-CT was found to be cost-effective in numerous high risk groups, such as in patients with N3 disease or in higher risk groups within nasopharyngeal or hypopharyngeal cancer. These different results in subgroup analysis reflect both the higher risk of distant metastases as well as the greater potential for cost savings and QoL benefits as treatments in later stages are more costly and have a greater morbidity risk. It was also found that a strategy of no imaging

was cost-effective in the lowest risk groups (T1N0 and T2N0), reflecting the low likelihood of distant metastases being detected in these groups.

There were a few limitations to the analysis that should be noted. As with most economic analyses, the analysis is, to a large extent, dependent on the data upon which it is based. The primary source used in the analysis was the Head and Neck Cancer Audit data. While this data has the advantage of being applicable to the UK context there are notable limitations. Firstly, the data focused on newly diagnosed head and neck cancer patients only and so does not account for recurrent cancers. Secondly, the dataset only provided information on the rate of distant metastases. Therefore, there were no data available to be able to model some of the other benefits of imaging, such as the detection of synchronous primaries. Thirdly, it was unclear how and at what time point distant distant disease was detected in the dataset. Therefore, it is possible that the prevalence data may not accurately reflect the true prevalence in the cohort (i.e. if it was dependent upon a diagnostic test then the prevalence data would be influenced by the diagnostic accuracy of that test).

Another limitation of the analysis was the uncertainty over the proportion of patients whose management changes as a result of distant disease detection. Due to a lack of data in this area, the proportion of patients with a change in management was not evidence based but was instead based on an assumption. However, the guideline committee themselves had disparate views on this aspect of the analysis (although the majority thought that it would have a substantial impact on managemet). To account for the uncertainty in this area, extensive sensitivity analyses were performed whereby it was found that this parameter is a crucial determinant of the results. This was unsurprising as this aspect was really a fundamental aspect of the model as it informs the benefits of PET staging in cost-effectiveness terms. However, this dependency on an assumption is far from ideal and clearly research in this area would be welcome.

A further limitation of the analysis was that some of the benefits of imaging could not be captured in a cost-effectiveness analysis as some of the benefits of imaging are not readily measurable in terms of costs or effectiveness. For example, benefits of imaging such as patient reassurance or having a more accurate prognosis could not be captured in the analysis. It is perhaps possible that such aspects could be captured (for example by varying QoL weights) but there is currently insufficient evidence to inform such an analysis.

There was also found to be a paucity of quality of life data in this area. Unfortunately, no QoL evidence was identified that was directly applicable to the context of the decision problem. In the absence of such data, QoL benefits were applied based on the QoL decrements that could be avoided by being spared ‘unnecessary’ treatment. As described in detail in the QoL section of this report, there are issues with the individual QoL studies as well as issues with applying them in this context. Overall, it could probably be concluded that the QoL data in this context is of generally poor quality. Therefore, there is considerable uncertainty around the QALY benefits that may be obtained from distant disease detection. However, it should be noted the quantity of QALY benefits was not found to be a crucial determinant of the model result as conventional imaging was found to be dominant (i.e. more effective and cheaper). Therefore, it is really the direction of the QoL values that is of most importance and the guideline committee were in agreement that the direction of the QoL values seemed right. However, further research into QoL in this area (if possible) would be welcomed.

A.14 Conclusion

The results showed that using conventional imaging as the systemic staging strategy was effective and cost-effective in the majority of patient populations. Notable exceptions were the T1N0 and T2N0 patient subgroups, in which no imaging was found to be the optimal strategy because of the low number of patients with systemic disease. Despite the better diagnostic accuracy of PET-CT, its use was not found to be a cost-effective strategy to use in the pooled group of all head and neck cancer patients. In this group of patients, it was found

that the benefits were too small to justify the substantial additional cost associated with PET-CT. However, PET-CT was found to be more cost-effective than conventional imaging in high risk groups (i.e. groups with high prevalence of distant metastases). This was most evident in patients with N3 disease at any subsite, T4 nasopharynx or T4 hypopharynx cancer, where FDG PET-CT was found to be dominant.

Sensitivity analysis showed that there were some scenarios in which the conclusion of the analysis changed. The most notable uncertainty was found to be the proportion of patients with a change in management as a result of distant disease detection.

References

Ara R, Brazier J. Deriving an Algorithm to Convert the Eight Mean SF-36 Dimension Scores into a Mean EQ-5D Preference-Based Score from Published Studies (Where Patient Level Data Are Not Available). Value in Health (2008) 11(7): 1131-1143

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

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

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

Higgins, KM. What treatment for early-stage glottic carcinoma among adult patients: CO2 endolaryngeal laser excision versus standard fractionated external beam radiation is superior in terms of cost utility? Laryngoscope 2011; 121(1): 116-134.

Hollenbeak, CS, Lowe, VJ, and Stack, BC. The cost-effectiveness of fluorodeoxyglucose 18-F positron emission tomography in the NO neck (Structured abstract). Cancer 2001; 92(9): 2341-2348.

Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press

Lassig AAD, Duffy SA, Fowler KE, Ronis DL, Chepeha DB, Terrell JE. The effect of neck dissection on quality of life after chemoradiation. Otolaryngol Head Neck Surg. 2008 Oct;139(4):511-8.

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

Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P (2010) The Average Body Surface Area of Adult Cancer Patients in the UK: A Multicentre Retrospective Study. PLoS ONE 5(1): e8933. doi:10.1371/journal.pone.0008933

Sher, DJ et al. Cost-effectiveness of CT and PET-CT for determining the need for adjuvant neck dissection in locally advanced head and neck cancer (Provisional abstract). Annals of Oncology 2010; 21(5): 1072-1077.

Xu, G., Li, Junkai, Zuo, Xiaoyan, and Li, Chunyan. Comparison of whole body positron emission tomography (PET)/PET-computed tomography and conventional anatomic imaging for detecting distant malignancies in patients with head and neck cancer: a meta-analysis. Laryngoscope 2012. 122(9): 1974-1978

A.15 Supplementary tables (detailed costs by disease site)

A.15.1 Hypopharyngeal cancer

Stage grouping and treatment	Proportion	Cost	Source
Stage I	**0%**	**£3,689.36**	
Excision and neck dissection	20%	£4,728.53	
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	53%	£5,891.25	NHS reference costs 2013/14 - elective inpatient
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	47%	£3,414.15	NHS reference costs 2013/14 - elective inpatient
RT	80%	£3,429.56	
Preparation for Complex Conformal Radiotherapy, with Technical Support (SC52Z)	-	£906.16	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 20 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£2,523.40	NHS reference costs 2013/14 - outpatient radiotherapy
Stage II	**3%**	**£3,559.46**	
Excision and neck dissection	10%	£4,728.53	
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	53%	£5,891.25	NHS reference costs 2013/14 - elective inpatient
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	47%	£3,414.15	NHS reference costs 2013/14 - elective inpatient
RT	90%	£3,429.56	
Preparation for Complex Conformal Radiotherapy, with Technical Support (SC52Z)	-	£906.16	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 20 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£2,523.40	NHS reference costs 2013/14 - outpatient radiotherapy
Stage III	**8%**	**£12,421.16**	
chemoRT	50%	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy

Stage grouping and treatment	Proportion	Cost	Source
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Laryngopharyngectomy and neck dissection	10%	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
Laryngopharyngectomy and neck dissection + RT	20%	£19,592.14	
Laryngopharyngectomy and neck dissection	-	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Laryngopharyngectomy and neck dissection + ChemoRT	20%	£20,250.29	
Laryngopharyngectomy and neck dissection	-	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient

Stage grouping and treatment	Proportion	Cost	Source
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/1414 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/1414 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/1414 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/1414 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Stage IV	**89%**	**£18,832.17**	
Laryngopharyngectomy and neck dissection + chemoRT	90%	£20,250.29	
Laryngopharyngectomy and neck dissection	-	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/1414 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/1414 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/1414 - elective inpatient
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/1414 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/1414 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14- outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14-

Stage grouping and treatment	Proportion	Cost	Source
			outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
ChemoRT alone	10%	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/1414 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/1414 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Weighted average	**100%**	**£17,820.65**	

A.15.2 Laryngeal cancer

Stage grouping and treatment	Proportion	Cost	Source
Stage I	**3%**	**£2,960.32**	
Excision	56%	£2,034.92	
Intermediate, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	57%	£2,124.76	NHS reference costs 2013/14 - elective inpatient
Intermediate, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	43%	£1,916.17	NHS reference costs 2013/14 - elective inpatient
Excision and neck dissection (for supraglottic tumours)	24%	£4,728.53	
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	53%	£5,891.25	NHS reference costs 2013/14 - elective inpatient
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	47%	£3,414.15	NHS reference costs 2013/14 - elective inpatient
RT	20%	£3,429.56	
Preparation for Complex Conformal Radiotherapy, with Technical Support (SC52Z)	-	£906.16	NHS reference costs 2013/14 - outpatient radiotherapy

Stage grouping and treatment	Proportion	Cost	Source
Deliver 20 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£2,523.40	NHS reference costs 2013/14 - outpatient radiotherapy
Stage II	**7%**	**£3,312.25**	
Excision	14%	£2,034.92	
Intermediate, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	57%	£2,124.76	NHS reference costs 2013/14 - elective inpatient
Intermediate, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	43%	£1,916.17	NHS reference costs 2013/14 - elective inpatient
Excision and neck dissection (for supraglottic tumours)	6%	£4,728.53	
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	53%	£5,891.25	NHS reference costs 2013/14 - elective inpatient
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	47%	£3,414.15	NHS reference costs 2013/14 - elective inpatient
RT	80%	£3,429.56	
Preparation for Complex Conformal Radiotherapy, with Technical Support (SC52Z)	-	£906.16	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 20 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£2,523.40	NHS reference costs 2013/14 - outpatient radiotherapy
Stage III	**13%**	**£11,543.70**	**£11,543.70**
chemoRT	50%	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Laryngectomy and neck dissection	25%	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 -

Stage grouping and treatment	Proportion	Cost	Source
			elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
Laryngectomy and neck dissection + RT	15%	£19,592.14	
Laryngopharyngectomy and neck dissection	-	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Laryngectomy and neck dissection + ChemoRT	10%	£20,250.29	
Laryngectomy and neck dissection	-	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy

Stage grouping and treatment	Proportion	Cost	Source
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Stage IV	**77%**	**£18,536.00**	**£18,536.00**
ChemoRT	10%	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Laryngectomy and neck dissection + RT	45%	£19,592.14	
Laryngectomy and neck dissection	-	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Laryngectomy and neck dissection + ChemoRT	45%	£20,250.29	
Laryngopharyngectomy and neck dissection	-	£14,181.18	

Stage grouping and treatment	Proportion	Cost	Source
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Weighted average	**100%**	**£16,120.76**	

A.15.3 Nasal cavity and sinus cancer

Stage grouping and treatment	Proportion	Cost	Source
Stage I	**4%**	**£5,096.75**	
Excision	50%	£2,391.27	
Intermediate Nose Procedures	10%	£1,831.68	NHS reference costs 2013/14 - elective inpatient
Major Nose Procedures	52%	£2,177.73	NHS reference costs 2013/14 - elective inpatient
Very Major Nose Procedures	21%	£2,517.02	NHS reference costs 2013/14 - elective inpatient
Complex Nose Procedures	17%	£3,224.09	NHS reference costs 2013/14 - elective inpatient
Excision + RT	50%	£7,802.22	

Stage grouping and treatment	Proportion	Cost	Source
Wide local excision		£2,391.27	
Intermediate Nose Procedures	10%	£1,831.68	NHS reference costs 2013/14 - elective inpatient
Major Nose Procedures	52%	£2,177.73	NHS reference costs 2013/14 - elective inpatient
Very Major Nose Procedures	21%	£2,517.02	NHS reference costs 2013/14 - elective inpatient
Complex Nose Procedures	17%	£3,224.09	NHS reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Stage II	**0%**	**£5,096.75**	
Excision	50%	£2,391.27	
Intermediate Nose Procedures	10%	£1,831.68	NHS reference costs 2013/14 - elective inpatient
Major Nose Procedures	52%	£2,177.73	NHS reference costs 2013/14 - elective inpatient
Very Major Nose Procedures	21%	£2,517.02	NHS reference costs 2013/14 - elective inpatient
Complex Nose Procedures	17%	£3,224.09	NHS reference costs 2013/14 - elective inpatient
Excision + RT	50%	£7,802.22	
Wide local excision		£2,391.27	
Intermediate Nose Procedures	10%	£1,831.68	NHS reference costs 2013/14 - elective inpatient
Major Nose Procedures	52%	£2,177.73	NHS reference costs 2013/14 - elective inpatient
Very Major Nose Procedures	21%	£2,517.02	NHS reference costs 2013/14 -

Stage grouping and treatment	Proportion	Cost	Source
			elective inpatient
Complex Nose Procedures	17%	£3,224.09	NHS reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Stage III	**13%**	**£17,363.19**	
Surgery including neck dissection + RT.	100%	£17,363.19	
Very Complex Maxillofacial Procedures	50%	£16,976.78	NHS Reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures	50%	£6,927.69	
Complex Maxillofacial Procedures with CC Score 1+	45%	£9,081.24	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures with CC Score 0	55%	£5,166.20	NHS reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Stage IV	**83%**	**£17,363.19**	
Surgery including neck dissection + RT.	100%	£17,363.19	
Very Complex Maxillofacial Procedures	50%	£16,976.78	NHS Reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures	50%	£6,927.69	
Complex Maxillofacial Procedures with CC Score 1+	45%	£9,081.24	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures with CC Score 0	55%	£5,166.20	NHS reference costs 2013/14 - elective inpatient

Stage grouping and treatment	Proportion	Cost	Source
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Weighted average	**100%**	**£16,852.09**	

A.15.4 Oral cavity cancer

Stage grouping and treatment	Proportion	Cost	Source
Stage I	**4%**	**£4,761.44**	
Excision	40%	£2,485.06	
Intermediate, Mouth or Throat Procedures, 19 years and over	75%	£2,034.92	
Intermediate, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	57%	£2,124.76	NHS reference costs 2013/14 - elective inpatient
Intermediate, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	43%	£1,916.17	NHS reference costs 2013/14 - elective inpatient
Major Maxillofacial Procedures, 19 years and over	25%	£3,835.48	
Major Maxillofacial Procedures, 19 years and over, with CC Score 1+	30%	£4,378.08	NHS reference costs 2013/14 - elective inpatient
Major Maxillofacial Procedures, 19 years and over, with CC Score 0	70%	£3,599.54	NHS reference costs 2013/14 - elective inpatient
Excision and neck dissection.	55%	£5,828.11	
Complex, Mouth or Throat Procedures	50.0%	£4,728.53	
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	53%	£5,891.25	NHS reference costs 2013/14 - elective inpatient
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	47%	£3,414.15	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures	50.0%	£6,927.69	
Complex Maxillofacial Procedures with CC Score 1+	45.0%	£9,081.24	NHS reference costs 2013/14 - elective inpatient

Stage grouping and treatment	Proportion	Cost	Source
Complex Maxillofacial Procedures with CC Score 0	55.0%	£5,166.20	NHS reference costs 2013/14 - elective inpatient
Excision, neck dissection and RT	5%	£11,239.06	
Complex, Mouth or Throat Procedures	50.0%	£4,728.53	
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	53%	£5,891.25	NHS reference costs 2013/14 - elective inpatient
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	47%	£3,414.15	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures	50.0%	£6,927.69	
Complex Maxillofacial Procedures with CC Score 1+	45.0%	£9,081.24	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures with CC Score 0	55.0%	£5,166.20	NHS reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Stage II	**5%**	**£7,451.39**	
Excision and neck dissection.	70%	£5,828.11	
Complex, Mouth or Throat Procedures	50.0%	£4,728.53	
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	53%	£5,891.25	NHS reference costs 2013/14 - elective inpatient
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	47%	£3,414.15	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures	50.0%	£6,927.69	
Complex Maxillofacial Procedures with CC Score 1+	45.0%	£9,081.24	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures with CC Score 0	55.0%	£5,166.20	NHS reference costs 2013/14 - elective inpatient
Excision, neck dissection + RT	30%	£11,239.06	

Stage grouping and treatment	Proportion	Cost	Source
Complex, Mouth or Throat Procedures	50.0%	£4,728.53	
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	53%	£5,891.25	NHS reference costs 2013/14 - elective inpatient
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	47%	£3,414.15	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures	50.0%	£6,927.69	
Complex Maxillofacial Procedures with CC Score 1+	45.0%	£9,081.24	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures with CC Score 0	55.0%	£5,166.20	NHS reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Stage III	**6%**	**£20,989.94**	
Surgery including neck dissection + RT.	100%	£20,989.94	
Very Complex, Mouth or Throat Procedures	50%	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
Very Complex Maxillofacial Procedures	50%	£16,976.78	NHS Reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy

Stage grouping and treatment	Proportion	Cost	Source
Stage IV	**85%**	**£21,319.02**	
Surgery including neck dissection + RT	50%	£20,989.94	
Very Complex, Mouth or Throat Procedures	50%	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
Very Complex Maxillofacial Procedures	50%	£16,976.78	NHS Reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Surgery including neck dissection + chemo RT	50%	£21,648.09	
Very Complex, Mouth or Throat Procedures	50%	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
Very Complex Maxillofacial Procedures	50%	£16,976.78	NHS Reference costs 2013/14 - elective inpatient
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy

Stage grouping and treatment	Proportion	Cost	Source
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Weighted average	**100%**	**£19,976.19**	

A.15.5 Oropharyngeal cancer

Stage grouping and treatment	Proportion	Cost	Source
Stage I	**1%**	**£3,969.24**	
RT	77.5%	£3,429.56	
Preparation for Complex Conformal Radiotherapy, with Technical Support (SC52Z)	-	£906.16	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 20 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£2,523.40	NHS reference costs 2013/14 - outpatient radiotherapy
Surgery including neck dissection	22.5%	£5,828.11	
Complex, Mouth or Throat Procedures	50.0%	£4,728.53	
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	53%	£5,891.25	NHS reference costs 2013/14 - elective inpatient
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	47%	£3,414.15	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures	50.0%	£6,927.69	
Complex Maxillofacial Procedures with CC Score 1+	45.0%	£9,081.24	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures with CC Score 0	55.0%	£5,166.20	NHS reference costs 2013/14 - elective inpatient
Stage II	**4%**	**£3,849.31**	
RT	82.5%	£3,429.56	
Preparation for Complex Conformal Radiotherapy, with Technical Support (SC52Z)	-	£906.16	NHS reference costs 2013/14 - outpatient radiotherapy

Stage grouping and treatment	Proportion	Cost	Source
Deliver 20 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£2,523.40	NHS reference costs 2013/14 - outpatient radiotherapy
Surgery including neck dissection	17.5%	£5,828.11	
Complex, Mouth or Throat Procedures	50.0%	£4,728.53	
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 2+	53%	£5,891.25	NHS reference costs 2013/14 - elective inpatient
Complex, Mouth or Throat Procedures, 19 years and over, with CC Score 0-1	47%	£3,414.15	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures	50.0%	£6,927.69	
Complex Maxillofacial Procedures with CC Score 1+	45.0%	£9,081.24	NHS reference costs 2013/14 - elective inpatient
Complex Maxillofacial Procedures with CC Score 0	55.0%	£5,166.20	NHS reference costs 2013/14 - elective inpatient
Stage III	**7%**	**£7,868.40**	
chemoRT	75%	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Surgery +RT	10%	£20,989.94	
Laryngectomy and neck dissection	50%	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 -

Stage grouping and treatment	Proportion	Cost	Source
			elective inpatient
Very Complex Maxillofacial Procedures	50%	£16,976.78	NHS Reference costs 2013/14 - elective inpatient
RT	-	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Surgery + chemoRT	2.5%	£21,648.09	
Laryngectomy and neck dissection	50%	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
Very Complex Maxillofacial Procedures	50%	£16,976.78	NHS Reference costs 2013/14 - elective inpatient
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
RT	12.5%	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy

Stage grouping and treatment	Proportion	Cost	Source
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Stage IV	**88%**	**£7,594.10**	
chemoRT	85%	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Surgery + chemoRT	10%	£21,648.09	
Laryngectomy and neck dissection	50%	£14,181.18	
Very Complex, Mouth or Throat Procedures, with CC Score 5+	34%	£18,483.27	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 2-4	37%	£12,972.73	NHS Reference costs 2013/14 - elective inpatient
Very Complex, Mouth or Throat Procedures, with CC Score 0-1	29%	£10,578.56	NHS Reference costs 2013/14 - elective inpatient
Very Complex Maxillofacial Procedures	50%	£16,976.78	NHS Reference costs 2013/14 - elective inpatient
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 -

Stage grouping and treatment	Proportion	Cost	Source
			outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
RT	5%	£5,410.96	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - outpatient radiotherapy
Weighted average	**100%**	**£7,434.22**	

A.15.6 Nasopharyngeal cancer

Stage grouping and treatment	Proportion	Cost	Source
Stage I	**0%**	**£3,429.56**	
RT	100%	£3,429.56	
Preparation for Complex Conformal Radiotherapy, with Technical Support (SC52Z)	-	£906.16	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 20 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£2,523.40	NHS reference costs 2013/14 - in outpatient radiotherapy
Stage II	**0%**	**£6,869.01**	
ChemoRT	70%	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
ChemoRT + adjuvant chemotherapy	30%	£8,735.44	
ChemoRT	-	£6,069.11	

Stage grouping and treatment	Proportion	Cost	Source
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Adjuvant chemotherapy (assuming 3 cycles)	-	£2,666.33	
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£531.70	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cisplatin cost per dose (80mg/m2)	-	£27.68	Unit costs from eMit
Cost for four doses of fluorouracil (on days 1, 2, 3 and 4)	-	£15.60	Unit costs from eMit
Stage III	**17%**	**£8,111.95**	
ChemoRT	40%	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
ChemoRT + neck dissection in people with poor response to RT	10%	£9,617.47	
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy

Stage grouping and treatment	Proportion	Cost	Source
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Neck dissection	-	£3,548.36	
Intermediate Maxillofacial Procedures (CA94Z)	-	£3,548.36	NHS reference costs 2013/14 - elective inpatient
ChemoRT + adjuvant chemotherapy	40%	£8,735.44	
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Adjuvant chemotherapy (assuming 3 cycles)	-	£2,666.33	
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£531.70	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cisplatin cost per dose (80mg/m2)	-	£27.68	Unit costs from eMit
Cost for four doses of fluorouracil (on days 1, 2, 3 and 4)	-	£15.60	Unit costs from eMit
ChemoRT + adjuvant chemotherapy + Neck dissection in people with poor response to RT	10%	£12,283.80	
ChemoRT	-	£6,069.11	

Stage grouping and treatment	Proportion	Cost	Source
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Adjuvant chemotherapy (assuming 3 cycles)	-	£2,666.33	
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£531.70	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cisplatin cost per dose (80mg/m2)	-	£27.68	Unit costs from eMit
Cost for four doses of fluorouracil (on days 1, 2, 3 and 4)	-	£15.60	Unit costs from eMit
Neck dissection	-	£3,548.36	
Intermediate Maxillofacial Procedures (CA94Z)	-	£3,548.36	NHS reference costs 2013/14 - elective inpatient
Stage IV	**83%**	**£9,000.05**	
ChemoRT	15%	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
ChemoRT + neck dissection in people with poor response to RT	15%	£9,617.47	

Stage grouping and treatment	Proportion	Cost	Source
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Neck dissection	-	£3,548.36	
Intermediate Maxillofacial Procedures (CA94Z)	-	£3,548.36	NHS reference costs 2013/14 - elective inpatient
ChemoRT + adjuvant chemotherapy	55%	£8,735.44	
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - in outpatient radiotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Adjuvant chemotherapy (assuming 3 cycles)	-	£2,666.33	
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£531.70	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cisplatin cost per dose (80mg/m2)	-	£27.68	Unit costs from eMit
Cost for four doses of fluorouracil (on days 1, 2, 3 and 4)	-	£15.60	Unit costs from eMit

Stage grouping and treatment	Proportion	Cost	Source
ChemoRT + adjuvant chemotherapy + Neck dissection in people with poor response to RT	15%	£12,283.80	
ChemoRT	-	£6,069.11	
Preparation for Intensity Modulated Radiation Therapy, with Technical Support (SC41Z)	-	£1,625.86	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver 30 fractions of complex treatment on a megavoltage machine (SC23Z)	-	£3,785.10	NHS reference costs 2013/14 - in outpatient radiotherapy
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£265.85	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cost for two doses of cisplatin 100mg (on day 1 and day 22)	-	£78.51	Unit costs from eMit
Adjuvant chemotherapy (assuming 3 cycles)	-	£2,666.33	
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£531.70	NHS reference costs 2013/14 - outpatient chemotherapy
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	-	£313.80	NHS reference costs 2013/14 - outpatient chemotherapy
Cisplatin cost per dose (80mg/m2)	-	£27.68	Unit costs from eMit
Cost for four doses of fluorouracil (on days 1, 2, 3 and 4)	-	£15.60	Unit costs from eMit
Neck dissection	-	£3,548.36	
Intermediate Maxillofacial Procedures (CA94Z)	-	£3,548.36	NHS reference costs 2013/14 - elective inpatient
Weighted average	**100%**	**£8,852.03**	

Appendix B: The cost-effectiveness of initial treatments for newly diagnosed T1 or T2 carcinoma of the larynx?

B.1 Background

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

B.2 Aims

To estimate the cost-effectiveness of initial treatments for newly diagnosed T1 or T2 carcinoma of the larynx.

B.3 Existing Economic Evidence

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

B.4 De Novo Economic Model

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel. A Markovian approach was adopted because it seemed well suited to the decision problem, especially in relation to the modelling of disease progression over time, which can be easily handled with the approach. The model operated with an annual cycle length with a half-cycle correction applied. This model was based upon treatment pathways agreed by the GC for patient initially receiving radiotherapy or TLM (figures 3 and 4 below).

Patients diagnosed with T1-T2 carcinoma of the larynx enter the model and receive primary tumour treatment with either radiotherapy or TLM. Following treatment with radiotherapy, there is a small chance that patients may have a non-functioning larynx that necessitates a total laryngectomy, after which the patient will be monitored in a follow-up programme. All other patients treated with either TLM or radiotherapy will be entered into a follow-up programme following treatment. There is then a chance that the patient may experience a recurrence at which point further treatment would be required. Following a recurrence, patients may undergo one of multiple options to treat the recurrent tumour. For example, patients initially treated with radiotherapy that experience a recurrence may undergo TLM, a partial laryngectomy or a total laryngectomy as the treatment of their recurrent tumour. The proportion of patients receiving each of the treatment options were estimated by the guideline committee and are discussed in greater detail in a later section of the report. It should be noted that the subsequent treatment options are dependent upon preceding treatments (for example radiotherapy is an option for recurrent tumours in patients initially treated with TLM but not for patients initially treated with radiotherapy).

Following treatment of the recurrent tumour, the patient is once again monitored in a follow-up schedule where further recurrences may be detected. The patient will then, once more, undergo one of multiple options to treat the recurrent tumour. This pattern continues until the patient undergoes a total laryngectomy at which point treatments for localised disease have been exhausted.

Patients could also die from cancer of the upper aerodigestive tract or other cause mortality at any point in the process.

Figure 3: Treatment pathway for patients initially treated with radiotherapy

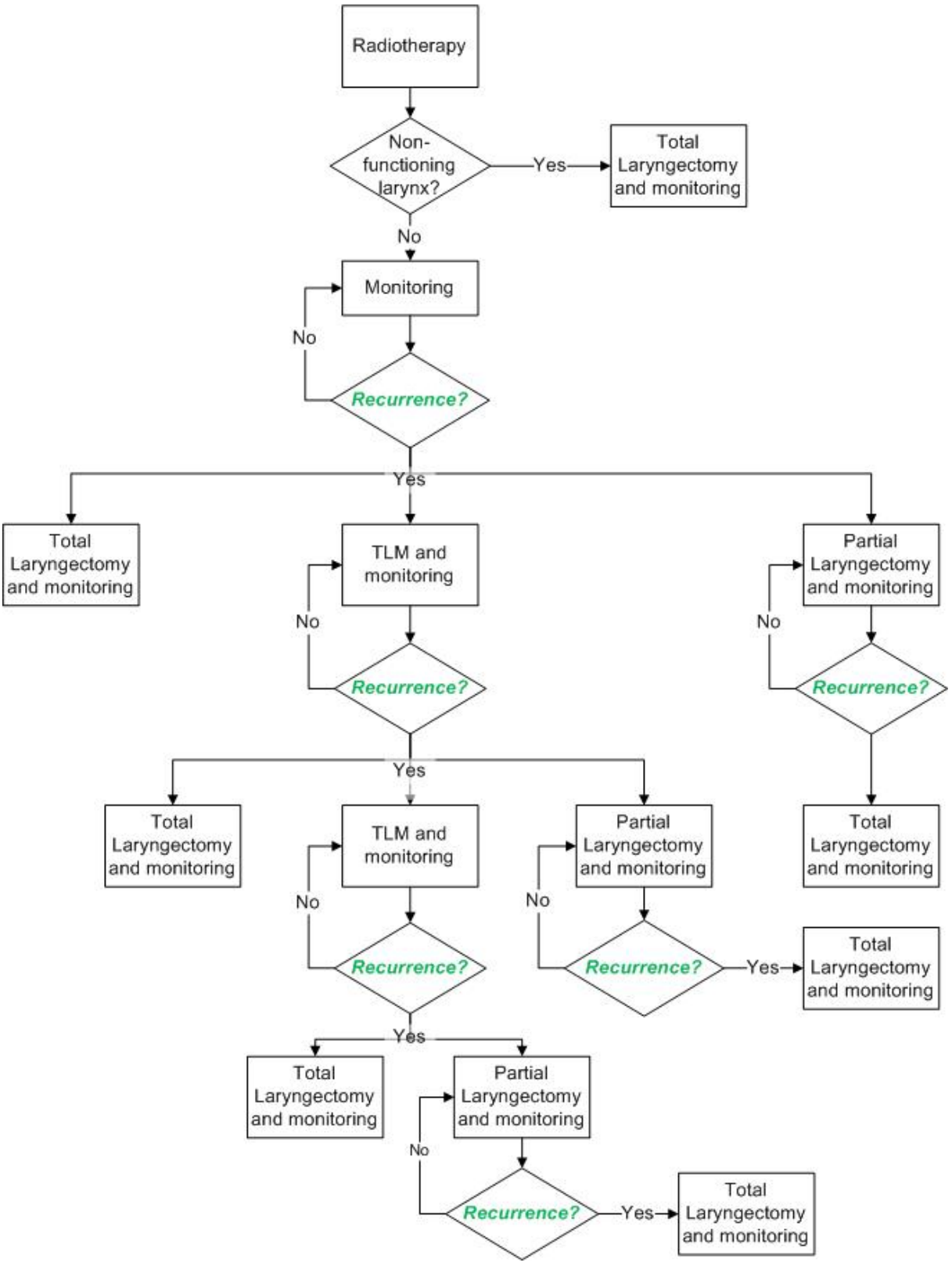
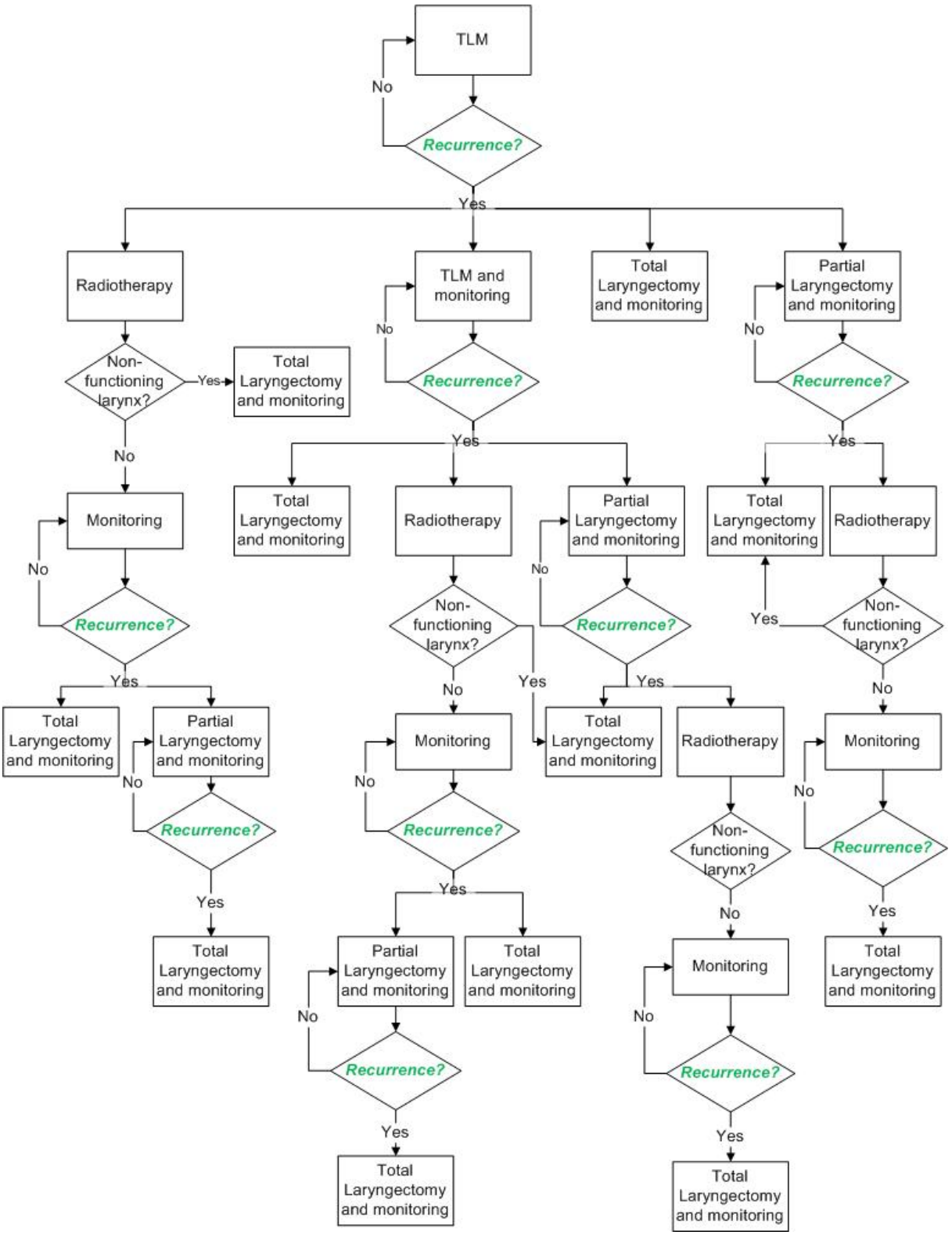


Figure 4: Treatment pathway for patients initially treated with TLM



B.5 Clinical data

B.5.1 Recurrence rates

The recurrence rates for T1a laryngeal cancer patients undergoing radiotherapy or TLM were estimated using data on progression free survival from the clinical evidence review

conducted for this guideline. A meta-analysis of 14 observational studies in patients with stage T1a disease treated with TLM and radiotherapy reported an odds ratio (OR) of 0.92 for local control rates, suggesting a slight benefit in patients treated with radiotherapy.

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

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

Evidence for the T1b-T2 laryngeal cancer was more difficult to source as there seemed to be a paucity of high quality evidence addressing this particular group. Most of the available evidence focused on lower stage cancer (T1a) or did not compare the interventions of interest (many studies compared partial laryngectomy with radiotherapy or TLM with partial laryngectomy).

The evidence that was used was sourced from another paper identified in the clinical evidence review; O'Hara et al. 2013. This systematic review included a comparison of local control rates in patients with T1b laryngeal cancer treated with TLM and radiotherapy. It was found that three year local control rates were lower in patients treated with TLM (76.8%) rather than radiotherapy (86.2%). These were converted to annual recurrence estimates of 6.56% and 2.99% for the TLM and radiotherapy arms respectively (assuming a constant rate of recurrence over the time period).

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

B.5.2 Mortality

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

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

Death from other causes was captured using 2011-2013 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender with the model assuming that 70% of patients were male (estimate by the guideline committee) and that the average age was 66.7 years old (based on data from the National Head and Neck Cancer Auditdatabase). These annual probabilities were converted to three-monthly probabilities for use in the model.

B.5.3 Radiotherapy damage to larynx function

The GC suggested that a small proportion of patients undergoing radiotherapy would have a non-functioning larynx as a result of damage caused by radiotherapy. Such patients would then undergo a total laryngectomy. The proportion of patients with a non-functioning larynx as a result of radiotherapy was estimated to be 0.7% based upon a crude average of rates from Mendenhall et al. and Cellai et al.

B.6 Treatment proportions following a recurrence

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

The proportions of patients receiving each one of these treatments (in the event of a recurrence) are shown in the tables below for patients initially treated with radiotherapy and TLM. The proportions differ depending on the stage of cancer at initial diagnosis with a different set of rates for T1a and T1b-T2 laryngeal cancer.

B.6.1 T1a laryngeal cancer

Table 18: Post-recurrence treatment options for patients with T1a laryngeal cancer initially treated with radiotherapy

Treatment	After first recurrence	After second recurrence	After third recurrence
Total	78%	78%	92%
Partial	7%	7%	8%
TLM	15%	15%	0%
Radiotherapy	0%	0%	0%
Proportions were varied in PSA using dirichlet distributions			

Table 19: Post-recurrence treatment options for patients with T1a laryngeal cancer initially treated with TLM

Treatment	After TLM		After radiotherapy	After partial laryngectomy*
	First recurrence	Second recurrence		
Total	20%	27%	85%	75%
Partial	15%	20%	15%	0%
TLM	25%	0%	0%	0%
Radiotherap	40%	53%	0%	25%

Treatment	After TLM		After radiotherapy	After partial laryngectomy*
	First recurrence	Second recurrence		
y				
*In patients without previous radiotherapy				
Proportions were varied in PSA using dirichlet distributions				

B.6.2 T1b-T2 laryngeal cancer

Table 20: Post-recurrence treatment options for patients with T1b-T2 laryngeal cancer initially treated with radiotherapy

Treatment	After first recurrence	After second recurrence	After third recurrence
Total	90%	90%	92%
Partial	7%	7%	8%
TLM	3%	3%	0%
Radiotherapy	0%	0%	0%
Proportions were varied in PSA using dirichlet distributions			

Table 21: Post-recurrence treatment options for patients with T1b-T2 laryngeal cancer initially treated with TLM

Treatment	After TLM		After radiotherapy	After partial laryngectomy*
	First recurrence	Second recurrence		
Total	30%	32%	85%	75%
Partial	15%	16%	15%	0%
TLM	5%	0%	0%	0%
Radiotherapy	50%	53%	0%	25%
*In patients without previous radiotherapy				
Proportions were varied in PSA using dirichlet distributions				

B.7 Costs

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

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

B.7.1 Initial treatment costs

The costs of initial treatments are shown in table 22 and table 23 below for the radiotherapy arm and TLM arm, respectively. The radiotherapy costs are based upon 20 fractions of

complex conformal radiotherapy. The costs of TLM are weighted based upon the occurrence of co-morbidities and complications (using procedure numbers from NHS reference costs).

Table 22: Treatment costs for initial radiotherapy treatment

Treatment aspect	Cost	PSA distribution‡	Source
Radiotherapy preparation			
Preparation for Complex Conformal Radiotherapy, with Technical Support (SC52Z)	£906.16	Gamma (SE =193.62, alpha =22, beta =41)	NHS reference costs 2013/14 - outpatient radiotherapy
Radiotherapy delivery			
Deliver a fraction of complex treatment on a megavoltage machine (SC23Z)	£126.17	Gamma (SE =39.87, alpha =10, beta =13)	NHS reference costs 2013/14 - outpatient radiotherapy
Number of fractions	20	Gamma (SE =3.71, alpha = 29, beta =1)	Guideline committee estimate
Total radiotherapy cost	***£3,429.56***		
‡Alpha and beta values estimated using upper and lower estimates from NHS reference costs 2013/14			

Table 23: Initial TLM treatment costs

Treatment	Value	PSA distribution‡	Source
Procedures with major CC† - proportion	57%	Dirichlet (alpha =58)	NHS reference costs 2013/14 - elective inpatient
Procedures without CC* - proportion	43%	Dirichlet (alpha =44)	NHS reference costs 2013/14 - elective inpatient
Procedures with major CC† - cost	£2,124.76	Gamma (SE =838.46, alpha =6, beta =331)	NHS reference costs 2013/14 - elective inpatient
Procedures without CC* - cost	£1,916.17	Gamma (SE =808.60, alpha =6, beta =341)	NHS reference costs 2013/14 - elective inpatient
Weighted average cost of TLM	***£2,034.92***		
†Intermediate Mouth or Throat Procedures, 19 years and over with major CC (CA84A)			
*Intermediate Mouth or Throat Procedures, 19 years and over without CC (CA84B)			
‡Alpha and beta values estimated using upper and lower estimates from NHS reference costs 2013/14			

B.7.2 Salvage treatment costs

Patients that experience a recurrence will receive treatments in line with the estimated proportions outlined earlier. Those patients receiving a TLM or radiotherapy will be treated in the same manner as in the initial treatment and so the same costs are incurred.

However, some patients receiving radiotherapy are assumed to receive more intensive treatment with intensity modulated radiotherapy (IMRT) used in patients with late stage recurrences (T3 or T4). In the base case, it was assumed that 30% of patients receiving radiotherapy for a recurrence would receive IMRT. In addition, it was assumed that 50% of patients receiving IMRT would also receive concomitant chemotherapy. The costs of IMRT

and concomitant radiotherapy are shown in the table below. Note that it was assumed that Cisplatin would be given in two doses of 100mg/m2.

Table 24: IMRT costs with and without concomitant chemotherapy

Chemoradiotherapy treatment cost elements	Cost	PSA distribution‡	Source
IMRT			
Preparation for Intensity Modulated Radiation Therapy, with Technical Support	£1,625.86	Gamma (SE =511.55, alpha =10, beta =161)	NHS reference costs 2013/14 - - outpatient radiotherapy (–SC41Z)
Deliver a fraction of complex treatment on a megavoltage machine	£126.17	Gamma (SE =39.87, alpha =10, beta =13)	NHS reference costs 2013/14 - - outpatient radiotherapy–(SC23Z)
Number of fractions	30	Gamma (SE =3.71, alpha =66, beta =0)	Guideline committee estimate
Total IMRT cost	***£5,410.96***	**-**	**-**
Concomitant chemotherapy			
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance*	£265.85	Gamma (SE =88.17, alpha =9, beta =29)	NHS reference costs 2013/14 -- outpatient chemotherapy (SB14Z)
Deliver subsequent elements of a chemotherapy cycle	£313.80	Gamma (SE =265.61, alpha =1, beta =225)	NHS reference costs 2013/14 -– outpatient chemotherapy (SB15Z)
Cisplatin cost per dose (100mg/m2)†	£39.25	Gamma (SE =14.59, alpha =7, beta =5)	Unit cost from eMIT
Cost for two doses of cisplatin (on day 1 and day 22)	£78.51	-	-
Total cisplatin cost	***£658.15***	**-**	**-**
Total chemoradiotherapy cost	**£6,069.11**		
* Based on information in the Thames Cancer Valley Network report on chemotherapy regimens, which states an infusion time of 2-4 hours			
† Based on average body surface area for patients with head and neck cancer from Sacco et al. 2010 (1.85m2 for males and 1.65m2 for females)			
^Based on the cost of one 100ml vial (£16.69), one 50ml vial (£11.21) and four 10ml vials (£3.55) for men and one 100ml vial, one 50ml vial and two 10ml vials for women. ‡Alpha and beta values estimated using upper and lower estimates from NHS reference costs 2013/14, standard deviations from eMit and with upper and lower estimates of ± 50% for values based on assumptions.			

The costs of salvage treatment with a partial laryngectomy or total laryngectomy for patients that experience a recurrence are shown in the table below. It was also assumed that adjuvant IMRT would be performed for 60% of patients undergoing total laryngectomy if they have not previously been irradiated. It was further assumed that 50% of those patients that receive IMRT would receive concomitant chemotherapy with two doses of cisplatin. The IMRT and chemotherapy costs shown above (for patients with a late stage recurrence receiving IMRT) were also applied in this context.

Table 25: Salvage treatment costs

Treatment (± complications and comorbidities)	Value	PSA distribution‡	Source
Total laryngectomy			
Procedures* with CC Score 5+	34%	Dirichlet (alpha =35)	NHS Reference costs 2013/14 - elective inpatient
Procedures† with CC Score 2-4	37%	Dirichlet (alpha =38)	NHS Reference costs 2013/14 - elective inpatient
Procedures‡ with CC Score 0-1	29%	Dirichlet (alpha =30)	NHS Reference costs 2013/14 - elective inpatient
Procedures* with CC Score 5+	£18,483.27	Gamma (SE =5518.76, alpha =11, beta =1648)	NHS Reference costs 2013/14 - elective inpatient
Procedures† with CC Score 2-4	£12,972.73	Gamma (SE =6238.67, alpha =4, beta =3000)	NHS Reference costs 2013/14 - elective inpatient
Procedures^ with CC Score 0-1	£10,578.56	Gamma (SE =4696.51, alpha =5, beta =2085)	NHS Reference costs 2013/14 - elective inpatient
Weighted average cost of total laryngectomy	£14,181.18		-
Partial laryngectomy			
Procedures‡ with CC Score 0-1	£10,578.56	Gamma (SE =4696.51, alpha =5, beta =2085)	NHS Reference costs 2013/14 - elective inpatient
*Very Complex, Mouth or Throat Procedures, with CC Score 5+			
†Very Complex, Mouth or Throat Procedures, with CC Score 2-4			
‡Very Complex, Mouth or Throat Procedures, with CC Score 0-1 ‡Alpha and beta values estimated using upper and lower estimates from NHS reference costs 2013/14			

B.7.3 Follow-up costs

There is a general consensus that patients require regular follow-up after treatment with TLM or radiotherapy in order to detect recurrences. While there is likely to be some variation in clinical practice, the GC estimated that the following protocols would best reflect current UK practice:

Table 26: Frequency of surgical consultant follow-up

Year and follow-up frequency	Average number of sessions per year	PSA distribution‡	Source
Year 1 (after TLM): 3 weeks, then every 6-8 weeks	8.58	Gamma (SE =6.36, alpha =2, beta =5)	Guideline committee estimate
Year 1 (after RT): Every 6-8 weeks	7.58	Gamma (SE =5.62, alpha =2, beta =4)	Guideline committee estimate
Year 2: Every 8-10 weeks	5.85	Gamma (SE =4.34, alpha =2, beta =3)	Guideline committee estimate

Year and follow-up frequency	Average number of sessions per year	PSA distribution‡	Source
Year 3: Every 12-15 weeks	3.90	Gamma (SE =2.89, alpha =2, beta =2)	Guideline committee estimate
Year 4: Every 6 months, then discharge	2.00	Gamma (SE =1.48, alpha =2, beta =1)	Guideline committee estimate
1‡Alpha and beta values estimated using upper and lower estimates of ± 50%			

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

B.7.4 Speech and language therapy (SLT) and dietetics costs

Patients undergoing treatment for laryngeal cancer require regular speech and language therapy and dietetics sessions. These sessions are typically tailored to the individual needs of the patient. However, for the purposes of the model, it was necessary to approximate the average number of sessions that would typically be required after each treatment in order to reflect current clinical practice in the UK. The table below shows the GC's estimate of the average number of sessions typically required after each treatment that was applied in the model base case.

Table 27: Number of speech and language therapy sessions and dietetics sessions during and after treatment

Treatment	Number of sessions	PSA distribution‡	Source
Speech and language therapy			
TLM	5	Gamma (SE =3.71, alpha =2, beta =3)	Guideline committee estimate
Radiotherapy	10	Gamma (SE =7.41, alpha =2, beta =5)	Guideline committee estimate
Partial laryngectomy	16	Gamma (SE =11.86, alpha =2, beta =9)	Guideline committee estimate
Total laryngectomy	16	Gamma (SE =10.38, alpha =2, beta =8)	Guideline committee estimate
Dietetics			
TLM	5	Gamma (SE =3.71, alpha =2, beta =3)	Guideline committee estimate
Radiotherapy	10	Gamma (SE =7.41, alpha =2, beta =5)	Guideline committee estimate
Partial laryngectomy	16	Gamma (SE =11.86, alpha =2, beta =9)	Guideline committee estimate
Total laryngectomy	16	Gamma (SE =10.38, alpha =2, beta =8)	Guideline committee estimate
‡Alpha and beta values estimated using upper and lower estimates of ± 50%			

It was additionally assumed that 10% of patients would require lifelong speech and language therapy sessions after a total laryngectomy, with sessions taking place every 6 months.

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

B.7.5 Valve change costs (after laryngectomy)

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

B.7.6 Systemic chemotherapy and palliative care

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

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

The systemic chemotherapy costs applied in the model are shown in the table below.

Systemic Chemotherapy cost elements	Value	PSA distribution‡	Source
Proportion assumed to receive systemic chemotherapy	50%	Beta (alpha =50, beta =50)	Assumption
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£265.85	Gamma (SE =88.17, alpha =9, beta =29)	NHS reference costs 2013/14 -– outpatient chemotherapy (SB14Z)
Deliver subsequent elements of a chemotherapy cycle	£313.80	Gamma (SE =265.61, alpha =1, beta =225)	NHS reference costs 2013/14 -– outpatient chemotherapy SB15Z
Cisplatin cost per dose (80mg/m2)	£27.68	Gamma (SE =10.47, alpha =7, beta =4)	Unit cost from eMit
Fluorouracil cost per dose (750mg/m2)	£3.90	Gamma (SE =1.91, alpha =4, beta =1)	Unit cost from eMit
Cost for four doses of fluorouracil (on days 1, 2, 3 and 4)	£15.60	-	-
Total chemotherapy cost per cycle	£888.78	-	-
Average number of cycles	4	Gamma (SE =2.97, alpha =2, beta =2)	Assumption
Total systemic chemotherapy cost	**£3,555.10**		

Systemic Chemotherapy cost elements	Value	PSA distribution‡	Source
‡Alpha and beta values estimated using upper and lower estimates from NHS reference costs 2013/14, standard deviations from eMit and with upper and lower estimates of ± 50% for values based on assumptions			

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

Type of care	Average cost per cancer patient	PSA distribution‡	Source
Cost of all hospital contacts	£5,890	Gamma (SE =4366.20, alpha =2, beta =3237)	Exploring the cost of care at the end of life (Nuffield Trust, Georghiou 2014)
Local authority-funded care	£444	Gamma (SE =329.13, alpha =2, beta =244)	
District nursing care	£588	Gamma (SE =435.88, alpha =2, beta =323)	
GP contacts	£365	Gamma (SE =270.57, alpha =2, beta =201)	
Average palliative care cost per patient	**£7,287**		
‡Alpha and beta values estimated using upper and lower estimates of ± 50%			

It should be noted that this cost is generic to all cancers and is not specifically related to cancers of the upper aerodigestive tract. However, in the absence of more robust data, it has been assumed that the costs in upper aerodigestive tract would not differ substantially. The influence of changing the cost of palliative care was explored in sensitivity analysis.

B.8 Health related quality of life (QoL) values

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs were estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state.

There is a paucity of high quality of life (QoL) data available in laryngeal cancer. However, it is recognised that QALYs need to be estimated in order to assess cost-effectiveness using the thresholds employed by NICE (£20,000 - £30,000 per QALY) and thus it is useful to utilise QoL data, even if they are of relatively poor quality. It is however recognised as a limitation of the analysis and the QoL values were subjected to sensitivity analysis to assess how influential they are on the final decision.

For the purposes of this economic evaluation, the following QoL data were utilised, which were primarily identified from an existing cost-utility analysis by Higgins et al. 2011. The QoL data are differentiated depending on whether the patient is alive with the voice box entirely intact, partially intact (i.e. after a partial laryngectomy) or without voice box (i.e. after a total laryngectomy).

In addition, a QoL value from the NICE HTA on Cetuximab was used as an estimate for the quality of life of patients in a metastatic disease state. As described above, a metastatic health state was not explicitly modelled as such but it has been assumed that patients dying from upper aerodigestive tract cancer were likely to have developed metastatic disease. Thus, the QoL decrement associated with metastatic disease was retrospectively applied under the assumption that patients would spend 6 months in this state. However, it should be

noted that in the case of patients alive without a voice box, no further decrement was applied as the evidence suggested that this QoL state was worse than metastatic disease.

Table 28: Quality of life values applied in the economic model

Health state	Utility	PSA distribution‡	Source
Alive with voice box entirely intact	0.8718	Beta (alpha =26, beta =4)	Higgins et al. 2011
Alive with part of voice box intact	0.7060	Beta (alpha =21, beta =9)	Higgins et al. 2011
Alive without voice box	0.3650	Beta (alpha =11, beta =19)	Higgins et al. 2011
End of life (metastatic disease)	0.6500	Beta (alpha =65, beta =35)	NICE HTA on Cetuximab
‡Alpha and beta values estimated using patient numbers from the QoL studies			

B.9 Base Case Results

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

The deterministic base case results of the analysis for are presented in the tables below. It can be seen that, in both T1a and T1b-T2 laryngeal cancer, using radiotherapy as the initial treatment strategy was more expensive (£2,654 and £623 in T1a and T1b-T2 laryngeal cancer, respectively) and less effective (reduction of 0.14 and 0.04 in T1a and T1b-T2 laryngeal cancer, respectively) than transoral laser microsurgery (TLM). Therefore, in cost-effectiveness terms, TLM can be considered the dominant strategy i.e. more effective and less costly.

B.9.1 T1a laryngeal cancer

Table 29: Deterministic base case cost-effectiveness results for T1a laryngeal cancer

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

B.9.2 T1b-T2 laryngeal cancer

Table 30: Deterministic base case cost-effectiveness results for T1b-T2 laryngeal cancer

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

In addition to the deterministic results above, the base case results were also generated probabilistically. In this analysis the mean total costs and QALYs were recorded after 10,000 probabilistic runs of the analysis (sufficient for stability in the ICER). The probabilistic base

case results are presented in Table 31 and Table 32 for T1a and T1b-T2 laryngeal cancer, respectively.

As in the deterministic analysis, it can be seen that using radiotherapy as the initial treatment strategy was more expensive (£2,744 and £847 in T1a and T1b-T2 laryngeal cancer, respectively) and less effective (reduction of 0.19 and 0.14 in T1a and T1b-T2 laryngeal cancer, respectively) than TLM. Therefore the conclusion is unchanged with TLM found to be the dominant strategy.

Table 31: Probabilistic base case cost-effectiveness results for T1a laryngeal cancer

	Cost		QALYs		
Initial treatment	Total	Incremental	Total	Incremental	ICER (cost per QALY)
Transoral laser microsurgery (TLM)	£8,093	-	6.53	-	-
Radiotherapy	£10,837	£2,744	6.34	-0.19	Dominated

Table 32: Probabilistic base case cost-effectiveness results for T1b-T2 laryngeal cancer

	Cost		QALYs		
Initial treatment	Total	Incremental	Total	Incremental	ICER (cost per QALY)
Transoral laser microsurgery (TLM)	£10,970	-	6.33	-	-
Radiotherapy	£11,651	£681	6.24	-0.09	Dominated

B.10 Deterministic sensitivity analysis

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

Table 33: One-way sensitivity analysis results for T1a and T1b-T2 laryngeal cancer

	ICER (cost per QALY gained with RT)	
Change made	T1a	T1b-T2
No Damage following RT	RT Dominated	RT Dominated
No difference in local control	RT Dominated	RT Dominated
Lower local control odds ratio (RR = 0.62)	RT Dominated	-
Lower DSS odds ratio (RR = 0.75)	RT Dominated	RT Dominated
Lower recurrence and mortality odds ratio	RT Dominated	-
No difference in recurrence rates	RT Dominated	RT Dominated
No difference in QoL values	RT Dominated	RT Dominated
No discounting	RT Dominated	RT Dominated
Day case costs for TLM	RT Dominated	RT Dominated
TLM cost increased by 50%	RT Dominated	£8,995
TLM cost = radiotherapy cost	RT Dominated	£17,492
Same treatments in TLM and RT after first recurrence	RT Dominated	RT Dominant
Post treatment QoL with RT 0.01 higher than with TLM	RT Dominated	£26,232
Post treatment QoL with RT 0.05 higher than with TLM	£12,280	£2,093

Change made	ICER (cost per QALY gained with RT)	
	T1a	T1b-T2
Recurrence rates maintained over 10 years	RT Dominated	RT Dominated
16 fraction (50 Gy) radiotherapy schedule	RT Dominated	RT Dominated

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

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

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

B.11 Probabilistic sensitivity analysis (PSA)

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

The results of 10,000 runs of the probabilistic sensitivity analysis are shown using an ICER scatter plot and cost-effectiveness acceptability curve (CEAC). The ICER scatter plot shows the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graph shows the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis. The ICER scatterplot and CEACs for T1a laryngeal cancer are shown in figures 5, 6, 7 and 8 for T1a and T1b-T2 laryngeal cancer.

Figure 5: ICER scatter plot for TLM in comparison to radiotherapy in T1a laryngeal cancer patients

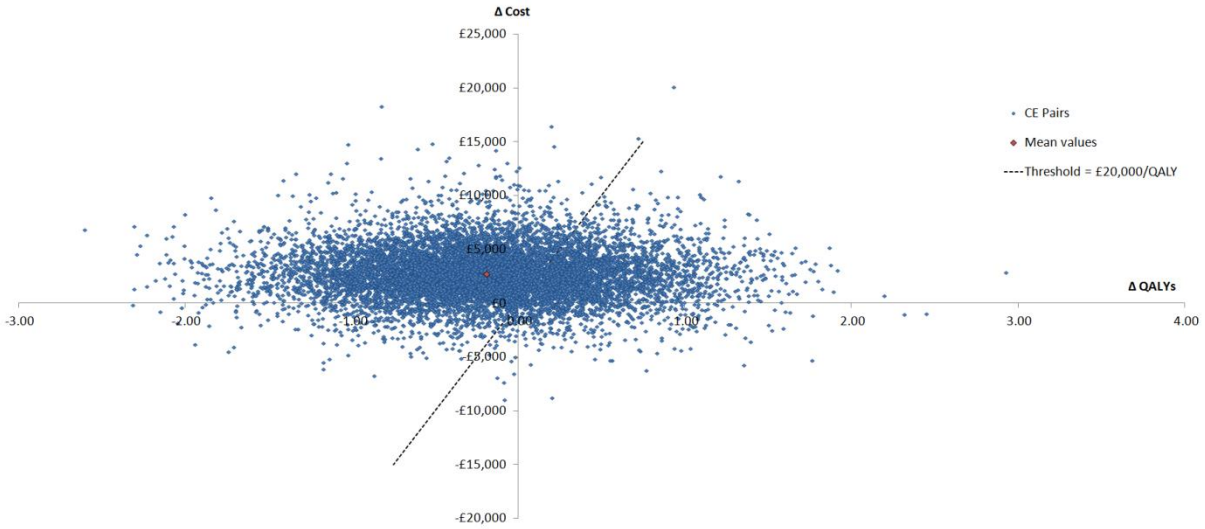


Figure 6: Cost-effectiveness acceptability curve (CEAC) for TLM and radiotherapy in T1a laryngeal cancer patients

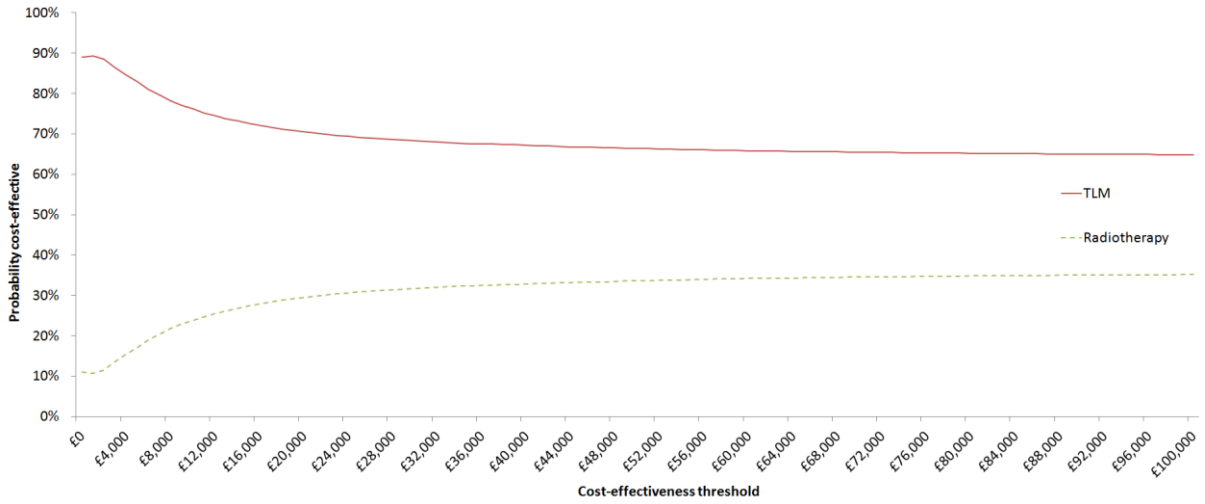


Figure 7: ICER scatter plot for TLM in comparison to radiotherapy in T1b-T2 laryngeal cancer patients

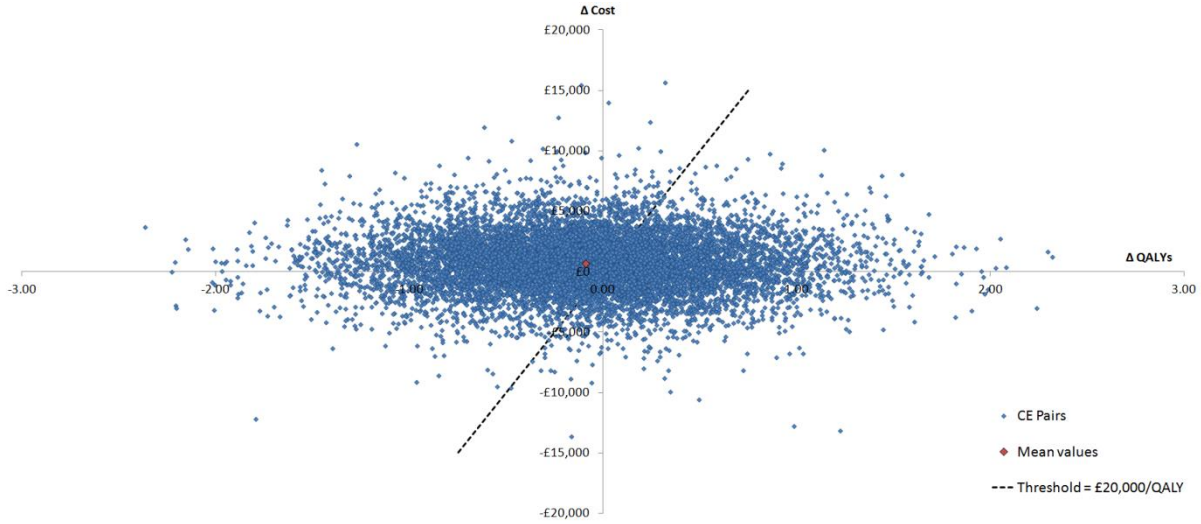
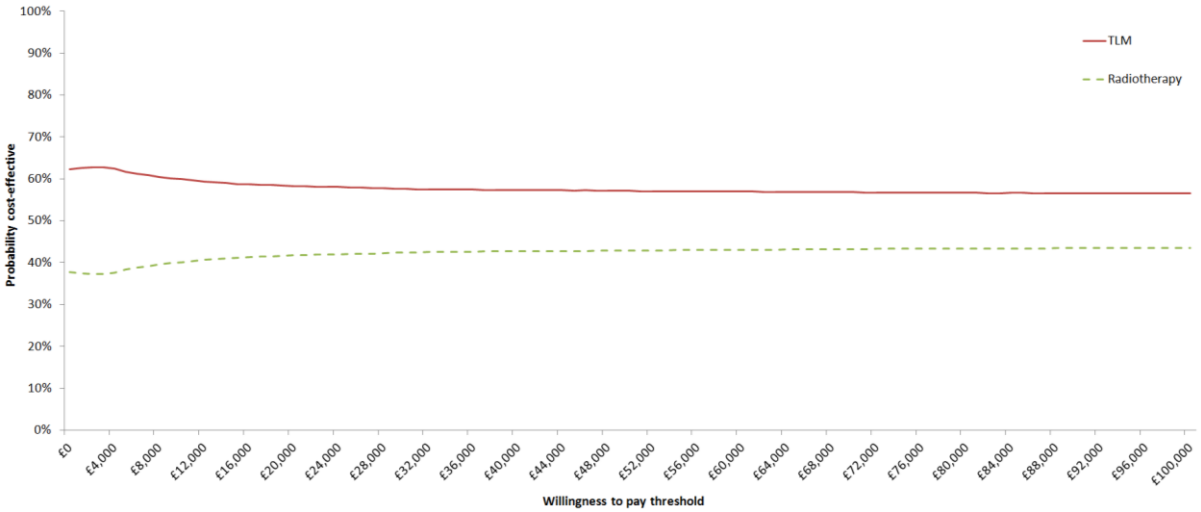


Figure 8: Cost-effectiveness acceptability curve (CEAC) for TLM and radiotherapy in T1b-T2 laryngeal cancer patients



It can be seen that in the scatterplot for the T1a laryngeal cancer group, the majority of the results clearly reside in the North West quadrant where radiotherapy is less effective and more expensive than TLM (i.e. dominated by TLM). In the CEAC for the T1a laryngeal cancer group, it can be seen that, at a willingness to pay threshold of £20,000 per QALY, TLM has a 71% probability of being cost-effective.

In the scatterplot for the T1b-T2 laryngeal cancer group, the results are spread across all four quadrants of the cost-effectiveness plane suggesting that there is considerable uncertainty. In the CEAC for the T1b-T2 laryngeal cancer group, it can be seen that, at a willingness to pay threshold of £20,000 per QALY, TLM has a 58% probability of being cost-effective.

B.12 Discussion

This analysis aimed to estimate the cost-effectiveness of initial treatments (TLM or radiotherapy) for newly diagnosed T1 or T2 carcinoma of the larynx. To our knowledge, this is the first model that has investigated these treatment approaches in the UK context. One previous analysis (Higgins et al. 2011) was identified that conducted a similar analysis but this analysis considered the Canadian health care system and was therefore not directly applicable to the UK context.

The results of the base case analysis suggest that using TLM as the initial treatment for early stage laryngeal cancer is a cost-effective strategy in T1a and T1b-T2 laryngeal cancer. Indeed, in both cases, TLM was found to be dominant i.e. more effective and less expensive. This result is similar to the result found in the analysis by Higgins et al. 2011 in which TLM was again found to dominate radiotherapy.

However, while the base case results for T1a and T1b-T2 laryngeal cancer were similar, the sensitivity results showed that there was a difference in the level of certainty around results. In T1a laryngeal cancer, the result was found to be insensitive to the majority of changes made in deterministic analysis and, in probabilistic sensitivity analysis, TLM was shown to have a high probability of being cost-effective. In the case of T1b-T2 laryngeal cancer, the result was found to be very sensitive to the changes made in deterministic sensitivity analysis and in probabilistic sensitivity analysis, the probability of TLM being cost-effective was found to be 58%.

A particularly noteworthy issue in the T1b-T2 laryngeal cancer analysis was the sensitivity of the result to the relative QoL in patients treated with TLM or radiotherapy. The base case analysis assumed an equivalent QoL in both patient groups reflecting the evidence identified in the systematic review for the guideline (Spielmann et al. 2010), which did not show a statistically significant difference in QoL between the two. However, this was known to be an area of some contention, with uncertainty still remaining over the relative QoL benefits of the two approaches. Indeed, amongst the guideline committee, there were some suggestions that radiotherapy may be more beneficial (in QoL terms) than TLM in the more advanced cancer group (i.e. T1b-T2). Therefore, extensive sensitivity analysis was conducted in this area. Most notably, a threshold analysis revealed that radiotherapy would become cost-effective with a QoL improvement of 0.011. Such a QoL difference could be plausible, casting further uncertainty on the result. Further research in this area would be highly valuable and could help to settle the debate around the two treatments in the T1b-T2 laryngeal cancer group.

There were a few limitations to the analysis that should be noted. As with most economic analyses, the analysis is, to a large extent, dependent on the clinical data upon which it is based. While a systematic review was undertaken to ensure that the model inputs reflect the best clinical evidence currently available, the evidence base was found to have limitations. In both T1a and T1b-T2 laryngeal cancer groups, observational studies were used as the main source of clinical data. As such, the clinical evidence identified in both disease groups was considered to be of very low quality in the appraisal for this guideline. Therefore, there is a clear need for higher quality (ideally RCT) evidence in this area, particularly in T1b-T2 laryngeal cancer patients where there is greater uncertainty over the result.

There was also found to be a paucity of quality of life data in this area. This is a common issue in cost-effectiveness evaluations but is nevertheless a significant one. The key QoL values applied in this model were sourced from Higgins et al. 2011 which was not without limitations. Firstly, the study was Canadian and so it may not be directly applicable to the UK context. Secondly, QoL was measured using the Health Utilities Index Mark 3, which not be the preferred measure under NICE methodology (QoL values should ideally be derived using the EQ-5D survey). Thirdly, the small sample size (n=30) limits the certainty that can be placed in the QoL values that were obtained.

While these limitations hinder the QALY side of the model, it should be noted the quantity of QALY benefits was not found to be a crucial determinant of the model result. In both scenarios, TLM was found to be dominant (i.e. more effective and cheaper), thus it is really the direction of the QoL values that is of most importance and the guideline committee were in agreement that the direction of the QoL values seemed right. However, as mentioned above, further research into QoL in this area would be welcomed.

B.13 Conclusion

The results showed TLM to be the preferred strategy in T1a and T1b-T2 cancer of the larynx. In the case of T1a cancer of the larynx, this result appears to be very robust suggesting a strong case for the use of TLM. However, in T1b-T2 cancer of the larynx, there was far more uncertainty around the result and radiotherapy could be preferred under plausible alternative assumptions. Therefore, the optimal strategy, in cost-effectiveness terms, remains somewhat uncertain in this group.

References

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

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

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

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

Georghiou T, Bardsley M. Exploring the cost of care at the end of life. Nuffield Trust 2014

Higgins, KM. What treatment for early-stage glottic carcinoma among adult patients: CO2 endolaryngeal laser excision versus standard fractionated external beam radiation is superior in terms of cost utility? Laryngoscope 2011; 121(1): 116-134.

Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press

National Life Tables, United Kingdom, 1980-82 to 2011-13. Office for National Statistics (www.ons.gov.uk)

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

O'Hara, J., Markey, A., & Homer, J. J. (2013). Transoral laser surgery versus radiotherapy for tumour stage 1a or 1b glottic squamous cell carcinoma: systematic review of local control outcomes. Journal of Laryngology & Otology, 127, 732-738.

Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P (2010) The Average Body Surface Area of Adult Cancer Patients in the UK: A Multicentre Retrospective Study. PLoS ONE 5(1): e8933. doi:10.1371/journal.pone.0008933

Appendix C: The Cost-Effectiveness of Management Strategies for the Clinically and Radiologically N0 Neck.

C.1 Background

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

This balance between overtreatment and under treatment has been considered elsewhere (Weiss et al. 1994) and has led to many centres offering an elective neck dissection when the incidence of clinically occult metastases is thought to be greater than a threshold of 15%-20%. However, the cost-effectiveness of these strategies in the UK context is not known.

Recently, the use of sentinel lymph node biopsy has been introduced as a further option. This could be used to stratify patients into those that require an elective neck dissection and those that can be observed under watchful waiting, which could minimise the potential for overtreatment and under treatment. However, the use of sentinel lymph node biopsy would represent an additional procedure for these patients and its cost-effectiveness is unknown.

C.2 Aims

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

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

C.3 Existing Economic Evidence

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

1. Elective neck dissection
2. Watchful waiting
3. Gene expression profiling then neck dissection or watchful waiting
4. Sentinel lymph node biopsy then neck dissection or watchful waiting
5. Gene expression profiling (GEP) and sentinel lymph node biopsy (for positive GEP) then neck dissection or watchful waiting

The results of the analysis suggested that that sentinel lymph node biopsy followed by neck dissection or watchful waiting was the most effective and cost-effective strategy (with an ICER of €3,356 per QALY below the author's chosen cost-effectiveness threshold of €80,000 per QALY). In sensitivity analysis the result was found to be particularly sensitive to the

percentage of occult metastases. Sentinel lymph node biopsy was found to remain the most cost-effective strategy with occult metastases of 11%-53%. Elective neck dissection was found to be cost-effective with occult metastases >53% and watchful waiting was found to be cost-effective with occult metastases <11%.

In the probabilistic sensitivity analysis (PSA), sentinel lymph node biopsy was found to be the preferred strategy when the willingness to pay threshold was higher than €7,500 per QALY.

However, as this study considered the Dutch health care system it was not deemed sufficient to address the decision problem in the UK context.

C.4 De Novo Economic Model

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel. A Markovian approach was adopted because it seemed well suited to the decision problem, especially in relation to the modelling of disease progression over time, which can be easily handled with the approach. The model operated with an annual cycle length with a half-cycle correction applied. The diagram below illustrates the modelled treatment pathway.

Oral cavity cancer patients with a clinically and radiological N0 neck enter the model following a tumour resection. The patient may then undergo further treatment with an elective neck dissection (END) or sentinel lymph node biopsy (SLNB) or be entered into a 'watchful waiting' surveillance programme.

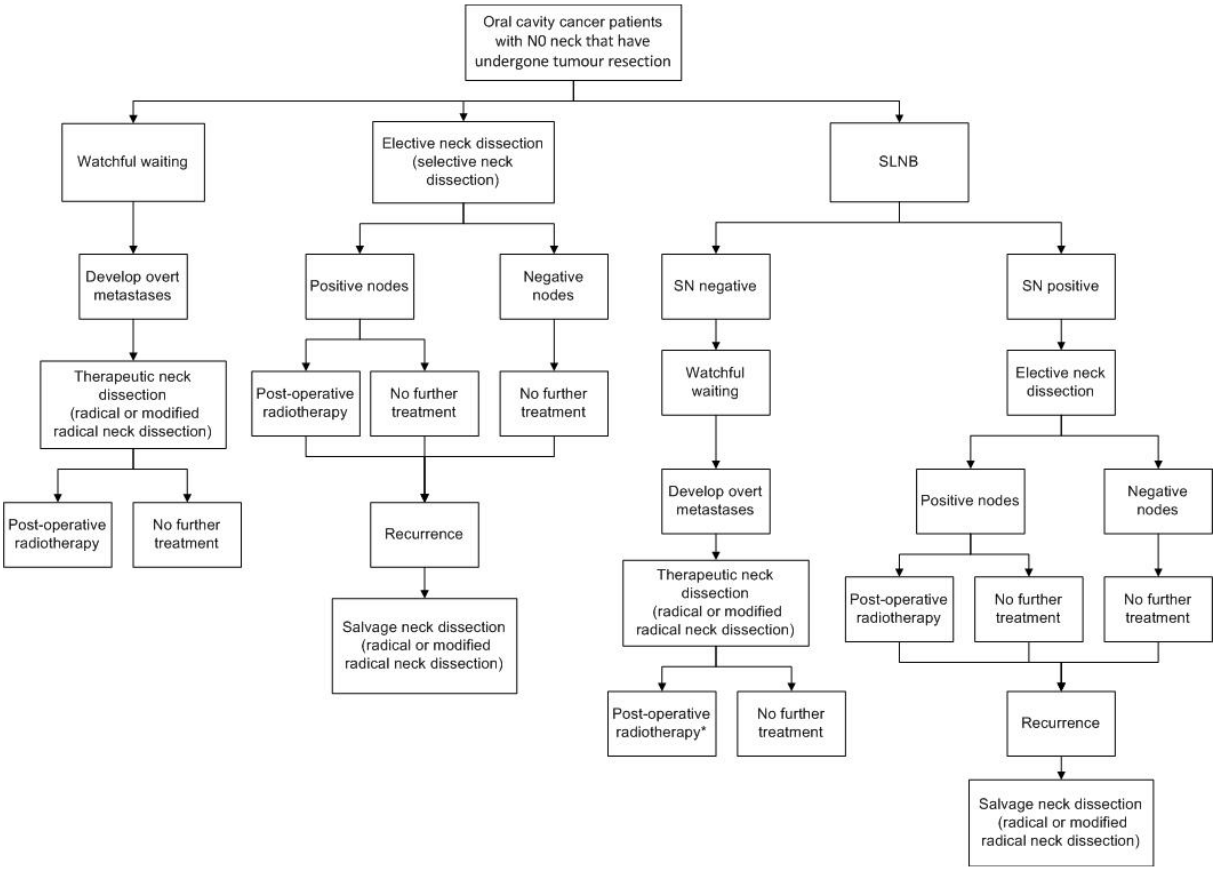
In patients that undergo an END, positive nodes may or may not be detected. For patients with negative nodes, no further treatment is required. For a proportion of patients with positive nodes that are found to have more advanced disease (e.g. extracapsular spread), the END procedure will be followed by post-operative radiotherapy (the proportion of patients receiving this is discussed in more detail in a later section of the report). For other node positive patients with less advanced disease, the END itself will be deemed sufficient with no further treatment required. Following treatment, patients are entered into a follow-up programme to detect possible recurrences. In the event of a recurrence, patients will undergo a salvage neck dissection.

Patients in the watchful waiting arm are monitored closely for the development of overt metastases. (i.e. node positive disease that is clinically or radiologically detectable). If the patient develops overt metastases then further treatment is required and the patient will undergo a therapeutic neck dissection. As above, following the neck dissection, patients may receive post-operative radiotherapy if the disease is found to be more advanced.

In patients that undergo a SLNB, positive sentinel nodes may or may not be detected. Patients with negative sentinel nodes will be entered into a watchful waiting programme and essentially follow the same process outlined above for patients initially managed with watchful waiting (note that the possibility of sentinel node negative patients developing overt metastases is determined by the specificity of the SLNB procedure). Patients with positive sentinel nodes will undergo an elective neck dissection, and essentially follow the same process outlined above for patients initially managed with END (note that the probability of positive nodes being found after the END procedure in sentinel node positive patients is determined by the sensitivity of the SLNB procedure).

Patients could also die from cancer of the upper aerodigestive tract or other cause mortality at any point in the process.

Figure 9: Modelled treatment pathway



C.5 Clinical data

C.5.1 Occult metastases and regional failure rates

For the purposes of the economic model, regional recurrence was parameterised in two steps. Firstly, the proportion of T1N0 patients with occult metastases was estimated and secondly, the regional failure rate in patients with occult metastases was estimated.

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

An underlying assumption in the model (and much of the clinical literature) is that all occult metastases will become overt metastases. Therefore, in patients in the observation arm, the regional failure rate is equivalent to the proportion of patients with occult metastases (46%). For patients in the elective neck dissection arm, the results of the clinical evidence review were used, which showed that the risk of locoregional recurrence with elective neck dissection is approximately half that associated with observation (pooled RR estimate of 0.49). Therefore, the regional failure rate in patients undergoing an elective neck dissection was 21.1%.

C.5.2 Neck dissection related morbidity and mortality

The neck dissection procedure is an invasive one and is associated with some degree of morbidity, such as accessory nerve damage. In addition, it is sometime postulated that a delayed, therapeutic neck dissection (in those patients initially undergoing observation) is a

more morbid procedure than an elective neck dissection. However, the clinical evidence review conducted for this guideline suggested that there was uncertainty as to whether delaying neck dissection until nodes are clinically positive means a more morbid procedure.

In the base case analysis, the morbidity rates were based on alternative data identified in the clinical evidence review on selective neck dissections in comparison to radical neck dissections (Brentani et al. 1998). It has been assumed that patients undergoing an elective neck dissection would undergo a selective neck dissection while patients undergoing a therapeutic neck dissection would undergo a radical neck dissection. Therefore, patients undergoing an elective neck dissection arm have a morbidity risk of 25.0% and patients undergoing a therapeutic neck dissection have a morbidity risk of 41.3%.

It should be noted that, the important aspect to consider in an economic model is whether the morbidity associated with neck dissection translates into cost and QALY consequences. The influence of neck dissections on these aspects is discussed in more detail in the relevant sections below.

There is also a potential mortality risk associated with the procedure. However, the mortality risk was thought to be so small that it was necessary to consider it in the modelled base case (less than 1 in 1000). However, the influence of including operative mortality is assessed in sensitivity analysis where it is assumed that a small proportion of patients will die.

C.5.3 Disease related and other cause mortality

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

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

Variations in disease related mortality were explored in sensitivity analysis, including a scenario where it was assumed that there was no survival advantage (as was the case in the Yuen et al. 2009 study).

Death from other causes was captured using 2011-2013 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. These annual probabilities were converted to three-monthly probabilities for use in the model. The starting age and gender data applied in the model were sourced from the Data for Head and Neck Oncology (National Head and Neck Cancer Audit) national dataset. Thus, in the modelled cohort, 59.9% of patients were male and the average age was 64.4 years old.

C.5.4 Diagnostic accuracy of sentinel lymph node biopsy

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

A more recent meta-analysis (Yamauchi et al. 2015) was identified in an update of the clinical evidence review conducted for the guideline, in which a pooled sensitivity of 91% (95% CI 85% to 95%) was reported while specificity was again assumed to be 100%. Since the results of the results were very similar to the results of Govers et al. 2013, it was not considered necessary to update the analysis with the new data from Yamauchi et al. 2015.

It should be noted that all studies on SLNB in this patient population assume a specificity of 100%. This is because the reference standard is a neck dissection which would also assess whether there is a positive node. However, the wider issue of whether all occult metastases would become overt disease is not assessed in the studies.

There is also reason to be cautious about the high sensitivity values reported in most diagnostic accuracy studies. END was used as the reference standard in most of these studies and there may be limitations with this approach as it is likely that some occult metastases are missed by END. Indeed, this may be evidenced by the apparent discrepancy between the incidence of node positivity at the time of END (around 30%) and the occurrence of nodal relapse in the WW group (around 45%) in D'Cruz et al. 2014 and Yuen et al. 2009. In both studies this issues is discussed and attributed to the likelihood that occult metastases were missed under pathological examination. In an attempt to capture the consequences of this uncertainty, the use of alternative sensitivity values was explored in sensitivity analysis. In particular, the pooled sensitivity from studies using clinical/radiological follow-up from Yamauchi et al. 2015 were utilised, in which sensitivity was estimated to be 84% (95% CI 75% to 90%).

It should further be noted that no comparative evidence was identified that assessed the impact of SLNB on overall survival or disease recurrence. Therefore, the estimates attained in this economic evaluation will be entirely model based and should therefore be interpreted with a degree of caution.

In the model, it is assumed that patients with positive sentinel lymph nodes will undergo an elective neck dissection. Those patients correctly identified as being sentinel node positive (true positives) were assumed to have the same regional recurrence rate as patients found to be node positive in the elective neck dissection arm. If patients were found to be erroneously positive (i.e. false positive) then they would receive an unnecessary neck dissection. However, the specificity of 100% means that this scenario did not arise in the model.

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

C.6 Costs

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

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

C.7 Neck dissection

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

It is sometimes postulated that therapeutic neck dissections carry a greater morbidity risk, which could result in therapeutic neck dissections taking longer and thus carrying a greater cost. However, no distinction was made between the procedures in NHS reference costs. Thus, in the base case, it has been assumed that there is no difference in the cost of a therapeutic neck dissection and an elective neck dissection. This assumption is varied in the sensitivity analysis where the influence of making therapeutic neck dissections more costly is evaluated.

C.7.1 Sentinel lymph node biopsy

Obtaining an accurate cost for sentinel lymph node biopsy in the context of head and neck cancer proved to be problematic. Procedural codes associated with sentinel lymph node biopsy (T862, T873, T911 and O142) currently map to HRG codes associated with breast cancer – "Intermediate breast procedure" with and without complications.

The coding of SLNB under an umbrella procedure code for breast cancer most likely reflects the fact that the most common usage of sentinel lymph node biopsy is in breast cancer. It is not clear to what extent the cost of performing the procedure in the context of head and neck cancer patients would differ. It should also be noted that as the code is relatively generic, it is likely that other breast procedures also map to this code.

However, in the absence of better data on the cost of SLNB in this context, the NHS cost associated with an intermediate breast procedure was used as the base case estimate for a SLNB. Note that the SLNB procedure can be performed as an elective inpatient or day case procedure, with a current best practice tariff designed to incentivise more day case procedures. In the absence of data on the relative proportions of SLNBs performed as day case and elective inpatient procedures in head and neck cancer, procedure proportions were based on the number of intermediate breast procedures in NHS Reference costs.

In addition, patients undergoing a SLNB would receive imaging to identify the sentinel node(s). The cost of imaging before the SLNB was also estimated from NHS Reference Cost using Nuclear Medicine Category 3 (£233.94).

The costs associated with SLNB that were applied in the model are shown in the table below.

Table 34: Sentinel lymph node biopsy cost

Treatment	Proportion	Cost	Source
Imaging			
Lymphoscintigraphy	-	£233.94	NHS reference costs 2013/14 - Nuclear Medicine, Category 3 in outpatient diagnostic imaging
Unilateral intermediate breast procedure cost			
Elective inpatient	18%	£2,185.01	NHS reference costs 2013/14
With CC Score 6+	3%	£3,305.86	NHS reference costs 2013/14 – (JA24D)
With CC Score 3-5	14%	£2,360.10	NHS reference costs 2013/14 – (JA24E)
With CC Score 0-2	83%	£2,109.74	NHS reference costs 2013/14 – (JA24F)
Day case	**82%**	**£1,258.81**	**NHS reference costs 2013/14**

Treatment	Proportion	Cost	Source
With CC Score 6+	1%	£1,227.88	NHS reference costs 2013/14 – (JA24D)
With CC Score 3-5	6%	£1,274.22	NHS reference costs 2013/14 – (JA24E)
With CC Score 0-2	93%	£1,258.01	NHS reference costs 2013/14 – (JA24F)
Weighted average procedure cost		£1,426.53	
Total cost of SLNB		£1,659.47	

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

Post operative radiotherapy

For the purposes of the model it was estimated that 67% of patients undergoing neck dissection will also receive post-operative radiotherapy. This estimate was based on the study by Yuen et al. 2009, in which the 33% of patients with pN1 disease without extracapsular spread did not receive radiotherapy. Reflecting advances in clinical practice, it was assumed that all patients undergoing radiotherapy would receive intensity modulated radiotherapy (IMRT).

In addition, it was estimated that 46% of patients would receive chemotherapy in conjunction with radiotherapy. This estimate was based on the proportion of patients with extracapsular spread after nodal recurrence from Yuen et al. 2009, under the assumption that all patients with extracapsular spread would receive concomitant chemotherapy.

The costs of IMRT and concomitant chemotherapy are shown in the table below. Note that it was assumed that Cisplatin would be given in two doses of 100mg/m^2.

Table 35: IMRT costs with and without concomitant chemotherapy

Chemoradiotherapy treatment cost elements	Cost	PSA distribution‡	Source
IMRT			
Preparation for Intensity Modulated Radiation Therapy, with Technical Support	£1,625.86	Gamma (SE =511.55, alpha =10, beta =161)	NHS reference costs 2013/14 – outpatient radiotherapy –(SC41Z)
Deliver a fraction of complex treatment on a megavoltage machine	£126.17	Gamma (SE =39.87, alpha =10, beta =13)	NHS reference costs 2013/14 –- outpatient radiotherapy (SC23Z)
Number of fractions	30	Gamma (SE =3.71, alpha =66, beta =0)	Guideline committee estimate
Total IMRT cost	***£5,410.96***		**-**
Concomitant chemotherapy			
Deliver Complex Chemotherapy, including	£265.85	Gamma (SE	NHS reference

Chemoradiotherapy treatment cost elements	Cost	PSA distribution‡	Source
Prolonged Infusional Treatment, at First Attendance*		=88.17, alpha =9, beta =29)	costs 2013/14 -– outpatient chemotherapy (SB14Z)
Deliver subsequent elements of a chemotherapy cycle	£313.80	Gamma (SE =265.61, alpha =1, beta =225)	NHS reference costs 2013/14 -– outpatient chemotherapy (SB15Z)
Cisplatin cost per dose (100mg/m2)†	£39.25^	Gamma (SE =14.59, alpha =7, beta =5)	Unit cost from eMIT
Cost for two doses of cisplatin (on day 1 and day 22)	£78.51	-	-
Total cisplatin cost	***£658.15***	**-**	**-**
Total chemoradiotherapy cost	**£6,069.11**		
† Based on average body surface area for patients with head and neck cancer from Sacco et al. 2010 (1.85m2 for males and 1.65m2 for females)			
^Based on the cost of one 100ml vial (£16.69), one 50ml vial (£11.21) and four 10ml vials (£3.55) for men and one 100ml vial, one 50ml vial and two 10ml vials for women.			
‡ Alpha and beta values estimated using upper and lower estimates from NHS reference costs 2013/14 and standard deviations from eMit			

C.7.2 Follow-up costs

There is a general consensus that patients require regular follow-up after treatment in order to detect recurrences. While there is likely to be some variation in clinical practice, the guideline committee estimated that the following protocols would best reflect current UK practice:

Table 36: Frequency of surgical consultant follow-up

Year and follow-up frequency	Average number of sessions per year	PSA distribution‡	Source
Year 1: 3 weeks, then every 6-8 weeks	8.58	Gamma (SE =6.36, alpha =2, beta =5)	Guideline committee estimate
Year 2: Every 8-10 weeks	5.85	Gamma (SE =4.34, alpha =2, beta =3)	Guideline committee estimate
Year 3: Every 12-15 weeks	3.90	Gamma (SE =2.89, alpha =2, beta =2)	Guideline committee estimate
Year 4: Every 6 months, then discharge	2.00	Gamma (SE =1.48, alpha =2, beta =1)	Guideline committee estimate
‡Alpha and beta values estimated using upper and lower estimates of ± 50%			

The average number of sessions per year was estimated using the follow-up frequencies estimated by the guideline committee. Where a range was provided, the annual estimate was calculated using the average of the upper and lower estimate.

It was assumed that surgical consultants would carry out the clinical examination at each follow-up visits. The cost per consultation was estimated to be £86.92 based upon the

average cost of a 'Consultant Led Non-Admitted Face to Face Attendance' (WF01A) from NHS reference costs in ENT and Maxillo-facial surgery.

C.7.3 Physiotherapy sessions

It was assumed that some patients would require physiotherapy after neck dissection. However, estimating the proportion of patients that would require physiotherapy proved to be difficult as there was thought to be variation in clinical practice. In the base case, it was assumed that only those patients reporting difficulty after an END require physiotherapy. Thus, in the base case, it was assumed that 50% of patients undergoing TND and 26% of patients undergoing END would require physiotherapy based patients reporting severe activity disability in a survey by El Ghani et al. 2002.

In those patients undergoing physiotherapy, it was assumed that the patient would be seen once or twice as an inpatient with a further six sessions as an outpatient. The inpatient visits were assumed to be captured in the reference costs for a neck dissection and so only the additional costs of the outpatient attendances were considered in the model. The cost per consultation was estimated to be £57.94 based on the cost of 'Consultant Led Non-Admitted Face to Face Attendances' from NHS reference costs in Physiotherapy.

C.7.4 Systemic chemotherapy and palliative care

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

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

The systemic chemotherapy costs applied in the model are shown in the table below.

Table 37: Systemic chemotherapy costs

Systemic Chemotherapy cost elements	Value	PSA distribution‡	Source
Proportion assumed to receive systemic chemotherapy	50%	Beta (alpha =50, beta =50)	Assumption
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£265.85	Gamma (SE =88.17, alpha =9, beta =29)	NHS reference costs 2013/14 -– outpatient chemotherapy (SB14Z)
Deliver subsequent elements of a chemotherapy cycle	£313.80	Gamma (SE =265.61, alpha =1, beta =225)	NHS reference costs 2013/14 -– outpatient chemotherapy (SB15Z)
Cisplatin cost per dose (80mg/m2)	£27.68	Gamma (SE =10.47, alpha =7, beta =4)	Unit cost from eMit
Fluorouracil cost per dose (750mg/m2)	£3.90	Gamma (SE =1.91, alpha =4, beta =1)	Unit cost from eMit

Systemic Chemotherapy cost elements	Value	PSA distribution‡	Source
Cost for four doses of fluorouracil (on days 1, 2, 3 and 4)	£15.60	-	-
Total chemotherapy cost per cycle	£888.78	-	-
Average number of cycles	4	Gamma (SE =2.97, alpha =2, beta =2)	Assumption
Total systemic chemotherapy cost	**£3,555.10**		
‡Alpha and beta values estimated using upper and lower estimates from NHS reference costs 2013/14, standard deviations from eMit and with upper and lower estimates of ± 50% for values based on assumptions.			

C.7.5 Palliative care costs

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

Table 38: Palliative care costs

Type of care	Average cost per cancer patient	PSA distribution‡	Source
Cost of all hospital contacts	£5,890	Gamma (SE =4366.20, alpha =2, beta =3237)	Exploring the cost of care at the end of life (Nuffield Trust, Georghiou 2014)
Local authority-funded care	£444	Gamma (SE =329.13, alpha =2, beta =244)	
District nursing care	£588	Gamma (SE =435.88, alpha =2, beta =323)	
GP contacts	£365	Gamma (SE =270.57, alpha =2, beta =201)	
Average palliative care cost per patient	£7,287		
‡Alpha and beta values estimated using upper and lower estimates of ± 50%			

It should be noted that this cost is generic to all cancers and is not specifically related to cancers of the upper aerodigestive tract. However, in the absence of more robust data, it has been assumed that the costs in upper aerodigestive tract would not differ substantially. The influence of changing the cost of palliative care was explored in sensitivity analysis.

C.8 Health related quality of life (QoL) values

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs were estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state.

Sourcing data on QoL proved to be problematic as there seems to be a paucity of suitable data available in laryngeal cancer. This is illustrated by previous economic studies in this area, which have generally relied upon author assumptions or estimates from clinicians. Under NICE methodology, these methods would not be preferable as QoL values should be based on estimations obtained directly from patients and ideally using the EQ-5D survey.

However, it is recognised that QALYs need to be estimated in order to assess cost-effectiveness using the thresholds employed by NICE (£20,000 - £30,000 per QALY) and thus it is useful to utilise QoL data, even if they are of relatively poor quality. It is however

recognised as a limitation of the analysis and the QoL values were subjected to sensitivity analysis to assess how influential they are on the final decision.

For the purposes of this economic evaluation, the QoL data shown in table 40 were utilised.

Table 39: Quality of life values applied in the economic model

Health state	Utility	PSA distribution‡	Source
No evidence of disease (N0 patient)	0.9130	Beta (alpha = 7, beta = 1)	Sher et al. 2010 and Hollenbeak et al. 2001
Neck dissection disutility	0.0386	Beta (alpha = 55, beta = 10) - Beta (alpha = 31, beta = 7)	Difference in QoL values for patients treated with and without neck dissection from Lassig et al. 2008 (converted to EQ-5D using Ara et al. 2008†)
End of life (metastatic disease)	0.6500	Beta (alpha = 65, beta = 35)	NICE HTA on Cetuximab
† SF-36 values from Lassig et al 2008 converted to EQ-5D values using mapping algorithm from Ara et al. 2008 ‡Alpha and beta values estimated using patient numbers from QoL studies			

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

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

It should be noted that this study also has limitations. Most notably, the study population does not match the population being modelled. The study was based on patients with more advanced cancer (stage IV oropharyngeal cancer) than those in the modelled. It is possible that the QoL decrement would be different in patients with more advanced cancer. However, as there are no better alternative available, the use of this QoL data was thought to be appropriate. Furthermore, the effect of using alternative QoL values is explored in sensitivity analysis.

In the base case, it was assumed that there is no QoL decrement associated with a sentinel lymph node biopsy. This assumption was tested in sensitivity analysis where various QoL decrements were applied.

A QoL value from the NICE HTA on Cetuximab was used as an estimate for the quality of life of patients in a metastatic disease state. As described above, a metastatic health state was not explicitly modelled as such but it has been assumed that patients dying from upper aerodigestive tract cancer were likely to have developed metastatic disease. Thus, the QoL decrement associated with metastatic disease was retrospectively applied under the assumption that patients would spend 6 months in this state.

C.9 Base Case Results

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

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

Table 40: Deterministic base case cost-effectiveness results against common baseline (watchful waiting)

	Cost		QALYs		
Initial treatment	Total	Incremental	Total	Incremental	ICER (cost per QALY)
Watchful waiting	£7,284	-	4.87	-	-
Elective neck dissection	£9,509	£2,225	5.77	0.89	£2,490
SLNB	£9,175	£1,891	5.84	0.96	£1,960

Table 41: Deterministic Base case cost-effectiveness results using dominance rank

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

In addition to the deterministic results above, the base case results were also generated probabilistically. In this analysis the mean total costs and QALYs were recorded after 10,000 probabilistic runs of the analysis (sufficient for stability in the ICER). The probabilistic base case results are presented in tables 43 and 44 below for the comparison against a common baseline and the dominance rank approach.

It can be seen that, while there are some small changes in values, the conclusions of the analyses remain unchanged. In comparison to watchful waiting, SLNB and elective neck dissection are again found to be cost-effective with ICERS of £1,316 and £250 per QALY, respectively while SLNB was found to be the optimal strategy using dominance rank (with elective neck dissection dominated by SLNB).

Table 42: Probabilistic base case cost-effectiveness results against common baseline (watchful waiting)

	Cost		QALYs		
Initial treatment	Total	Incremental	Total	Incremental	ICER (cost per QALY)
Watchful waiting	£235	-	4.95	-	-
Elective neck dissection	£492	£2,256	5.87	0.92	£2,450
SLNB	£9,151	£1,916	5.94	0.99	£1,930

Table 43: Probabilistic Base case cost-effectiveness results using dominance rank

Initial treatment	Cost	QALYs	ICER (cost

	Total	Incremental	Total	Incremental	per QALY)
Watchful waiting	£235	-	4.95	-	-
SLNB	£9,151	£1,916	5.94	0.99	£1,930
Elective neck dissection	£492	£340	5.87	-0.07	Dominated

C.10 Deterministic sensitivity analysis

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

Table 44: One-way sensitivity analysis results

Change made	Optimal strategy
Prevalence of occult metastases = 30%	SLNB
Prevalence of occult metastases = 20%	SLNB
Proportion occult metastases that become overt = 75%	SLNB
Proportion occult metastases that become overt = 50%	SLNB
Proportion occult metastases that become overt = 25%	**WW**
Yamauchi SLNB sensitivity = 84%	SLNB
SLNB sensitivity = 80%	**END**
Equivalent morbidity with END and SND	SLNB
No survival benefit with END	**WW**
SLNB costs + 50%	SLNB
SLNB costs - 50%	SLNB
Neck dissection costs + 50%	SLNB
Neck dissection costs - 50%	SLNB
Conventional RT instead of IMRT	SLNB
Neck dissection disutility - 50%	SLNB
No neck dissection disutility	**END**
Disease specific mortality from Fasunla et al. 2011	SLNB
Disease specific mortality from D'Cruz et al. 2015	SLNB
Locoregional recurrence from D'Cruz et al. 2015	SLNB
Recurrence and mortality from D'Cruz et al. 2015	SLNB
WW Scenario - same effectiveness with ultrasound scans	SLNB
WW Scenario – Yuen effectiveness with ultrasound scans	**WW**
WW Scenario – Yuen effectiveness without ultrasound scans	**WW**
100% Elective inpatient SLNB	SLNB
100% Day case SLNB	SLNB
SLNB cost from melanoma model	SLNB
SLNB Best practice day case PbR tariff	SLNB
SLNB Ordinary elective PbR tariff	SLNB
Additional pathology cost = £200	SLNB
Additional pathology cost = £400	SLNB
Radiotherapy QoL decrement	SLNB

It can be seen that the conclusion of the analysis is unchanged in most modelled scenarios i.e. SLNB is found to be the dominant strategy in most analyses. However, there were notable exceptions where watchful waiting or elective neck dissection became the most cost-effective strategy. Watchful waiting was found to be cost-effective in the scenarios where the effectiveness estimates from Yuen et al. were applied (with and without ultrasound scans included in follow-up) or when the proportion of occult metastases that become overt disease was lowered to 25%. These findings are unsurprising given that they effectively reduce (or completely remove) the effectiveness that could be expected from the neck dissection procedure.

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

C.11 Threshold analysis

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

Elective neck dissection versus watchful waiting (SLNB not included)

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

All comparators (SLNB included)

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

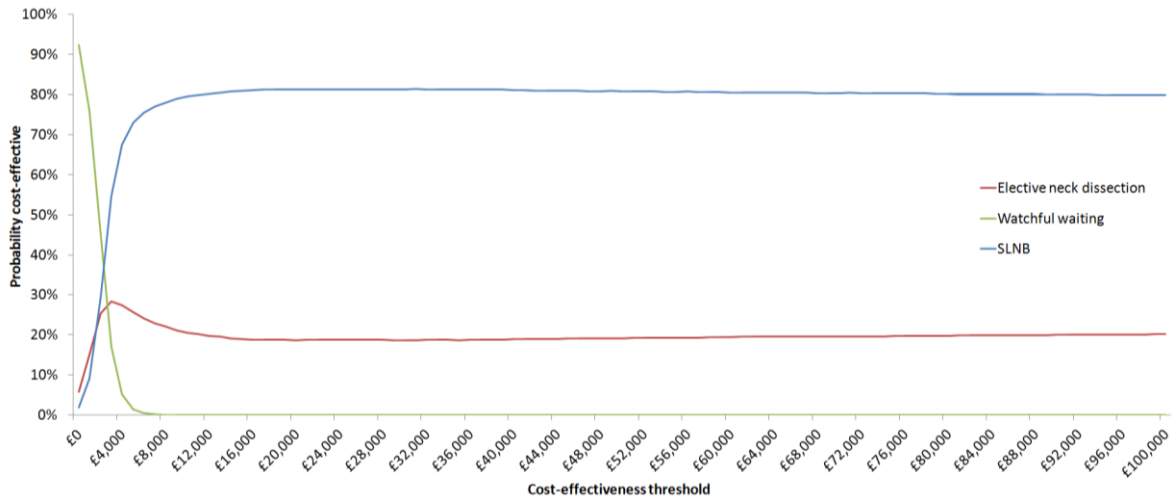
In addition, due to concerns about the reliability of SLNB sensitivity estimates in the clinical literature, a further threshold analysis was conducted on this parameter. It was found that SLNB is no longer cost-effective if its sensitivity ≤ 83.7%, at which point END becomes the preferred strategy.

C.12 Probabilistic sensitivity analysis (PSA)

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

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

Figure 10: Cost-effectiveness acceptability curve (CEAC) for management strategies for the clinically and radiologically N0 neck



C.13 Discussion

This analysis aimed to estimate the cost-effectiveness of management strategies for the clinically and radiologically N0 neck. To our knowledge, this is the first model that has investigated these treatment approaches in the UK context. One previous analysis (Govers et al. 2013) was identified that conducted a similar analysis but this analysis considered the Dutch health care system and was therefore not directly applicable to the UK context.

The results of the base case analysis suggest that SLNB was the most cost-effective strategy. In comparison to a watchful waiting strategy, SLNB was found to provide an additional QALY at a cost of £1,960, substantially below the NICE threshold of £20,000 per QALY. In comparison to elective neck dissection, SLNB was found to be dominant (i.e. more effective and less expensive). This result is similar to the result found in the analysis by Govers et al. 2013 in which SLNB was also found to be the most effective and cost-effective strategy (with an ICER of €3,356 per QALY).

One-way sensitivity analysis showed that the result was relatively robust with the conclusion of the analysis remaining unchanged in most modelled scenarios. However there were a few notable exceptions where the conclusion of the analysis changed in some scenarios where alternative inputs or assumptions were used. In particular, END was found to be cost-effective under some plausible assumptions with lower SLNB sensitivity. The result of the probabilistic sensitivity analysis also suggested that the result was robust showing that at, a threshold of £20,000 per QALY, SLNB had an 81% probability of being cost-effective.

There were a few limitations to the analysis that should be noted. As with most economic analyses, the analysis is, to a large extent, dependent on the clinical data upon which it is based. While a systematic review was undertaken to ensure that the model inputs reflect the best clinical evidence currently available, the evidence base was not found to directly address the decision problem. There was relatively good evidence showing a reduction in recurrence for patients treated with END instead of WW. However, there was no evidence identified that directly compared a SLNB approach with either of these approaches. Therefore, a modelling approach was adopted using diagnostic accuracy data on SLNB in conjunction with the available evidence on END and WW. While this approach is relatively common in health economic modelling, it would clearly be preferable to have clinical trial

data that directly compared SLNB with END or WW. Therefore, further research in this area would be desirable.

There was also found to be a paucity of quality of life data in this area. This is a common issue in cost-effectiveness evaluations but is nevertheless a significant one. The key QoL data applied in the model was the disutility associated with an elective neck dissection identified in a study by Lassig et al. 2008.

While this data was thought to be the best evidence available, it was not without limitations. Firstly, the study population did not match the population that was modelled. The study considered patients with stage IV oropharyngeal cancer treated with chemoradiotherapy alone and chemoradiotherapy in addition to neck dissection. Therefore it is likely that that the baseline utility for these patients is different as their cancer is more advanced and the treatment (with chemoradiotherapy) could be more intensive. However, while the baseline utility may be different, it has been assumed that the difference between the two treatments i.e. that which could be apportioned to neck dissection would be the same. Secondly, the study measured QoL using the SF-36 survey rather than the nice preferred EQ-5D survey. This issue was addressed by converting the SF-36 values to EQ-5D values using a mapping algorithm but the use of such algorithms also involves some uncertainty as it depends upon the predictive capability of the algorithm. However, the effect of the latter was hopefully mitigated by the use of the validated and widely used mapping algorithm by Ara et al. 2008.

There was also uncertainty over the cost of the SLNB procedure and associated pathology costs. While there is a cost code available for the procedure in NHS reference costs, there were concerns over the applicability of the code in this disease area (as the code seems to be related to SLNB procedures in breast cancer patients). Furthermore, the guideline committee expressed concerns that the cost estimate seemed to be too low with particular concerns over the potential extra resources that would be required in pathology. However, concerns in this area were largely addressed by the extensive sensitivity analyses that were conducted, in which the conclusions of the analysis remained unchanged.

C.14 Conclusion

The results showed SLNB to be the preferred management strategy for the clinically and radiologically N0 neck. Sensitivity analysis suggested that the result was generally robust with a relatively high level of certainty in the conclusion of the analysis. However, there were some scenarios identified in sensitivity analysis, in which the conclusion of the analysis changed. In particular, the influence of changes in SLNB sensitivity on the results was noteworthy as END was found to be cost-effective under some plausible assumptions with lower sensitivity.

References

Ara R, Brazier J. Deriving an Algorithm to Convert the Eight Mean SF-36 Dimension Scores into a Mean EQ-5D Preference-Based Score from Published Studies (Where Patient Level Data Are Not Available). Value in Health (2008) 11(7): 1131-1143

Bessell, A., Glenny, A. M., Furness, S., Clarkson, J. E., Oliver, R., Conway, D. I. et al. (2011). Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database of Systematic Reviews.

Brentani, R. R., Kowalski, L. P., Soares, J. F., Torloni, H., Camargo, A. C., Pereira, R. N. et al. (1998). Results of a prospective trial on elective modified radical classical versus supraomohyoid neck dissection in the management of oral squamous carcinoma. American Journal of Surgery, 176, 422-427.

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

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

D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R et al. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. N Engl J Med 2015. Epub ahead of print.

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

Fakih AR, Rao RS, Borges AM, Patel AR. (1989) Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. American Journal of Surgery, 158(4):309-13.

Fasunla AJ, Greene BH, Timmesfeld N, Wiegand S, Werner JA, Sesterhenn AM. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. Oral Oncol. 2011 May;47(5):320-4.

Georghiou T, Bardsley M. Exploring the cost of care at the end of life. Nuffield Trust 2014

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

Govers TM, Takes RP, Baris Karakullukcu M, Hannink G, Merkx MA, Grutters JP, Rovers MM. Management of the N0 neck in early stage oral squamous cell cancer: a modeling study of the cost-effectiveness. Oral Oncol. 2013 Aug;49(8):771-7

Hollenbeak, CS, Lowe, VJ, and Stack, BC. The cost-effectiveness of fluorodeoxyglucose 18-F positron emission tomography in the NO neck (Structured abstract). Cancer 2001; 92(9): 2341-2348.

Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press

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

Lassig AAD, Duffy SA, Fowler KE, Ronis DL, Chepeha DB, Terrell JE. The effect of neck dissection on quality of life after chemoradiation. Otolaryngol Head Neck Surg. 2008 Oct;139(4):511-8.

National Life Tables, United Kingdom, 1980-82 to 2011-13. Office for National Statistics (www.ons.gov.uk)

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

Vandenbrouck C, Sancho-Garnier H, Chassagne D, Saravane D, Cachin Y, Micheau C. (1980) Elective versus therapeutic radical neck dissection in epidermoid carcinoma of the oral cavity: results of a randomized clinical trial. Cancer. 1980 Jul 15;46(2):386-90.

Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P (2010) The Average Body Surface Area of Adult Cancer Patients in the UK: A Multicentre Retrospective Study. PLoS ONE 5(1): e8933. doi:10.1371/journal.pone.0008933

Sher, DJ et al. Cost-effectiveness of CT and PET-CT for determining the need for adjuvant neck dissection in locally advanced head and neck cancer (Provisional abstract). Annals of Oncology 2010; 21(5): 1072-1077.

Weiss MH, Harrison LB, Isaacs RS. Use of Decision Analysis in Planning a Management Strategy for the Stage NO Neck. Arch Otolaryngol Head Neck Surg. 1994;120(7):699-702

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

Yuen, A. P. W., Ho, C. M., Chow, T. L., Tang, L. C., Cheung, W. Y., Ng, R. W. M. et al. (2009). Prospective Randomized Study of Selective Neck Dissection Versus Observation for No Neck of Early Tongue Carcinoma. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck, 31, 765-772.

Appendix D: Abbreviations

BMI	Body mass index
CCRT	Radiotherapy and concomitant chemotherapy
CT	Computed tomography
CUADT	Cancer of the upper aerodigestive tract
DNA	Deoxyribonucleic acid
ECS	Extracapsular spread
FDG	Fluorodeoxyglucose
FNAC	Fine-needle aspiration cytology
GC	Guideline committee
GRADE	Grading of recommendations, assessment, development and evaluation
HBO	Hyperbaric oxygen
HNC	Head and neck cancer
HPV	Human papilloma virus
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
ISH	In-situ hybridisation
IMRT	Intensity modulated radiotherapy
LETR	Linking evidence to recommendations
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NBI	Narrow band imaging
ND	Neck dissection
NPV	Negative predictive value
ORN	Osteoradionecrosis
PCR	Polymerase chain reaction
PET	Positron emission tomography
PEG	Percutaneous endoscopic gastrostomy
PET-CT	Positron emission tomography-computed tomography
PICO	Population, Intervention, Comparator, Outcome
PFS	Progression free survival
PPV	Positive predictive value
PRT	Progressive resistance training
PSA	Probabilistic sensitivity analysis
RCTs	Randomised controlled trials
RNA	Ribonucleic acid
QALY	Quality adjusted life years
QArfLY	Quality adjusted relapse free life-years
QoL	Quality of Life
QUADAS	Quality assessment of diagnostic accuracy studies
RT	Radiotherapy
SCC	Squamous cell carcinoma
SLNB	Sentinel lymph node biopsy
TLM	Transoral laser microsurgery
TORS	Transoral robotic surgery

UADT	Upper aerodigestive tract

Appendix E: Glossary

Adjuvant treatment

A treatment given after the main treatment for cancer to reduce the risk of recurrence.

Adverse event

Detrimental change in health occurring in a person receiving the treatment whether or not it has been caused by the treatment.

Biological therapy

Biological therapy involves the use of substances derived from living organisms, or laboratory-produced versions of such substances, such as antibodies, which interfere with specific molecules involved in tumour growth and progression.

Biomedical scientist

A person with professional qualifications who is registered to test samples and specimens in order to assist doctors to make diagnoses and plan treatment.

Biopsy

Removal of a sample of tissue from the body to assist in diagnosis or inform the choice of treatment of a disease.

Body Mass Index

A measure of body weight relative to height used to determine whether people are underweight, at a healthy weight, over weight or obese.

Chemotherapy

The use of medication (drugs) that is toxic to cancer cells, given with the aim of killing the cells or preventing or slowing their growth.

Cohort studies

In case control studies groups of patients with a particular condition or specific characteristic are compared with matched groups who do not have it. Patients within the cohort are then compared with each other.

Computed tomography (CT)

Imaging technique in which the person lies on a table within a X-ray gantry. The images are acquired using a spiral (helical) path and banks of detectors, allowing presentation of the internal organs and blood vessels in different projections including 3-D views.

Concomitant chemotherapy

Chemotherapy that is administered during a course of radiotherapy.

Core biopsy

A small sample of tissue removed from the body using a needle in order to make a diagnosis or inform the choice of treatment of a disease.

Cost utility analysis

A special form of cost effectiveness analysis where benefit is measured in quality adjusted life years. A treatment is assessed in terms of its ability to extend or improve the quality of life.

Cross-sectional imaging

Imaging based on obtaining data at an angle perpendicular to the axis of the body and usually refers to MRI, CT, and FDG PET-CT. It does not include plain film imaging and ultrasound.

Curative treatment

Curative treatment is defined as a treatment which is intended to lead to patient survival beyond the time after which the risk of treatment failure approaches zero.

Cutaneous melanoma

Melanoma of the skin.

Cytologist

A doctor who specialises in making diagnoses by viewing cells under the microscope.

Deterministic sensitivity analysis

A method for assessing uncertainty in economic analyses. Alternative inputs or assumptions are explored in the analysis to assess their influence on the cost-effectiveness results and conclusions.

Disease-free survival

Length of time after treatment during which no disease is found.

DNA in-situ hybridisation (ISH)

A technique to show whether particular genes are present when tissues are inspected through a microscope.

Dysfunctional

Abnormal or impaired functioning.

Dyspnoea

Subjective experience of breathlessness.

Elective neck dissection

Planned removal of cervical lymph nodes.

End of life

People who are approaching the end of life when they are likely to die within the next 12 months including those whose death is imminent.

Endoscopic assessment

A technique that is used to assess lesions of the UADT using various endoscopes and telescopes through the mouth and the nose.

Enteral feeding

Nutrition support directly into the gut via a tube.

Extracapsular spread (ECS)

Spread of tumour outside the lymph node capsule.

False negative

Where a diagnostic test classifies an individual with a disease as disease free.

False positive

Where a diagnostic test classifies an individual who is disease free as having the disease.

Fine needle aspiration Cytology (FNAC)

The sampling of cells, rather than pieces of tissue for examination by a cytopathologist.

Flexible transnasal oesphagoscopy

A technique performed under topical anaesthesia that uses a thin, flexible endoscope passed through the nose, to examine the oesophagus.

Follow-up

Continuing examination or observation of a patient to monitor the success of earlier treatment.

Functional swallow

Swallow that is abnormal or altered but where there is no aspiration risk of either oral secretions or oral intake.

Gastrostomy tube

Enteral tube inserted through the abdominal wall into the stomach for the purpose of nutrition support.

GRADE

The GRADE approach is a method of grading the quality of evidence and strength of recommendations in healthcare guidelines. It is developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.

Histological margins

The measurement of the closest distance between edge of the tumour to the surface of the specimen. This measurement is usually, but not always, made using the microscope.

Hypopharynx

Area of the throat where the oesophagus and voice box meet.

Hyperbaric oxygen therapy

Therapeutic use of pressurised oxygen to increase tissue oxygenation or promote healing. It is used to treat injury to tissues exposed to radiotherapy, either where osteoradionecrosis has occurred or where teeth in an irradiated part of the jaw need to be extracted.

Immunohistochemistry

Immunohistochemistry (IHC) is a technique that uses specific antibodies to show whether particular proteins are present when tissues are inspected through a microscope.

Incidence

The number of new cases of a disease in a given time period.

Intensity modulated radiation therapy (IMRT)

Specialised form of radiation therapy where the radiation can be adjusted to vary the doses given to different parts of an organ.

Interventional tube feeding

A feeding tube that is placed prior to treatment to manage factors such as significant nutritional compromise, swallowing problems, or other clinical and non clinical criteria.

Ipsilateral

On, or affecting, the same side.

Laryngeal function

The action of the larynx during speaking, coughing and swallowing.

Laryngectomy

Partial or complete removal of the voicebox.

Larynx

The voicebox.

Larynx-preserving surgery

Surgery to the voice box aiming to preserve function of speech and swallowing.

Long Term Feeding

A feeding tube that is placed for example greater than 4 weeks.

Malnutrition

A state of nutrition in which a deficiency of energy, protein and/or other nutrients causes measurable adverse effects on tissue/body form, composition, function or clinical

Magnetic resonance imaging (MRI)

A type of scan which uses a magnetic field and radio waves to produce images of sections of the body.

Mandible

Lower jaw or jawbone supporting the lower teeth.

Meta-analysis

A form of statistical analysis used to synthesise results from a collection of individual studies.

Metastases/metastatic disease

Spread of cancer away from the primary site to somewhere else through the bloodstream or the lymphatic system.

Morbidity

Detrimental effects on health.

Mortality

Either (1) the condition of being subject to death; or (2) the death rate, which is usually expressed as the number of deaths in a fixed number of the population e.g. per 100,000 people.

Mucosa

The lining of the mouth, throat and nose.

Mucosal melanoma

Rare type of melanoma that occurs on the mucous membranes which are moist surfaces which line the mouth, throat and nose.

Multi disciplinary team (MDT)

A team with members from different health care professions and specialties (e.g. oncology, pathology, radiology, and nursing). Cancer care in the NHS uses this system to ensure that all relevant health professionals are engaged to discuss the best possible care for all patients.

Multi disciplinary team meeting (MDTM)

A meeting where members of the Multi Disciplinary Team discuss and make recommendations about the care of people.

Multi Modality

The use of more than one treatment type for patients.

Nasogastric tube

Nutrition support provided through a tube inserted through the nose via the oesophagus into the stomach.

Nasopharynx

The air cavity lying at the back of the nose and above the roof of the mouth.

National Peer Review Programme

National Peer Review Programme is a quality assurance programme that is aimed at reviewing clinical teams and services to determine their compliance against national measures, as well as the assessment of quality aspects of clinical care and treatment.

Neck dissection

Surgical removal of lymph nodes in the neck.

Observational studies

A study in which participants receive different interventions without randomisation. Instead, the interventions received may be influenced by factors such as patient choice, patient characteristics, time of treatment, treatment location, etc. These factors may influence outcomes independent of the intervention, and therefore these studies are at greater risk of bias than randomised controlled trials.

Occult metastases

The presence of tumour which has spread from the primary to a regional or distant site within the body but which is not detectable clinically.

Open partial laryngectomy

Removal of part of the larynx through a skin incision.

Oropharynx

The part of the throat at the back of the mouth behind the oral cavity.

Oral cavity

The mouth.

Osteoradionecrosis

A complication of radiotherapy where bone in the irradiated field dies. It most commonly affects the mandible.

Overall survival

The length of time from either the date of diagnosis or the start of treatment for a disease that patients diagnosed with the disease are still alive. This is usually expressed as the proportion of patients who are alive at a certain time point after diagnosis or treatment.

p16

A protein involved in regulating the life cycle of a cell that is used as a surrogate marker for high-risk human papillomavirus infection.

Palliative

Anything which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it.

Paranasal

Around or near the nasal passages.

Polymerase chain reaction (PCR)

The laboratory technique used to identify whether a particular gene is present within a specimen.

Primary tumour

Original site of the first cancer.

Probabilistic sensitivity analysis

A method for assessing uncertainty in economic analyses. Models are run multiple times with values drawn from probability distributions instead of the mean values used in the base case.

Prognosis

A prediction of the likely outcome or course of a disease; the chance of recovery, recurrence or death.

Prognostic factors

Specific characteristics of a cancer or the person who has it which might affect their prognosis.

Progression-free survival

The length of time that a patient lives with a disease without it getting worse usually measured from either the date of diagnosis or the start of treatment.

Prophylactic tube feeding

A feeding tube that is placed prior to treatment to pro-actively manage factors such as significant nutritional compromise, swallowing problems, or other clinical and non-clinical criteria.

Psychosocial support

A general term for any non-therapeutic intervention that helps a person cope with stressors in the home or at work.

Qualitative data

Data in which the outcomes are usually recorded in words, rather than with numbers.

Qualitative research

Research in which the outcomes are usually recorded in words, rather than with numbers. Often used to explore and understand peoples' beliefs, experiences, attitudes, behaviour and interactions.

Quality adjusted life years (QALYs)

A measure of health outcome, which looks at both length of life and quality of life. QALYs are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a 0-1 scale). One QALY is equal to 1 year of life in perfect health, or 2 years at 50% health, and so on.

Quality of life

An overall appraisal of well being.

Quantitative research

Research which uses numerical measurement techniques (e.g. measuring survival times after treatment).

Radiotherapy

The use of radiation, usually high energy x-rays to control the growth of cancer cells.

Randomised controlled trial (RCT)

An experimental clinical trial (study) comparing the effectiveness of different treatments. Participants are assigned at random to the different treatment groups one of which will be the current standard of care. RCTs give the most reliable (i.e. least biased) form of evidence on clinical effectiveness.

Rapid access clinic

A clinic where patients referred with suspected cancer are seen within 2 weeks of the date of the referral.

Reactive tube feeding

A feeding tube that is only placed during treatment if it becomes clinically indicated.

Reconstruction

Surgery that is done to reshape or rebuild (reconstruct) a part of the body changed by previous surgery.

Recurrence

Recurrence is when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body.

Regional control

The control of cancer in sites that represent the first stages of spread from the local origin.

Rehabilitation

The process of improving, maintaining or optimising physical, cognitive or psychological impairment that has occurred as a consequence of a disease or its treatment.

RNA in-situ hybridisation (ISH)

A technique to show whether a particular gene is active when tissues are inspected through a microscope.

Salvage surgery

Surgery undertaken after cancer has progressed, following previous treatments.

Secondary Cancer

A primary cancer is where a cancer starts. Sometimes cancer cells can break away from the primary cancer and settle and grow in another part of the body. This new cancer growth is called secondary cancer.

Selective neck dissection

Surgery to remove selected neck lymph nodes whilst preserving key anatomical structures.

Sensitivity

In this context the term is used to mean the proportion of individuals with a disease who have that disease correctly identified by the study test.

Sensitivity analysis

A means of representing uncertainty in the results of economic evaluations. Sensitivity analysis also allows for exploring the generalisability of results to other setting.

Sentinel lymph node biopsy (SLNB)

Surgical removal of the first lymph node or group of nodes (the sentinel node) draining a cancer.

Skin excoriation

A raw, irritated area of skin.

Specificity

In diagnostic testing, it refers to the chance of having a negative test result given that you do not have the disease.

Spinal accessory nerve

A nerve in the neck partly responsible for shoulder movement that is potentially at risk of damage during surgery.

Squamous cell carcinoma

Cancer that begins in squamous cells. Squamous cells are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the passages of the respiratory and digestive tracts.

Staging

Clinical description of the size and spread of a patient's tumour, fitting into internationally agreed categories.

Stent

A tube or other device placed in the body to relieve a blockage in a passage.

Stridor

A high pitched sound resulting from narrowing in the upper airway (usually trachea or main bronchi).

Surgical margins

The margin of apparently normal tissue that a surgeon removes in order to ensure complete removal of a tumour.

Survival

Survival is the time alive after diagnosis of a disease.

Synchronous primary cancer

Two or more histologically distinct, simultaneously detected malignancies.

Systemic disease

A systemic disease is one that affects a number of organs and tissues, or affects the body as a whole.

Systematic review

A review of the literature carried out in order to address a defined question and using quantitative methods to summarise the results.

Systemic staging

Investigations carried out to determine if a cancer has spread beyond the primary site.

Systemic treatment

Treatment, usually given by mouth or by injection, that reaches and affects cancer cells throughout the body rather than targeting one specific area.

Therapeutic neck dissection

Surgery carried out to treat established nodal disease in the neck.

Tracheostomy

Surgically created stoma (hole) in the front wall of the trachea below the larynx, either temporary or permanent, to enable improved air flow into the lungs.

Transoral laser micro surgery (TLM)

A minimally-invasive surgical technique that uses a laser under microscopic magnification to remove lesions of the upper aerodigestive tract through the mouth.

Trismus

Limitation of opening of the mouth.

Tumour debulking

Removal of part of the tumour by any surgical method, with the aim of alleviating symptoms rather than curing the patient of the tumour.

Ultrasound

A type of scan in which high-frequency sound waves are used to outline a part of the body.

Upper aerodigestive tract cancer

Upper aerodigestive tract cancers encompass cancers arising at different sites in the airways of the head and neck. These comprise cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and nasal sinuses.

Unknown primary

The presence of metastatic malignancy, with no identifiable primary site.

Unilateral

One-sided.

Watchful waiting

A method of managing people with cancer, involving treatment only if and when they develop symptoms.

Appendix F:Guideline Scope

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SCOPE

F.1 Guideline title

Cancer of the upper aerodigestive tract: assessment and management of upper aerodigestive tract mucosal cancers

F.1.1 Short title

Cancer of the upper aerodigestive tract

F.2 The remit

The Department of Health has asked NICE to develop a clinical guideline on the assessment and management of upper airways tract cancers.

F.3 Need for the guideline

F.3.1 Epidemiology

- Upper airways tract (UAT) cancers encompass a number of cancers arising at different sites in the airways of the head and neck. These comprise cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and nasal sinuses.
- Squamous cell cancers predominate but other less common cancers can also occur.
- In 2013 the Cancer Research UK website published incidence and survival data on all oral cancers which included the lip, mouth, oropharynx and hypopharynx. In 2010, 6539 people were diagnosed with oral cancer in the UK and there were 1985 deaths from oral cancer. It is twice as common in men as in women – incidence rates have almost doubled in the last 25 years, and rates for women have also been increasing in recent years. Oral cancers are more common in older people (mean age 64 years) but the number of younger people developing these cancers is increasing. Incidence rates are higher in Scotland but similar in England, Wales and Northern Ireland, although there are regional variations. Around 50% of adults diagnosed with oral cancer survive for 5 years or more.
- Laryngeal cancer is almost 5 times more common in men than in women. In 2010, 2337 people were diagnosed with laryngeal cancer in the UK and there were 760 deaths from laryngeal cancer. It is rarely diagnosed in people aged under 40. But over 40 years, the incidence of laryngeal cancer rises steeply with nearly three quarters of cases in people aged 60 and over. Around 85% of people with laryngeal cancer will survive the disease for at least 1 year. The 5-year survival rate is around 67%.
- Figures for other cases of upper airways tract cancers diagnosed each year in the UK are:
  - 460 nasal sinuses
  - 240 nasopharynx
  - 1346 oropharynx
  - 238 hypopharynx.

- Nasopharyngeal cancer is more common in some ethnic groups such as people of Chinese origin.
- The association between human papilloma virus (HPV) and oropharyngeal cancer is increasingly being recognised. But as the natural history and transmission of oral and oropharyngeal HPV infection is not fully understood, the opportunities for reducing this risk are unclear. Oropharyngeal cancer tends to affect a younger population (mean age 59 years) without traditional risk factors such as smoking and alcohol.
- The major risk factors for upper airways tract squamous cell cancer in the UK are tobacco smoking and alcohol consumption. Control of these environmental carcinogens remains the focus for primary and secondary prevention.

F.3.2 Current practice

- A multidisciplinary team approach involving ear, nose and throat surgeons, maxillofacial surgeons, plastic surgeons, radiologists, pathologists and specialist oncologists is essential to provide high quality care. Providers of rehabilitation services (such as speech and language therapists and dietitians), restorative dentists, therapy radiographers, clinical nurse specialists, supportive and palliative care practitioners and research staff are also integral members of the upper airways tract cancer multidisciplinary team.
- The proximity of upper airways tract cancers to critical structures such as the spinal cord, brain, eyes and major blood vessels poses challenges to treatment.
- Over the last 10 years, increasing use of chemoradiotherapy (with or without induction chemotherapy) has resulted in a decrease in the amount of surgery being performed. However, there is wide variation across the UK in the rates of these procedures.
- There has also been a change in the treatment of laryngeal cancer over the last decade, with increasing use of laser treatment for early stage disease instead of radiotherapy.
- Since the publication of Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck (NICE technology appraisal guidance 145) it has become standard treatment for people not fit enough to have chemoradiotherapy.
- There has been an increase in the use of intensity modulated radiotherapy (IMRT) techniques to treat upper airways tract cancer.
- Positron emission tomography (PET) is also increasingly used for investigating upper airways tract cancers, but there is uncertainty about the indications for its use.
- h) The involvement of multiple health professionals can lead to fragmentation of care. Service guidance on improving outcomes in head and neck cancers (NICE cancer service guidance CSGHN) recommended the composition and organisation of services for upper airways tract cancers in England and its implementation continues to be assessed against peer review measures published in the Department of Health's Manual for cancer services, 2008: Head and neck measures.
- The findings from the latest 'National peer review of UAT services in England' (scheduled for publication in October 2013) show that there are currently 49 upper airways tract cancer multidisciplinary teams. The median compliance of upper airways tract cancer services with the measures increased from 79% in 2011/2012 to 90% in 2012/2013. However, some issues of concern were identified including:
  - • treatment management decisions and protocols not always communicated clearly between oncologists in different multidisciplinary teams
  - • lack of restorative dentists and dietitians
  - • limited availability and lack of continuity of trained nursing staff to support clinicians during surgery
  - • delays in diagnosis, resulting in a failure to meet waiting time targets.
- Several areas of good practice were identified. These included:
  - surgery performed at a single designated site within a region

- routine provision of intensity modulated radiotherapy for all people for whom it is appropriate
- development of enhanced recovery programmes and day-of-surgery admissions
- dedicated slots provided for dental assessments before radiotherapy
- use of craniofacial 3D modelling.

Data collection using the National Head and Neck Cancer Audit (DAHNO audit dataset) continues to improve.

F.4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

F.4.1 Population

F.4.1.1 Groups that will be covered

- Adults and young people (16 years and older) referred from primary care with suspected cancer of the upper airways tract (including cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and nasal sinuses).
- Adults and young people (16 years and older) with newly diagnosed or recurrent cancer of the upper airways tract (including cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and nasal sinuses).
- Subgroups identified as needing specific consideration will be considered during the development of the guideline.

F.4.1.2 Groups that will not be covered

- Adults and young people (16 years and older) with cancer of the thyroid.
- Adults and young people (16 years and older) with cancer of the orbit.
- Adults and young people (16 years and older) with cancers of the middle ear.
- Adults and young people (16 years and older) with cancers of the cutaneous (sun-exposed) lip.
- Adults and young people (16 years and older) with skull base cancers.
- Adults and young people (16 years and older) with salivary gland cancer.
- Adults and young people (16 years and older) with sarcoma.
- Adults and young people (16 years and older) with lymphoma.
- Children under 16 years.

F.4.2 Setting

- All settings in which NHS-funded care is received.

F.4.3 Management

F.4.3.1 4.3.1 Key issues that will be covered

a) The information and support needs of people with upper airways tract cancers and their carers at diagnosis, at treatment planning, and during and after treatment.

b) The most effective investigative pathways for assessing undiagnosed neck lumps.
c) The most effective investigative pathways for staging newly diagnosed and recurrent upper airways tract cancer (including unknown primary of presumed upper airways tract origin).
d) The most effective treatment for carcinoma of the larynx (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies).
e) The most effective treatment for carcinoma of the hypopharynx (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies).
f) The most effective treatment for carcinoma of the oral cavity (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies).
g) The most effective treatment for carcinoma of the nasopharynx (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies).
h) The most effective treatment for carcinoma of the nasal sinuses (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies).
i) The most effective treatment for carcinoma of the oropharynx (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies).
j) The most effective treatment for unknown primary of presumed upper airways tract origin (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies).
k) The specific identification and management issues for HPV-associated cancers of the upper airways tract.
l) The most effective treatment for upper airways tract mucosal melanoma (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)?
m) The optimum follow-up pathway for people with upper airways tract cancer (including duration, frequency, investigations).
n) The effectiveness of palliative therapies (including surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies) in the management of locally advanced and/or metastatic upper airways tract cancer.
o) Management of the long-term consequences of upper airways tract cancer treatment (including rehabilitation).
p) The effect of smoking cessation on treatment outcome in people with upper airways tract cancer.
q) The most appropriate nutritional and speech and language support for people having treatment for upper airways tract cancer.

4.3.2 Issues that will not be covered

- Referral from primary care with suspected upper airways tract cancer (this will be covered by ‘Suspected cancer’, the update of Referral guidelines for suspected cancer [NICE clinical guideline 27]).

4.4 Main outcomes

- Overall survival.
- Disease-free survival.
- Disease-related morbidity.
- Treatment-related morbidity.
- Treatment-related mortality.
- Diagnostic accuracy.
- Number and length of admissions to hospital after diagnosis.
- Health-related quality of life.
- Cost effectiveness.

F.4.4 Review questions

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

- What are the information and support needs of people diagnosed with upper airways tract cancer (at first diagnosis, during treatment, post treatment)? (4.3.1.a)
- What are the most effective investigative pathways for assessing undiagnosed neck lumps (for example, fine needle aspiration cytology, core biopsy, imaging techniques)? (4.3.2.b)
- What are the most effective investigative pathways for staging newly diagnosed upper airways tract cancer (for example, computerised tomography (CT), magnentic resonance imaging (MRI), positron-emission tomography with comupterised tomography (PET-CT), fine-needle aspiration cytology (FNAC), ultrasound (US), contrast swallow)? (4.3.1.c)
- What are the most effective investigative pathways for staging recurrent upper airways tract cancer (for example, CT, MRI, PET-CT, FNAC, US, contrast swallow)? (4.3.1.c)
- What are the most effective investigative pathways for staging unknown primary cancers of presumed upper airways tract origin (for example, CT, MRI, PET-CT, FNAC, US, contrast swallow)? (4.3.1.c)
- What is the most effective treatment for carcinoma of the larynx (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)? (4.3.1.d)
- What is the most effective treatment for carcinoma of the hypopharnyx (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)? (4.3.1.e)
- What is the most effective treatment for carcinoma of the oral cavity (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)? (4.3.1.f)
- What is the most effective treatment for carcinoma of the nasopharynx (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)? (4.3.1.g)
- What is the most effective treatment for carcinoma of the nasal sinuses (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)? (4.3.1.h)
- What is the most effective treatment for carcinoma of the oropharynx (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)? (4.3.1.i)
- What is the most effective treatment for unknown primary of presumed upper airways tract origin (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)? (4.3.1.j)
- What are the indications for HPV testing in people with upper airways tract cancer? (4.3.1.k)
- What is the most effective HPV testing strategy for people with upper airways tract cancer? (4.3.1.k)
- What are the most effective treatments for HPV-positive people diagnosed with upper airways tract cancer? (4.3.1.k)
- What is the most effective treatment for upper airways tract mucosal melanoma (for example, surgery, radiotherapy, chemoradiotherapy, chemotherapy or other systemic therapies)? (4.3.1.l)
- In people who are asymptomatic and who have undergone treatment for upper airways tract cancer with curative intent, what is the optimal method(s), frequency, and duration of follow-up? (4.3.1.m)

- What is the most effective palliative treatment for people with locally advanced and/or metastatic upper airways tract cancer (for example, dyspnoea, dysphagia, fistulas)? (4.3.1.n)
- What are the most effective methods of managing the long-term consequences of upper airways tract cancer treatment (for example, xerostomia, radionecrosis, fatigue, dysphagia, tracheostomy)? (4.3.1.o)
- Does smoking cessation affect outcomes for people with upper airways tract cancer? (4.3.1.p)
- What is the most effective protocol for nutritional support in people having treatment for upper airways tract cancer? (4.3.1.q)
- What is the most effective protocol for speech and language support in people having treatment for upper airways tract cancer? (4.3.1q)

F.4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in The guidelines manual.

F.4.6 Status

F.4.6.1 Scope

This is the final version of the scope.

F.4.6.2 Timing

The development of the guideline recommendations will begin in December 2013.

F.5 Related NICE guidance

F.5.1 Published guidance

F.5.1.1 NICE guidance to be updated

This guideline will not update or replace any NICE guidance.

F.5.1.2 NICE guidance to be incorporated

This guideline will not incorporate any NICE guidance.

F.5.1.3 Other related NICE guidance

- Opioids in palliative care. NICE clinical guideline 140 (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Metastatic malignant disease of unknown primary origin. NICE clinical guideline 104 (2010).
- Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck. NICE technology appraisal guidance 172 (2009).
- Medicines adherence. NICE clinical guideline 76 (2009).

- Metastatic spinal cord compression. NICE clinical guideline 75 (2008).
- Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck. NICE technology appraisal guidance 145 (2008).
- Service guidance on improving outcomes in head and neck cancers. NICE cancer service guidance (2004).
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).

F.5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Referral for suspected cancer (update). NICE clinical guideline. Publication date to be confirmed.

F.6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS: 5th edition
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.

Appendix G: People and organisations involved in production of the guideline

G.1 Members of the Guideline Committee

GC Chair	
Dr Martin Robinson	Consultant Clinical Oncologist, Sheffield Teaching Hospital and Honorary Reader in Clinical Oncology University of Sheffield
GC Lead Clinician	
Mr Cyrus Kerawala	Consultant in Maxillofacial/Head and Neck Surgery, The Royal Marsden NHS Foundation Trust
Committee Members	
Dr Shreerang Bhide	Consultant in Clinical Oncology, Royal Marsden Hospital, Surrey
Dr Margred Capel	Consultant in Palliative Medicine, George Thomas Hospice Care, Cardiff and Honorary Lecturer Cardiff University
Leah Cox	Senior Therapeutic Radiographer, Ysbyty Glan Clwyd, Betsi Cadwaladar University Health Board, N Wales
Prof Michael Fenlon	Professor of Prosthodontics, King's College London Dental Institute and Consultant in Restorative Dentistry, Guy's & St Thomas' NHS Foundation Trust
Mr Laurence Newman	Consultant Maxillofacial / Head & Neck Surgeon, The Queen Victoria Hospital NHS Foundation Trust, West Sussex
Sarah Orr	Lead Clinical Nurse Specialist Head and Neck Cancer, University College Hospital London
Prof Vinidh Paleri	Consultant Head & Neck Surgeon, Newcastle upon Tyne Hospitals NHS Foundation Trust and Honorary Professor of Head & Neck Surgery, Newcastle University
Dr Tom Roques	Consultant Clinical Oncologist, Norfolk and Norwich University Hospitals NHS Foundation Trust
Anthony Smith	Patient and carer member
Stephen Spraggett	Patient and carer member
Bella Talwar	Clinical Lead Dietitian, Head & Neck Cancer Services, University College London Hospitals NHS Foundation Trust
Dr Selvam Thavaraj[i]	Honorary Consultant in Head and Neck Pathology, Guy's & St. Thomas' NHS Foundation Trust and Lecturer in Oral & Maxillofacial Pathology, King's College London Dental Institute
Jane Thornton	Clinical Lead Speech and Language Therapist, Sheffield Teaching Hospital NHS Foundation Trust
Mr Stuart Winter	ENT, Head & Neck Consultant, Oxford University Hospitals Trust

GC Chair	
Dr Julia Woolgar[ii]	Senior lecturer in Oral Pathology, University of Liverpool and Honorary Consultant Histopathologist, Aintree University Hospitals NHS Foundation Trust; The Royal Liverpool and Broadgreen University Hospitals NHS Trust
Dr Wai Lup Wong	Consultant Radiologist (Nuclear Medicine), Mount Vernon Hospital, Northwood and PET/CT Lead, Paul Strickland Scanner Centre Northwood

G.1.1 Declarations of interest

Member	Interest declared	Type of interest	Decision taken
Martin Robinson (Chair)	Honorarium received from the Christie Hospital for reviewing grant applications.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) payment is for general advice and non-specific.
	Received travel expenses from CRUK to attend a CTRad committee meeting.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required.
	Wife is principal investigator for a trial on ADHD run by Shire Pharmaceuticals. She receives fees for lecturing and running meetings about the trial.	Personal, family interest	Declare and can participate in discussions on all topics - interest is non-specific.
	Chief investigator of VORTEX trial (adjuvant external beam radiotherapy in patients with previously resected extremity soft tissue sarcoma). Funded by CRUK/ Birmingham Trials Unit.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Local principal investigator for LUX2 trial (Phase III trial of afatinib (BIBW 2992) v placebo for the treatment of head and neck squamous cell cancer after treatment with chemoradiotherapy).	Non-personal pecuniary, specific	Declare and must withdraw from discussion of any topics which include adjuvant afatanib after chemo-radiotherapy as an intervention in stage III+ H&N cancer until 12 months has expired.

Member	Interest declared	Type of interest	Decision taken
	Funded by Boehringer Ingelheim Pharmaceuticals. Handed over at retirement May 2013.		
	Local principal investigator for trial investigating surgery plus lapatinib in patients with advanced head and neck cancer. Funded by GSK. Handed over at retirement May 2013.	Non-personal pecuniary, specific	Declare and must withdraw from discussion of any topics which include lapatinib plus surgery as an intervention in advanced H&N cancer until 12 months has expired.
	Local principal investigator for trial investigating chemoradiotherapy plus lapatinib in patients with advanced head and neck cancer. Funded by GSK. Handed over at retirement May 2013.	Non-personal pecuniary, specific	Declare and must withdraw from discussion of any topics which include lapatinib plus chemoradiotherapy as an intervention in advanced H&N cancer until 12 months has expired.
Cyrus Kerawala (Clinical Lead)	Received honorarium from the GMC for being on a GMC registration and certification appeals panel.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - payment is for general advice and non-specific.
	Received honorarium from the Health Service Ombudsman for acting as an expert advisor on surgery in a complaint.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) payment is for general advice and non-specific.
	Received travel expenses and an honorarium from the Institute of Rural Health in Wales for giving a presentation on robotic head and neck surgery.	Personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
	Gave a lecture on head and neck cancer to the Yorkshire Oncology Group (no fee received).	Personal non-pecuniary	Declare and can participate in discussions on all topics - lecture was on general head and neck cancer issues.
	Written an editorial on research in oral and maxillofacial surgery.	Personal non-pecuniary	Declare and can participate in discussions on all topics as editorial was on research and not diagnosis and

Member	Interest declared	Type of interest	Decision taken
			management.
	Council member of BAHNO.	Personal non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Honorary Secretary of the British Association of Oral and Maxillofacial Surgeons.	Personal non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Section editor for oncology for the British Journal of Oral and Maxillofacial Surgery.	Personal non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Examiner for the Intercollegiate FRSC on head and neck oncology.	Personal non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Member of the Statutory Advisory Committee for Oral and Maxilofacial Surgery (oversee training).	Personal non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Expert advisor to the DAHNO database of head and neck oncology.	Personal non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Principle investigator for PANDORA trial (Point-of-care Analysis by Non-invasive Dielectrophoresis for ORAl cancer diagnosis) looking at electrophoresis of brush samples in diagnosis of oral cavity malignancy. Funded by NHIR.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
Shreerang Bhide	Received travel expenses from ORACLE Cancer Trust to attend a head and neck conference.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required and conference non-specific.
	Advised on the trial protocol and recruits patients to the ART-DECO trial (randomised Phase III trial of dose-escalation in	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.

Member	Interest declared	Type of interest	Decision taken
	laryngeal/hypopharyngeal cancer). Funded by CRUK.		
	Provided quality assurance of radiotherapy plan for the PARSPORT trial (randomised Phase III trial of IMRT v 3DCRT for parotid sparing). Funded by CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Member of trial management group (involved in developing trial protocol) for co-star trial (randomised Phase III trial of IMRT v 3DCRT for cochlear sparing). Funded by CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
Margred Capel	Clinical lead for George Thomas Hospice (funding from the Big Lottery Fund).	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) non-specific.
	Member of RCP, Association of Palliative Medicine and BMA.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Teaching aspects of palliative medicine at Cardiff University (short course, diploma and Masters in Palliative Medicine).	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Taking part in a telephone interview about integrated palliative care for patients with advanced cancer and chronic disease with pan-European research. No financial payment was received.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
Leah Cox	Involved in piloting, trialling and analysing a patient questionnaire about radiotherapy for patients with head and neck cancer. No funding. No payment received.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Radiotherapy representative on the NSAG for Wales head and neck cancer	Personal, non-pecuniary	Declare and can participate in discussions on all

Member	Interest declared	Type of interest	Decision taken
	group.		topics as not specific.
Michael Fenlon	Received honorarium from the Society of Clinical Dental Technicians (key note speaker on the evidence base behind complete denture construction and methods for making successful dentures).	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as not specific and 12 months has passed.
	Member of the British Society for Prosthodontics Maxillofacial Prosthodontics Group.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Treasurer of the British Society for Prosthodontics (learned society) - no involvement in funding decisions.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Author on an opinion based paper making recommendations on how dentists should care for patients following head and neck radiotherapy and when patients should be referred back in to secondary care.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as 12 months has passed.
	Holds shares in Victrex (manufacturer of polyaryletherketones used in industries such as automotive, aerospace and some denture applications).	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as non-specific.
	Member of Restorative Dentistry UK and UCLPartners – London Cancer	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
Laurence Newman	Received an honorarium from the RCS for running FRCS examinations.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) payment is for general advice and non-specific.
	Receives reimbursement of travel expenses and subsistence from the specialty Advisory Committee of the RCS for assessing surgical	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably

Member	Interest declared	Type of interest	Decision taken
	training.		required and non-specific.
	Member of the Council of the British Association of Oral and Maxillofacial Surgeons.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Recruited patients into the Head and Neck 5000 trial. Funded by University Hospital Bristol.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
	Recruited patients into the LUGOL's-iodine in head and neck squamous cell carcinoma trial (now closed) LIHNCS Trial. Funded by CRUK.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
Sarah Orr	Received honorarium from the Institute of Cancer Research for a presentation on supporting head and neck cancer patients as part of the MSc Oncology.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) payment is for presentation on general head and neck cancer support issues and non-specific.
	Received travel expenses from Eusapharma for attending a BAHNO committee meeting.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required.
	Received travel expenses from Macmillan to attend a workshop on the recovery package.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required and workshop non-specific.
	Received travel expenses from Macmillan for a presentation on survivorship at a 'learn and share' workshop.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required and workshop non-specific.
	Received travel expenses and	Personal pecuniary,	Declare and can participate in

Member	Interest declared	Type of interest	Decision taken
	conference fees from Eusa Pharma to attend the European Congress on Head and Neck Oncology.	non-specific	discussions on all topics - expenses not beyond reasonably required.
	Taking part in CADIAS (Cancer diagnosis in the acute setting) patient interviews for research into lung and colorectal cancer, funded by DoH.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry and non-specific.
	Received travel and subsistence expenses as well as conference fees from Macmillan to attend the UKONS conference.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - expenses not beyond reasonably required.
	Received travel expenses to give a presentation titled 'A whistlestop tour of Head and Neck Cancer' at BACO 2015 (British Academic Conference in Otolaryngology) on 9th July, funded by BACO.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - expenses not beyond reasonably required.
Vinidh Paleri	Received honorarium from Merck for a symposium on swallowing outcomes after radiation therapy.	Personal pecuniary, specific	Declare and must withdraw from discussion of any topics which include swallowing outcomes after radiation therapy until 12 months has expired.
	Received travel expenses and subsistence from Olympus KeyMed for speaking on narrow band imaging at the Portsmouth Laryngopharyngeal Laser Course.	Personal pecuniary, specific	Declare and can participate in discussions on all topics - expenses not beyond reasonably required.
	Received travel expenses from DP Medical for teaching a course on trans nasal oesophagoscopy.	Personal pecuniary, specific	Declare and can participate in discussions on all topics - expenses not beyond reasonably required.
	Received travel expenses and subsistence from RSM for attending a meeting on trans oral robotic surgery.	Personal pecuniary, specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably

Member	Interest declared	Type of interest	Decision taken
			required.
	Course organiser for the Newcastle Head and Neck course. Dinner supported by Cooper Surgical.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - as Cooper Surgical do not manufacture anything related to head and neck cancer.
	Chief investigator (involved in designing the trial protocol) for the TUBE trial (A feasibility randomised controlled trial of pre-treatment gastrostomy tube versus oral feeding plus as-needed nasogastric tube feeding in patients undergoing chemoradiation for head and neck cancer). Funded by NIHR.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry
	Principal investigator for the PET NECK trial (neck dissection versus PET scan in managing neck metastases). Local administrator of the trial. Funded by NIHR.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
	Principal investigator for Head and Neck 5000 trial. Responsible for administering the trial locally. Funded by NIHR.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
	Responsible for the Newcastle upon Tyne Hospital NHS Charity TN005 fund. Supports research in head and neck cancer at the unit. Authorises what the funds are spent on (only be research related). Fund generated from donations and fundraising (no contributions from the healthcare industry).	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) and non-specific.
	Advisor to the Throat Cancer Foundation.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.

Member	Interest declared	Type of interest	Decision taken
	Setting up a trial on a tissue glue (Tisseel produced by Baxter). No payment.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Worked with Olympus KeyMed to develop an adaptor to integrate narrow-band imaging into the operating microscope for oesophageal diseases and ENT. The adaptor is at prototype stage and being tested, once completed, a trial will be set up. No payment.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Company Director and Trustee of JLO (1984) Limited (a registered charity) from March 2015. The role involves joint responsibility with the other Trustees for the strategic direction of the charity, ensuring it meets its charitable objectives and is managed in accordance with the requirements of the Charities Act and company law. The main income stream of the charity is the publication of The Journal of Laryngology and Otology and its associated supplements.	Personal non-pecuniary, non-specific	Declare and can participate in discussions on all topics as not specific.
	Associate Editor for Head and Neck Journal. The role involves agreeing what goes into the journal and ensuring peer review processes are followed for other author's articles, but he does not write the articles or express a personal opinion. Topics covered by the journal are wider than the UAT scope.	Personal non-pecuniary, non-specific	Declare and can participate in discussions on all topics as not specific.
	Senior Reviews Editor for the Journal of Laryngology and	Personal pecuniary, non-specific	Declare and can participate in discussions on all

Member	Interest declared	Type of interest	Decision taken
	Otology in 2013. The role involves agreeing what goes into the journal and ensuring peer review processes are followed for other author's articles, but he does not write the articles or express a personal opinion. Topics covered by the journal are wider than the UAT scope.		topics - payment is for general advice and non-specific.
	Reimbursement of travel expenses and subsistence from the Medrobotics for attendance at European TORS meeting.	Personal pecuniary, specific	Declare and can participate in discussions on all topics - expenses not beyond reasonably required.
Tom Roques	Reimbursement of travel expenses from the RCR for attendance at quarterly meetings at PSSB committee and clinical lead meetings.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required.
	Member of the trial management group for the ART DECO trial (randomised Phase III trial of dose-escalation in laryngeal/hypopharyngeal cancer). Funded by CRUK.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
	Local principal investigator (not involved in trial set up) for CONVERT (fractionation of radiotherapy in SCLC. Funded by CRUK / Royal Marsden.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Local principal investigator (not involved in trial set up) for DeteQT (QoL instruments in thyroid cancer). Funded by Macmillan / Coventry.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Local principal investigator (not involved in trial set up) for Head and Neck 5000. Funded by University Hospital	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.

Member	Interest declared	Type of interest	Decision taken
	Bristol.		
	Local principal investigator (not involved in trial set up) for IoN (I-131 in low risk thyroid cancer). Funded by UCL/CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Local principal investigator (not involved in trial set up) for SCORAD-III (radiotherapy dose for spinal cord compression). Funded by UCL / CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Local principal investigator (not involved in trial set up) for ICBP-4 (survey on diagnostic delays). Funded by DoH / Eve Appeal.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Local principal investigator (not involved in trial set up) for COSTAR (Cochlear sparing radiotherapy for parotid cancer). Funded by CRUK / Royal Marsden.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Local principal investigator (not involved in trial set up) for FRAGMATIC trial (standard therapy +/- heparin in lung cancer). Funded by Velindre NHS Trust.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Local principal investigator (not involved in trial set up) for HiLo (I-131 dose in thyroid cancer). Funded by UCL / CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Local principal investigator (not involved in trial set up) for a local study on the effect of radiotherapy treated volume on taste. Funded by Norwich / Anthony Long Charity.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Co-author on a paper entitled 'Functional Organ Preservation in	Personal, non-pecuniary	Declare and participate in discussion on all topics

Member	Interest declared	Type of interest	Decision taken
	Locally Advanced Laryngeal Squamous Cell Carcinoma: Is there a Role for Induction Chemotherapy?'		as conclusions of the paper were based on a review of the published evidence.
	Co-author on a paper entitled 'DeCIDE and PARADIGM: nails in the coffin of induction chemotherapy in head and neck squamous cell carcinoma?'	Personal, non-pecuniary	Declare and participate in discussion on all topics as conclusions of the paper were based on a review of the published evidence.
	Co-investigator for the DARS trial - dysphagia optimized intensity modulated radiotherapy (do-IMRT) versus standard IMRT in head and neck cancer. Grant application submitted to CRUK.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
	Radiotherapy advisor to the De-escalate study (comparing different therapies in combination with RT in HPV+ oropharyngeal cancer. Funded by CRUK.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
Anthony Smith	Patient representative on East London Head and Neck Pathway Group	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Vice President of the National Association of Laryngectomy Clubs (funding from Macmillan) - no involvement in allocation of funds.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Chairman of the Harrow Laryngectomy Club (voluntary).	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
Stephen Spraggett	Founder member of the Ipswich Head and Neck Cancer Support Group (funding from Macmillan and private companies).	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
Bella Talwar	Advisor for the Rarer Cancers Forum providing nutritional advice (no input since 2010).	Personal non-pecuniary	Declare and can participate in discussions on all topics as not specific.

Member	Interest declared	Type of interest	Decision taken
	Previous Chair of the British Dietetics Association, Oncology Group.	Personal non-pecuniary	Declare and can participate in discussions on all topics as not specific and 12 months has passed.
	Worked on the Rehabilitation Care Pathway with NCAT.	Personal non-pecuniary	Declare and can participate in discussions on all topics as not specific and 12 months has passed.
	Expert advisor on dietetics for Map of Medicine.	Personal non-pecuniary	Declare and can participate in discussions on all topics as not specific and 12 months has passed.
	Carried out a systematic review and is the primary author of nutrition chapter in the BAHNO guidelines. No payment received.	Personal non-pecuniary	Declare and participate in discussion on all topics as conclusions of the guideline were based on a review of the published evidence.
	Member of guideline development group for COSA. No payment received.	Personal non-pecuniary	Declare and participate in discussion on all topics as conclusions of the guidelines are based on a review of the published evidence.
Selvam Thavaraj	Co-investigator for the FiGaRO study (phase I pilot study of FDG-PET in Guiding Intensity Modulated Radiotherapy to Oropharyngeal tumours). Funded by the King's Health Partners - Research and Development Challenge Fund. Involved in designing the HPV testing protocol.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
	Local investigator for the BOHEMIAN trial (Biomarkers of Hypoxia Evaluation with Molecular and 64Copper (II) diacetylbis (N4)methylthiosemicarbazone (CuATSM) Positron Emission Tomography/Compute	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.

Member	Interest declared	Type of interest	Decision taken
	d Tomography (PET/CT) Imaging Techniques in Head and Neck Squamous Cell Carcinomas). Funded by King's Health Partners Research.		
	Local investigator for the PREDICTR trial (Improving treatment selection using predictive and prognostic classifiers of treatment response for head and neck cancers and dysplasia). Funded by CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) and non-specific.
	Principle Investigator for the Evaluation of Epidermal Growth Factor Receptor Status in Biopsy Samples and Correlation with Outcome to Targeted Therapy in HPV associated Head & neck cancer. Funded by the charity Friends of Guy's Hospital.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) and non-specific.
	Local investigator for Biomarker classifiers to predict prognosis following treatment of oropharyngeal carcinoma (PreticTr-OPC). Funded by CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) and non-specific.
	Primary supervisor for PhD student thesis entitled Mechanisms of the Differential Response between HPV+ and HPV- HNC cells to Therapeutic Agents in vitro. Funded by the Commonwealth Scholarship Commission.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) and non-specific.
	Invited to review a chapter for a book entitled 'Histopathology: Methods and Protocols' in the series Methods in Molecular	Personal, non-pecuniary	Declare and participate in discussion on all topics as based on a review of the published evidence.

Member	Interest declared	Type of interest	Decision taken
	Biology published July 2014. Methods in Molecular Biology: Human Papillomavirus Testing in Head and Neck Squamous Cell Carcinoma: Best Practice for Diagnosis. In press. No payment received.		
	Guest Editor for a special issue of the journal Diagnostic Histopathology. A mini-symposium on HPV in Head and Neck Cancer 1. HPV-associated Head and Neck Cancer: Epidemiology, Clinical Behaviour and Oncogenic Mechanisms. 2. The Role of the Pathologist in the Multidisciplinary Management of HPV-associated Head and Neck Cancer. 3. Histopathology of HPV-associated Oropharyngeal Squamous Cell Carcinoma. 4. HPV testing in Diagnostic Head and Neck Histopathology. Due for publication June 2015. Honorarium will be received from Elsevier.	Personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
	Reviewer for Research Grants Council of Hong Kong, SAR (Serological biomarkers of human papillomavirus and the risk of nasopharyngeal carcinoma: a case-control study in Hong Kong). Honorarium due from Research Grants Council of Hong Kong).	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry and non-specific.
	Reviewer for the Wellcome Trust DBT India Alliance Scheme on Prognostic implications of Human	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.

Member	Interest declared	Type of interest	Decision taken
	Papilloma Virus (HPV) on overall survival and disease free survival in Indian oral squamous cell carcinoma (OSCC).		
	Pathology Representative on Council of the British Association of Head and Neck Oncology.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Member of NCRI clinical studies group for head and neck cancer.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
Jane Thornton	Received reimbursement for travel expenses from RCPsych for attending a working group meeting which produced guidelines on the management of gender identity disorder.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required and meeting non-specific.
	Received reimbursement for travel expenses from NCAT for peer review work.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required and non-specific.
	Received reimbursement for travel expenses to attend NCIN clinical reference group on head and neck cancer.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required.
Stuart Winter	Received an honorarium from Oxford GP Training Scheme for providing training to local GPs on ENT.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - payment is for general advice and non-specific.
	Received reimbursement of travel expenses from the NCRN for attending a DAHNO committee meeting.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required.
	Working with Oxford University on	Non-personal	Declare and can participate in

Member	Interest declared	Type of interest	Decision taken
	screening Dastatinib for synergistic effects with existing drugs or drug candidates that have passed clinical phase I/II trials. Funded by Oxford University.	pecuniary, non-specific	discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Local principle investigator for the Head and Neck 5000 trial. Funded by NCRI.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
	Co-supervisor of a PhD student researching the IGF axis in head and neck cancer. Funded by Heads Up (Oxford charity) and RCS.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) non-specific.
	Local principle investigator for trial investigating the use of molecular biomarkers in selecting the management of individual patients with oropharyngeal and laryngeal cancer. Local administrator. Funded by Hisham Mehanan.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics as not specific.
	Chair of Heads Up charity board (funds research at the University of Oxford on head and neck cancer)	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Confidential discussions with Norgine Ltd providing advice on something they were developing. No fee received and no further involvement.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Member of NCRI clinical studies group for head and neck cancer	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific.
	Accepted to be recognised as a Macmillan Cancer Consultant. As yet has not been asked to do anything. SW advised to notify NCC-C if Macmillan asks him to do anything so the	Personal, non-pecuniary	Declare and can participate in discussions on all topics as not specific. SW advised to notify NCC-C if Macmillan ask him to do anything so the interest can be categorised on a case

Member	Interest declared	Type of interest	Decision taken
	interest can be categorised on a case by case basis.		by case basis.
Wai Lup Wong	Received an honorarium from Lilly for attending an advisory board on moderate memory failure.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - payment is for presentation on moderate memory failure and non-specific.
	PET CT lead and on the clinical management team for BACCHUS trial (Bevacizumab and Combination Chemotherapy in Rectal Cancer until Surgery). Funded by CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Co-investigator on a trial of Imaging Radiation Effects with 18F-CHOLINE PET AND MRI: relating early pneumonitis to subsequent fibrosis. Funded by CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Co-investigator and protocol writer for trial on Induction TPF therapy for advanced Head and Neck Cancer. Funded by CRUK.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.
	Co-investigator and protocol writer for trial on Positron Emission Tomography-Computerised Tomography scan (PET-CT) for the management of patients with pancreatic cancer and suspected pancreatic cancer. Funded by DoH.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific
	Co- investigator and protocol writer for trial on PET-CT guided watch and wait policy versus planned neck dissection for the management of locally advanced (N2/N3) nodal metastases in	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics - not funded by the healthcare industry.

Member	Interest declared	Type of interest	Decision taken
	patients with head neck squamous carcinoma treated with radical chemoradiotherapy (CRT). Funded by DoH		
	Co-investigator and Imaging expert for trial on Phase II study to evaluate the toxicity and efficacy of a modified German Paediatric protocol (HD95) in (aged 18-30) patients with Hodgkin's lymphoma. Funded by CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Co-investigator/ Protocol writer/ Imaging expert for pilot study to determine the correlation between the uptake of the tracers 18F-FDG and 18F-FLT as detected in PET CT and tumour cell proliferation within biopsy specimens in patients with NHL. Funded by CRUK.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Co-investigator/ Protocol writer/ Imaging expert for evaluation of FLT PET CT in predicting response to primary systemic therapy in patients with operable breast cancer. Funded by Gunner Nielsen Cancer Trust.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) the trial is non-specific.
	Published article in Clinical Oncology on the recommendations made in the Ontario guidelines on Head and Neck cancer about the use of PET CT.	Personal, non-pecuniary	Declare and participate in discussion on all topics as conclusions of the paper were based on a review of the published evidence.
Julia Woolgar	Received travel expenses from Public Health England for attending NCIN meeting.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics - (not funded by the healthcare industry) expenses not beyond reasonably required.

Member	Interest declared	Type of interest	Decision taken
	Plans to be pathologist for A Phase III, Open-label, Randomized, Multi-centre Study of the Effects of Leukocyte Interleukin, Injection [Multikine] Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects With Advanced Primary Squamous Cell Carcinoma of the Oral Cavity / Soft Palate Versus Standard of Care Only. Not involved in designing the trial protocol. JW did not begin work on the trial.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics - JW did not begin work on the trial.

G.2 Organisations invited to comment on the guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

5 Borough's Partnership NHS Foundation Trust	National Institute for Health Research
Aintree University Hospital NHS Foundation Trust	National Patient Safety Agency
Allocate Software PLC	Newcastle upon Tyne Hospitals NHS Foundation Trust
AngioDynamics	NHS Barnsley Clinical Commissioning Group
Association for Palliative Medicine of Great Britain	NHS Choices
Association for Respiratory Technology and Physiology	NHS Chorley and South Ribble CCG
Association of Anaesthetists of Great Britain and Ireland	NHS Cumbria Clinical Commissioning Group
Association of Chartered Physiotherapists in Oncology and Palliative Care	NHS East Staffordshire CCG
Association of Chartered Physiotherapists in Respiratory Care in	NHS England
Barnsley Hospital NHS Foundation Trust	NHS Gloucestershire CCG
Belfast Health and Social Care Trust	NHS Hardwick CCG
Boehringer Ingelheim	NHS Health at Work
Boehringer Ingelheim Ltd	NHS Plus
British Association of Head and Neck Nurses	NHS Sheffield
British Association of Oral and Maxillofacial Surgeons	NHS Sheffield CCG

British Dental Association	NHS Somerset CCG
British Dietetic Association	NHS South Cheshire CCG
British Medical Association	NHS Wakefield CCG
British Medical Journal	NHS Warwickshire North CCG
British National Formulary	NHS West Cheshire CCG
British Nuclear Cardiology Society	NHSCC
British Nuclear Medicine Society	NIHR CCRN ENT Specialty Group
British Psychological Society	North of England Commissioning Support
British Red Cross	Northern Health and Social Care Trust
British Society for Oral and Maxillofacial Pathology	Northern Ireland Cancer Network
British Society for Oral Medicine	Nottingham City Council
British Society of Dental Hygiene & Therapy	Nursing and Midwifery Council
British Society of Paediatric Gastroenterology Hepatology and Nutrition	Nutricia Advanced Medical Nutrition
British Society of Thoracic Imaging	Older People's Advocacy Alliance
BSPGHAN	Oxfordshire Clinical Commissioning Group
Cancer Commissioning Team	
Cancer Laryngectomee Trust	Pathfinders Specialist and Complex Care
Cancer Research UK	Pfizer
Caplond Services	Primary Care Pharmacists Association
Care Quality Commission	Primrose Bank Medical Centre
Central Manchester University Hospitals NHS Foundation Trust	Public Health England
Chartered Society of Physiotherapy	Queen Elizabeth Hospital King's Lynn NHS Trust
Cheshire and Merseyside SCN	Restorative Dentistry UK
Chesterfield Royal Hospital NHS Foundation Trust	Roche Diagnostics
City Hospitals Sunderland NHS Foundation Trust	Roche Products
Cochrane Oral Health Group	Royal Brompton Hospital & Harefield NHS Trust
College of Paramedics	Royal College of Anaesthetists
Cook Medical Inc.	Royal College of General Practitioners
County Durham and Darlington NHS Foundation Trust	Royal College of General Practitioners in Wales
Covidien Ltd.	Royal College of Midwives
Croydon Council	Royal College of Nursing
Croydon University Hospital	Royal College of Obstetricians and Gynaecologists
CWHHE Collaborative CCGs	Royal College of Paediatrics and Child Health
Department of Health	Royal College of Pathologists
Department of Health, Social Services and Public Safety Northern Ireland	Royal College of Physicians
East and North Hertfordshire NHS Trust	Royal College of Physicians and Surgeons of Glasgow
East Kent Hospitals University NHS Foundation Trust	Royal College of Psychiatrists
East of England Strategic Clinical Network	Royal College of Radiologists

Ethical Medicines Industry Group	Royal College of Speech and Language Therapists
Faculty of Dental Surgery	Royal College of Surgeons of Edinburgh
False Allegations Support Organisation	Royal College of Surgeons of England
Five Boroughs Partnership NHS Trust	Royal Cornwall Hospitals NHS Trust
Gastroenterology specialist group	Royal Devon and Exeter NHS Foundation Trust
Gloucestershire Hospitals NHS Foundation Trust	Royal Pharmaceutical Society
GP update / Red Whale	Royal Surrey County Hospital NHS Trust
Greater Manchester, Lancashire and South Cumbria Strategic Clinical Network	Sandoz Ltd
Health and Care Professions Council	Scottish Intercollegiate Guidelines Network
Health and Social Care Information Centre	Sheffield Teaching Hospitals NHS Foundation Trust
Healthcare Improvement Scotland	Social Care Institute for Excellence
Healthcare Infection Society	Society and College of Radiographers
Healthcare Quality Improvement Partnership	Society of British Neurological Surgeons
Healthwatch East Sussex	South Eastern Health and Social Care Trust
Herts Valleys Clinical Commissioning Group	South London & Maudsley NHS Trust
Hywel Dda University Health Board	South Wales Cancer Network
Intuitive Surgical	South West Yorkshire Partnership NHS Foundation Trust
Isabel Hospice	Southern Health & Social Care Trust
Joint Royal Colleges Ambulance Liaison Committee	Staffordshire and Stoke on Trent Partnership NHS Trust
King Fahd Military Medical Complex	Stockport Clinical Commissioning Group
Launch Diagnostics	Teenage Cancer Trust
Leeds Teaching Hospitals NHS Trust	The African Eye Trust
Local Government Association	The Institute of Cancer Research
London cancer alliance	The Patients Association
London Respiratory Team	Throat Cancer Foundation
Manchester Cancer	UCL Partners
Maquet UK Ltd	UK National Screening Committee
Mastercall Healthcare	University Hospital Birmingham NHS Foundation Trust
Medicines and Healthcare Products Regulatory Agency	University Hospitals Birmingham
Mid Staffordshire NHS Foundation Trust	Velindre NHS Trust
Ministry of Defence	Welfare Enough Festival Harm Reduction Services
Muslim Doctors and Dentists Association	Welsh Government
National Association of Laryngectomee Clubs	Welsh Scientific Advisory Committee
National Clinical Guideline Centre	West Suffolk Hospital NHS Trust
National Collaborating Centre for Cancer	Western Health and Social Care Trust
National Collaborating Centre for Mental Health	Western Sussex Hospitals NHS Trust
National Collaborating Centre for Women's and Children's Health	Wigan Borough Clinical Commissioning Group
National Deaf Children's Society	York Hospitals NHS Foundation Trust
National Institute for Health Research Health	

Technology Assessment Programme	

G.3 Individuals carrying our literature reviews and complementary work

Overall Co-ordinators	
Dr John Graham	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Project Manager	
Victoria Titshall	National Collaborating Centre for Cancer, Cardiff
Senior Researcher	
Dr Nathan Bromham	National Collaborating Centre for Cancer, Cardiff
Researchers	
Dr David Jarrom	National Collaborating Centre for Cancer, Cardiff
Jennifer Hilgart[iii]	National Collaborating Centre for Cancer, Cardiff
Dr Susan O'Connell	National Collaborating Centre for Cancer, Cardiff
Health Economists	
Victoria Kelly[iv]	National Collaborating Centre for Cancer, Cardiff
Matthew Prettyjohns	National Collaborating Centre for Cancer, Cardiff
Information Specialists	
Stephanie Arnold	National Collaborating Centre for Cancer, Cardiff
Sabine Berendse	National Collaborating Centre for Cancer, Cardiff
Elise Hasler	National Collaborating Centre for Cancer, Cardiff
Delyth Morris[v]	National Collaborating Centre for Cancer, Cardiff

G.4 Expert advisors to the Guideline Committee

Val Jones	Lead Physiotherapist, Sheffield Shoulder and Elbow Unit, Sheffield Teaching Hospital Foundation Trust

G.4.1 Declarations of interest

None declared

[i] From June 2014
[ii] Until May 2014
[iii] Until September 2014
[iv] Until September 2014
[v] Until April 2014