National Institute for Health and Care Excellence

Version 1.0 Pre-consultation

Oesophago-gastric cancer: assessment and management in adults

Appendix I

Clinical Guideline

Cost-effectiveness analyses

12 May 2017

Draft for Consultation

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

ISBN:

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I.1 Background

The staging of oesophageal and oesophago-gastric junctional cancer can alter patient management, for instance it can determine whether disease is suitable for radical treatment with curative intent, or whether the disease is too advanced for such treatment. Advances in imaging modalities and techniques have facilitated more accurate staging and thus more appropriate referral of patients for curative interventions.

The various imaging modalities and techniques used in the staging of oesophageal cancer all serve different functions. There is potentially scope for improving the choice and sequencing of staging investigations to optimise the use of the investigations. In particular, it is thought that endoscopic ultrasound (EUS) could be used more selectively based upon the results of the initial CT scan. EUS is routinely used to characterise tumour size and stage but it is not helpful for more detailed staging of mucosal or nodal disease. In terms of altering management, EUS is primarily of value in distinguishing between T1 and T2 disease and T3 and T4 disease.

I.1.1 Aim

To estimate the cost-effectiveness of a strategy of selectively using EUS in the staging of patients with oesophageal cancer.

I.2 Methods

I.2.1 Existing Economic Evidence

A systematic literature review was conducted to identify economic evaluations that may be applicable to the current decision problem. No relevant economic studies were identified. However, a study by Findlay et al. 2015 was identified in which a similar staging algorithm to that suggested by the committee had been proposed and validated.

I.2.2 De novo economic evaluation

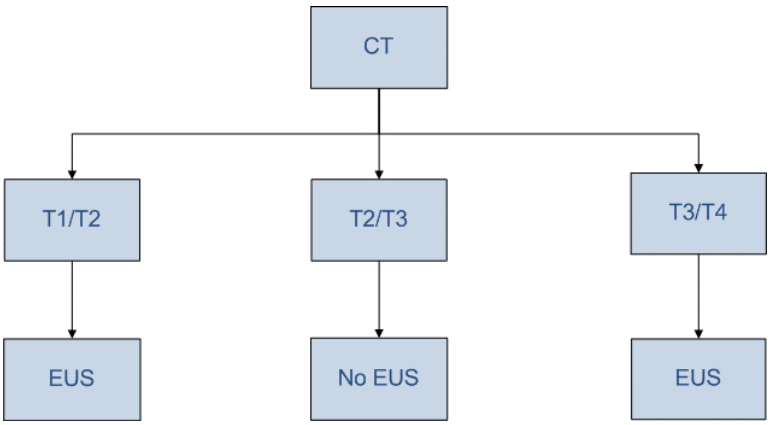
Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (The guidelines manual, NICE November 2012). The model considered a one year time horizon and as such discount rates were not applied.

I.2.3 Staging strategies

The diagram below depicts the staging algorithm suggested by the guideline committee. It shows that EUS would only be used in those patients found to have T1/T2 or T3/T4 disease following the CT scan. However, after assessing the available evidence, it became clear that it would not be possible to model this particular algorithm as the T stage categories used in the evidence did not match those in the proposed algorithm. There was variation in how T

stages were combined in the evidence but in most of the studies, the T stages were presented individually with an additional notation for those patients where it was not possible to determine the T stage (typically “T0” or “Tx”).

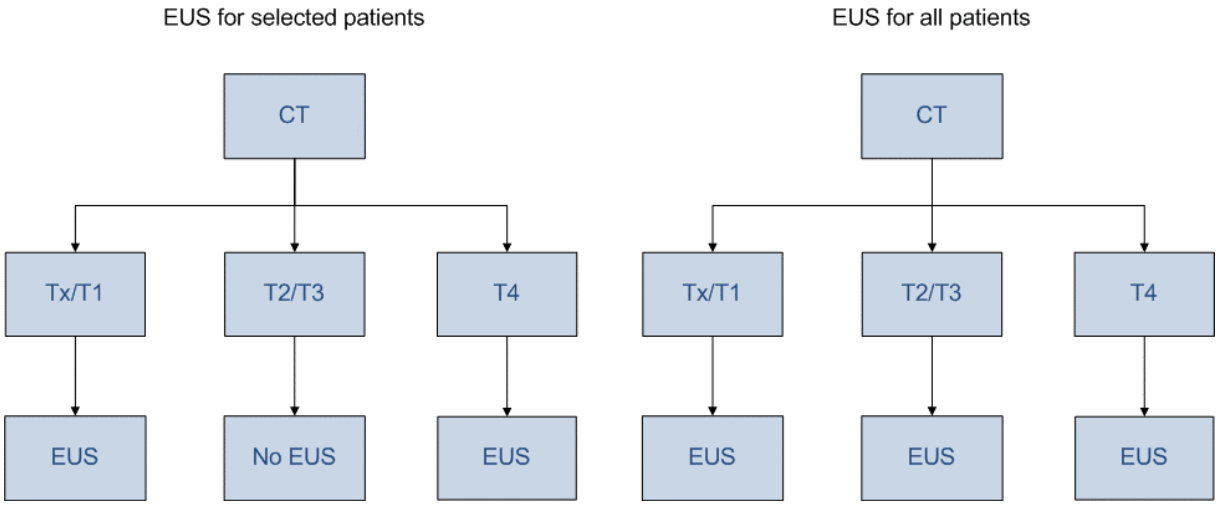
Figure 1: Staging algorithm proposed by guideline committee



A pragmatic approach was taken to restructure the staging algorithm to match the available data.It was assumed that EUS would only be used in those patients found to have Tx/T1 or T4 disease following the CT scan. While this is a variation on the approach suggested by the committee, it was thought to be sufficiently similar and crucially it maintains the principal that there is a group of patients with T2/T3 disease that possibly do not require EUS.

The diagram below depicts the modelled staging algorithms, showing the pragmatic selection algorithm described above as well as the ‘EUS for all patients’ strategy which is used as the comparator.

Figure 2: Modelled staging algorithms



The use of PET-CT was also considered in the modelled staging algorithms for patients with T4 disease. It was assumed that patients with metastatses identified by PET-CT would not be offered EUS (as their management would be altered by the identification of metastases and the results of the EUS would not change this). Since the risk of metastases is very low in patients with T1a disease, PET-CT is not routinely offered. However, it would not be known whether patients have T1a disease until an EUS has been performed. This suggests that,

unlike in the T4 group, PET-CT would be performed after an EUS (in patients without T1a disease). However, in the committee's estimation, the PET-CT and EUS are often ordered simultaneously and it is unlikely that the decision on whether to offer EUS selectively would have any bearing on the use of PET-CT. Therefore the use of PET-CT was not considered in the analysis for the T1 group (as it would be the same in both arms).

I.2.4 Clinical data

I.2.4.1 T Stage at presentation

It was found that there was limited data available on T stage at presentation. The available large cohort studies (including the available audit data) presented stage groupings based upon the TNM stage classification (i.e. Stage I, Stage II etc) rather than the individual T stage. In the absence of direct data, the individual T stage at presentation was estimated using data on TNM stage groups from Findlay et al. 2015. The dataset from Findlay et al. 2015 was selected in preference to other datasets because it included more detailed stage group (in particular Stage II is broken down into Stage IIa and Stage IIb).

The T stage was estimated from TNM stage groupings by making some crude assumptions about the proportion of patients with each T stage within each stage group. The table below depicts the TNM stage groups. Where multiple T stages occur within a stage group it has been assumed that they are equal distributed. For example within Stage IIA, it has been assumed that there is an equivalent proportion of T2 and T3 records (i.e. 50% each).

Table 1: TNM Stage groups

TNM Stage groups	T	N	M
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

The table below depicts the total estimated T stages at presentation, based on the TNM groups from Findlay. These values were applied in the base case version of the model. However, clearly there are methodological drawbacks to the approach taken to estimating T stage at presentation. However, in the absence of more specific data, it was thought to be the best approach that could be taken. In addition, the proportion of patients within each T stage was adjudged to have reasonable 'face validity' by the guideline committee. In recognition of the uncertainty in this area, alternative proportions were tested in one-way and probabilistic sensitivity analysis.

Data from Findlay was also used to estimate the proportion of T1a and T4b tumours. It was estimated that 64% of T1 tumours were T1a and 36% of T4 tumours were T4b.

Table 2: Estimated T stage at presentation

T Stage	Proportion
T1	10%
T2	21%
T3	39%

T Stage	Proportion
T4	30%

I.2.4.2 Staging accuracy

In order to populate the model, data was required on the staging accuracy of EUS, CT and PET-CT. The staging accuracy of CT was not reported in our systematic review since the population of interest specified in our review protocol was "people who have been found at endoscopy and whole body CT to be potentially suitable for curative treatment". In other words, the starting point for the population included in the systematic review was after the initial CT.

The staging accuracy of CT was therefore estimated separately for the purposes of the economic evaluation. Data on the sensitivity and specificity of CT were sourced from a subset of studies in a systematic review (Luo et al. 2016), in which CT and EUS were compared. It was assumed that patients without visible tumour on CT (usually noted as "Tx" or "T0" in the studies) would be put forward as part of the T1 stage and proceed to EUS (i.e. they were counted in the sensitivity statistic for the Tx/T1 group). The CT sensitivity and specificity estimates for each T stage are shown in the table below.

Table 3: Accuracy of CT staging by T stage

T Stage	Sensitivity	Specificity	Reference
T1	82%	97%	Luo et al. 2016
T2	52%	89%	Luo et al. 2016
T3	88%	73%	Luo et al. 2016
T4	59%	94%	Luo et al. 2016

The staging accuracy of EUS was sourced from the clinical evidence review, focusing primarily on a meta-analysis presenting accuracy by T stage (Luo et al. 2016), supplemented with additional data from Pech et al. 2010. The EUS sensitivity and specificity estimates for each of the T stages under consideration are shown in the table below.

Table 4: Accuracy of EUS staging by T stage

T Stage	Sensitivity	Specificity	Reference
T1	74%	97%	Luo et al. 2016 and Pech et al. 2010
T4	84%	97%	Luo et al. 2016

Data on the accuracy of PET-CT in the detection of distant disease was not identified in the clinical evidence review. It is thought that there is a lack of evidence on this aspect because previous studies, based on PET alone, had already established the clear utility of using this modality to detect distant disease. Therefore, accuracy data from studies using PET alone have been used to approximate the accuracy of using PET-CT to detect distant disease. Based on a meta-analysis by Vliet et al. 2008, the sensitivity and specificity of PET-CT for the detection of distant disease is estimated to be 71% and 93%, respectively.

I.2.5 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 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using unit cost data

from the electronic market information tool (eMit) 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 guideline committee.

I.2.5.1 Imaging costs

The cost associated with EUS was estimated from NHS Reference costs 2015/16 using cost code GB13Z, which relates to an 'Endoscopic Ultrasound Examination, of Hepatobiliary or Pancreatic Duct'. There was uncertainty around the relevance of this cost code for the oesophageal cancer population since it does not feature in the description. However, there is not a similar procedure code for the oesophageal duct. Therefore this procedure code was thought to provide the best estimation of the cost for the procedure and so was used in the base case analysis. It was assumed that the procedure would be performed as a 'day case' procedure (95% of the procedures in NHS Reference Costs were coded as such) and it was estimated to cost £603.59. The cost of the procedure was agreed to have face validity with the guideline committee as it seemed to be similar to costs that they had heard quoted for the procedure.

I.2.5.2 Costs associated with changes in management

A key aspect of the analysis is capturing the consequences of changes in staging outcomes in terms of changes in patient management. As mentioned above, this applies only to patients with T1 disease and T4 disease as differences in EUS staging only have the potential to change management in these patients (not the case in patients with T2/T3 disease). More specifically, in patients with T1 disease, the value of staging is in identifying or refuting T1a disease whereas in patients with T4 disease, the value of staging is in identifying or refuting T4b disease.

Of particular importance to this analysis, are the patients with T1a or T4b disease that have been incorrectly staged by the initial CT as T2/T3 disease. Under the selective EUS strategy, these patients would not go on to receive an EUS and it is therefore possible that these patients may receive suboptimal management.

Patients with T1a disease are typically treated by surgical resection or definitive radiotherapy. For patients with T1a disease that was incorrectly upstaged, it was assumed that the consequence would be that unnecessary neoadjuvant chemotherapy or chemoradiotherapy would be received in addition to surgical resection or definitive radiotherapy.

It has been assumed that patients with T4b disease are typically treated with systemic chemotherapy. For patients with T4b disease that was incorrectly down-staged, it is assumed that unnecessary radical treatment would be received instead (assumed to be either chemoradiotherapy and surgery or chemoradiotherapy alone).

The tables below show the estimated costs of unnecessary or suboptimal treatment for patients with T1a and T4b disease.

Table 5 details the average cost of chemotherapy per cycle. The average cost was based upon the cost of the five chemotherapy regimens which were most likely to be used (as identified by the guideline committee). The chemotherapy delivery costs were sourced from NHS Reference Costs 2015/16 and drug costs were sourced from eMit. It can be seen that the chemotherapy costs per cycle were similar for each of the regimens and the average cost per cycle was estimated to be £824.68.

Table 6 shows the estimated cost of radiotherapy. The cost of radiotherapy preparation and delivery (per fraction) were sourced from NHS Reference costs 2015/16. It was assumed that

23 fractions of radiotherapy would be delivered in the average radiotherapy regimen (based on the committee's estimation of the dosage that is most likely to be administered). The estimated cost of radiotherapy treatment was £3,563.59.

Table 7 shows the estimated cost of surgery. The cost was sourced from NHS Reference costs 2015/16 based on the cost of a 'very complex, oesophageal, stomach or duodenum procedure' (FZ80).

Table 8 shows the overall estimated cost of the unnecessary or suboptimal treatment in patients with T1a or T4b disease. In patients with T1a disease that was incorrectly upstaged, the estimated cost of the unnecessary treatment was £3,934.87, based on a crude average of the cost of neoadjuvant chemotherapy (when used in combination with surgery or radiotherapy) and chemoradiotherapy.

In patients with T4b disease that was incorrectly downstaged, the estimated cost of the unnecessary treatment was £7,442.93, based on a crude average of the cost of chemoradiotherapy and surgery and chemoradiotherapy alone (£12,391.02), minus the cost of systemic chemotherapy (£4,948.09).

Table 5: Estimated chemotherapy costs per cycle

Treatment	Cost	Source
Cisplatin and FU		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Cisplatin	£26.60	eMit
Fluorouracil 750mg/m2 days 1-5	£10.34	eMit
Cost per cycle	**£804.60**	
Carboplatin and paclitaxel		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Carboplatin AUC 2 weekly x 5 (days 1,8,15,22,29)	£55.95	eMit
Paclitaxel 50mg/m2 weekly x 5 (days 1,8,15,22,29)	£42.50	eMit
Cost per cycle	**£866.12**	
Cisplatin and capecitabine		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Cisplatin 60mg/m2 on day 1 of cycle	£12.46	eMit
Capecitabine 625mg/m2 twice daily (days 1-21)	£24.65	eMit
Cost per cycle	**£804.78**	
Carboplatin and capecitabine		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Carboplatin AUC 5 on day 1 of cycle	£21.65	eMit
Capecitabine 625mg/m2 twice daily (days 1-21)	£24.65	eMit

Treatment	Cost	Source
Cost per cycle	**£813.97**	
Oxaliplatin and capecitabine		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Oxaliplatin dose 130mg/m2 on day 1	£41.62	eMit
Capecitabine 625mg/m2 twice daily (days 1-21)	£24.65	eMit
Cost per cycle	**£833.94**	

Table 6: Estimated radiotherapy costs

Cost item	Value	Source
Preparation for complex conformal radiotherapy (SC51Z)	£654.57	NHS Reference costs 2015/16
Deliver a fraction of complex treatment on a megavoltage machine (SC23Z)	£126.48	NHS Reference costs 2015/16
Number of fractions	23	
Total	**£3,563.59**	

Table 7: Estimated surgery cost

Procedure	Proportion*	Cost	Source
Very complex, oesophageal, stomach or duodenum procedure, 19 years and over (FZ80)			
with CC score 6+	18%	£18,934.89	NHS Reference costs 2015/16
with CC score 3-5	22%	£11,700.19	NHS Reference costs 2015/16
with CC score 0-2	60%	£8,439.60	NHS Reference costs 2015/16
Weighted average		***£11,057.41***	

Table 8: Estimated cost of 'unnecessary' or suboptimal treatment in patients with T1a and T4b disease

Cost item	Value
T1a disease	
Two cycles of neoadjuvant chemotherapy (when used in combination with surgery)	£1,648.20
Four cycles of neoadjuvant chemotherapy (when used in combination with radiotherapy)	£3,296.41
Chemoradiotherapy	£6,859.99
Average cost	***£3,934.87***
T4b disease	
Chemoradiotherapy and surgery	£17,917.41
Chemoradiotherapy	£6,859.99
Average cost	***£12,388.70***
Normal treatment for t4b disease - six cycles of systemic chemotherapy	£4,944.61
Average cost minus normal treatment cost	***£7,444.09***

I.2.6 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.

The QALY side of the model was focused on the outcomes that might differ between the two staging strategies. Specifically, we sought to capture the consequences of changes in management as a result of changes in staging outcomes. As mentioned in the above section, this applies only to patients with T1 disease and T4 disease as differences in EUS staging only have the potential to change management in these patients.

For patients with T1a disease that was incorrectly upstaged, it was assumed that there would be a QoL decrement as a result of the unnecessary neoadjuvant chemotherapy or chemoradiotherapy that would be received in addition to surgical resection or definitive radiotherapy. The QoL decrement was estimated using values from a cost-effectiveness analysis of treatments for locally advanced oesophageal cancer by Graham et al. 2007. In the analysis, QoL values of 0.67 and 0.63 were estimated for surgery and multi-modal treatment, respectively at 6 to 12 months after treatment. The difference between these two values (0.04) was used to inform the decrement associated with neodadjuvant chemotherapy or chemoradiotherapy in the analysis,

For patients with T4b disease that was incorrectly down-staged, it is assumed that there would be a QoL decrement associated with the unnecessary radical treatment that would be received instead of systemic chemotherapy. Graham et al. 2007 was again used to inform the QoL decrement. In this analysis, the QoL score in patients treated with surgery was estimated to be 0.63 at 0 to 6 months and 0.70 at 12 to 36 months. The difference between these two values was used to inform the decrement associated with radical treatment in the analysis.

It should be noted that a conservative approach has been adopted when considering the QALY aspects of the analysis. The analysis is focused only on the QoL decrements associated with the potential misstaging when using the selective EUS staging strategy. However, there is the potential for QALY differences in the opposite direction. Since EUS is not 100% specific, using the EUS strategy in all patients carries a greater potential for ‘false positives’. For example, when using EUS in all patients, it is possible that some patients with T2 disease after a CT may be incorrectly staged as T1 disease.

I.3 Results

I.3.1 Base case results

The base case results of the analysis are presented in the table below. It can be seen that the selective use of EUS was found to be less costly (£185) and marginally less effective (0.0024 QALYs) than using EUS for all patients and resulted in an ICER of £77,363 per QALY. This can be interpreted as £77,363 saved for each QALY that is lost. Therefore, the strategy of selectively using EUS was found to be cost-effective as this saving is above the NICE threshold for cost-effectiveness.

Table 9: Base case analysis results

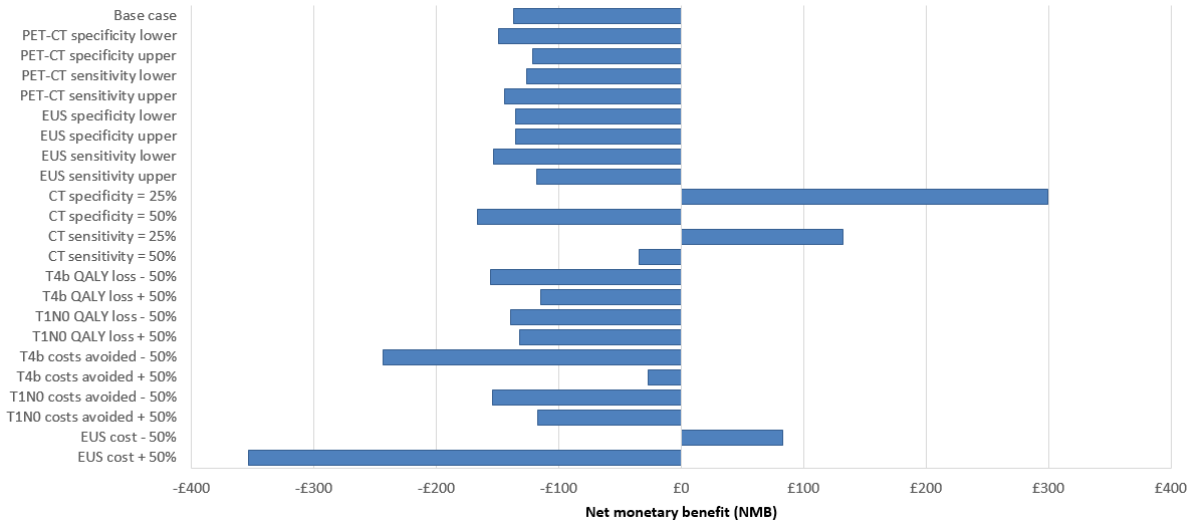
Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
EUS for all patients	£657	-	-0.0005	-	-
EUS for selected patients	£472	-£185	-0.0029	-0.0024	£77,363

I.3.2 Deterministic sensitivity 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 graph below shows the results of the one-way sensitivity analysis with the result presented in net monetary benefit terms using the NICE threshold of £20,000 per QALY (i.e. QALY values are converted into monetary values by multiplying by the NICE threshold and are costs are subtracted). Values to the left side of the vertical zero line show that EUS for selected patients is cost-effective while values to the right side of the vertical line show that the conclusion of the analysis has changed and EUS for all patients is cost-effective.

Figure 3: Deterministic sensitivity analysis results



It can be seen that the conclusion of the analysis is unchanged in most modelled scenarios. The notable exceptions were decreasing the cost of EUS by 50% or decreasing either the sensitivity or specificity of CT scans to 25%. Decreasing the cost of EUS reduces the marginal cost of the 'EUS for all patients' strategy (as it reduces the cost of testing the additional patients. The accuracy of CT scans is important as it determines whether the right patients have been selected for EUS or not. Reducing the sensitivity of CT scan means that more T1a patients will be missed by the selective EUS strategy while reducing specificity increases the number of patients that 'unnecessarly' receive an EUS.

While this scenarios are of interest as they show some of the key drivers of the analysis, none of them were thought likely to be plausible by the guideline committee. Therefore the conclusion of the analysis appears to be robust.

It is also notable that the analysis is relatively insensitive to changes in the QoL outcomes. Increasing the QoL decrements increases the incremental QALY losses associated with the selective EUS strategy. Therefore, the 'selective EUS' strategy is less cost-effective in these scenarios. However, the change was not large enough to change the conclusion of the analysis. This is most likely because the proportion of patients that are mis-staged by the strategy is relatively small.

I.3.3 Probabilistic sensitivity results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using ICER scatterplots and cost-effectiveness acceptability curves (CEAC) in figure 4 and figure 5, respectively. The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

Figure 4: ICER scatterplot

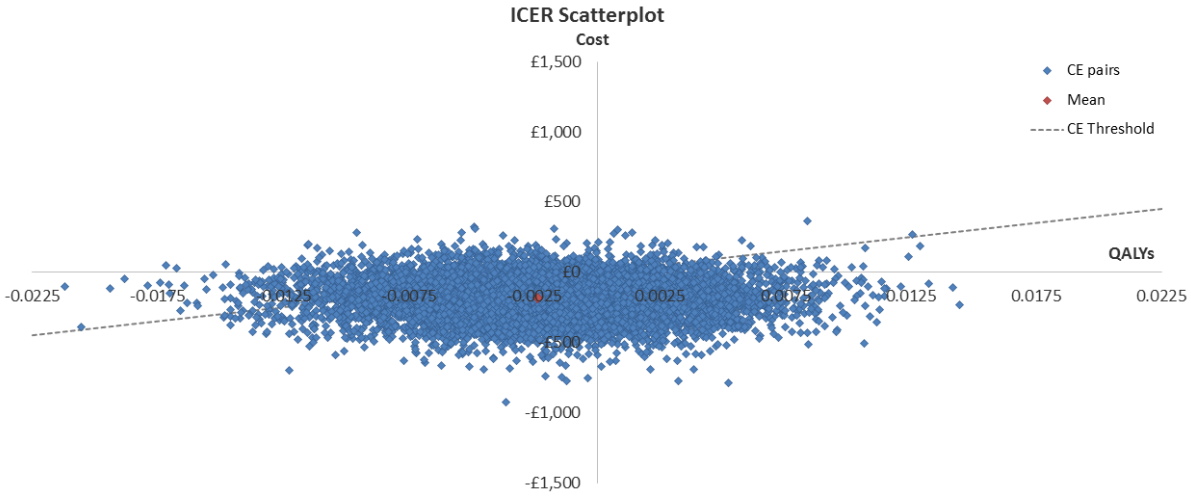
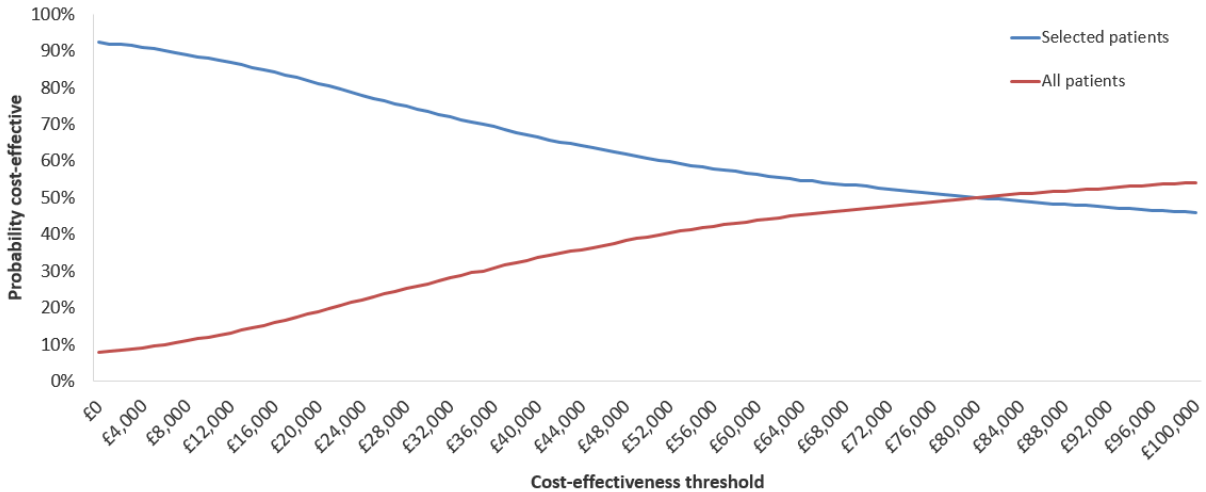


Figure 5: Cost-effectiveness acceptability curve



From the ICER scatterplot it can be seen that, while the results are spread across all four domains of the scatterplot, the majority of the results reside in the South West quadrant. This indicates that in the majority of cases, the selective EUS strategy was found to be less effective and less expensive than the strategy of staging all patients with EUS (as it was in

the base case analysis). Furthermore, it can also be seen that the majority of the cost-effectiveness pairs reside below the cost-effectiveness threshold line (£20,000 per QALY) meaning that in the majority of cases, the selective EUS strategy was found to be cost-effective.

From the CEAC it can be seen that the likelihood of the selective EUS strategy being deemed cost-effective decreases as the cost-effectiveness threshold increases. This makes intuitive sense as the cost savings conferred by the strategy become less valuable as the threshold increases. At the commonly applied NICE threshold of of £20,000 per QALY, the selective EUS strategy was found to have an 81% probability of being cost-effective, while the strategy of staging all patients was found to have a 19% probability of being cost-effective.

I.3.4 Probabilistic base case results

In addition to the deterministic results presented above (in section I.3.1), 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. The probabilistic base case results are presented in the table below.

Table 10: Probabilistic base case results

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
EUS for all patients	£656	-	-0.0029	-	-
EUS for selected patients	£471	-£184	-0.0005	-0.0024	£78,376

It can be seen that the mean results of the probabilistic results do not differ substantially from the deterministic analysis. The selective use of EUS was again found to be less costly and marginally less effective than using EUS in all patients. The ICER value shows that £78,376 is saved for each QALY that is lost and so it can again be concluded that the selective EUS strategy is cost-effective.

I.4 Discussion

This analysis aimed to estimate the cost-effectiveness of a selective EUS staging strategy in comparison to EUS staging in all patients. To our knowledge, this is the first model that has investigated the cost-utility of such a strategy in the UK context.

The results of the base case analysis suggest that the selective use of EUS is less costly and marginally less effective than using EUS for all patients. The resulting ICER showed that £77,363 would be saved for each QALY that is lost and therefore the strategy of selectively using EUS was found to be cost-effective.

In the deterministic sensitivity analysis, these findings were found to be robust with the conclusion remaining unchanged in the majority of modelled scenarios. Furthermore, in probabilistic sensitivity analysis, the selective EUS strategy was found to have a reasonably high probability of being cost-effective (81%) at the £20,000 per QALY threshold.

While the results suggest a clear result in favour of the selective EUS strategy, there were a few limitations to the analysis that should be considered. The analysis focused only on the costs and QoL decrements associated with false negative results i.e. the potential ‘overtreatment’ of T1a disease and unnecessary surgery in T4b disease. However, there is also the potential for cost and QoL changes resulting from false positive results i.e. wrongly staging patients as having T1a or T4b disease. This could lead to the undertreatment of

disease, which has wrongly been staged as T1a and the incorrect treatment approach being taken in patients with T4b disease (i.e. palliative chemotherapy instead of radical treatment). It is likely that using the incorrect treatment in these patients would affect the effectiveness of the treatment and possibly the patient's survival chances. While, the exclusion of this aspect affects the completeness of the analysis, it was not thought to affect the conclusion of the analysis. This is because there is likely to be a greater potential for 'false positives' in the EUS for all patients strategy than in the selective EUS strategy. Therefore, the inclusion of this aspect would only further strengthen the results of the analysis. Our approach could therefore be described as 'conservative'.

The analysis was run over a short time horizon of one year. This time horizon was selected as part of the pragmatic approach adopted in the model whereby the complexity of treatment choices and outcomes were simplified in order to make the modelling exercise manageable. As part of this approach, it was assumed that the adverse QoL outcomes of incorrect treatment would not persist beyond one year. In patients with T1a disease, this means that the QoL decrement associated with the 'unnecessary' addition of neoadjuvant chemotherapy would last for one year and would not persist beyond this. In patients with T4b disease, this means that the QoL decrement associated with the incorrect treatment of T4b disease with surgery would also last for one year and would not persist beyond this. While these assumptions are clearly simplifications, it is thought that they are more likely to overestimate the QoL impact rather than underestimate it. While chemotherapy can be toxic, it is unlikely that the side-effects of treatment would still be a problem in patients with T1a disease after one year. In patients with T4b disease, the low life expectancy means that it is unlikely that all patients would be alive at one year. Therefore, our approach has again been conservative as the analysis potentially overestimates the QALY loss associated with the selective EUS strategy.

A further limitation was around the accuracy data applied in the analysis. Sensitivity and specificity values for T1 and T4 disease have been used to estimate the accuracy of EUS in detecting T1a and T4b disease. In reality, it is possible that the accuracy would differ between the two approaches. Sensitivity and specificity values were also considered to be independent when varied in the probabilistic sensitivity analysis. In reality, there is a clear relationship between the two with a trade-off between sensitivity and specificity. The inclusion of a covariance estimate between the two parameters might alter the resulting probability of the selective EUS strategy being cost-effective. However, it was thought to be unlikely that this change would alter the probability to the extent that the selective EUS strategy is not preferred.

There was found to be a paucity of quality of life data in patients with oesophageal cancer that could be used to inform utility weights in the model. Therefore assumptions were made in order to apply existing QoL values in the analysis. Most notably, a 'radical treatment' disutility has bee defined for use in the model and this is the same regardless of the the radical treatment received. It has therefore been assumed that receiving chemoradadiotherapy carries the same utility decrement as chemoradiotherapy plus surgery (when compared to palliative chemotherapy). Clearly, it is unlikely to be the case that the radical treatments have the same disutility and it would have been preferrable to have estimates that better represent the individual treatments. However, given the paucity of QoL data, the approach taken was thought to be a pragmatic solution. Furthermore, the results of the one-way sensitivity analysis suggested that the model was relatively insensitive to changes in these parameters with variation of ± 50% not affecting the conclusion of the analysis.

I.5 Conclusions

The results of the analysis showed that selectively using EUS resulted in substantial savings with a minimal reduction in effectiveness. Overall, the results suggest that the selective EUS

strategy was cost-effective, saving £77,363 for each QALY lost. The result was found to be robust in deterministic sensitivity analysis with the conclusion of the analysis remaining unchanged in all plausible scenarios. In probabilistic sensitivity analysis, the strategy of selectively using EUS was found to have an 81% probability of being cost-effective at a threshold of £20,000 per QALY.

Appendix I: B. The cost-effectiveness of operative approaches in the surgical treatment of oesophageal cancer

I.1 Background

Surgery, combined with neo-adjuvant chemotherapy or chemoradiation is often the preferred definitive treatment of oesophageal cancer for adults with acceptable performance status. The type of surgical resection and operative approach used can vary between one, two or three-stage procedures; open, laparoscopic, thoracoscopic or a combination of all three.

Traditionally, the discussion of technique has mainly focused on a comparison of the transthoracic and transhiatal approach but the emergence of minimally invasive procedures have increased the surgical techniques available. There are perceived advantages to both partial and completely minimally invasive approaches such as reduced pain, blood loss and hospital stay but there are concerns about the adequacy of resection and extent of nodal harvest to control residual disease.

I.1.1 Aim

To estimate the cost-effectiveness of operative approaches for the surgical treatment of oesophageal cancer.

I.2 Methods

I.2.1 Existing Economic Evidence

A systematic literature review was conducted to identify economic evaluations that may be applicable to the current decision problem. One published cost-utility analysis was identified. Lee et al. 2013a compared the short-term cost and QALY consequences of minimally invasive and open surgical approaches from the Candian health care perspective. The minimally invasive approach was estimated to be more costly initially due to equipment costs and a longer operative time. However, it was found to be cheaper when incorporating reductions in complications and length of stay. Overall, the minimally invasive approach was found to be less costly and more effective than the open approach (i.e. ‘dominant’).

While the analysis was thought to be of generally high quality, it was deemed to be only partially applicable to the UK health care system. Therefore it was not considered sufficient to address the decision problem in the UK context.

I.2.2 De novo economic evaluation

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (The guidelines manual, NICE November 2012). The model considered a forty year time horizon with future costs and benefits discounted at a rate of 3.5% (as recommended in the NICE reference case).

I.2.3 Clinical data and model approach

The clinical evidence review conducted for this topic revealed that there is a lack of clear differences between the various surgical approaches. This is particularly true for the longer term outcomes. Therefore the primary focus of the model is on short term outcomes and in particular differences in complication rates.

However, there is a lack of consistency in the complication outcomes reported for each of the comparisons. Therefore, it was not possible to draw indirect comparisons between the comparators which were not directly compared in any of the studies identified in the evidence review (such as a comparison between a minimally invasive and hybrid surgical approach). The analysis was therefore restricted to a series of pairwise comparisons for which direct clinical evidence was available. The comparisons considered in the analysis were as follows:

- Minimally invasive in comparison to open surgical approach (transthoracic)
- Hybrid in comparison to open surgical approach (transthoracic)
- Transhiatal in comparison to two-stage transthoracic approach
- Transhiatal in comparison to three-stage transthoracic approach

Note that in the studies where the open approach was compared to a minimally invasive or hybrid approach, open surgery was performed as a transthoracic procedure. The diagrams below depict the model comparisons. It can be seen that following each surgical approach, patients may die from 30-day mortality (typically used as an estimate of procedure related mortality) or they may experience a major complication (such as anastomotic leak) or they may have survive with no complications. In the comparison of open and minimally invasive or hybrid approaches, it can be seen that some patients may convert to the open approach as it is not possible to perform the procedure in all patients. The subsequent sections detail the clinical data informing the probabilities of each of these events occurring.

Figure 6: Modelled comparison of open and minimally invasive or hybrid surgical approaches

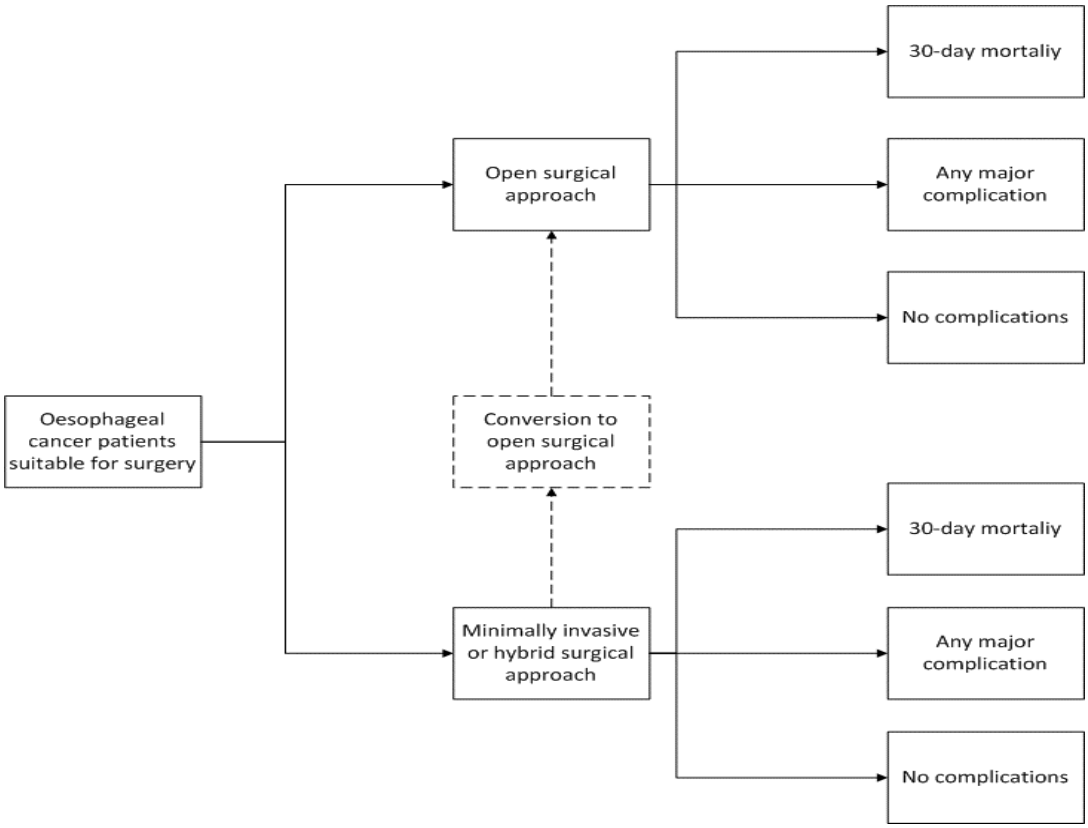
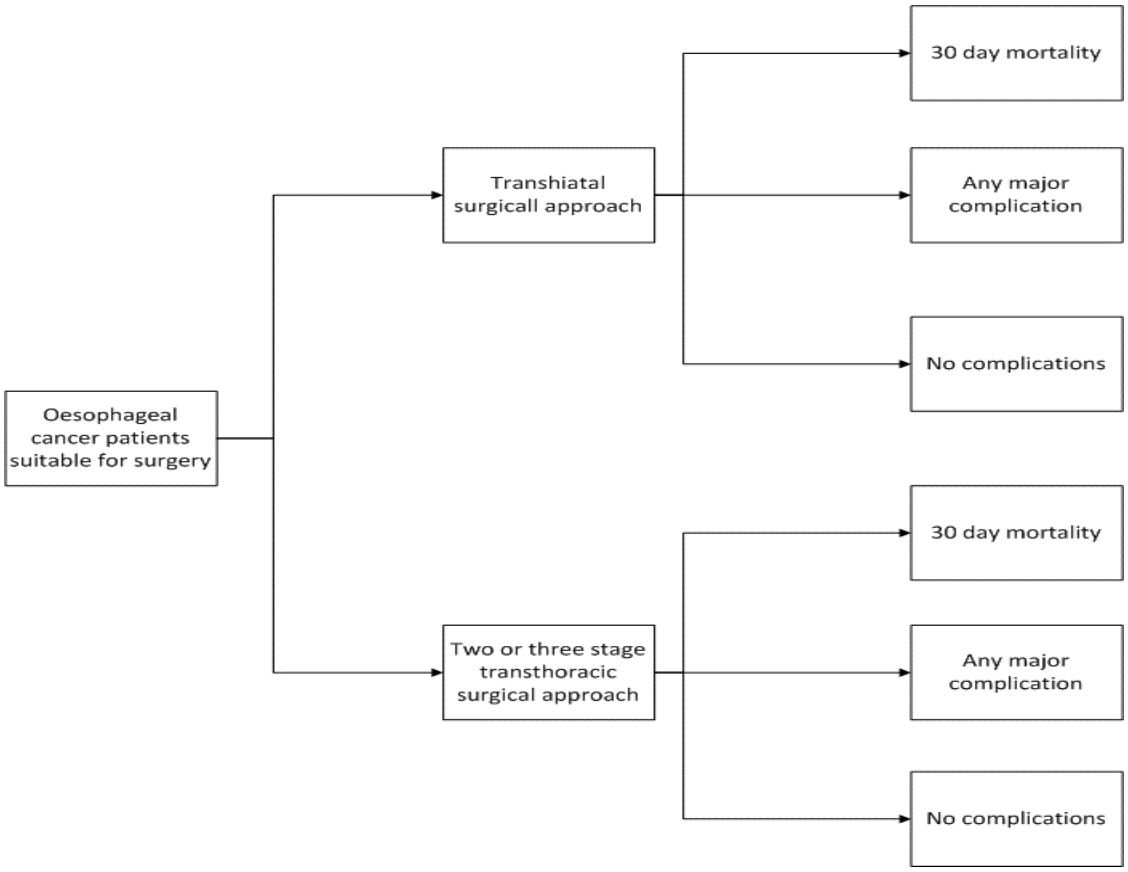


Figure 7: Modelled comparison of transhiatal and two or three stage transthoracic surgical approaches



I.2.3.1 Complications and 30 day mortality

Data on complications and 30 day mortality were sourced from the studies identified for each of the comparisons in the clinical evidence review conducted for this topic. The clinical evidence review showed that there were differences in complications and 30 day mortality rates between the surgical approaches. The tables below show the complication and 30 day mortality rates for each of the surgical approaches considered in the comparisons. Note that in the comparison of minimally invasive and open surgical approaches, there was no 30 day mortality reported for the open approach. Since this seemed unlikely it has been assumed that baseline 30 day mortality for the open approach is equal to that reported in the comparison against the hybrid approach. Similarly, in the comparison of transhiatal and two-stage transthoracic open surgical approaches, there were no pneumonia or 30 day mortality rates reported for the approaches. Baseline data has therefore been estimated using data from the comparison of transhiatal and three-stage transthoracic open surgical approaches (based on events in the transhiatal arm). It has also been assumed that there is no difference between the approaches in terms of 30 day mortality (which is consistent with the evidence for the comparison of transhiatal and three-stage transthoracic open surgical approaches).

It should also be noted that there is only evidence of statistically significant differences in the comparison between the hybrid and open approach. Therefore, there is likely to be a high degree of uncertainty around the results from the other comparisons.

Table 11: Major complications for the comparison of minimally invasive and open surgical approaches

Parameter	Open approach	RR	Minimally invasive
Pulmonary complications	6.6%	0.44 (0.16-1.26)	3.0%

Parameter	Open approach	RR	Minimally invasive
Anastomotic leak	3.6%	1.28 (0.46-3.55)	4.7%
30 day mortality	4.8%	2.90 (0.12-72.62)	0.0%

Table 12: Major complications for the comparison of hybrid and open surgical approaches

Parameter	Open approach	RR	Hybrid
Pulmonary complications	29.8%	0.59 (0.35-0.98)	17.6%
Total complications	64.4%	0.56 (0.42-0.75)	36.1%
30 day mortality	4.8%	1.10 (0.30-3.38)	4.9%

Table 13: Major complications for the comparison of transhiatal and two-stage transthoracic open surgical approaches

Parameter	Transthoracic	RR	Transhiatal
Anastomotic leak	5.3%	0.32 (0.01-7.35)	1.7%
Pneumonia	2.8%	4.76 (0.24-93.19)	13.1%
30 day mortality	6.3%	1.00	6.3%

Table 14: Major complications for the comparison of transhiatal and three-stage transthoracic open surgical approaches

Parameter	Transthoracic	RR	Transhiatal
Anastomotic leak	18.5%	0.48 (0.11-2.14)	8.9%
Pneumonia	19.3%	0.68 (0.29-1.62)	13.1%
30 day mortality	6.3%	1.00 (0.07-14.64)	6.3%

I.2.3.2 Other cause mortality

Mortality from other causes was captured using 2013-2015 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. A starting age of 60 and a male proportion of 68.2% were applied in the model based on averages reported in Biere et al. 2012 and Guo et al. 2013.

I.2.3.3 Disease specific mortality

Mortality from disease specific causes was estimated using data from two studies identified in the clinical evidence review; Hulscher et al. 2002 and Omloo et al. 2007. Omloo et al. 2007 reported disease specific mortality rates of 62% and 54% at five years for the transhiatal and transthoracic approaches respectively. Hulscher et al. 2002 reported overall mortality rates of 70% and 60% for the transhiatal and transthoracic approaches respectively. Disease specific mortality was estimated by removing in-hospital mortality (reported in study) and other cause mortality. Other cause mortality was estimated using ONS life tables (as described above) informed by the average age and gender reported in Hulscher et al. 2002. After removing 30-day and other cause mortality, disease specific mortality at five years was estimated to be 58% and 49% at five yars for the transhiatal and transthoracic approaches respectively.

Data on the transhiatal and transthoracic approaches in each study were combined to give an overall disease specific mortality estimate of 56% at five years. This was converted to an annual mortality rate of 15%.

I.2.3.4 Recurrence

Recurrence rates were estimated using data from Hulscher et al. 2002 (selected as it presented outcomes in sufficient detail for recurrences to be estimated). Hulscher et al. 2002 reported recurrences rates of 65% and 54% at five years for the transhiatal and transthoracic approaches respectively. Data on both arms was combined to give an estimated recurrence rate rate of 59% at five years. This was converted to an annual recurrence rate of 16%.

I.2.3.5 Conversion to open approach

For various reasons, some patients that are planned to undero a minimally invasive or hybrid surgical approach are unable to do so. In such cases, an open surgical approach would be performed instead. Based on data from Biere et al. 2012, it was estimated that 13.8% of patients due to undergo a minimally invasive or hybrid approach would would have to convert to the open approach.

I.2.4 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 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) 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 guideline committee.

I.2.4.1 Procedure and complications costs

One of the key aspects to be captured in the economic analysis is the difference in costs between the various surgical approaches. However, this presents a problem because NHS reference costs have a standard cost for the procedure regardless of the approach taken. Therefore, the analysis used the procedure cost as the starting point for all surgical approaches and then introduced cost variations based on differences in procedure time, equipment costs, complication rates and length of stay.

The cost of a ‘very complex, oesophageal, stomach or duodenum procedures’ (FZ80) from NHS Reference costs 2015/16 was identified as the code most likely to be used for the procedure. The table below details this cost, which varies according to complications and co-morbidity (CC) scores.

In the model, a ‘base cost’ of £8,439.60 was used for the procedure. The cost of complications associated with each surgical technique were then added to this figure. The cost of complications was estimated to be £6,481.20 based on the difference between the weighted average cost of the procedure with complications (£14,920.80) and without complications (£8,439.60).

Table 15: Surgical procedure cost

Procedure	Proportion*	Cost	Source
Very complex, oesophageal, stomach or duodenum procedure, 19 years and over (FZ80)			
with CC score 6+	18%	£18,934.89	NHS Reference costs 2015/16
with CC score 3-5	22%	£11,700.19	NHS Reference costs 2015/16

Procedure	Proportion*	Cost	Source
with CC score 0-2	60%	£8,439.60	NHS Reference costs 2015/16
Weighted average		***£11,057.41***	

*Based on number of recorded procedures in NHS reference costs

I.2.4.2 Equipment costs

In the cost-effectiveness analysis by Lee et al. 2013a, it was estimated that the additional equipment required to perform the minimally invasive approach was $1,510 (Canadian dollars). This cost has been converted and inflated to UK 2015 prices and has been estimated at £891.30. It should be noted that there are limitations to converting between currencies in this way as there may be differences other than the exchange rate which are not captured in the conversion.

In the absence of any better alternative data, it was also assumed that the same equipment cost would apply to the hybrid approach too. However, in the opinion of the guideline committee, the equipment costs associated with the hybrid approach are likely to be lower than that associated with the minimally invasive approach. Therefore, a conservative approach has been adopted where the cost-effectiveness of the hybrid approach may be underestimated in the analysis.

To reflect the uncertainty around the equipment costs both in respect to the conversion to UK prices and the application to the hybrid approach, this variable was varied in the deterministic sensitivity analysis.

I.2.4.3 Operation time costs

One of the key differences between surgical approaches identified in the clinical evidence review was in the time taken to perform the operation. The additional costs associated with the additional operation time were captured in the analysis by estimating an average cost per minute of surgical time and multiplying the additional time by this figure.

The average minimally invasive and open procedure time (from the evidence review) was estimated to be 256.76 minutes. This figure has been used in conjunction with the procedure cost (£11,057.41) to estimate a cost per minute of operation time (£43.06). This is then used to estimate the additional time costs to perform minimally invasive, hybrid and transthoracic procedures.

The table below details the calculation of the cost per minute of surgical procedure time and the cost of the extra time for each type of surgical procedure.

Table 16: Surgical operation time costs

Procedure	Value	Source
Procedure cost (A)	£11,057.41	NHS Reference costs 2015/16
Average time taken to perform procedure in minutes (B)	256.76	Clinical evidence review
Cost per minute of procedure time (C)	£43.06	Estimated as (A) divided by (B)
Extra minutes to perform minimally invasive or hybrid procedure in comparison to open approach (D)	48.06	Clinical evidence review
Additional time costs to perform minimally invasive or hybrid procedure	£2,069.67	Estimated as (C) multiplied by (D)

Procedure	Value	Source
Extra minutes to perform two-stage transthoracic approach compared to transhiatal procedure (E)	27.05	Clinical evidence review
Additional time costs to perform two-stage transthoracic procedure	£1,164.89	Estimated as (C) multiplied by (E)
Extra minutes to perform three stage transthoracic approach compared to transhiatal procedure (F)	121.10	Clinical evidence review
Additional time costs to perform three-stage transthoracic procedure	£5,215.09	Estimated as (C) multiplied by (F)

I.2.4.4 Length of stay costs

One of the reported benefits of the minimally invasive or hybrid surgical procedures is that there is a reduced length of stay after surgery. Based on data reported in Biere et al. 2012 and Guo et al. 2013, it was assumed that the length of stay with minimally invasive or hybrid surgical approaches is reduced by 2.2 days. The cost per additional day (£316.34) was estimated using costs for excess bed days from NHS reference costs.

Note that the inclusion of this aspect runs the risk of double counting the benefit associated with reduced morbidity in the hybrid, minimally invasive and transhiatal treatment arms (as the LOS reduction may already be captured in the morbidity cost estimates). For this reason, it was varied in sensitivity analysis (including a scenario where it was removed entirely).

I.2.4.5 Recurrence costs

It was assumed that recurrences would be treated with six cycles of chemotherapy, based on an average cost of the five chemotherapy regimens that are most likely to be used in clinical practice (as identified by the guideline committee). The chemotherapy delivery costs were sourced from NHS Reference Costs 2015/16 and drug costs were sourced from eMit.

The table below details the average cost of each chemotherapy regimen per cycle. It can be seen that the chemotherapy costs per cycle were similar for each of the regimens. The average cost per cycle was estimated to be £824.68 with a cost of £4,948.09 for six cycles.

Table 17: Estimated chemotherapy costs per cycle

Treatment	Cost	Source
Cisplatin and FU		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Cisplatin	£26.60	eMit
Fluorouracil 750mg/m2 days 1-5	£10.34	eMit
Cost per cycle	**£804.60**	
Carboplatin and paclitaxel		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Carboplatin AUC 2 weekly x 5 (days 1,8,15,22,29)	£55.95	eMit
Paclitaxel 50mg/m2 weekly x 5 (days 1,8,15,22,29)	£42.50	eMit

Treatment	Cost	Source
Cost per cycle	**£866.12**	
Cisplatin and capecitabine		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Cisplatin 60mg/m2 on day 1 of cycle	£12.46	eMit
Capecitabine 625mg/m2 twice daily (days 1-21)	£24.65	eMit
Cost per cycle	**£804.78**	
Carboplatin and capecitabine		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Carboplatin AUC 5 on day 1 of cycle	£21.65	eMit
Capecitabine 625mg/m2 twice daily (days 1-21)	£24.65	eMit
Cost per cycle	**£813.97**	
Oxaliplatin and capecitabine		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Oxaliplatin dose 130mg/m2 on day 1	£41.62	eMit
Capecitabine 625mg/m2 twice daily (days 1-21)	£24.65	eMit
Cost per cycle	**£833.94**	

I.2.4.6 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. The table below details the palliative care cost applied in the model.

Table 18: Estimated palliative care cost per patient in the last three months of life

Type of care	Average cost per cancer patient	Source
Cost of all hospital contacts	£5,890	Exploring the cost of care at the end of life (Nuffield Trust, Georghiou 2014)
Local authority-funded care	£444	
District nursing care	£588	
GP contacts	£365	
Average palliative care cost per patient	**£7,287**	

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

I.2.5 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.

The QoL values applied in the model were sourced from the cost-effectiveness analysis by Lee et al. 2013a and are shown in the table below. Lee et al. 2013a used data from Biere et al. 2012 to estimate QoL values for various health states in patients treated with open and minimally invasive surgical approaches.

The QoL value for the postoperative health state (0.6775) was estimated as the average of the QoL values for the postoperative states following an open or minimally invasive procedure in Lee et al. 2013a (0.649 and 0.706, respectively). As in Lee et al. 2013a, a utility decrement of 0.043 was applied for any of the major complications experienced with the surgical approaches.

A QoL increment was applied in the analysis to capture the potential benefits associated with a better postoperative period following a minimally invasive or hybrid surgical procedure. This value was estimated based on the difference between the minimally invasive and open procedure estimated in Lee et al. 2013a (0.057). It was assumed that the QoL benefit would only apply for the first three months after the procedure. A further QoL benefit was applied for the reduced length of stay associated with the minimally invasive and hybrid surgical procedures. A QoL value of 0.0018 was applied based on the QoL value for the inhospital postoperative period from Lee et al. 2013a (0.300) estimated per day and multipled by the reduction in length of stay.

A QoL decrement was estimated for patients experiencing recurrence based on data from Graham et al. 2007, a cost-effectiveness analysis of treatments for locally advanced oesophageal cancer. As part of the analysis, QoL values were estimated for surgical and multi-modal treatments at various time points. For the present analysis it was assumed that the pre-treamtent values would best represent the QoL value with disease while the post-treatment value would best represent the QoL value for patients that are disease-free. A QoL decrement of 0.040 was estimated as the difference between patients with disease (0.63) and without disease (0.67) after surgical treatment.

Table 19: Health-related quality of life values

Health state	Value	Source
Postoperative health state	0.6775	Lee et al. 2013a – average of postoperative states for open (0.6490) and MIE (0.7060) approaches
QoL increments and decrements		
Postoperative complication disutility	0.0430	Lee et al. 2013a
3-month postoperative QoL benefit with minimally invasive or hybrid approach	0.0143	Lee et al. 2013a – difference (0.057) between open and MIE approaches divided by 4
QoL benefit through reduced LOS with minimally invasive	0.0018	Lee et al. 2013a – in-hospital postoperative period QoL (0.30) estimated per day and multiplied by LOS reduction.
Recurrence	0.0400	Graham et al. 2007 - based on the difference between patients with and without disease after surgical treatment

I.3 Results

I.3.1 Base case results

The base case results of each of the pairwise analyses are presented in the tables below.

It can be seen that the minimally invasive surgical approach was found to be more costly (£1,002) and less effective (-0.26 QALYs) than the open surgical approach and was therefore dominated.

The hybrid surgical approach was found to be more costly (£351) and more effective (0.02 QALYs) than the open surgical approach and resulted in an ICER of £18,036 per QALY. Therefore the hybrid approach can be considered cost-effective in comparison to the open approach as this value is lower than the NICE threshold of £20,000 per QALY.

For the comparisons between the types of open surgical approaches, it can be seen that the transhiatal approach was found to be more costly and less effective than the two-stage transthoracic approach and was therefore dominated. In comparison to the three stage transthoracic approach, the transhiatal approach was found to be less costly and more effective. It was therefore dominant.

When interpreting the results of the deterministic analysis, it is important to remember that many of the differences in clinical effectiveness that have been modelled were not statisitically significant. This limits the reliability of the base case estimates.

Table 20: Base case results for minimally invasive approach in comparison to open approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Open approach	£17,373	-	2.71	-	**-**
Minimally invasive approach	£18,375	*£1,002*	2.45	*-0.26*	**Dominated**

Table 21: Base case results for hybrid approach in comparison to open approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Open approach	£20,766	-	2.68	-	**-**
Hybrid approach	£21,117	*£351*	2.70	*0.02*	**£18,036**

Table 22: Base case results for transhiatal in comparison to two-stage transthoracic approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Transthoracic	£17,099	-	2.66	-	**-**
Transhiatal	£17,523	*£424*	2.66	*-0.00*	**Dominated**

Table 23: Base case results for transhiatal in comparison to three-stage transthoracic approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Transthoracic	£18,965	-	2.65	-	**-**
Transhiatal	£17,975	*-£991*	2.65	*0.01*	**Dominant**

I.3.2 Deterministic sensitivity 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 results of the deterministic sensitivity analyses are shown in the table below. The table shows the optimal strategy (in cost-effectiveness terms) for each of the modelled scenarios.

For the comparison of the minimally invasive and open surgical open approaches, it can be seen that the conclusion of the analysis remains unchanged in all modelled scenarios (i.e. the open approach is always preferred).

For the comparison of the hybrid and open surgical open approaches, it can be seen that the conclusion of the analysis changes in a number of modelled scenarios including a scenario where the upper RR for complications is applied as well as scenarios where QoL assumptions are changed around complications.

For the comparisons between the open approaches, it can be seen that the transhiatal approach remains the preferred strategy in the majority of modelled scenarios. The only exception is in the scenarios where the upper or lower RR is used for complications. In these scenarios it was found that the strategy with the lowest complications was always preferred. This reflects the high degree of uncertainty in the effectiveness estimate for complications.

Table 24: Deterministic sensitivity analysis results

Change made	MI vs open	Hybrid vs open	Transhiatal vs two-stage transthoracic approach	Transhiatal vs three-stage transthoracic approach
Base case	**Open**	**Hybrid**	**Transthoracic**	**Transhiatal**
Upper RR for complications	Open	Open	Transthoracic	Transthoracic
Lower RR for complications	Open	Hybrid	Transhiatal	Transhiatal
No differences in 30 day mortality	Open	Hybrid	-	-
6-month postop QoL benefit	Open	Hybrid	-	-
No postop QoL benefit	Open	Open	-	-
No QoL benefit through reduced LOS	Open	Hybrid	-	-
No complication disutilities	Open	Open	Transthoracic	Transhiatal
Recurrence disutility + 50%	Open	Hybrid	Transthoracic	Transhiatal
Recurrence disutility - 50%	Open	Hybrid	Transthoracic	Transhiatal
No recurrence disutility	Open	Hybrid	Transthoracic	Transhiatal
Removal of cost savings due to LOS reduction	Open	Open	-	-

Change made	MI vs open	Hybrid vs open	Transhiatal vs two-stage transthoracic approach	Transhiatal vs three-stage transthoracic approach
Equipment costs +50%	Open	Open	-	-
Equipment costs -50%	Open	Hybrid	-	-
No equipment costs	Open	Hybrid	-	-
Complication costs 50% higher	Open	Hybrid	Transthoracic	Transhiatal
Complication costs 50% lower	Open	Open	Transthoracic	Transhiatal
No conversions	Open	Hybrid	-	-

I.3.3 Probabilistic sensitivity results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using ICER scatterplots and cost-effectiveness acceptability curves (CEAC). The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

The figures below show the ICER scatterplots and CEAC for the comparison between the minimally invasive and open surgical approach. From the ICER scatterplot, it can be seen that the results are spread across all four quadrants but the majority of the results reside in the North half of the graph, indicating that the minimally invasive approach is more expensive than the open approach in most modelled scenarios. The CEAC shows that the probability of the minimally invasive approach being cost-effective increases as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, the minimally invasive approach was found to have a 35% probability of being cost-effective while the open approach had an 65% probability of being cost-effective.

Figure 8: ICER Scatterplot for minimally invasive approach in comparison to open approach

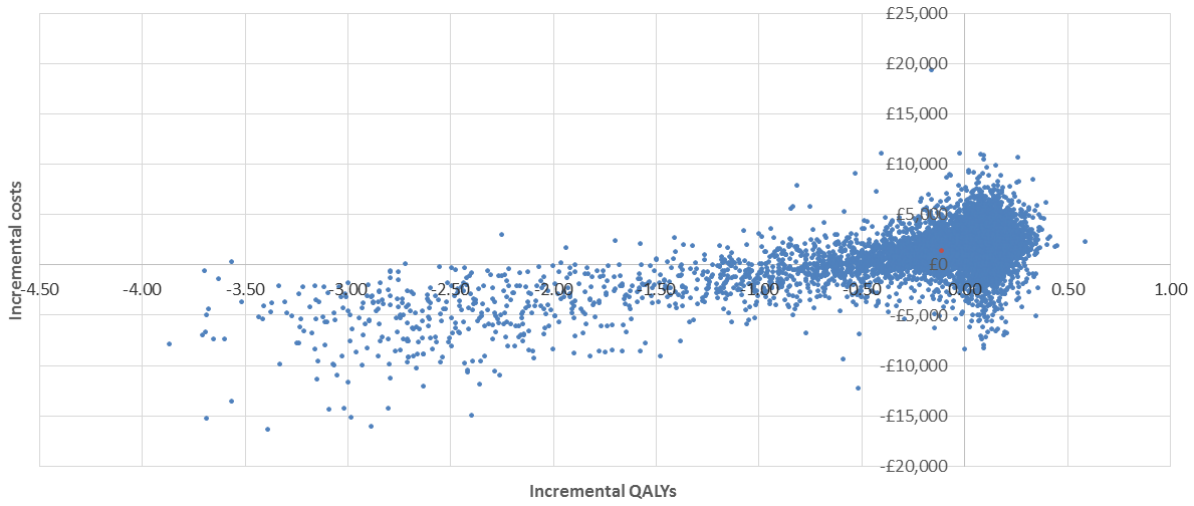
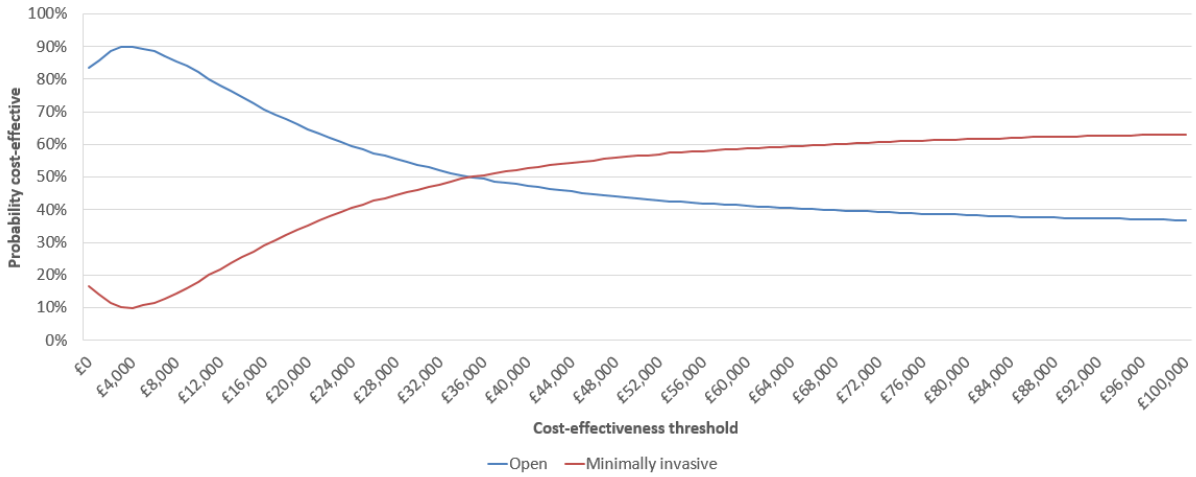


Figure 9: Cost-effectiveness acceptability curve for minimally invasive approach in comparison to open approach



The figures below show the ICER scatterplots and CEAC for the comparison between the hybrid and open surgical approach. From the ICER scatterplot, it can be seen that the majority of the results reside in the North East quadrant, indicating that the hybrid approach is more effective and more expensive than the open approach. The CEAC shows that the probability of the minimally invasive approach being cost-effective increases as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, the hyrbid approach was found to have a 54% probability of being cost-effective while the open approach had a 46% probability of being cost-effective.

Figure 10: ICER Scatterplot for hybrid approach in comparison to open approach

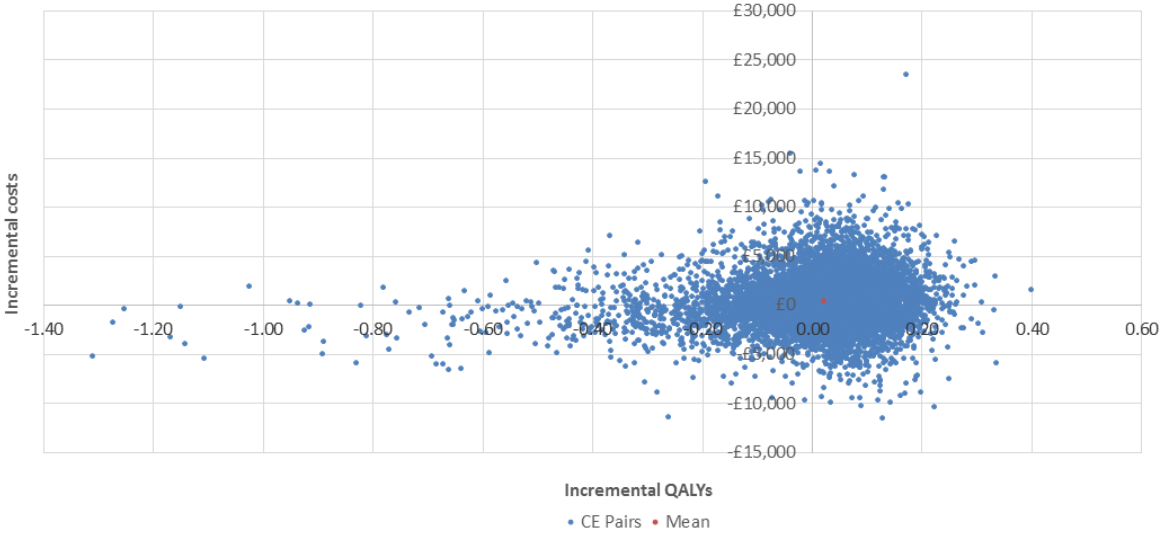
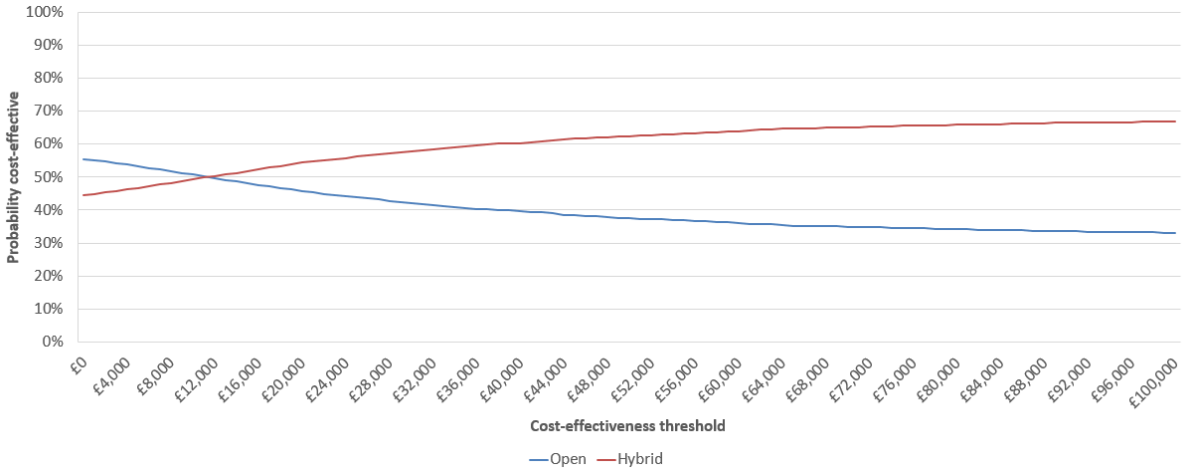


Figure 11: Cost-effectiveness acceptability curve for hybrid approach in comparison to open approach



The figures below show the ICER scatterplots and CEAC for the comparison between the two stage transthoracic and transhiatal approach. From the ICER scatterplot, it can be seen that the majority of the results reside in the South West quadrant, indicating that the transhiatal approach was more effective and less expensive than the two stage transthoracic approach. The CEAC shows that the probability of the transhiatal approach being cost-effective increases as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, the transhiatal approach was found to have a 76% probability of being cost-effective while the two stage transthoracic approach had a 24% probability of being cost-effective.

Figure 12: ICER Scatterplot for transhiatal approach in comparison to two-stage transthoracic approach

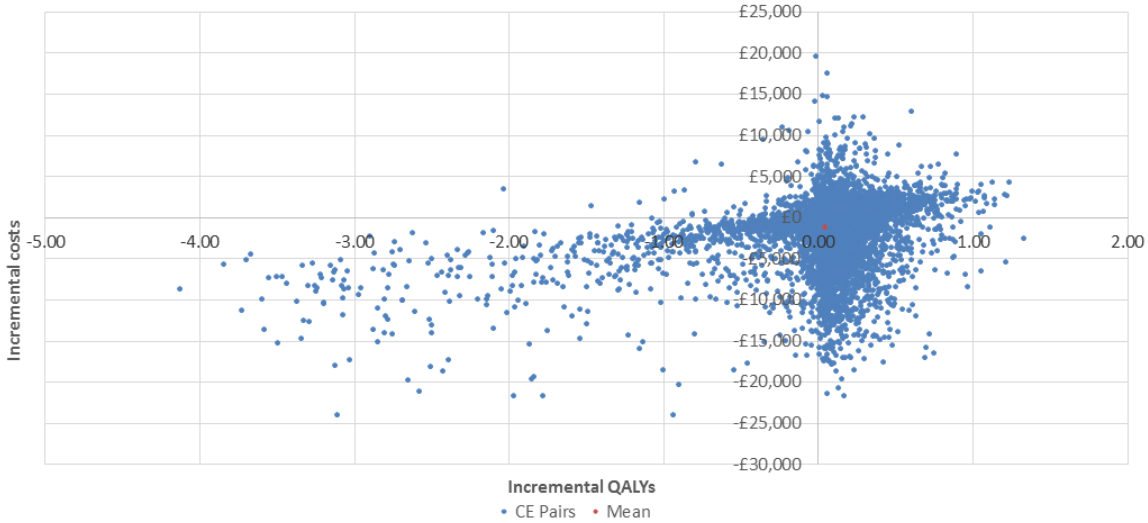
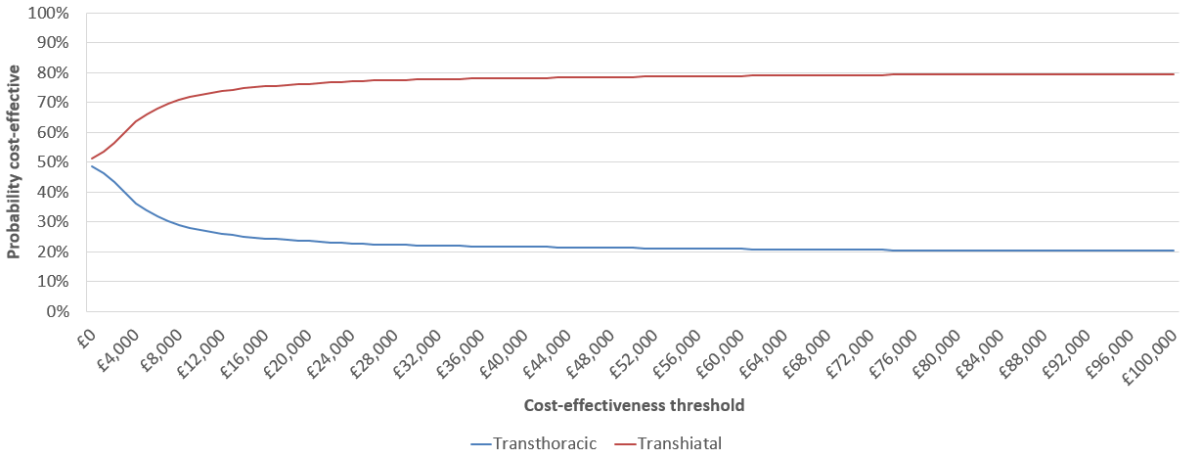


Figure 13: Cost-effectiveness acceptability curve for transhiatal approach in comparison to two-stage transthoracic approach



The figures below show the ICER scatterplots and CEAC for the comparison between the three stage transthoracic and transhiatal approach. From the ICER scatterplot, it can be seen that the results are spread across all four quadrants but the majority reside in the lower half, indicating that the transhiatal approach was found to be less expensive than the three stage transthoracic approach in most cases. The CEAC shows that the probability of the transhiatal approach being cost-effective remains fairly constant as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, the transhiatal approach was found to have a 82% probability of being cost-effective while the three stage transthoracic approach had a 18% probability of being cost-effective.

Figure 14: ICER Scatterplot for transhiatal approach in comparison to three-stage transthoracic approach

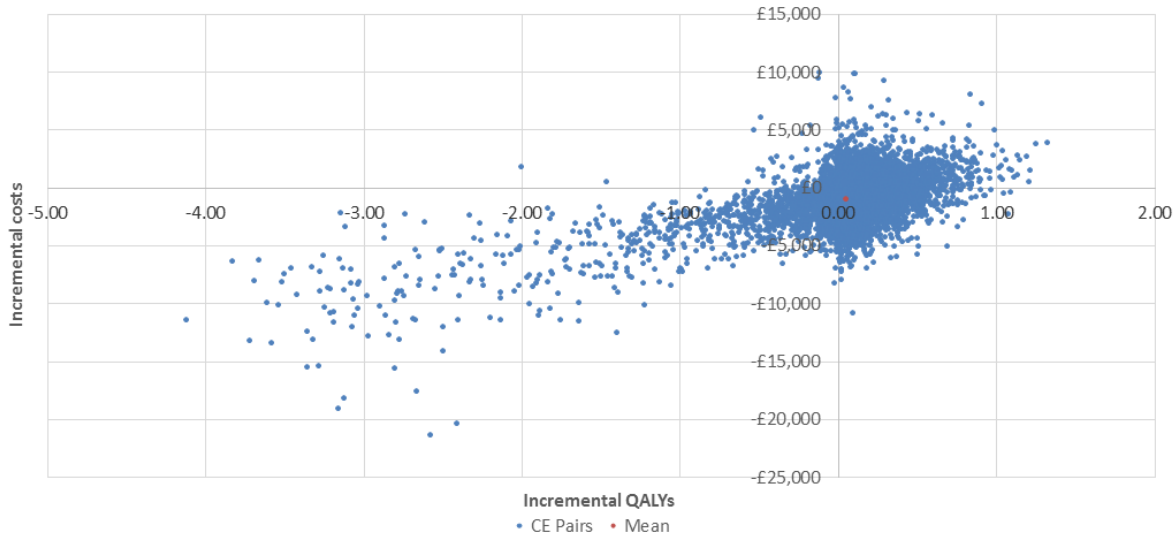
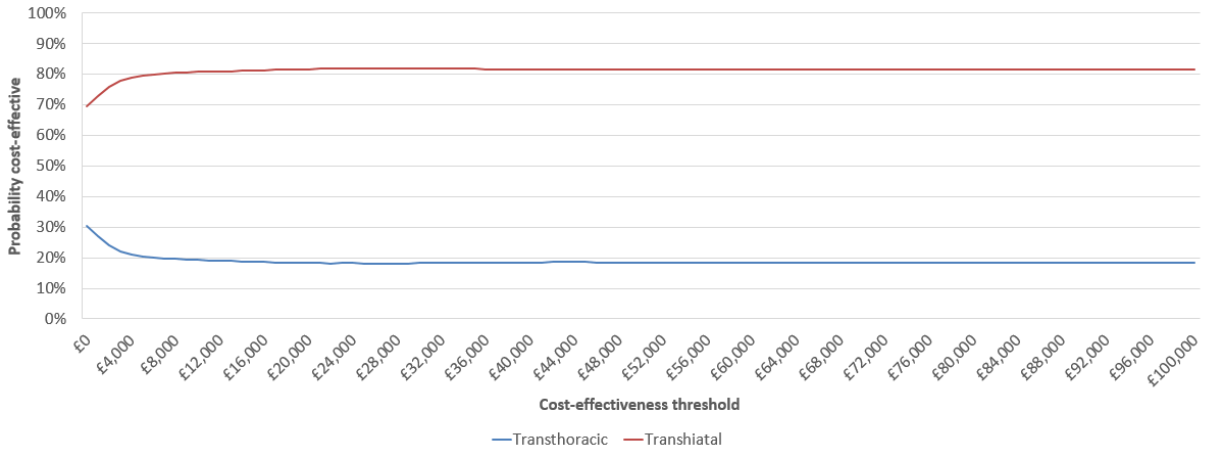


Figure 15: Cost-effectiveness acceptability curve for transhiatal approach in comparison to three-stage transthoracic approach



I.3.4 Probabilistic base case results

In addition to the deterministic results presented above (in section I.3.1), 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. The probabilistic base case results are presented in the tables below.

In the comparison between the minimally invasive and open approach, it can be seen that the result doesn't differ substantially from the deterministic analysis with the minimally invasive approach again found to be more costly and less effective than the open approach. Therefore, as in the deterministic base case the minimally invasive approach is dominated by the open approach.

In the comparison between the hybrid and open approach, it can be seen that the results do not differ substantially from the deterministic analysis. The hybrid approach is again found to be more costly and more effective than the open surgical approach. However, the increased ICER of £22,034 per QALY is marginally above the the NICE threshold of £20,000 per QALY and so in strict terms, the hybrid approach is no longer considered cost-effective.

In the comparison between the transhiatal and two-stage transthoracic approach, it can be seen that the probabilistic result is substantially different to the deterministic base case. The transhiatal approach was found to be dominated in the deterministic base case (i.e. less effective and more expensive) but it is found to be dominated in the probabilistic base case (i.e. less expensive and more effective).

In the comparison between the transhiatal and three-stage transthoracic approach, it can be seen that the result doesn't differ substantially from the deterministic analysis with the transhiatal approach again found to be less costly and more effective than the three-stage transthoracic approach. Therefore, as in the deterministic base case, the transhiatal approach is found to be dominant in comparison to the three-stage transthoracic approach.

Table 25: Probabilistic base case results for minimally invasive approach in comparison to open approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Open approach	£17,152	-	2.62	-	-

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Minimally invasive approach	£18,661	*£1,509*	2.52	*-0.11*	**Dominated**

Table 26: Probabilistic base case results for hybrid approach in comparison to open approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Open approach	£20,528	-	2.60	-	**-**
Hybrid approach	£20,967	*£439*	2.62	*0.02*	**£22,034**

Table 27: Probabilistic base case results for transhiatal in comparison to two-stage transthoracic approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Transthoracic	£18,463	-	2.57	-	**-**
Transhiatal	£17,403	*-£1,059*	2.61	*0.04*	**Dominant**

Table 28: Probabilistic base case results for transhiatal in comparison to three-stage transthoracic approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Transthoracic	£18,733	-	2.57	-	**-**
Transhiatal	£17,854	*-£880*	2.61	*0.04*	**Dominant**

I.4 Discussion

This analysis aimed to estimate the cost-utiltiy of surgical approaches in the treatment of oesophageal cancer. In the comparison between the minimally invasive and open approach, the base case results suggested that the minimally invasive approach was more costly and less effective than the open approach and was therefore dominated. The result was not found to vary in deterministic sensitivity analysis with the conclusion remaining unchanged in numerous scenarios. In probabilistic sensitivity analysis, the minimally invasive approach was found to have only a 35% probability of being cost-effective at a threshold of £20,000 per QALY.

In the comparison between the hybrid and open approach, the base case results suggested that the hybrid approach was more costly and more effective than the open approach and resulted in an ICER of £18,036 per QALY. Therefore the hybrid approach can be considered cost-effective in comparison to the open approach as this value is lower than the NICE threshold of £20,000 per QALY. The result was not found to be robust in deterministic sensitivity analysis with the conclusion changing in numerous plausible scenarios. Furthermore, in probabilistic sensitivity analysis, the hybrid approach was found to have a 51% probability of being cost-effective at a threshold of £20,000 per QALY.

In the comparisons between the types of open surgical approaches, it was found that the transhiatal approach was more costly and less effective than the two-stage transthoracic approach and was therefore dominated. In comparison to the three stage transthoracic approach, the transhiatal approach was found to be less costly and more effective and was therefore dominant. The result was not found to change in most deterministic sensitivity analysis. However, the conclusion of the analyses was found to change when upper or lower

RR estimates were used for complications. In probabilistic sensitivity analysis, the transhiatal approach was found to have a 76% and 82% probability of being cost-effective at a threshold of £20,000 per QALY when compared against the two-stage and three-stage transthoracic approach, respectively.

However, the lack of robust clinical data has limited the strength of the analyses that have been undertaken. This is particularly true for the comparison between the minimally invasive and open approach and the comparisons between open approaches (transhiatal and transthoracic). The results of the analyses were largely dependent upon the clinical effectiveness data and since differences in this data were not statistically significant, the results (and in particular the base case results) do not provide a reliable estimate of cost-effectiveness. The evidence for the comparison between the hybrid and open approach was thought to be of higher quality and suggested that there were statistically significant differences between the two approaches.

To our knowledge, this is the first model that has investigated the cost-utility of surgical approaches in the UK context. A previous cost-utiltiy analysis by Lee et al. 2013a estimated the cost-utiltiy of a minimally invasive approach in comparison to an open surgical approach from the Candian health care perspective. It is worth noting that the results of the present analysis are not in accordance with the results in Lee et al. 2013a. In Lee et al 2013a, the minimally invasive approach was found to be less costly and more effective than the open approach (i.e. dominant) whereas in this analysis it was found to be more costly and less effective (i.e. dominated). The reason for the cost difference seems to relate to differences in the elements used in the cost estimates (particularly, the estimated reduction in LOS with the minimally invasive approach and estimated costs of additional theatre time). The reason for the difference in effectiveness partly relates to differences in the clinical evidence used to inform the model (such as a reduction in 30 day mortality in Lee et al. 2013a rather than the increase modelled in this analysis). There were also differences in the QoL values applied in the analyses, with more conservative assumptions made in this analysis (thereby reducing the potential QoL benefit with the minimally invasive approach). For example, in this analysis it was assumed that the post-operative QoL benefit after minimally invasive surgery would only persist for one year.

There were a few limitations to the analysis that should be considered. The analysis was primarily focused on the short-term outcomes associated with the various surgical approaches (specifically, 30-day mortality and complications). While the time horizon of forty years does capture subsequent recurrences, further treatment and disease-related mortality, it has been assumed that these aspects do not differ between strategies. This is in accordance with the available evidence base, which does not indicate that there are differences between the approaches in disease-related outcomes. However, longer-term data from high quality studies is required to be able to conclusively make such a judgement.

It was thought that there was likely to be differences in the costs of the surgical approaches as a result of differences in procedure time, equipment costs, length of stay and complications. However, it was not easy to estimate appropriate costs for each of the procedures as the cost of the procedure in NHS reference costs does not vary according to the approach adopted. A pragmatic approach has been adopted to attempt to estimate the likely cost differences and this has necessitated making simplifying assumptions. Most notably, the additional procedure time costs have been estimated by estimating a cost per minute of procedure time, which was estimated by dividing the procedure cost from NHS reference costs by the average time taken to perform the procedure. This approach is likely to overestimate the procedure time costs as the reference cost will include fixed costs that would not vary as the time increases. Therefore the marginal cost has been overestimated. While this is clearly a limitation, it fits in with the conservative approach that has been adopted in the analysis whereby we have aimed to bias against the intervention.

There was found to be a paucity of quality of life data in patients with oesophageal cancer undergoing surgery that could be used to inform utility weights in the model. The QoL values used in the analysis were based on the QoL values applied in the analysis by Lee et al. 2013a. As discussed above, these QoL values were modified slightly in order to reduce potential bias in favour of the hybrid and minimally invasive approaches. Thereby making the QoL values more conservative. However, it remains the case that there is uncertainty around the QoL values applied in the analysis and it would appear to be an area where furher research is needed.

I.5 Conclusion

Conducting a robust economic analysis in this area is very difficult due to a lack of high quality clinical evidence showing clear differences between the surgical approaches. The clearest differences in the clinical evidence were observed in the comparison between the hybrid and open surgical approach.

The base case results for the comparison between the hybrid and open surgical approaches showed that the hybrid approach was more costly and more effective with an ICER below the NICE threshold for cost-effectiveness. This suggests that there may be a role for the hybrid surgical approach in the management of these patients. However, it should be noted that the probabilistic sensitivity analysis showed that there was uncertainty over this result.

In all other comparisons, the results were thought to be too uncertain to draw any firm conclusions. This was made clear in the uncertainty observed in the sensitivity analysis. Overall, it is clear that further research is needed before robust conclusions can be drawn about the cost-effectiveness of the various surgical approaches.

Appendix I: C. The cost-effectiveness of curative treatments for squamous cell carcinoma of the oesophagus

I.1 Background

Treatment options for patients with squamous cell carcinoma of the oesophagus include surgery, radiotherapy and chemotherapy; either as single modalities, or in combination (multi-modality). There is currently uncertainty over the effectiveness and cost-effectiveness of the treatment options available. In particular, there is debate around whether non operative treatment is as effective as surgery based treatment, and whether multimodal is superior to unimodal treatment.

I.1.1 Aim

To estimate the cost-effectiveness of curative treatment strategies for people with squamous cell carcinoma of the oesophagus.

I.2 Methods

I.2.1 Existing Economic Evidence

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

I.2.2 De novo economic evaluation

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (The guidelines manual, NICE November 2012). The model considered a forty year time horizon with future costs and benefits discounted at a rate of 3.5% (as recommended in the NICE reference case).

I.2.3 Comparisons considered in the analysis

As a result of inconsistency and incoherence in the effectiveness data as well as concerns about differences in the patient populations indicated for each treatment, it was not possible to model all treatments against each other. Therefore, the analysis has been run as a series of pairwise comparisons.

The economic analysis was restricted to the primary comparisons of interest as identified by the guideline committee. However, due to limitations in the available data, it was not possible to model a comparison of chemoradiotherapy plus surgery and chemoradiotherapy alone, which was the comparison of most interest to guideline committee. Arguably, there is sufficient data to be able to undertake a mixed treatment comparison of chemoradiotherapy plus surgery and chemoradiotherapy alone. However, it was thought that there was too much hetereogneity in the populations to make a meaningful comparison. Specifically, patients receiving chemoradiotherapy and surgery are generally fitter than patients receiving chemoradiotherapy alone.

The following comparisons were considered in the analysis:

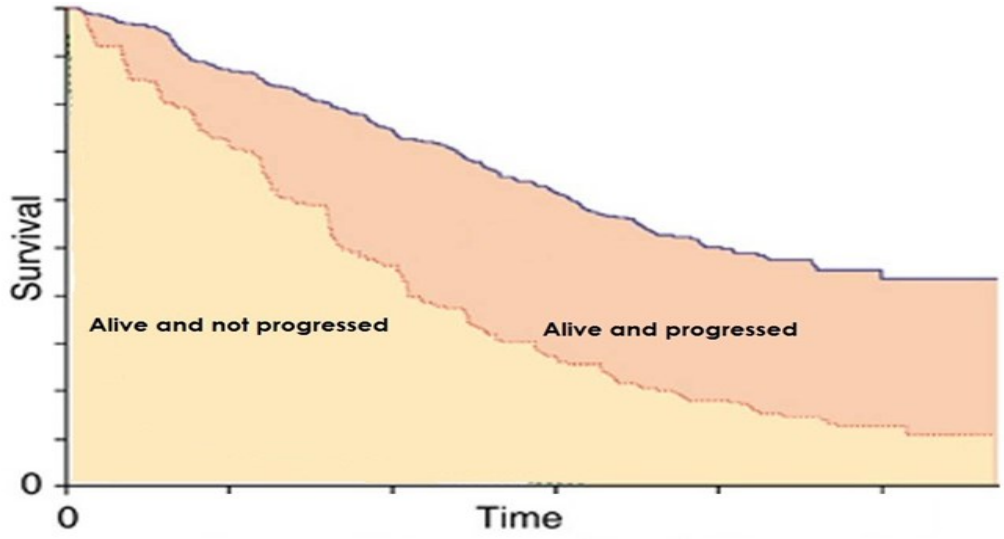
- Chemoradiotherapy followed by surgery in comparison to surgery
- Chemoradiotherapy followed by surgery in comparison to chemotherapy followed by surgery
- Chemoradiotherapy in comparison to surgery
- Chemotherapy followed by surgery in comparison to surgery

I.2.4 Clinical data and model approach

The economic analysis was based on overall survival and progression free survival estimates for each of the treatments included in the analysis. The analysis essentially took the form of a simplistic partitioned survival analysis (as illustrated in the diagram below), in which three mutually exclusive health states were derived from the overall survival and progression free survival estimates:

- Alive without progressed disease
- Alive with progressed disease
- Death

Figure 16: Illustrative example of partitioned survival analysis



I.2.4.1 Overall and disease free survival

Overall and disease free survival values were derived based on the treatment effects estimated in the clinical evidence review conducted for this topic (measured using relative risk (RR) estimates). The treatment effects were applied in conjunction with baseline estimates of overall and disease free survival in patients with squamous cell carcinoma from the CROSS trial (Shapiro et al. 2015). Data from the CROSS trial was used to inform the baseline estimates as it was adjudged by the guideline committee to be the most representative of current clinical practice.

In the majority of the comparisons considered in the analysis, interventions have been compared against surgery alone. In these cases, five-year overall and disease free survival estimates of 30.2% and 27.9%, respectively have been used as the baseline estimates for the surgery arm (Shapiro et al. 2015). RR estimates for the respective comparators are then applied to this baseline data. For overall survival, RR estimates of 1.42, 2.08 and 1.39 were applied for chemoradiotherapy plus surgery, chemoradiotherapy and chemotherapy plus surgery, respectively. For progression free survival, RR estimates of 1.69, 1.73 and 2.09 were applied for chemoradiotherapy plus surgery, chemoradiotherapy and chemotherapy plus surgery, respectively.

For the comparison of chemoradiotherapy plus surgery in comparison to chemotherapy plus surgery, three-year overall and disease free survival estimates of 68.3% and 61.0%, respectively have been used as the baseline estimates for the chemoradiotherapy plus surgery arm (Shapiro et al. 2015). Note that three year data has been used for this comparison to match the time point for the observed treatment effect. Survival outcomes for chemotherapy plus surgery were estimated using RR estimates of 0.79 and 0.93 for overall and disease free survival, respectively.

Note that due to uncertainty and inconsistency in the overall and disease free survival estimates, the estimated disease free survival was sometimes higher than the overall survival estimate. Since such a scenario is implausible, it was assumed that disease free survival was equal to overall survival in these instances. Note that this scenario reflects the high level of uncertainty around the effect estimates and that this uncertainty is likely to be reflected in the results of the economic analysis.

Mortality from other causes was captured using 2013-2015 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. A starting age of 60 and a male proportion of 78.1% were applied in the model based on averages reported in Shapiro et al. 2015 for the chemoradiotherapy plus surgery and surgery alone arms. The other cause mortality esimates were used in conjunction with the overall survival estimates above to estimate the proportion of patients that died of disease-specific and other causes.

I.2.5 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 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) 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 guideline committee.

I.2.5.1 Surgery costs

Surgery costs were estimated using the cost of a 'very complex, oesophageal, stomach or duodenum procedure' (FZ80) in NHS reference costs 2015/16. The table below details this cost, which varies according to complications and co-morbidities. A weighted average across the complication and co-morbidity scores was estimated for use in the economic model, weighted by the number of recorded procedures in NHS reference costs.

Table 29: Surgery costs

Procedure	Proportion*	Cost	Source
Very complex, oesophageal, stomach or duodenum procedure, 19 years and over (FZ80)			
with CC score 6+	18%	£18,934.89	NHS Reference costs 2015/16
with CC score 3-5	22%	£11,700.19	NHS Reference costs 2015/16
with CC score 0-2	60%	£8,439.60	NHS Reference costs 2015/16
Weighted average		***£11,057.41***	

*Based on number of recorded procedures in NHS Reference costs

I.2.5.2 Radiotherapy costs

The table below shows the estimated cost of radiotherapy. The cost of radiotherapy preparation and delivery (per fraction) were sourced from NHS Reference costs 2015/16. It was assumed that 23 fractions of radiotherapy would be delivered in the average radiotherapy regimen. The estimated cost of radiotherapy treatment was £3,563.59.

Table 30: Estimated radiotherapy costs

Cost item	Value	Source
Preparation for complex conformal radiotherapy (SC51Z)	£654.57	NHS Reference costs 2015/16
Deliver a fraction of complex treatment on a megavoltage machine (SC23Z)	£126.48	NHS Reference costs 2015/16

Cost item	Value	Source
Number of fractions	23	
Total	**£3,563.59**	

I.2.5.3 Chemotherapy costs

The table below details the average cost of chemotherapy per cycle. The average cost was based upon the cost of the five chemotherapy regimens which were most likely to be used (as identified by the guideline committee). The chemotherapy delivery costs were sourced from NHS Reference Costs 2015/16 and drug costs were sourced from eMit. It can be seen that the chemotherapy costs per cycle were similar for each of the regimens and the average cost per cycle was estimated to be £824.68.

When used in conjunction with surgery, it was assumed that two cycles of chemotherapy would be administered at a cost of £1,649.36. When used in conjunction with radiotherapy, it was assumed that four cycles of chemotherapy would be administered at a cost of £3,298.73. When used as monotherapy (following a recurrence) it was assumed that six cycles of chemotherapy would be administered at a cost of £4,948.09.

Table 31: Estimated chemotherapy costs per cycle

Treatment	Cost	Source
Cisplatin and FU		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Cisplatin	£26.60	eMit
Fluorouracil 750mg/m2 days 1-5	£10.34	eMit
Cost per cycle	**£804.60**	
Carboplatin and paclitaxel		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Carboplatin AUC 2 weekly x 5 (days 1,8,15,22,29)	£55.95	eMit
Paclitaxel 50mg/m2 weekly x 5 (days 1,8,15,22,29)	£42.50	eMit
Cost per cycle	**£866.12**	
Cisplatin and capecitabine		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Cisplatin 60mg/m2 on day 1 of cycle	£12.46	eMit
Capecitabine 625mg/m2 twice daily (days 1-21)	£24.65	eMit
Cost per cycle	**£804.78**	
Carboplatin and capecitabine		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Carboplatin AUC 5 on day 1 of cycle	£21.65	eMit

Treatment	Cost	Source
Capecitabine 625mg/m2 twice daily (days 1-21)	£24.65	eMit
Cost per cycle	**£813.97**	
Oxaliplatin and capecitabine		
Deliver Complex Chemotherapy, incl. Prolonged Infusional Treatment, at First Attendance (SB14Z)	£406.63	NHS Reference costs 2015/16
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£361.04	NHS Reference costs 2015/16
Oxaliplatin dose 130mg/m2 on day 1	£41.62	eMit
Capecitabine 625mg/m2 twice daily (days 1-21)	£24.65	eMit
Cost per cycle	**£833.94**	

Chemotherapy and chemoradiotherapy morbidity costs were estimated based on morbidity data from the CROSS trial, which showed that 22.8% of patients experience events of grade ≥3 during chemoradiotherapy. It was assumed that the cost of an adverse event would be £121.88, which is equal to the cost of a 'consultant led face to face follow-up attendance' (WF01A) in 'Upper Gastrointestinal Surgery' from NHS Reference Costs 2015/16.

I.2.5.4 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. The table below details the palliative care cost applied in the model.

Table 32: Estimated palliative care cost per patient in the last three months of life

Type of care	Average cost per cancer patient	Source
Cost of all hospital contacts	£5,890	Exploring the cost of care at the end of life (Nuffield Trust, Georghiou 2014)
Local authority-funded care	£444	
District nursing care	£588	
GP contacts	£365	
Average palliative care cost per patient	**£7,287**	

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

I.2.6 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.

QoL values were estimated using data from Graham et al. 2007, a cost-effectiveness analysis of treatments for locally advanced oesophageal cancer (including adenocarcinoma and squamous cell carcinoma). As part of the analysis, QoL values were estimated for surgical and multi-modal treatments at various time points. For the present analysis it was assumed that the pre-treamtent values would best represent the QoL value with disease while the post-treatment value would best represent the QoL value for patients that are disease-free. A QoL value of 0.595 was applied for patients with disease, based on the average of the QoL values at 0 to 6 months in patients treated with surgery (0.630) and

multimodal treatment (0.560). A QoL value of 0.650 was applied for patients that are disease-free, based on the average of the QoL values at 6 to 12 months in patients treated with surgery (0.670) and multimodal treatment (0.630).

I.3 Results

I.3.1 Base case results

The base case results of the analysis are presented in the tables below. It can be seen that chemoradiotherapy and surgery was found to more costly (£6,511) and more effective (0.48 QALYs) than surgery alone and resulted in an ICER of £13,704 per QALY. Therefore chemoradiotherapy and surgery was deemed to be cost-effective in comparison to surgery alone as this value is below the NICE threshold of £20,000 per QALY. Chemoradiotherapy and surgery was found to be more costly (£5,021) and more effective (0.34 QALYs) than chemotherapy and surgery and resulted in an ICER of £14,940 per QALY. Therefore chemoradiotherapy and surgery was deemed to be cost-effective in comparison to chemotherapy and surgery as this value is lower than the NICE threshold of £20,000 per QALY. Chemoradiotherapy was found to be less costly (£4,916) and more effective (1.48 QALYs) than surgery alone. Therefore chemoradiotherpy was considered to be dominant in comparison to surgery alone. Chemotherapy and surgery was found to be more costly (£1,326) and more effective (0.44 QALYs) than surgery alone and resulted in an ICER of £3,025 per QALY. Therefore chemotherapy and surgery was deemed to be cost-effective in comparison to surgery alone as this value is below the NICE threshold of £20,000 per QALY..

Table 33: Base case results for chemoradiotherapy and surgery in comparison to surgery alone

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Surgery	£17,655	-	4.33	-	**-**
ChemoRT + surgery	£24,166	*£6,511*	4.81	*0.48*	**£13,704**

Table 34: Base case results for chemoradiotherapy and surgery in comparison to chemotherapy and surgery

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Chemo + surgery	£19,145	-	4.47	-	**-**
ChemoRT + surgery	£24,166	*£5,021*	4.81	*0.34*	**£14,940**

Table 35: Base case results for chemoradiotherapy in comparison to surgery

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Surgery	£17,655	-	4.33	-	**-**
ChemoRT	£12,739	*-£4,916*	5.81	*1.48*	**Dominant**

Table 36: Base case results for chemotherapy and surgery in comparison to surgery alone

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Surgery	£17,655	-	4.33	-	**-**

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Chemo+surgery	£18,981	*£1,326*	4.77	*0.44*	**£3,025**

I.3.2 Deterministic 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.

It can be seen that the conclusion of the analysis remains unchanged in the majority of modelled scenarios. Notable exceptions are the scenarions in which the lower RR estimates are applied for overall survival outcomes.

Table 37: Deterministic sensitivity analysis results

Change made	ChemoRT+surgery vs surgery	ChemoRT+surgery vs chemo+surgery	ChemoRT vs surgery	Chemo+surgery vs surgery
Base case	**ChemoRT+surgery**	**ChemoRT+surgery**	**ChemoRT**	**Chemo+surgery**
Upper RR for OS	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Lower RR for OS	Surgery	Chemo+surgery	ChemoRT	Surgery
Upper RR for DFS	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Lower RR for DFS	ChemoRT+Surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Upper RR for OS and DFS	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Lower RR for OS and DFS	Surgery	Chemo+surgery	ChemoRT	Surgery
Disease free QoL = 0.700	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Disease free QoL = 0.595	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Lower QoL for patients treated with chemo or chemoRT +surgery	Surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
ChemoRT or chemo morbidity + 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
ChemoRT or chemo morbidity - 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
ChemoRT or chemo morbidity cost + 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
ChemoRT or chemo morbidity cost - 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Chemotherapy cost + 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery

Change made	ChemoRT+surgery vs surgery	ChemoRT+surgery vs chemo+surgery	ChemoRT vs surgery	Chemo+surgery vs surgery
Chemotherapy cost - 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Radiotherapy cost + 50%	ChemoRT+surgery	Chemo+surgery	ChemoRT	Chemo+surgery
Radiotherapy cost - 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Surgery cost + 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Surgery cost - 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Palliative care cost + 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery
Palliative care cost - 50%	ChemoRT+surgery	ChemoRT+surgery	ChemoRT	Chemo+surgery

I.3.3 Probabilistic sensitivity results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using ICER scatterplots and cost-effectiveness acceptability curves (CEAC) in figure 3 and figure 4, respectively. The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

The figures below show the ICER scatterplot and CEAC for chemoradiotherapy and surgery in comparison to surgery alone. From the ICER scatterplot, it can be seen that the majority of the results reside in the North East quadrant of the scatterplot, indicating that chemoradiotherapy and surgery is more effective and more costly than surgery in most analyses. The CEAC shows that the probability of chemoradiotherapy and surgery being cost-effective increases as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, chemoradiotherapy and surgery was found to have a 66% probability of being cost-effective while surgery alone had a 34% probability of being cost-effective.

Figure 17: ICER scatterplot for chemoradiotherapy and surgery in comparison to surgery alone

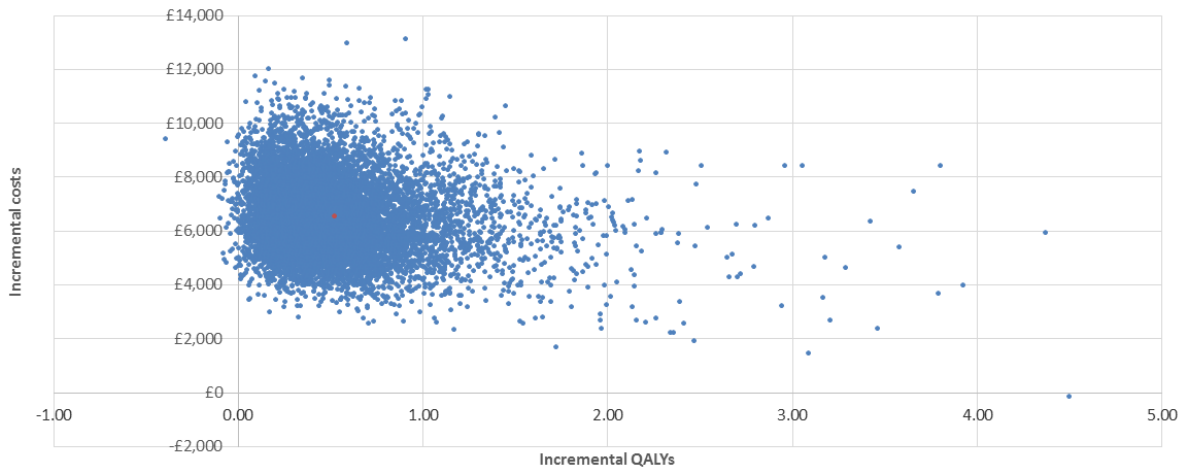
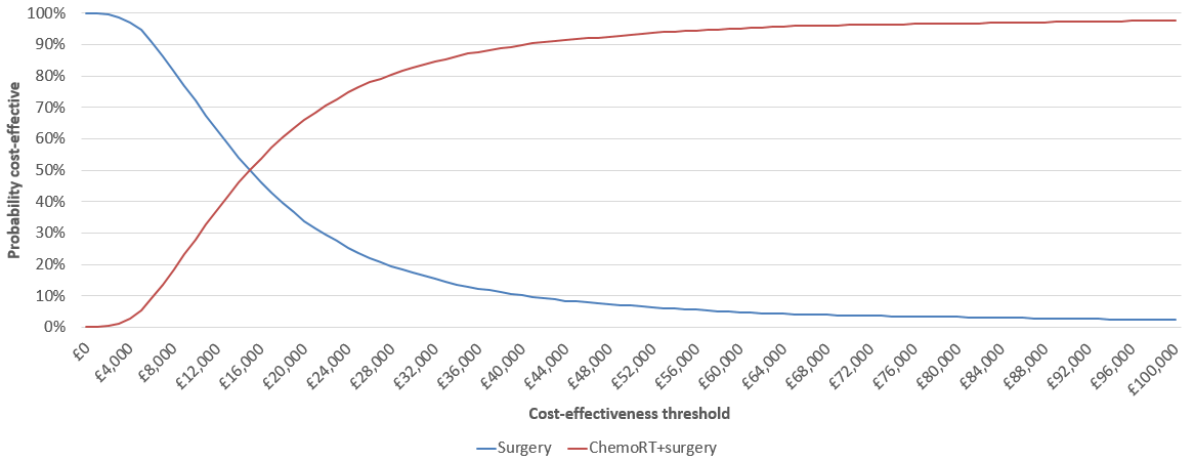


Figure 18: CEAC for chemoradiotherapy and surgery in comparison to surgery alone



The figures below show the ICER scatterplot and CEAC for chemoradiotherapy and surgery in comparison to chemotherapy and surgery. From the ICER scatterplot, it can be seen that the majority of the results reside in the North East quadrant of the scatterplot, indicating that chemoradiotherapy and surgery is more effective and more costly than chemotherapy and surgery in most analyses. The CEAC shows that the probability of chemoradiotherapy and surgery being cost-effective increases as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, chemoradiotherapy and surgery was found to have a 51% probability of being cost-effective while chemotherapy and surgery had a 49% probability of being cost-effective.

Figure 19: ICER scatterplot for chemoradiotherapy and surgery in comparison to chemotherapy and surgery

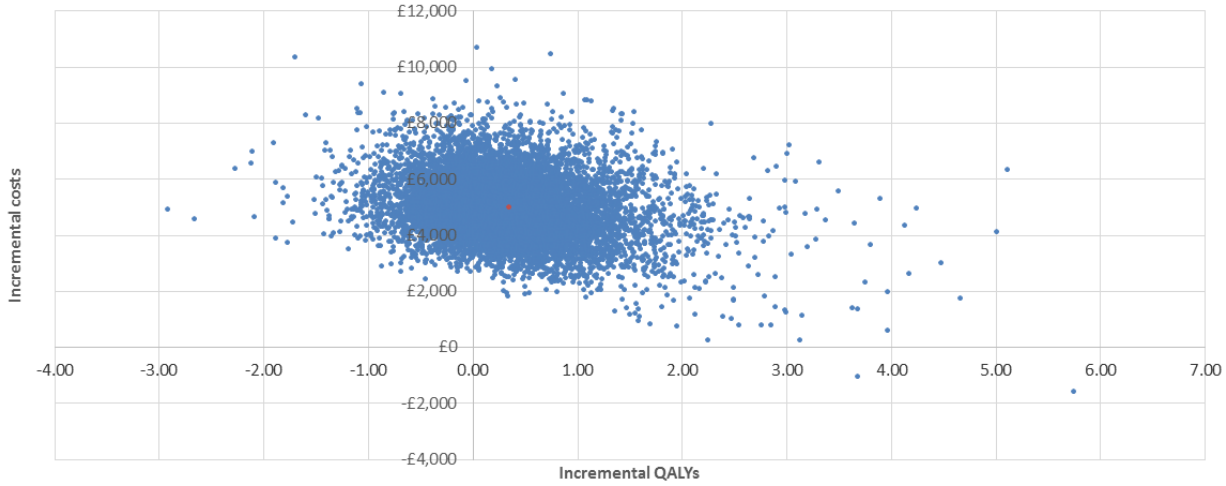
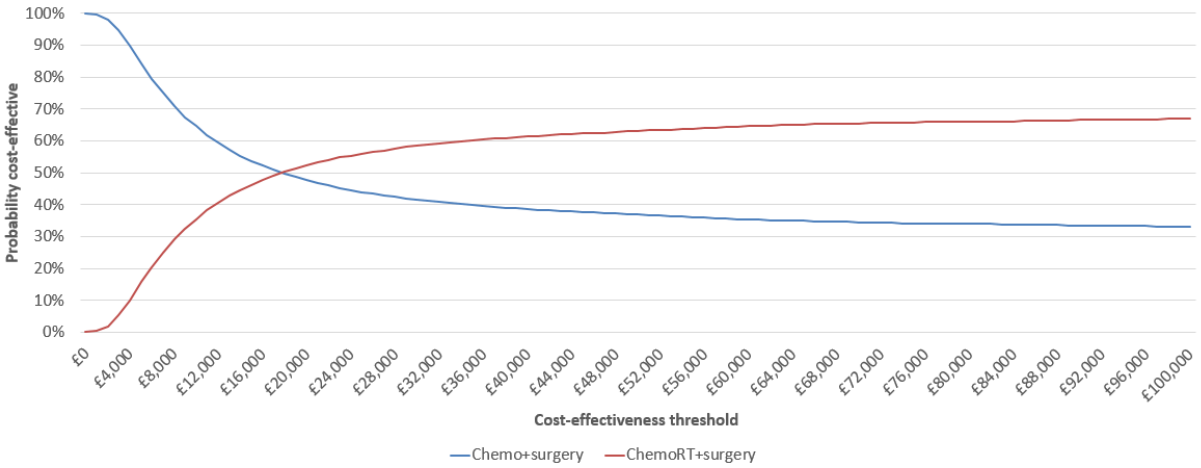


Figure 20: CEAC for chemoradiotherapy and surgery in comparison to chemotherapy and surgery



The figures below show the ICER scatterplot and CEAC for chemoradiotherapy in comparison to surgery. From the ICER scatterplot, it can be seen that the majority of results reside in the South East quadrant showing that chemoradiotherapy is dominant in the majority of modelled scenarios. The CEAC shows that the probability of chemoradiotherapy being cost-effective remains fairly constant as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, chemoradiotherapy was found to have a 98% probability of being cost-effective while surgery had a 2% probability of being cost-effective.

Figure 21: ICER scatterplot for chemoradiotherapy in comparison to surgery

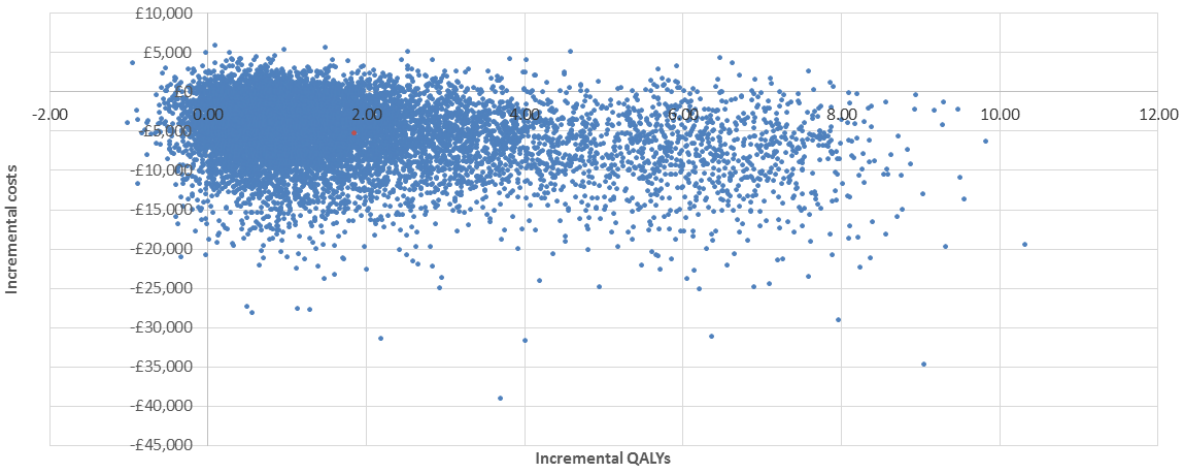
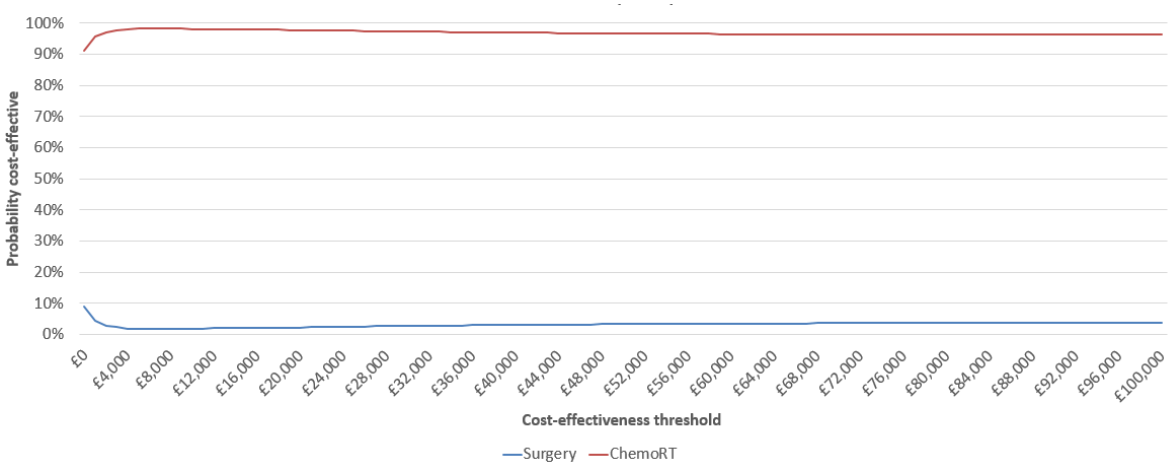


Figure 22: CEAC for chemoradiotherapy in comparison to surgery



The figures below show the ICER scatterplot and CEAC for chemotherapy and surgery in comparison to surgery alone. From the ICER scatterplot, it can be seen that the majority of results reside in the North East quadrant showing that chemotherapy and surgery was more effective and more costly than surgery in the majority of modelled scenarios. The CEAC shows that the probability of chemotherapy and surgery being cost-effective increases as the cost-effectiveness threshold increases and becomes fairly constant above £20,000 per QALY. At the NICE threshold of £20,000 per QALY, chemotherapy and surgery was found to have a 73% probability of being cost-effective while surgery had a 27% probability of being cost-effective.

Figure 23: ICER scatterplot for chemotherapy and surgery in comparison to surgery alone

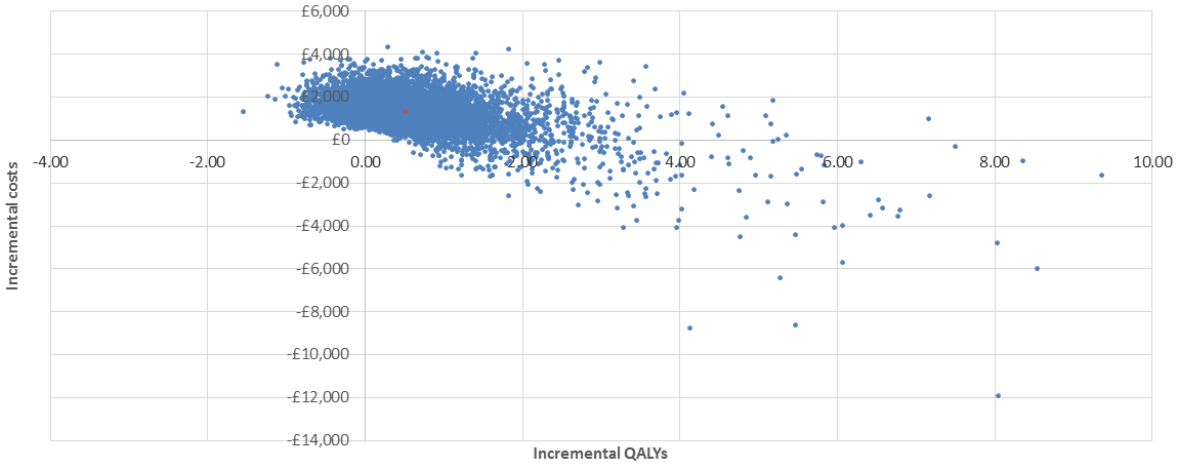
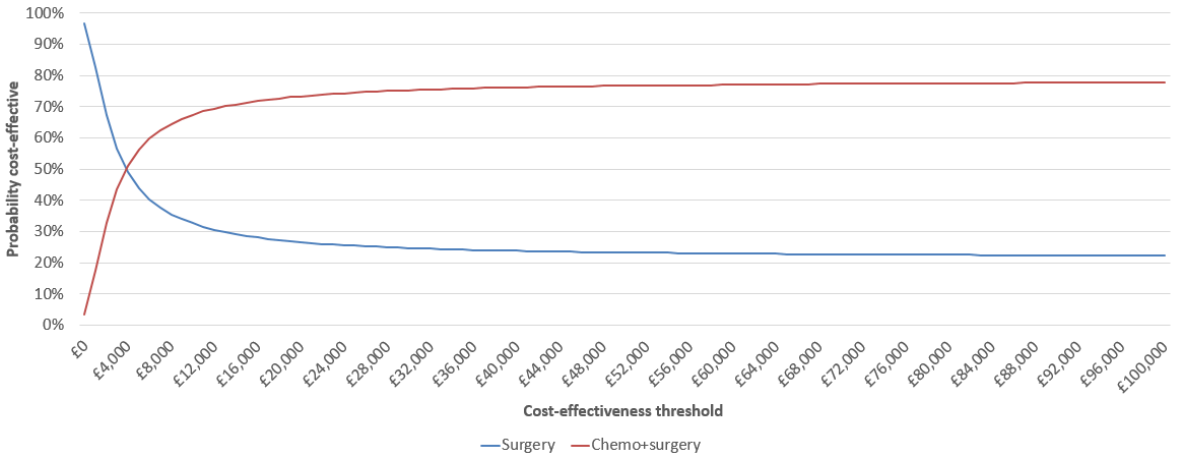


Figure 24: CEAC for chemotherapy and surgery in comparison to surgery alone



I.3.4 Probabilistic base case results

In addition to the deterministic results presented above (in section I.3.1), 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. The probabilistic base case results are presented in the tables below.

Overall, the results did not differ substantially from the results in the deterministic base case analysis with the conclusions of the analysis unchanged..

Table 38: Base case results for chemoradiotherapy and surgery in comparison to surgery alone

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Surgery	£17,672	-	4.31	-	-
ChemoRT + surgery	£24,285	*£6,613*	4.83	*0.51*	**£12,853**

Table 39: Base case results for chemoradiotherapy and surgery in comparison to chemotherapy and surgery

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Chemo + surgery	£19,252	-	4.49	-	-
ChemoRT + surgery	£24,285	*£5,033*	4.83	*0.33*	**£15,120**

Table 40: Base case results for chemoradiotherapy in comparison to surgery alone

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Surgery	£17,672	-	4.31	-	-
ChemoRT	£12,479	*-£5,192*	6.12	*1.81*	**Dominant**

Table 41: Base case results for chemotherapy and surgery in comparison to surgery alone

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Surgery	£17,672	-	4.31	-	-
Chemo+surgery	£19,005	*£1,333*	4.83	*0.52*	**£2,587**

I.4 Discussion

The aim of the analysis was to estimate the cost-effectiveness of treatments for squamours cell carcinoma of the oesophagus. However, due to a lack of evidence, it was not possible to directly compare all the interventions against each other. The analysis therefore took the form of pairwise comparisons, which limits the conclusions that can be drawn.

The results of the base case analysis suggest that chemoradiotherapy and surgery was cost-effective in comparison to surgery alone with an ICER of £13,704 per QALY below the NICE threshold of £20,000 per QALY. Chemotherapy and surgery was also found to be cost-effective in comparison to surgery alone with an ICER of £3,025 per QALY. When comparing chemoradiotherapy and surgery against chemotherapy and surgery, chemoradiotherapy and surgery was found to be cost-effective with an ICER of £14,940 per QALY. Chemoradiotherapy was found to be less costly and more effective than surgery alone and was therefore dominant.

In deterministic sensitivity analysis, it was found that the conclusion of the analyses remained unchanged in the majority of modelled scenarios. The most notable excpetion was where the lower RR estimate was applied for overall survival outcomes. In the probabilistic sensitivity analysis it was found that, in comparison to surgery alone, chemoradiotherapy and surgery had a 66% probability of being cost-effective at the NICE threshold of £20,000 per QALY. Chemotherpay and surgery was found to have a 73% probability of being cost-effective in comparison to surgery. When comparing chemoradiotherapy and surgery against chemotherapy and surgery, chemoradiotherapy and surgery was found to have a 51% probability of being cost-effective while chemotherapy and surgery had a 49% probability of being cost-effective. In the comparison between chemoradiotherapy and surgery and surgery alone, chemoradiotherapy was found to have a very high probability of being cost-effective (98%).

While these results were of some interest, they were not thought to have practice changing implications. Indeed, the results essentially confirm that the two strategies that are most likely to be used in current practice; chemoradiotherapy or chemoradiotherapy plus surgery, are cost-effective in comparison to alternative treatments. However, there is some uncertainty around the results, particularly in regard to the comparison between chemotherapy and surgery and chemoradiotherapy and surgery.

There are also some limitations to the analysis that should be discussed. Firstly, it should be acknowledged that the analysis has not accompished its primary aim, which was to compare chemoradiotherapy and surgery to chemoradiotherapy. It was not possible to make a meaningful comparison between the two strategies because the current evidence base was thought to be insufficient. Arguably, a mixed treatment comparison could have been undertaken but it was thought that there was too much hetereogneity in the populations to make a meaningful comparison. Specifically, patients receiving chemoradiotherapy and surgery are generally fitter than patients receiving chemoradiotherapy alone.

A further limitation was around the QoL values applied in the analysis. As if often the case, it was found that there is a paucity of data that could be used to inform QoL values in the analysis. Therefore the model was heavily reliant upon the QoL data used in a cost-effectiveness analysis by Graham et al. 2007 coupled with some assumptions in-order to re-

purpose them for this analysis. Perhaps, most notably, it was assumed that the QoL values associated with being 'disease free' and 'with disease' did not vary by treatment. It is possible that some of the modalities might have more of a QoL impact. In particular, the addition of chemoradiotherpy or chemotherapy to surgery might carry an additional QoL impact when compared to surgery alone. Therefore, a sensivity analysis was conducted to estimate the impact of assuming a lower QoL value in these patients (using the multimodal QoL scores from Graham et al. 2007). In this scenario, it was found that chemotherapy and surgery was no longer cost-effective in comparison to surgery alone (although the result was marginal as the ICER was only slightly above £20,000 per QALY).

I.5 Conclusion

The analyses suggest that chemoradiotherapy and surgery was cost-effective in comparison to both surgery alone and chemotherapy plus surgery. The analysis also showed that chemoradiotherapy alone was cost-effective in comparison to surgery alone. Thus, essentially, the analysis confirms that the two approaches most likely to be used in current clinical practice are preferred against other treatment options.

Ideally, the analysis would have considered the comparison between chemoradiotherapy and surgery versus chemoradiotherapy alone. Indeed, the guideline committee identified this as the key comparison of interest in the analysis. However, there was insufficient clinical evidence to model this comparison in any meaningful way. Therefore, further research is required to address the aspect of the decision problem that is of most interest to clinical practice.