

# Oesophago-gastric cancer: assessment and management in adults

## Appendix L

*Clinical Guideline*

*Cost-effectiveness analyses*

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*Developed by the National Guideline Alliance, hosted  
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Gynaecologists*



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# Appendix L: Health economic evidence review

## I.1 Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO
- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

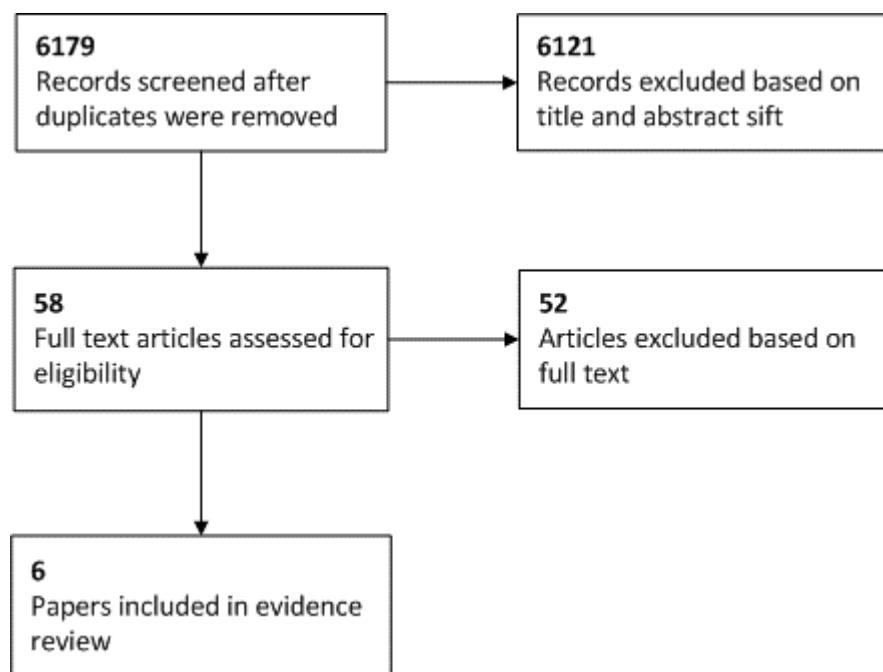
## I.2 Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

## I.3 Results

The diagram below shows the search results and sifting process.

**Figure 1:** Summary of health-economic evidence search and sifting process



It can be seen that 6,179 possibly relevant papers were identified. Of these, 6,121 papers were excluded at the initial sifting stage based on the title and abstract while 58 full papers were obtained for appraisal. A further 52 papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, six papers were included in the systematic review of the economic evidence; Hisashige et al. 2016, Lam et al. 2016, Meads et al. 2015, Lee et al. 2013, Rao et al. 2009 and Wang et al. 2008. All six studies included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

The identified studies were applicable to four review questions in the guideline. The applicable studies under each of these review questions are described in the relevant sections below.

## **I.4 Gastric Cancer**

**Review question: What is the optimal choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for gastric cancer?**

### **I.4.1 Evidence statement**

The base case results of Hisashige et al. 2016 showed that, in comparison to surgery alone, the addition of adjuvant chemotherapy provided one additional QALY at a cost of \$3,016. In probabilistic and deterministic sensitivity analysis, the addition of adjuvant chemotherapy was found to be cost-effective in most modelled scenarios.

The base case results of Wang et al. 2008 showed that, in comparison to surgery alone, the addition of adjuvant chemoradiotherapy provided one additional QALY at a cost of \$38,400. In probabilistic sensitivity analysis, the addition of adjuvant chemoradiotherapy was found to have a 67% probability of being cost-effective at a threshold of \$50,000 per QALY.

Overall, the analyses can be considered to show the potential cost-effectiveness of chemotherapy or chemoradiotherapy in addition to surgical treatment. However, decisive conclusions could not be drawn because the analyses were only partially applicable to the decision problem in the UK setting as they were based on the health care perspective of Japan and the United States. Furthermore, some potentially serious limitations were identified including the use of assumptions to quantify changes in QoL.

**Table 1: Summary table showing the included health economic evidence for the optimal choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for gastric cancer**

Study	Population	Comparators:	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Hisashige et al. 2016	Patients with completely resected stage II/III gastric Cancer.	S-1 therapy	\$13,057	8.65 QALYs	Reference standard			A Series of one- and two-way sensitivity analysis were conducted including variations in recurrence rate, utility values, acquisition costs and recurrence costs. Changes in the ICER value were minimal in all modelled scenarios.  S-1 therapy was found to be preferred in most modelled runs in the probabilistic sensitivity analysis (PSA). It was reported that at a threshold of \$6,220 per QALY, S-1 therapy has a 95% probability of being cost-effective.	The evaluation was deemed to be only partially applicable as it considered the Japanese health care system.  Potentially serious limitations were identified in the QoL data applied in the analysis, which were sometimes based on assumptions.
		Surgery alone	\$9,346	7.41 QALYs	\$3,722	1.24 QALYs	\$3,016 per QALY		
<b>Comments:</b> Study takes the perspective of the health care service in Japan. Costs are presented in US dollars.									
Wang et al. 2008	Patients with resectable adenocarcinoma of the stomach or gastroesophageal junction.	Chemoradiation	\$20,100	2.25 QALYs	Reference standard			Series of one- sensitivity analysis were conducted. It was found that variations in survival benefit, utility for gastrectomy and the cost of toxicity management had the greatest effect on the ICER.  In probabilistic sensitivity analysis, the addition of chemoradiation to surgery was found to have a 67% probability	The evaluation was deemed to be only partially applicable as it considered the US health care system.  Potentially serious limitations were identified in the QoL data applied in the analysis, which were sometimes drawn
		Surgery alone	-	1.72 QALYs	\$20,100	0.53 QALYs	\$38,400 per QALY		



Study	Population	Comparators:	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
								of being cost-effective at a threshold of \$50,000 per QALY.	from studies using non-generic measures, which necessitated assumptions to derive utility values. Some of the QoL data were also from different settings.
Comments: Study takes the perspective of the US healthcare system. Costs are presented in US dollars.									

## **I.5 Surgical treatment of oesophageal cancer**

**Review question: What is the most effective operative approach for the surgical treatment of oesophageal cancer?**

### **I.5.1 Evidence statement**

Lee et al. 2013 compared the short-term cost and QALY consequences of minimally invasive and open surgical approaches from the Canadian health care perspective. The minimally invasive approach was estimated to be more costly initially due to equipment costs and a longer operative time but 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').

However, the analysis was deemed to be only partially applicable to the decision problem in the UK setting as it was based on the perspective of the Canadian health care perspective. Furthermore some potentially serious limitations were identified with the analysis. Most notably the uncertainty around treatment effects was not fully captured in the probabilistic sensitivity analysis because event probabilities were varied individually rather than using a relative effect estimate (such as a relative risk). Overall, it was considered that the planned de novo economic analysis conducted for this guideline would still be required in order to adequately assess cost-effectiveness from the perspective of the NHS.

**Table 2: Summary table showing the included health economic evidence for the most effective operative approach for the surgical treatment of oesophageal cancer**

Study	Population	Comparators:	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Lee et al. 2013	Patients with resectable oesophageal cancer	Open surgery	\$47,533	0.601 QALYs	Reference standard			One-way and two-way deterministic sensitivity analyses were conducted. The analyses showed that differences in overall and intensive care unit length of stay were important determinants in the cost-effectiveness outcome.	The analysis was considered to be only partially applicable as it considered the Canadian health care system.
		Minimally invasive surgery	\$45,892	0.623 QALYs	-\$1,641	-0.022 QALYs	Dominant	Probabilistic sensitivity analysis was also conducted. It was shown that at, at a cost-effectiveness threshold of \$50,000/QALY, minimally invasive surgery was found to have a 77% probability of being cost-effective.	Some potentially serious limitations were also identified. Most notably, the uncertainty around treatment effects was not fully captured in the probabilistic sensitivity analysis. There was also a possibility that the quality of life benefits associated with the minimally invasive approach were overestimated in the analysis.
Comments: Analysis performed from the perspective of the Canadian healthcare perspective with costs reported in Canadian dollars (\$).									

## I.6 Second-line palliative chemotherapy

**Review question: What is the optimal palliative second-line chemotherapy for locally-advanced or metastatic oesophago-gastric cancer?**

### I.6.1 Evidence statement

The base case results of Lam et al. 2016 showed that, in cost-effectiveness terms, all chemotherapy regimens were preferred to palliative care with Irinotecan found to be the most cost-effective of the chemotherapy regimens.

The base case results of Meads et al. 2015 showed that, in comparison to active symptom control alone, the addition of docetaxel provided one additional QALY at a cost of £27,180. In probabilistic sensitivity analysis (PSA), the addition of docetaxel was found to have a 26% probability of being cost-effective at a threshold of £20,000 per QALY. At an increased threshold of £50,000 per QALY (applicable for treatments that meet the end of life criteria), docetaxel was found to have a 90% probability of being cost-effective.

The analysis by Lam et al. 2016 suggests that chemotherapy may be a cost-effective alternative to palliative care. However the analysis was only partially applicable to the decision problem in the UK setting as they were based on the health care perspective of the United States. Furthermore, some potentially serious limitations were identified in the analysis. The evidence used to inform the analysis was not identified through a systematic literature search and so it is possible that some useful data may have been missed. There were also concerns that the uncertainty around effectiveness estimates may have been underestimated in the probabilistic sensitivity analysis because event probabilities were varied individually (by  $\pm 25\%$ ) rather than using evidence based variations in relative effect estimates (such as a relative risk).

The analysis by Meads et al. 2015 suggests that docetaxel is not a cost-effective addition to active symptom control when considering the typical threshold of £20,000 per QALY. If the treatment was deemed to meet the end of life criteria, then the addition of docetaxel may be considered cost-effective at an increased threshold of £50,000 per QALY. However, some potentially serious limitations were identified in the analysis (including uncertainty around some of the cost estimates).

Overall, the analyses indicate that chemotherapy may be cost-effective in this setting but further research is required before drawing decisive conclusions.

**Table 3: Summary table showing the included health economic evidence for the optimal palliative second-line chemotherapy for locally advanced or metastatic oesophago-gastric cancer**

Study	Population	Comparator s:	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Lam et al. 2016	Patients with metastatic gastric cancer who have failed previous chemotherapy.	Irinotecan	\$39,264	0.35 QALYs	-			Series of one way sensitivity analysis were conducted on for the non-dominated strategies. It was found that the ICER for paclitaxel remained above a cost-effectiveness threshold of \$50,000 per QALY in the majority of analyses.  Probabilistic sensitivity analysis (PSA) was conducted. At a cost-effectiveness threshold of \$50,000 per QALY, irinotecan was found to have an 83% probability of being cost-effective.	The analysis was only partially applicable as it considered the US healthcare setting.  Potentially serious limitations were identified in the analysis, including the use of non-systematic searches to inform model inputs and a potential underestimate of uncertainty in the PSA.
		Docetaxel	\$47,244	0.37 QALYs	\$7,980	0.02 QALYs	Extended dominated		
		Paclitaxel	\$48,322	0.45 QALYs	\$9,058	0.10 QALYs	\$86,815		
		Palliative care	\$54,267	0.20 QALYs	\$15,003	-0.15 QALYs	Dominated		
Comments: Ramucirumab was included as an intervention in the analysis but has been excluded from consideration here as the cost-effectiveness of ramucirumab has already been assessed as part of a NICE technology appraisal (NICE TA378).									
Meads et al. 2015	Patients with refractory oesophagogastric adenocarcinoma.	Active symptom control	£6,218	0.186 QALYs	Reference standard			Series of deterministic sensitivity analysis were conducted (mostly involving varying inputs by 20%). Most of the analyses were found to have only a modest effect on the ICER.	Analysis was considered directly applicable since it considered the perspective of the UK NHS.

Study	Population	Comparators:	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
		Docetaxel and active symptom control	£9,352	0.302 QALYs	£3,134	0.116 QALYs	£27,180	In probabilistic sensitivity analysis (PSA), the addition of docetaxel was found to have a 26% probability of being cost-effective at a threshold of £20,000 per QALY. At an increased threshold of £50,000 per QALY (applicable for treatments under the end of life criteria), docetaxel was found to have a 90% probability of being cost-effective	Potential limitations were identified in the estimation of costs and a potential conflict of interest was identified as one of the authors received funding from the drug manufacturer.
Comments:									

## I.7 Luminal obstruction

**Review question: What is the optimal management of luminal obstruction for adults with oesophago-gastric cancer not amenable to treatment with curative intent?**

### I.7.1 Evidence statement

The base case results of Rao et al. 2009 showed that covered self-expanding metal stents were cost-effective and indeed dominant (i.e. less costly and more effective) in comparison to uncovered self-expanding metal stents and plastic stents. Probabilistic sensitivity analysis showed that at all thresholds below \$200,000 per QALY, there was a 97% probability that covered SEMS were more cost-effective than uncovered SEMS.

The analysis was deemed to be directly applicable to the decision problem in the UK setting as it was based on the health care perspective of the NHS. However, costs were converted from UK pound sterling (£) and presented in US dollars (\$). Some potentially serious limitations were identified in the analysis including the absence of deterministic sensitivity analyses and a potential conflict of interest for one of the study authors. There was also a concern that uncertainty had been underestimated in the probabilistic sensitivity analysis since triangular distributions were used for all parameters and effectiveness estimates were parameterised using variations in absolute effects rather than relative effects. Most notably, the clinical effectiveness estimates on which the analysis was based were drawn from a meta-analysis of randomised and non-randomised data. Given the lack of randomised data in this area, it is likely that the meta-analysis was primarily informed by non-randomised data thereby limiting the validity of the effectiveness estimates.

Overall, the analysis can be considered to show the potential cost-effectiveness of self-expanding metal stents over plastic stents. Furthermore, the analysis suggested that covered self-expanding metal stents are preferable (in cost-effectiveness terms) to uncovered self-expanding stents. However, given the potential limitations of the analysis, it is difficult to draw decisive conclusions.

**Table 4: Summary table showing the included health economic evidence for the optimal management of luminal obstruction for adults with oesophago-gastric cancer not amenable to treatment with curative intent**

Study	Population	Comparators:	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Rao et al. 2009	Patients with oesophageal cancer unsuitable for curative resection that require palliative stenting for dysphagia.	Covered self-expanding metal stent (SEMS)	\$4,498.69	0.3535 QALYs	Reference standard			Deterministic sensitivity analyses were not conducted.	The analysis was considered to be directly applicable as it considered the UK health care system. However, the costs were presented in US dollars.  Potentially serious limitations were identified including the lack of deterministic sensitivity analysis and an underestimation of uncertainty in the PSA. Furthermore, the effectiveness data on which the analysis was based was drawn from non-randomised data.  A potential conflict of interest was identified by one of the authors.
		Uncovered self-expanding metal stent (SEMS)	\$5,226.27	0.3522 QALYs	\$729.58	-0.0013 QALYs	Dominated	In probabilistic sensitivity analysis, it was shown that at all thresholds below \$200,000 per QALY, there was a 97% probability that covered SEMS were more cost-effective than uncovered SEMS. It was also shown that that there was a 99% probability that both types of SEMS were more cost-effective than plastic stents at all thresholds below \$150,000 per QALY.	
		Plastic stent	\$8,058.92	0.3324 QALYs	\$3,560.23	-0.0211 QALYs	Dominated		
Comments: Analysis performed from the perspective of the UK NHS. Costs were converted from UK pound sterling (£) are reported in US dollars (\$).									





## I.8 Included economic studies

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Lam, S.W., et al., Cost-Effectiveness Analysis of Second-Line Chemotherapy Agents for Advanced Gastric Cancer. *Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy*, 2017. 37(1): p. 94-103.

Lee, L., et al. Cost-effectiveness of minimally invasive versus open esophagectomy for esophageal cancer (Provisional abstract). *Annals of Surgical Oncology*, 2013. 20, 3732-3739.

Meads, D.M., et al., The Cost Effectiveness of Docetaxel and Active Symptom Control versus Active Symptom Control Alone for Refractory Oesophagogastric Adenocarcinoma: Economic Analysis of the COUGAR-02 Trial. *Pharmacoeconomics*, 2016. 34(1): p. 33-42.

Rao, C., et al., Economic analysis of esophageal stenting for management of malignant dysphagia. *Diseases of the Esophagus*, 2009. 22(4): p. 337-347.

Wang, S.J., et al., A cost-effectiveness analysis of adjuvant chemoradiotherapy for resected gastric cancer. *Gastrointestinal Cancer Research*, 2008. 2(2): p. 57-63.

## I.9 Excluded economic studies

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Balachandrakumar, V., et al., Day case oesophageal self expanding metallic stent (SEMS) placement is safe and saves bed days. *Gut*, 2015. 64: p. A207-A208.

Birch, J.F., et al., A cost-benefit comparison of self-expanding metal stents and Atkinson tubes for the palliation of obstructing esophageal tumors. *Diseases of the Esophagus*, 1998. 11(3): p. 172-176.

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