Systematic review of the efficacy and safety of minimally invasive oesophagectomy for cancer or high-grade dysplasia of the oesophagus

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Contributions of authors

Myfanwy Lloyd Jones and Heather Stegenga drafted the scope. Anna Macbeth devised the search strategies and conducted the searches. Heather Stegenga, Myfanwy Lloyd Jones, Fiona Campbell, and Lesley Uttley screened the search results and assessed studies for inclusion. Fiona Campbell, Lesley Uttley, and Myfanwy Lloyd Jones undertook data extraction and quality assessment, conducted data analysis, and drafted the review. Michael Rhodes provided expert clinical input. Heather Stegenga and Michael Rhodes commented on drafts of the review. Myfanwy Lloyd Jones acted as review lead.

Conflicts of interest

There are no known conflicts of interest.

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DEFINITION OF TERMS

Anastomosis	A connection between two hollow organs
Barrett’s oesophagus	A condition in which abnormal cells develop in the lower part of the oesophagus, probably as a consequence of acid reflux. In about 1% of cases, Barrett’s oesophagus develops into adenocarcinoma.
Chylothorax	Accumulation of lymphatic fluid (chyle) in the pleural cavity
Dehiscence	The premature "bursting" open of a wound along a surgical suture
Dysplasia	Abnormality of a cell. While the cell is not cancerous, it is more likely than a normal cell to develop into cancer, and cells with high-grade dysplasia have a high risk of turning cancerous at some point in the future.
EORTC QLQ-C30	A questionnaire developed to assess the quality of life of cancer patients
EORTC QLQ-OES18	An oesophageal cancer-specific module designed to be used with the EORTC QLQ-C30
EORTC QLQ-OES24	An oesophageal cancer-specific module designed to be used with the EORTC QLQ-C30; apparently superseded by EORTC QLQ-OES18
Hybrid oesophagectomy	Oesophagectomy performed using either laparascopically- or thoracoscopically-assisted procedures in combination with either a thoracotomy or laparotomy
Laparotomy	Access to the abdominal (intraperitoneal) cavity via an incision in the abdomen
Laparoscopically-assisted oesophagectomy	Oesophagectomy performed using laparascopically-assisted procedures in combination with a thoracotomy
Mediastinitis	Inflammation of the area between the lungs (mediastinum)
Minimally invasive oesophagectomy	Oesophagectomy undertaken using both thoracoscopy and laparoscopy
Thoracotomy	Access to the thoracic cavity via an incision in the chest
Thoracoscopically-assisted oesophagectomy	Oesophagectomy performed using thoracoscopically-assisted procedures in combination with a laparotomy
Transhiatal oesophagectomy	Oesophagectomy performed using incisions in the abdomen and neck, but not the chest
Transthoracic oesophagectomy	Oesophagectomy performed using either one continuous incision from the chest to the abdomen or separate incisions in the chest and abdomen

LIST OF ABBREVIATIONS

AC	Adenocarcinoma
ASA	American Society of Anaesthesiologists
BMI	Body mass index
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
HES	Hospital Episode Statistics
HMIO	Hybrid minimally invasive oesophagectomy
HR	Hazard ratio
ICD-10	International Classification of Disease (10^{th} revision)
LAO	Laparoscopically-assisted oesophagectomy
MIG	Minimally invasive gastrectomy
MIO (American MIE)	Minimally invasive oesophagectomy
MIT	Minimally invasive techniques
NHS	National Health Service
OG	Oesophago-gastric
OO	Open oesophagectomy
OR	Odds ratio
OPCS-4	Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4^{th} edition)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
RLNP	Recurrent laryngeal nerve paralysis
SCC	Squamous cell carcinoma
SD	Standard deviation
TAO	Thoracoscopically-assisted oesophagectomy
THO (American THE)	Transhiatal oesophagectomy
TTO (American TTE)	Transthoracic oesophagectomy
UICC	Union for International Cancer Control
VATS	Video-assisted thoracoscopic surgery

EXECUTIVE SUMMARY

Background

Oesophageal cancer is the ninth most common cancer in the UK. It is more common in men than in women, and most commonly occurs in people aged 60 or over. Patients may present with difficulty or pain in swallowing, regurgitation of food, weight loss, or hoarseness and coughing. Their prognosis is poor: for 2000/01, the latest year for which data are available, one-year survival rates in England and Wales were 30% for men and 27% for women, while 5-year survival rates were 8% for both men and women.

Oesophagectomy is the main curative treatment for patients whose cancer is not too advanced, and who are fit enough to undergo such surgery. It is also occasionally used to treat pre-malignant oesophageal disease such as high-grade dysplasia (precancerous changes in the cells) or severe benign disease such as oesophageal stricture.

However, open oesophagectomy is an extensive and traumatic procedure. The classic procedure involves the resection of the tumour, oesophageal tissue, and adjacent lymph nodes through a right-sided thoracotomy in combination with a laparotomy. This procedure necessitates postoperative care in the Intensive Care Unit, and carries a high risk of complications. Consequently, minimally invasive techniques have been developed with the aim of reducing the morbidity and mortality associated with open oesophagectomy. These include minimally invasive oesophagectomy (MIO), in which both the abdominal and thoracic stages of the procedure are either fully endoscopic or hand-assisted endoscopic, and hybrid MIO (HMIO) when one stage of the procedure (abdominal or thoracic) is open and other stage is endoscopic or hand-assisted endoscopic.

Objective

In 2006, NICE issued Interventional procedures guidance on thoracoscopically assisted oesophagectomy. This was informed by an overview prepared by the Interventional procedures team in July 2005. However, by 2010, the volume of new evidence was such that it was considered appropriate to review the existing guidance, at the same time expanding its scope to include transhiatal laparoscopically-assisted oesophagectomy.

The objective of this report is therefore to systematically review the evidence for the efficacy and safety of oesophagectomy performed for the treatment of cancer or high-grade dysplasia of the oesophagus using minimally invasive techniques compared with the efficacy and safety of open oesophagectomy.

Methods

Electronic databases were searched using terms designed to retrieve papers describing the clinical efficacy and/or safety of oesophagectomy performed using minimally invasive techniques. The searches covered the period from July 2005 (the date of the searches performed to inform the Interventional procedures team's overview of thoracoscopically-assisted oesophagectomy) to January 2011. Relevant studies prior to July 2005 were identified from that overview, and from relevant systematic reviews. Searches were restricted to studies published in the English language.

Studies were included if they met the following criteria:

Types of studies:

- Review of efficacy: comparative studies
- Review of safety: comparative studies, large observational studies ($\geq$200 patients), registry data, or case reports of rare adverse effects.

Types of participants

- Adult patients requiring oesophagectomy because of cancer or high-grade dysplasia of the oesophagus.

Types of intervention

- Oesophagectomy performed using minimally invasive techniques:
    - o Minimally invasive oesophagectomy (MIO) – oesophagectomy performed using thoracoscopic mobilisation of the oesophagus and laparoscopic mobilisation of the stomach
    - o Hybrid MIO (HMIO): oesophagectomy performed using minimally invasive techniques for mobilisation of either the oesophagus or the stomach (i.e. thoracoscopically-assisted oesophagectomy with laparotomy or laparascopically-assisted oesophagectomy with thoracotomy).

Types of comparator

- Open oesophagectomy – i.e. oesophagectomy performed using thoracotomy to mobilise the oesophagus and laparotomy to dissect and prepare the stomach (or sometimes intestine) for oesophageal reconstruction.

Types of outcome

- Survival, completeness of resection, adequacy of lymph node excision, conversion to open oesophagectomy, local/regional recurrence, length of hospital stay, return to normal activity, quality of life
- Adverse events: specifically in-hospital death (i.e. death within the index admission), return to theatre/reoperation, perioperative mortality (i.e. death within 30 days of surgery), tracheal perforation, damage to adjacent structures (including the spleen and aorta), damage to the laryngeal nerve or vocal cord, vascular injury and bleeding, anastomotic leak, thoracic duct injury/chyle leakage, infection, pulmonary embolism, reduction in lung capacity.

Results

Efficacy

26 studies were identified which compared patients who underwent oesophagectomy using minimally invasive techniques with patients who underwent oesophagectomy via open surgery, and reported relevant outcomes:

- 4 studies compared MIO with open surgery
- 16 compared HMIO with open surgery
- 3 compared MIO or HMIO with open surgery
- 2 compared MIO with both HMIO and open surgery
- 1 analysis of routinely-collected data compared MIO or HMIO with open surgery.

None were randomised controlled trials: 25 were non-randomised controlled studies, and one was an analysis of UK registry data which compared outcomes in patients who had undergone oesophagectomy for cancer of the oesophagus or gastro-oesophageal junction using open and minimally invasive techniques.

The degree of clinical heterogeneity in surgical techniques, patient selection, and the various criteria used for outcome measurement found in the comparative studies was such that meta-analysis was considered inappropriate, and the presentation of results is therefore limited to a narrative review. It should be noted that the quality of the controlled studies was not high, and the possibility of bias cannot be excluded.

The four studies which *compared MIO with open surgery* did not present a consistent picture. No consistent pattern was observed in relation to in-hospital mortality. Two studies found that the mean length of hospital stay was shorter in patients undergoing MIO than in controls, while two found it to be slightly longer. None of the studies reported rates of conversion from MIO to open surgery.

Two of the 16 studies which *compared HMIO with open surgery* found in-hospital mortality was higher with HMIO, whereas five found it was higher with open surgery; 8 had no mortality in either group, and one did not report this outcome. Only six studies presented data on mean length of hospital stay: five found that this was shorter in patients undergoing HMIO, although in some cases the difference was small. In addition, one study assessed quality of life; this suggested that recovery from HMIO was more rapid than recovery following open oesophagectomy. Six studies reported on cancer recurrence: although four studies found that recurrence rates were lower in patients undergoing HMIO than in those undergoing open surgery, the largest of these studies found no statistical association between operative approach and risk of cancer recurrence.

The three studies which *compared MIO/HMIO with open surgery* found that in-hospital mortality was lower, and length of hospital stay shorter, in patients undergoing MIO/HMIO than in those undergoing open surgery.

The two studies which *compared MIO with HMI and with open surgery* displayed no consistent pattern in relation to in-hospital mortality, but both found that length of hospital stay was slightly shorter in patients undergoing MIO than in those undergoing either HMIO or open surgery. It should be noted that these studies were particularly susceptible to selection bias.

The analysis of routinely-collected data which *compared MIO/HMIO with open surgery* found that, although MIO/HMIO appeared to be associated with lower in-hospital mortality, 30-day in-hospital mortality, and 365-day total mortality than open surgery, and to show a trend towards lower 30-day total mortality, following multiple regression analysis to control for age, gender, socio-economic deprivation, comorbidity score, year, and number of emergency admissions, the use of minimally invasive techniques was not associated with lower in-hospital mortality or 30-day in-hospital mortality rates relative to open procedures, but only with a non-significant reduction in 365-day mortality. Moreover, they considered that, in the absence of information relating to clinical factors (e.g. tumour stage, surgical procedure, number of lymph nodes retrieved, and completeness of resection), even if MIO/HMIO were associated with better outcomes than open surgery, it would not be clear whether this reflected the superiority of minimally invasive techniques or confounding due to the selection for MIO/HMIO of patients with better prognoses.

Thus, the evidence for the efficacy of MIO and HMIO relative to open oesophagectomy is not conclusive. Although more studies suggested that the use of minimally invasive techniques was associated with lower in-hospital mortality rates than open surgery, rather than vice versa, this may reflect bias in the data. There is no evidence of a consistent association between operative approach and either lymph node retrieval or cancer recurrence. Moreover, although the evidence suggests that the mean length of hospital stay may be shorter in patients undergoing MIO or HMIO than in those undergoing open surgery, in many cases the difference was not great. However, quality of life data from one study suggest that recovery from HMIO is more rapid than recovery following open oesophagectomy.

Safety

In addition to the 26 studies included in the review of efficacy, two case series were identified which included over 200 patients. There were also seven case reports of rare adverse events in patients who underwent oesophagectomy using minimally invasive techniques.

The three adverse effects most commonly reported in the comparative studies were anastomotic leak, pneumonia, and injury to the laryngeal nerve or vocal cord: however, the rates reported by these studies varied widely. The rates reported in the case series may provide the best indication of what can be achieved with MIO in a centre of excellence: overall major complication rates of 23-32%, with rates of 12-13% for anastomotic leak, 8-10% for pneumonia, and 4-5% for damage to the recurrent laryngeal nerve or vocal cord palsy, and a rate of conversion to open operation of around 7%. The major reported cause of conversion to open operation was adhesions, and few were necessitated by bleeding.

Conclusions

The evidence for the efficacy and safety of oesophagectomy performed using minimally invasive techniques is poor. The evidence for efficacy is drawn entirely from non-randomised studies in which it is impossible to exclude the possibility of bias, in terms of both the selection of patients to undergo MIO/HMIO and the use of historical controls. In addition, the paucity of information relating to the surgeons who performed the procedures, and their levels of competence, makes it difficult to exclude the possibility of performance bias.

Furthermore, it is difficult to compare studies because of variations in the techniques and equipment used in MIO/HMIO, shortcomings in the reporting of the procedures used in the open surgery, and inconsistency in either the outcomes which were reported or the way in which reported outcomes (particularly adverse events) were defined. Consequently, it was not considered appropriate to perform meta-analyses, and the evidence relating to the efficacy of MIO/HMIO is therefore not easy to summarise.

Some studies suggested that the use of minimally invasive techniques was associated with higher in-hospital mortality rates than open surgery, but more suggested that in-hospital mortality was higher with open surgery. However, this outcome is susceptible to bias arising from both patient selection and the use of historic controls, and multiple regression analysis of a large dataset found no significant difference between MIO/HMIO and open surgery in terms of in-hospital mortality. No evidence was found of a statistically significant difference in the risk of cancer recurrence between patients undergoing MIO/HMIO and open surgery.

Although mean hospital stays may be shorter in patients undergoing MIO/HMIO than in those undergoing open surgery, in many cases the difference was not great. None of the studies provided data relating to time to return to normal activity, although this is arguably one of the most important outcome measures, and one which may differ considerably between MIO and open surgery even when the length of hospital stay is similar. However, the one study which assessed quality of life suggested that recovery from HMIO may be more rapid than recovery following open oesophagectomy.

Because of the nature of the evidence, it is difficult to assess the safety of MIO/HMIO relative to open surgery. A very specialised centre reported major complication rates of 23-32% with MIO; unfortunately, comparable figures were not available for open surgery. The most commonly reported adverse events were anastomotic leak, pneumonia, and injury to the laryngeal nerve or vocal cord. The included studies reported widely varying rates of these events. The rates reported in a large case series from a specialised centre perhaps provide an indication of the best results which can be achieved in a centre of excellence: rates of 12-13% for anastomotic leak, 8-10% for pneumonia, and 4-5% for laryngeal nerve or vocal cord damage, with a rate of conversion to open operation of around 7%.

There is evidence that patient outcomes following open oesophagectomy are heavily influenced by the extent of the surgeon’s experience, or that of the institution in which he or she works, as measured by relevant caseload, and the same appears to be true of oesophagectomy performed using minimally invasive techniques. There is also evidence of the existence of a learning curve specifically in relation to MIO/HMIO. Such evidence supports the NHS Executive's guidance that surgery for cancer of the oesophagus should be performed in specialist centres by specialist surgeons who perform a relatively high volume of such procedures a year.

1 OBJECTIVE OF THE REVIEW

In 2006, NICE issued Interventional procedures guidance on thoracoscopically assisted oesophagectomy.[1] This was informed by an overview prepared by the Interventional procedures team in July 2005.[2] However, by 2010, the volume of new evidence was such that it was considered appropriate to review the existing guidance, at the same time expanding its scope to include transhiatal laparoscopically-assisted oesophagectomy.

The objective of this report is therefore to systematically review the evidence for the efficacy and safety of oesophagectomy performed for the treatment of cancer or high-grade dysplasia of the oesophagus using minimally invasive techniques compared with the efficacy and safety of open oesophagectomy.

2 BACKGROUND

Oesophagectomy is most commonly performed to treat oesophageal cancer. It is also occasionally used to treat pre-malignant oesophageal disease such as high-grade dysplasia (precancerous changes in the cells) or severe benign disease such as oesophageal stricture.

2.1 Description of Health Problem

Oesophageal cancer is the ninth most common cancer in the UK. In 2007, 6,487 people in England were diagnosed with oesophageal cancer: 4,269 of these (66%) were men. The incidence of oesophageal cancer increases with age: 82% of new cases reported in the UK in 2007 were in people aged 60 and over, and 42% were in people aged 75 and over. In England, the incidence is highest in urban areas of the north-west.[3]

There are two main histological types of oesophageal cancer: adenocarcinoma (AC) and squamous cell carcinoma (SCC). They tend to develop in different parts of the oesophagus: AC usually occurs in the lower third of the oesophagus and at the oesophago-gastric junction, while SCC usually occurs in the upper or middle oesophagus.[3;4] AC and SCC have different incidence trends, and probably also different causes. So, until the 1970s, SCC accounted for the vast majority of oesophageal cancers diagnosed in the UK;[3] major risk factors for SCC appear to be tobacco smoking and high alcohol consumption, particularly in combination.[5] However, since the 1970s, the incidence of AC has increased, and it is now the form of oesophageal cancer most frequently diagnosed in white men in the UK;[3] major risk factors for AC appear to be gastro-oesophageal reflux and obesity.[5]

Patients with oesophageal cancer may present with difficulty or pain in swallowing, regurgitation of food, weight loss, or hoarseness and coughing.[5] Their prognosis is poor. For 2000/01, the latest year for which data are available, one-year survival rates in England and Wales were 30% for men and 27% for women, while 5-year survival rates were 8% for both men and women.[6]

2.2 Oesophagectomy using Open and Minimally Invasive Techniques

2.2.1 What the Procedures Involve

Surgery for malignant disease of the oesophagus is an extensive and traumatic gastrointestinal surgical procedure.[7] For many years the classic procedure was a transthoracic oesophagectomy (TTO), in which the tumour, oesophageal tissue, and adjacent lymph nodes were resected through a right-sided thoracotomy in combination with a laparotomy to mobilise the stomach and prepare for oesophageal reconstruction; the anastomosis (connection) between the remaining oesophagus and stomach is usually located within the thorax. This procedure necessitates postoperative care in the Intensive Care Unit, and carries a high risk of patients developing a chest infection or, if a leak occurs at the anastomosis, mediastinitis. It also has a substantial impact on quality of life following hospital discharge. Quality of life (measured using the EORTC QLQ-C30 and the dysphagia scale from the EORTC QLQ-OES24) was reduced postoperatively in patients who underwent (open) oesophagectomy for cancer performed with curative intent in a UK hospital between November 1993 and May 1995: while quality of life scores returned to their preoperative levels in 6 to 9 months in those who survived at least 2 years, those who died within two years of surgery never regained their former quality of life except specifically in relation to the relief of dysphagia.[8]

The morbidity and mortality associated with TTO prompted the pursuit of alternative surgical procedures. One approach which evolved was transhiatal oesophagectomy (THO), in which the oesophagus is resected through a cervicoabdominal approach (i.e. using an upper abdominal incision to mobilise the oesophagus through the diaphragmatic hiatus and to move the stomach upwards, and a cervical incision to complete freeing the oesophagus, and remove it; in this case, the anastomosis is located in the neck). This approach avoided the need for a formal thoracotomy. The drawback of THO was the impossibility of performing a radical lymph node dissection of the mediastinum: this compromised the long-term survival of patients with cancer of the thoracic oesophagus.[9]

The use of thoracoscopy and/or laparoscopy was introduced in 1992 by Cuschieri et al,[10] who hoped that it would further reduce pulmonary morbidity while potentially improving the quality of the resection by enhancing visual control during the mediastinal dissection. Further developments in laparoscopic skills and equipment have led to many more techniques, including hybrid procedures in which only one stage (abdominal or thoracic) is open and the other stage is endoscopic or hand-assisted endoscopic. Video-assisted and robot-assisted techniques have also been developed.

However, although the use of minimally invasive techniques for oesophagectomy has potential advantages for the patient in terms of fewer perioperative complications, faster postoperative recovery, and shorter hospital stay,[7] there is scepticism concerning its oncological safety, in terms of the efficacy of tumour and lymph node clearance, as compared with the standard 'open' resections, and also concerning potential complications such as vocal cord palsy and anastomotic stricture. Despite the length of time since the introduction of minimally invasive techniques, there is still no evidence from randomised controlled trials (RCTs) to demonstrate whether such techniques confer any benefits in terms of efficacy and safety, when compared with open surgery.

In the literature, the term 'minimally invasive oesophagectomy' (MIO) has been broadly applied to oesophagectomy carried out using either thoracoscopy or laparoscopy or both. However, for our study, we classified procedures as MIO only when both the abdominal and thoracic stages were either fully endoscopic or hand-assisted endoscopic. Procedures were classified as transhiatal if they were either laparoscopic transhiatal or hand-assisted laparoscopic transhiatal. Procedures were classified as hybrid MIO (HMIO) when one stage of the procedure (abdominal or thoracic) was open and other stage was endoscopic or hand-assisted endoscopic.

Both MIO/HMIO are lengthy operations performed under general anaesthesia. They should be performed in specialist cancer centres.

2.2.2 The Nature of the Data

Assessing the safety and efficacy of oesophagectomy using minimally invasive techniques with the existing body of evidence is challenging. The techniques vary, as do the experience and competence of surgical teams. The lack of standardisation in the intervention technique, both between studies and also over time, means that any evaluation is rapidly out of date. There is also vast variability in patient selection, and diversity in the various criteria used for outcome measurement.

Because of the lack of randomised studies, there is a risk of bias in this body of evidence. Selection bias poses a threat to the validity of non-randomised studies as patients selected for minimally invasive surgery are unlikely to have been representative of the population of patients presenting to the reporting centres. Particularly in the early stages of their experience with minimally invasive surgery, surgeons are likely to have selected patients with smaller tumours, and to have avoided candidates with serious comorbidities.

2.3 Previous Systematic Reviews

The rationale for conducting the current systematic review might be questioned, given the existence of six published systematic reviews exploring the efficacy and safety of oesophagectomy performed using minimally invasive techniques (Gemmill & McCulloch 2007;[11] Biere et al 2009;[7] Decker et al 2009;[9] Nagpal et al 2009;[12] Verhage et al 2009;[13] and Sgourakis et al 2010[14]). However, the diversity of these reviews required exploration. Most obviously, they differed in the number of comparative studies relating to oesophagectomy performed using minimally invasive techniques which they included, ranging from 5 in the reviews by Decker et al[9] and Gemmill & McCulloch[11] to 12 in the review by Nagpal et al.[12] Decker et al[9] and Gemmill & McCulloch[11] also included case series, bringing their total number of included studies relating to oesophagectomy performed using minimally invasive techniques to 23 and 46 respectively. Moreover, the reviews were not consistent in terms of the comparative studies which they included: only two studies (Braghetto 2006[15] and Smithers 2007[16]) were included in all six reviews.

The six reviews are summarised in Table 1; Table 2 indicates which comparative studies were included in each of those reviews. Although all four reviews which excluded non-comparative studies cautiously suggest trends in favour of oesophagectomy performed using minimally invasive techniques in terms of shorter hospital stays, fewer surgical complications, and reduced morbidity, Sgourakis et al[14] suggest that the incidence of anastomotic strictures may be higher in patients undergoing oesophagectomy performed using minimally invasive techniques.

Table 1: Summary of reviews including comparative studies

Review	Inclusion criteria	Number of studies	Conclusion
Gemmill & McCulloch 2007[11]	All studies which reported ≥6 minimally invasive resections for gastric or oesophageal cancer or high-grade dysplasia and reported relevant outcomes	For MIO: 23 (of which 21 described as case series) For MIG: 23 (of which 14 described as case series)	Minimally invasive surgery for gastric and oesophageal cancer was considered feasible and safe; however, study quality was poor and the data should be treated with caution. Gemmill & McCulloch stated that 2 studies of MIO were comparative but did not specify which; the authors of the current review consider 5 of their included studies to be comparisons with open surgery
Biere et al 2009[7]	All comparative studies including case-matched studies. Studies comparing surgery using MIT with open surgery. English-language studies only.	10	Trends in favour of surgery using MIT were observed for the following outcome parameters: major morbidity, pulmonary complications, anastomotic leakage, mortality, length of hospital stay, operation time, and blood loss.
Decker et al 2009[9]	All studies which reported ≥10 minimally invasive resections for oesophageal cancer and reported a minimum set of surgical outcome data. English-language studies in peer-reviewed journals only.	46 (all referred to as 'series')	Oesophagectomy using MIT was considered feasible, but there was insufficient evidence to support its use to treat invasive oesophageal cancer. Decker et al did not identify any of their included studies as comparative. The authors of the current review consider 5 of their included studies to be comparisons with open surgery
Nagpal et al 2009[12]	All clinical studies comparing different techniques for oesophageal cancer	12	Compared with open surgery, MIO is associated with shorter hospital stay, lower respiratory complications and total morbidity. No significant difference in 30-day mortality, anastomotic leak, or vocal cord palsy. Compared with open surgery, HMIO is associated with a lower risk of anastomotic leak and respiratory complications. No significant difference in 30-day mortality, total morbidity, or vocal cord palsy.
Verhage et al 2009[13]	Articles published in 2000 or later. English-language studies only. Excluded studies using	10	Using data from case-control studies, surgery using MIT shows a tendency towards

	MIT for benign conditions.		better short-term outcomes when compared with conventional open surgery.
Sgourakis et al 2010[14]	Inclusion criteria: a) whole or part of the procedure done using MIT b) intent to treat analysis used c) all participants to have oesophageal cancer or Barrett's oesophagus with high grade dysplasia or upper aero-digestive tract primary tumour d) procedures: Ivor-Lewis oesophagectomy, left thoraco-abdominal approach, three-hole or McKeown oesophagectomy and transhiatal oesophagectomy	8	The MIT group was comparable to the open group in most outcomes. Although the MIT group reported fewer complications than the open group, it displayed a higher incidence of anastomotic strictures. The hybrid group was comparable in all outcomes to the open group.

Table 2: Comparative studies included in the six systematic reviews

	Biere et al 2009[7]	Gemmill & McCulloch 2007[11]	Decker et al 2009[9]	Nagpal et al 2009[12]	Verhage et al 2009[13]	Sgourakis et al 2010[14]	Comparison
Benzoni 2008[17]				y	y		MIO vs HMIO Other MIT
Bernabe 2005[18]	y	y	y	y	y		MIO vs open THO vs LSO THO
Bonavina 2004[19]				y			MIO vs HMIO
Braghetto 2006[15]	y	y	y	y	y	y	MIO vs open Other MIT TTO
Bresadola 2006[20]	y						THO
Fabian 2008[21]	y			y	y		MIO vs open TT and TH vs thoraco-laparoscopic O TTO
Kitagawa 2009[22]					y*		Other MIO
Kunisaki 2004[23]					y	y	MIO vs open TT and TH vs thoraco-laparoscopic O
Law 1997[24]		y	y	y		y	HMIO vs open
Martin 2005[25]				y			MIO vs HMIO
Morris 2007[26]	y					y	MIO vs open TTO
Nguyen 2000[27]				y	y	y	MIO vs open TT and TH vs thoraco-laparoscopic O
Osugi 2003[28]	y			y	y		HMIO vs open Other MIT TTO
Scheepers 2009[29]	y				y		THO vs LSO THO
Shiraishi 2006[30]	y			y			HMIO vs open TTO
Smithers 2007[16]	y	y	y	y	y	y	MIO vs open HMIO vs open TT and TH vs thoraco-laparoscopic O TTO
Taguchi 2003[31]						y	HMIO vs open
Van den Broek 2004[32]	y	y	y	y			MIO vs open THO
Zingg 2009[50]						y	HMIO vs open

* Date given in Verhage as 2008, i.e. the date of epub ahead of print
LSO: laparoscopic oesophagectomy
TLSO: thoraco-laparoscopic oesophagectomy
THO: transhiatal oesophagectomy
TTO: transthoracic oesophagectomy
HMIO: hybrid minimally invasive oesophagectomy
MIT: oesophagectomy performed using minimally invasive techniques

3 METHODS FOR REVIEWING SAFETY AND EFFICACY

3.1 Search Strategy

Comprehensive literature searches were performed by the NICE Information Services team in August 2010, and updated in January 2011. These searches were designed to retrieve papers describing the clinical efficacy and/or safety of oesophagectomy performed using minimally invasive techniques.

The following electronic bibliographic databases were searched:

1. Medline
2. Medline in-process
3. Embase
4. Cumulative index to nursing and allied health literature (CINAHL)
5. Cochrane Database of Systematic Reviews (CDSR)
6. Cochrane Central Register of Controlled Trials (CENTRAL)
7. NHS Database of Abstracts of Reviews of Effects (DARE)
8. NHS Health Technology Assessment (HTA) Database
9. Zetoc

Details of the search strategies used may be found in Appendix 1.

Because thorough searches of the earlier literature had been undertaken by the NICE Information Services team in July 2005 to inform their overview of thoracoscopically assisted oesophagectomy,[2] the searches performed in August 2010 were restricted to the period from July 2005 onwards. However, the earlier searches were limited to thoracoscopically-assisted oesophagectomy (for search strategies, see Appendix 2), and could therefore have excluded some procedures relevant to the current review of oesophagectomy performed using minimally invasive techniques. As there was insufficient time to extend the process of comprehensive searching and systematic study selection to the literature predating July 2005, relevant studies from that period were identified from the 2005 overview,[2] and supplemented by the systematic reviews by Biere et al,[7] Decker et al,[9] Gemmill & McCulloch,[11] Nagpal et al,[12] Sgourakis et al,[14] and Verhage et al.[13]

3.2 Study Selection

The Interventional procedures team sifted by title and abstract the results of the literature searches covering the period from July 2005 to January 2011. The abstracts of all studies which they identified as potentially relevant were then checked again by a member of the ReBIP team, resulting in some further exclusions. The full texts of all potentially relevant studies were then retrieved and assessed for relevance by a member of the ReBIP team against the inclusion criteria listed in sections 3.2.1-3.2.6. Decisions were checked by a second member of the ReBIP team with differences resolved by discussion.

For the period predating July 2005, the ReBIP team identified all potentially relevant studies which were included in either the 2005 overview of thoracoscopically-assisted oesophagectomy[2] or the systematic reviews by Biere et al,[7] Decker et al,[9] Gemmill & McCulloch,[11] Nagpal et al,[12] Sgourakis et al,[14] and Verhage et al.[13]

3.2.1 Types of Studies

Review of efficacy:

- Comparative studies

Review of safety:

- Comparative studies
- Large observational studies ($\geq$200 patients)
- Registry data
- Case reports of rare adverse effects.

The decision to exclude smaller observational studies from the review of safety was based on a desire to exclude small case series which might display particularly high rates of adverse event rates associated with limited experience of minimally invasive techniques on the part of the surgeon or institution. The decision to set the threshold for inclusion at 200 patients was taken a priori.

3.2.2 Types of Participants

Adult patients requiring oesophagectomy because of cancer or high-grade dysplasia of the oesophagus.

3.2.3 Types of Intervention

Oesophagectomy performed using minimally invasive techniques:

- Minimally invasive oesophagectomy (MIO) – oesophagectomy performed using thoracoscopic mobilisation of the oesophagus and laparoscopic mobilisation of the stomach
- Hybrid MIO (HMIO): oesophagectomy performed using minimally invasive techniques for mobilisation of either the oesophagus or the stomach, but not both (i.e. thoracoscopically-assisted oesophagectomy with laparotomy or laparascopically-assisted oesophagectomy with thoracotomy).

In both MIO and HMIO, the anastomosis may be cervical or intra-thoracic, depending on the location of the tumour.

3.2.4 Types of Comparator

Open oesophagectomy – i.e. oesophagectomy performed using thoracotomy to mobilise the oesophagus and laparotomy to dissect and prepare the stomach (or sometimes intestine) for oesophageal reconstruction.

3.2.5 Types of Outcome

Included studies had to report at least one of the following outcomes:

Review of efficacy:
- Completeness of resection
- Adequacy of lymph node excision
- Conversion to open oesophagectomy
- Survival
- Local/regional recurrence
- Length of hospital stay
- Return to normal activity
- Quality of life

Review of safety:
- In-hospital death (i.e. death within the index admission)
- Return to theatre/reoperation
- Perioperative mortality (i.e. death within 30 days of surgery)
- Tracheal perforation

- Damage to adjacent structures (including the spleen and aorta)
- Damage to the laryngeal nerve or vocal cord
- Vascular injury and bleeding
- Anastomotic leak
- Thoracic duct injury/chyle leakage
- Infection
- Pulmonary embolism
- Reduction in lung capacity

Length of hospital stay has been included as an efficacy outcome because of its obvious importance to patients. It also acts as a surrogate for postoperative recovery generally. However, it may also be regarded as a safety outcome in that it acts as a surrogate for pulmonary morbidity: hospital stays are longer in patients who have difficulty breathing and require longer ventilation, or who get chest infections.

3.2.6 Other Criteria

Because of time constraints, only studies published in the English language were eligible for inclusion.

3.3 Data Extraction

A data extraction form was developed and piloted. For comparative studies, relevant data were independently extracted by two reviewers, and any disagreements were resolved by discussion. Data extraction for observational studies was performed by a single reviewer.

3.4 Quality Assessment

Due to the lack of RCTs, this review draws on non-randomised research evidence. There is controversy, however, over the validity of non-randomised evidence, with concerns relating to the existence and magnitude of selection bias. In order to assess the extent of bias in these studies, we focused on three core quality domains: sample definition and selection; methods of creating treatment groups; and comparability of groups.[33]

In order to assess these quality domains, we collected and assessed the following data:

- Description of study design
- How allocation to treatment groups occurred
- Designs to balance groups
- Any blinding used
- Assessment of baseline comparability.

3.5 Data Analysis

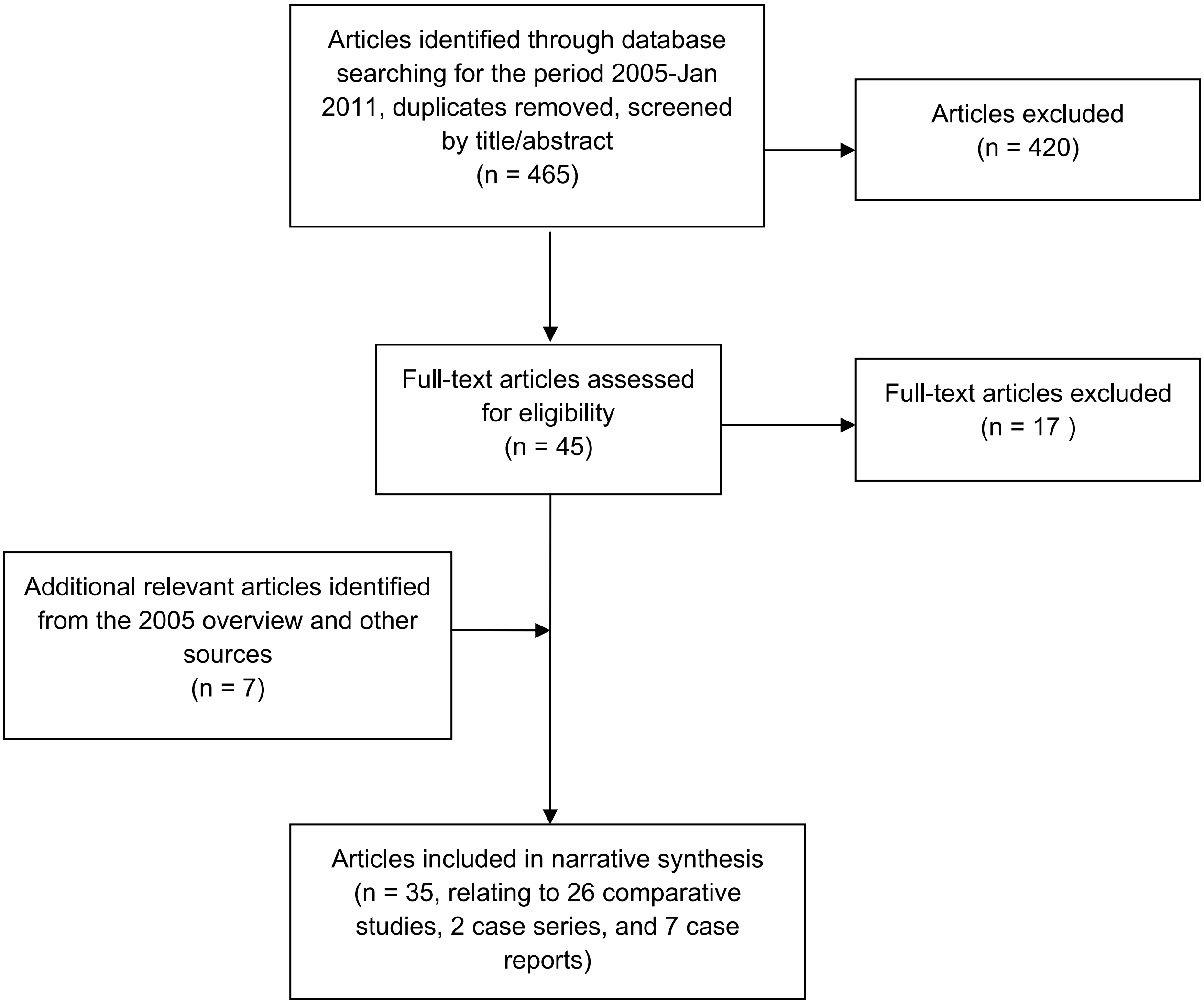
Studies which met the review's entry criteria were eligible for inclusion in meta-analyses if they were sufficiently comparable in terms of their study populations, interventions, and outcomes. However, the degree of clinical heterogeneity in surgical techniques, patient selection, and the various criteria used for outcome measurement was found to be such that pooling data from different studies was considered inappropriate, and the presentation of results is therefore limited to a narrative review.

4 RESULTS

4.1 Quantity and Quality of Research Available

The electronic literature searches conducted by the NICE Information Services team for the period July 2005 to January 2011 identified 465 potentially relevant citations. Of these, 420 were excluded at the title or abstract stage, leaving 45 which were obtained for examination of the full text; 17 of these were excluded after a full reading. Seven relevant articles (the comparative studies by Bernabe,[18] Buess,[34] Law,[24] Nguyen,[27] Osugi,[28] and van den Broek,[32] and the case series by Luketich[35]) were identified either from the 2005 overview of thoracoscopically-assisted oesophagectomy[2] or from citations from other sources. 26 studies were included in the review of efficacy, and a further nine in the review of safety (see Figure 1).

Figure 1: Modified PRISMA[36] flow diagram



4.1.1 Number and Type of Studies Included

4.1.1.1 Review of efficacy

26 studies were identified which compared patients who underwent oesophagectomy using minimally invasive techniques with patients who underwent oesophagectomy via open surgery, and reported relevant outcomes. None were randomised controlled trials: 25 were non-randomised controlled studies, and one was an analysis of UK registry data which compared outcomes in patients who underwent oesophagectomy for cancer of the oesophagus or gastro-oesophageal junction using open and minimally invasive techniques.[37]

Two studies, those by Smithers et al[16] and Thomson et al,[38] drew on the same database of patients treated in the Princess Alexandra Hospital, Woolagong, Australia. However, as they report different outcomes, there is no risk of double-counting, and therefore both studies have been retained in the review.

4.1.1.2 Review of safety

In addition to the studies included in the review of efficacy, two case series were identified which included over 200 patients, together with seven case reports of rare adverse events in patients who underwent oesophagectomy using minimally invasive techniques.

4.1.2 Number and Type of Studies Excluded, with Reasons

As may be seen from section 4.1 above, a substantial number of the references identified by the electronic searches related to studies which did not meet the review's inclusion criteria. These were excluded during the sifting process, and details are given only of those references which were excluded after a full reading for a reason other than a simple failure to meet the inclusion and exclusion criteria, or which were shown in Table 2 as included in the earlier systematic reviews. Such references are listed in Appendix 3, together with the reasons for their exclusion.

4.1.3 Study Characteristics

4.1.3.1 Comparative Studies

Of the 26 comparative studies which were identified, four compared MIO with open surgery, 16 compared HMIO with open surgery, three compared MIO or HMIO with open surgery, two compared MIO with both HMIO and open surgery, while one analysis of routinely-collected data compared MIO or HMIO with open surgery.

The quality of the comparative studies was not high. Despite the issues long known to be associated with the use of historical controls,[39] almost all studies used such controls for the open surgery comparison, either explicitly or, in the case of the analysis of routinely-collected data by Lazzarino et al,[37] implicitly. Moreover, few studies reported in adequate detail how the historical controls were selected. Consequently, the possibility of selection bias cannot be excluded.

4.1.3.2 Observational Studies

Two large case series were identified, by Luketich et al[35] and Kilic et al.[40] These relate to patients treated at one American centre during overlapping time periods, and therefore provide complementary rather than independent data.

4.1.3.3 Case Reports

Seven relevant case reports were identified, relating to five complications: hiatus hernia, tension capnothorax, complex tracheal lesion, injury to the thoracic aorta, and injury to an aberrant subclavian artery.

4.2 Assessment of Efficacy and Safety

Only comparative studies have been included in the assessment of efficacy. As noted above, these studies fall into five groups:

- MIO vs open surgery (4 studies)
- HMIO vs open surgery (16 studies)
- MIO/HMIO vs open surgery (3 studies)
- MIO vs HMIO vs open surgery (2 studies)
- MIO/HMIO vs open surgery – analysis of routinely-collected data (1 study).

The efficacy and safety data from each group of comparative studies are discussed in turn below, followed by a discussion of safety data from the case series and case reports.

4.2.1 Comparative Studies

4.2.1.1 MIO vs Open Surgery (4 studies)

4.2.1.1.1 Participants

The studies in this group included 269 participants, of whom 127 underwent MIO and 142 open surgery. The number included in the individual studies ranged from 45 to 90. Two studies were conducted in the USA, one in the UK, and one in Japan. The mean age participants was 64.3 (SD 1.9). Two studies reported average patient BMI prior to operation: this was 20.2 in the Japanese study and 28.5 in a study conducted in the USA. In the three studies which provided relevant data, patients were being treated for oesophageal cancer or high-grade dysplasia (see Table 3).

The reporting of pathology varied across studies (see Table 3). In the study by Pham et al,[41] data relating to pathologic stage were missing for 6 of the 85 patients with cancer (7%) – two in the intervention group and 4 in the control group. In a study which included 80 patients, Parameswaran et al[42] appear to report pathologic stage for 86 patients (108%) but tumour site for only 59 (74%); however, these data may perhaps refer to tumours rather than patients.

Table 3: MIO vs open surgery: baseline characteristics of participants

Author	Year	Country	N	Age	BMI	Gender (%)	
						Male	Female
Kunisaki[23]	2004	Japan	45	62.7	20.2	73	27
Nguyen[27]	2000	USA	54	65	~	67	33
Parameswaran[42]	2009	UK	80	67.5	~	83	17
Pham[41]	2010	USA	90	62	28.5	82	18

Author	Indication for oesophagectomy (%)			Pathologic (UICC) Stage (n)						Site of tumour (n)		
	Adeno	Squamous	Dysplasia	0	I	IIA	IIB	III	IV	Upper	Middle	Distal
Kunisaki[23]	~	~	~	~	~	~	~	~	~	0	20	25
Nguyen[27]	90	0	10	~	~	~	~	~	~	2	5	40
Parameswaran[42]	82	12	6	7	12	25*	-	36	6	6	43	10
Pham[41]	76	16	3	0	13	27*	-	36	3	~	~	~

~ Not reported
* stage II not differentiated into IIA and IIB

4.2.1.1.2 Intervention

In all four studies, the intervention was total MIO (i.e. thoracoscopic and laparoscopic oesophagectomy) with either cervical or intra-thoracic anastomosis. All four studies used a stapled anastomosis in the MIO group. Total MIO was compared with conventional open surgery: open transthoracic oesophagectomy in two studies, and either transthoracic or transhiatal oesophagectomy in the remaining two. Inclusion and exclusion criteria for each study are reported in Table 4.

Table 4: MIO vs open surgery: inclusion and exclusion criteria

Author	Inclusion Criteria	Exclusion Criteria	Intervention	I n	Control	C n
Kunisaki[23]	~	~	Hand-assisted laparoscopy with video-assisted thoracoscopy and mini-thoracotomy	15	Open thoracotomy and laparotomy	30
Nguyen[27]	Patients requiring oesophagectomy for stricture, Barrett's oesophagus, or carcinoma	Emergency oesophagectomy for oesophageal perforation; subtotal gastrostomy and primary colonic interposition; pharyngolaryngectomy with oesophagectomy; For MIO: history of right thoracotomy; T4 disease; morbid obesity (BMI>35kg/m^2)	Combined laparoscopically and thoracoscopically assisted oesophagectomy; cervical anastomosis	18	Open transthoracic (16) or transhiatal (20)	36
Parameswaran[42]	Patients with perceived distal oesophageal or junctional lesions (Siewert I and II)	Siewert III and gastric lesions	Thoracoscopic oesophageal mobilisation, laparoscopic gastric mobilisation, gastric conduit formation; open cervical anastomosis	50	Open transthoracic oesophagectomy (Ivor Lewis)	30
Pham[41]	Patients undergoing oesophagectomy for benign and malignant disease	~	Combined thoracoscopic and laparoscopic; cervical anastomosis	44	Open transthoracic oesophagectomy (Ivor Lewis)	46

~ Not reported

4.2.1.1.3 Summary of Surgical Techniques

Only one study (Nguyen[27]) explicitly stated where the gastric conduit was formed and where the specimen was removed from. Both Nguyen and Kunisaki referred to the surgeon responsible for the procedures, but only Kunisaki[23] provided details of the experience or skill of the operating surgeon (see Table 5).

Table 5: MIO vs open surgery: surgical details

Author	Gastric Conduit	Specimen Removal	Type of Anastomosis	Surgeon Experience	Neoadjuvant therapy	
					I	C
Kunisaki[23]	~	Chest	Staple and Sutures	Same experienced surgeon performed both open and VATS	~	~
Nguyen[27]	Intracorporeal	Neck	MIO=staple Open=Suture	4 different surgeons	9/18 (50%)	33/36 (92%)
Parameswaran[42]	~	~	Staple and suture	~	32/50 (64%)	12/30 (40%)
Pham[41]	~	~	I=Staple C=Suture	~	29/44 (66%)	23/4 (50%)

~ Not reported

4.2.1.1.4 Summary of Study Design and Quality

Three studies used historical controls in the form of the records of patients who had undergone oesophagectomy at the same centre using open surgery; in the fourth (Kunisaki[23]) there was some chronological overlap between the two groups, but they were not fully contemporary (for details, see Table 6). Although all four studies reported that intervention data were collected from consecutive patients, only Parameswaran[42] reported that the control data were also from consecutive patients. None of the studies provided any details of how controls were selected, other than the period of time during which the operations were performed, and therefore the possibility of selection bias cannot be excluded: even when the groups are comparable in terms of reported baseline characteristics, the selection criteria for the historical controls may have included some additional unreported factors which could have affected the outcome after treatment.

Three studies studied MIO prospectively, comparing outcomes with historical controls. Patients were recruited as they were admitted for the procedure on a consecutive basis. Historical controls were used but the methods for selecting the controls is not described in any of the studies. In one study (Kunisaki) the design was unclear. All four studies tested for baseline comparability, in two (Parameswaran,[42] Pham[41]) the control and intervention group were not statistically comparable. In Parameswaran's study, the patients in the MIO group were more likely to have received neoadjuvant therapy than those in the open group. There was also a higher proportion of women in the open group than in the MIO group. None of the studies described a method to blind at outcome assessment.

Table 6: MIO vs open surgery: study quality

Author	Study Design	Recruitment and group allocation	Baseline comparability A: tested stat and comparable B: tested stat and not comparable C: described as comparable D: described as not comparable E: not described	Blinding at outcome assessment
Kunisaki[23]	Unclear	Intervention: April 2002 to March 2003 Control: Apr 2000 to March 2003	A Age Y Gender Y BMI Y Pathology Y	None described
Nguyen[27]	Prospective comparative study with historical control	Consecutive	A Age Y Gender Y BMI ~ Pathology Y	None described
Parameswaran[42]	Prospective comparative study with historical control	Consecutive	B Age Y Gender N BMI ~ Pathology N Greater lymph node yield in MIO group Y and more patients had neoadjuvant therapy before procedure. More females in open group.	None described
Pham[41]	Prospective comparative study with historical control	Consecutive	B Age Y Gender more males BMI ~ Pathology Y	None described

4.2.1.1.5 Outcomes

Data on the outcomes of interest to this review are presented in Tables 7-9 below. Where no data are presented for an outcome listed in section 3.2.5, the studies did not report this outcome. Nguyen et al specified that they did not analyse survival data because of the short follow-up time in the MIO group.[27]

The four studies do not present a consistent picture. Two found the mean length of hospital stay to be shorter in patients undergoing MIO than in controls, while two found it to be slightly longer. Similarly, no consistent pattern was observed in relation to in-hospital mortality, lymph node retrieval, anastomotic leakage, pneumonia, or chyle leakage. However, three of the four studies found that MIO was associated with higher rates of laryngeal or vocal cord damage (for details, see Tables 7-9).

Table 7: MIO vs open surgery: efficacy outcomes

Author	In-hospital mortality (30 days)		Duration of follow-up (months)		Lymph node retrieval				Length of Stay (Days)			
	I %	C%	I	C	I Mean	I SD	C Mean	C SD	I Mean	I SD	C Mean	C SD
Kunisaki[23]	0	0	~	~	24.5	10	26.6	10.4	29.6	12.9	32.7	14
Nguyen[27]	0	0	6.3	~	10.8	8.4	6.6	5.7	11.3	14.2	22.7	19.2
Parameswaran[42]	2	3	19	38	10	range 7-49	23	range 2-23	12	range 8-86	10	range 6-56
Pham[41]	7	4	~	~	†13	range 9-15	†8	range 3-14	15	range 12-20	14	range 11-23

†Median value
~ Not reported

Table 8: MIO vs open surgery: safety outcomes (1)

Author	Anastomotic Leakage %		Anastomotic Leakage requiring reoperation %		Chyle Leakage %		Pulmonary Embolism %	
	I	C	I	C	I	C	I	C
Kunisaki[23]	13	3	13	3	~	~	~	~
Nguyen[27]	11	11	6	6	0	3	~	~
Parameswaran[42]	8	3	8	3	6	3	~	~
Pham[41]	9	11	0	0	~	~	0	4

Table 9: MIO vs open surgery: safety outcomes (2)

Author	Infection %			Laryngeal nerve or vocal cord damage %		Damage to adjacent structures %	
	Define	I	C	I	C	I	C
Kunisaki[23]	Pneumonia	0	3	20	10	~	~
Nguyen[27]		~	~	0	11	~	~
Parameswaran[42]	Pneumonia	8	7	12	0	~	~
Pham[41]	Pneumonia	25	15	14	0	0	2

4.2.1.2 HMIO vs Open Surgery (sixteen studies)

4.2.1.2.1 Participants

The studies in this group included 1706 participants, of whom 934 underwent HMIO and 772 open surgery. The number of patients included in the individual studies ranged from 28 to 419. Details of the country in which the studies were conducted are documented in Table 9 below. The mean age of participants in those studies ranged from 57 to 66.5 years. Only three studies reported average patient BMI prior to operation; these values ranged from 25.3 in an Italian study to 30 in a study from the USA. In those studies which provided data, patients were being treated for oesophageal cancer and also, in three studies, for high-grade dysplasia. The reporting on pathology varied across studies with several studies providing no data on severity of cancer (for details, see Table 10). In the study by Bernabe et al,[18] the 23 patients with cancer had their UICC stage recorded; the remaining 8 patients had Barrett's oesophagus with high-grade dysplasia.

Table 10: HMIO vs open surgery: baseline characteristics of patients

Author	Year	Country	N	Age	BMI	Gender %	
						Male	Female
Bernabe[18]	2005	USA	31	64	26.8	87	13
Buess[34]	1997	Germany	85	57	~	88	12
Braghetto[15]	2006	Chile	166	63.5	~	60	40
Bresadola[20]	2006	Italy	28	60.6	~	75	25
Caputo[43]	2005	Italy	71	63.3	25.3	77	23
Hamouda[44]	2010	UK	75	62	~	89	11
Kitagawa[22]	2009	Japan	36	62.1	~	78	22
Law[24]	1997	China	85	64.5	~	84	16
Osugi[28]	2003	Japan	149	63.9	~	81	19
Perry[45]	2009	USA	42	65	30	83	17
Saha[46]	2009	UK	44	64	~	84	16
Schroder[47]	2010	Germany	419	59.5	~	83	17
Shiraishi[30]	2006	Japan	153	63.1	~	82	18
Thomson[38]	2010	Australia	221	66.5	~	81	19
Van den Broek[32]	2004	Holland	45	63.5	~	73	27
Wang[48]	2010	China	56	59.5	~	68	32

Author	Indication for oesophagectomy (%)			Tumour Size (n)				Pathologic (UICC) Stage (n)						Site of tumour (n)		
	Adeno	Squamous	Dysplasia	T1n	T2n	T3n	T4n	0	I	IIA	IIB	III	IV	Upper	Middle	Distal
Bernabe[18]	74	0	26	~	~	~	~	3	20	~	~	~	~	~	~	~
Buess[34]	21	78	0	~	~	~	~	0	12	21*	-	47	4	9	47	29
Braghetto[15]	~	~	~	~	~	~	~	0	16	22	42	86	0	~	~	~
Bresadola[20]	~	~	~	~	~	~	~	~	~	~	~	~	~	8	9	11
Caputo[43]	~	~	~	~	~	~	~	~	~	~	~	~	~	1	15	36
Hamouda[44]	82	16	2	~	~	~	~	3	3	10*	-	53	5	~	~	~
Kitagawa[22]	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Law[24]	~	~	~	~	~	~	~	1	5	10	4	58	3	8	61	9
Osugi[28]	~	~	~	52	29	66	2	~	~	~	~	~	~	23	85	41
Perry[45]	45	0	55	~	~	~	~	~	~	~	~	~	~	~	~	~
Saha[46]	~	~	~	~	~	~	~	~	~	~	~	~	~	0	39	27
Schroder[47]	59	41	0	104	81	183	0	~	~	~	~	~	~	~	~	~
Shiraishi[30]	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Thomson[38]	81	19	~	70	28	107	16	0	56	33	29	103	0	0	34	187†
Van den Broek[32]	70	30		~	~	~	~	1	1	12	4	27	0	~	~	~
Wang[48]	5	92	0	~	~	~	~	0	11	28	9	8	0	9	37	10

~ Not reported
* stage II not differentiated into IIA and IIB
† Includes 34 at gastro-oesophageal junction

4.2.1.2.2 Intervention

In hybrid oesophagectomy, minimally invasive techniques are used for either the abdominal or the chest phase, but not both: thus, surgical procedures can be either laparoscopically-assisted with a thoracotomy (LAO) or thoracoscopically-assisted with a laparotomy (TAO). In either case, the anastomosis can be either cervical or intrathoracic. In each of the studies included in this section, the comparator was open oesophagectomy, which might be two-stage, transhiatal, left thoraco-abdominal, three-stage, or not described. Inclusion and exclusion criteria for each study are reported in Table 11.

Table 11: HMIO vs open surgery: inclusion and exclusion criteria

Author	Consecutive Patients	Inclusion Criteria	Exclusion Criteria	Intervention	I n	Control	C n
Bernabe[18]	~	Patients with stage 1 disease according to tumour node metastasis [TNM] staging system for oesophageal cancer	Patients with a history of upper abdominal or thoracic surgery.	Transhiatal laparoscopic oesophagectomy	17	Open transhiatal oesophagectomy	14
Buess[46]	~	~	~	Laparotomy and mediastinoscopy	37	Open thoraco-abdominal approach	48
Braghetto[15]	~	For HMIO: tumour located in the supracarineal oesophagus. Transhiatal oesophagectomy performed for infracarineal tumours	Patients with stage IV disease, for whom endoscopic palliative care was indicated.	Transthoracic video-assisted surgery or transhiatal laparoscopic oesophagectomy and gastric mobilisation	47	Open transthoracic or open transhiatal	119
Bresadola[20]	~	For HMIO: patient with no history of upper abdominal surgery and neoplasm preoperatively staged as T1 and T2	~	Transhiatal laparoscopic oesophagectomy or transthoracic laparoscopic oesophagectomy	14	Open surgery (procedure not described)	14
Caputo[43]	~	~	~	Transmediastinal laparoscopic oesophagectomy or transthoracic laparoscopic oesophagectomy	45	Standard open gastroplasty	26
Hamouda[44]	Consecutive	Oesophageal cancer fulfilling indication for an Ivor-Lewis oesophagectomy	~	Transthoracic laparoscopic oesophagectomy	51	Open transthoracic (Ivor-Lewis) oesophagectomy	24
Kitagawa[22]	~	Oesophageal cancer. Open surgery used in 20 patients treated before March 2005, and HMIO in 16 patients treated after that date	~	Transthoracic laparoscopic oesophagectomy	16	Open transthoracic oesophagectomy	20
Law[24]	~	~	~	Thoracoscopic oesophageal resection	22	Two-stage Lewis Tanner oesophagectomy	63
Osugi[28]	Control group consecutive	Pulmonary function capable of sustaining single-lung ventilation, absence of a serious concomitant medical condition such as liver cirrhosis, and patient preference for VATS	Extensive pleural adhesion, contiguous tumour spread, impaired pulmonary function, other concomitant disease, preference for open operation	Video-assisted Thoracoscopic oesophagectomy	77	Three-stage open surgery	72
Perry[45]	Consecutive	High grade dysphasia or stage 0 or	~	Laparoscopic inversion	21	Open transhiatal	21

		1 oesophageal cancer		oesophagectomy		oesophagectomy	
Saha[46]	Consecutive	Patients with pT1 oesophageal adenocarcinoma	~	Laparoscopic transhiatal oesophagectomy	16	Open oesophagectomy (transthoracic or transhiatal)	28
Schroder[47]	Consecutive	Patients undergoing an Ivor Lewis procedure for oesophageal carcinoma	~	Laparoscopic Ivor Lewis	238	Open transthoracic (Ivor Lewis) oesophagectomy	181
Shiraishi[30]	Consecutive	Oesophageal cancer, absence of contiguous tumour spread to an adjacent structure, no prior thoracic surgery, no extensive pleural adhesion, and pulmonary function capable of sustaining single-lung ventilation	Patients who had received induction chemoradiation therapy, patients with more than T2	Thoracoscopy and laparotomy oesophagectomy	116	Standard Thoracotomy	37
Thomson[47]	Non consecutive	Patients without neoadjuvant or adjuvant therapy	Patients who had any form of adjuvant therapy; cancers classified as Siewert III; in situ lesions; high-grade dysplasia; rare histology; transhiatal or open 3-stage surgery; tumour location in the upper thoracic or cervical oesophagus; evidence of distant metastasis	Video-assisted thoracoscopic oesophagectomy	165	Posterolateral thoracotomy oesophagectomy	56
Van den Broek[32]	Consecutive	Distal oesophageal or oesophageal-gastric cardia junction cancer and no signs of distal metastasis	Previous upper abdominal surgery, or needing a colon interposition	Transhiatal laparoscopic oesophagectomy	25	Open transhiatal oesophagectomy	20
Wang[48]	~	Oesophageal cancer	Local extension, massive lymph invasion, or organic metastasis	Video-assisted thoracoscopic surgery	27	Three-stage open surgery	29

4.2.1.2.3 Summary of Surgical Techniques

Only one study explicitly stated where the gastric conduit was formed, although the majority stated where the specimen was removed from. Two studies used a stapled anastomosis; five used a suture, and three used staples and sutures; one used a suture or staple and suture, and three did not report what was used. Two studies specified that a single surgeon was responsible for the procedures, and one further specified the surgeon's level of experience. The remaining 12 studies provided no details about the number of surgeons involved, or their experience or skill. Six studies reported administering chemo/radiotherapy prior to treatment. For details, see Table 12.

Table 12: HMIO vs open surgery: surgical procedure

Author	Gastric conduit	Specimen removal	Type of anastomosis	Surgeon experience	Baseline comparability	Neoadjuvant Therapy	
						I	C
Bernabe[18]	~	Abdomen	Staple and Sutures	~	Unclear: few descriptives provided	~	~
Buess[46]	~	Abdomen	Suture	~	Comparable	~	~
Braghetto[15]	~	Abdomen	Staple and Suture	~	No: only patients with early-stage disease underwent HMIO; those with more advanced disease underwent open surgery	~	~
Bresadola[20]	~	Neck	Suture	~	No: HMIO were lower stage than open surgery	~	~
Caputo[43]	~	Neck	Staple and Sutures	~	No: differences in tumour site location; more distal in open	~	~
Hamouda[44]	Intracorporeal	Chest	Suture	Single surgeon	Comparable	44/51 (86%)	20/24 (83%)
Kitagawa[22]	~	Neck	Suture	~	Unclear: data only provided for age and gender	~	~
Law[24]	~	~	Suture	~	No: differences in tumour site location & ECOG status	1	0
Osugi[28]	~	Abdomen	~	All operations performed by a single surgeon who had previously performed >150 oesophagectomies	Unclear: few descriptives provided	0	0
Perry[45]	~	Port site	Staple	~	No: control group younger but with higher BMI	~	~
Saha[46]	~	Neck or posterior mediastinum port site	Suture or staple + suture	~	No: patients in the I group had N0 disease and none received adjuvant treatment	0	1
Schroder[47]	~	~	Staple	~	No: patients in HMIO group older, more likely	144/238	66/181

					to have adenocarcinoma rather than squamous cell carcinoma, to have lower grade disease, and to have received adjuvant therapy.	(61%)	(36%)
Shiraishi[30]	~	Chest	~	~	No: open surgery group significantly older, more likely to have had surgery in 1995/99 rather than 2000/04, and to have deeper tumour penetration	17/78 (22%)	10/38 (26%)
Thomson[47]	~	~	~	~	Comparable but more severe cases in the open group	~	~
Van den Broek[32]	~	Neck	Suture	~	Comparable, except that HMIO group significantly more likely to have received neoadjuvant therapy	17/25 (68%)	4/20 (20%)
Wang[48]	~	Neck	~	~	Comparable	0	0

~ Not reported

4.2.1.2.4 Summary of Study Design and Quality

Fourteen studies used historical controls in the form of the records of patients who underwent oesophagectomy at the same centre using open surgery. In three studies (Hamouda,[44] Law,[24] Wang[48]) the data for the intervention and control group were collected during the same time period, although randomisation and allocation concealment was not performed so these groups are likely to be vulnerable to selection bias. The methods of selecting historical controls (other than the time period when the operations were performed) were rarely specified, again making these studies at high risk of selection bias.

In eleven studies, baseline comparability was tested statistically, although the number of baseline characteristics on which comparability was tested varied. The intervention and control groups were similar in terms of reported baseline data in only three (Bernabe,[18] Hamouda,[44] and Wang[48]) of the 14 studies; in nine studies, we did not consider the groups to be comparable, while the remaining two did not provide sufficient baseline data to assess comparability (for details, see Table 13). Moreover, because of the lack of detail of the methods used to select the controls, the selection criteria for the historical controls may have included some additional unreported factors which could have affected the outcome after treatment even in those studies in which the baseline patient characteristics appear comparable. No studies described efforts to blind at outcome assessment.

Table 13: HMIO vs open surgery: study quality

Author	Study Design	Recruitment and allocation to groups	Prospective/retrospective data collection	Baseline comparability A: tested stat and comparable B: tested stat and not comparable C: described as comparable D: described as not comparable E: not described	Blinding at outcome assessment
Bernabe[18]	Case control study	Matched control	Retrospective	A Age Y Gender Y BMI Y Pathology Y	None described
Buess[46]	Comparative	Matched control	Methods of recruitment and allocation not described	A Age Y Gender Y BMI ~ Pathology Y	Not described
Braghetto[15]	Retrospective comparative study with historical control		Methods of recruitment and allocation not described	E Age Y Gender Y BMI ~ Pathology N only patients with early-stage disease underwent HMIO; those with more advanced disease underwent open surgery	None described
Bresadola[20]	Non-randomised controlled trial	Not described	Prospective and historical control	B Age Y Gender Y BMI ~ Pathology N HMIO were lower stage than open surgery	None described
Caputo[43]	Comparative – unclear	Not described	Unclear	C Age Y Gender Y BMI Y Pathology Y	None described
Hamouda[44]	Non-randomised controlled trial	Consecutive	Prospective	A Age Y Gender Y BMI ~ Pathology Y	None described
Kitagawa[22]	Comparative.	Unclear	Unclear	A Age y Gender Y BMI ~ Pathology ~	None described
Law[24]	Non-randomised controlled study	Unclear	Unclear	B Age y Gender Y BMI ~ Pathology N	None described

				Patients in intervention group, higher surgical risk and more upper and lower third tumours.	
Osugi[28]	Comparative study with historical control	All patients who met inclusion criteria over particular time period were included (? A retrospective cohort study)	Unclear	C Age Y Gender More males BMI ~ Pathology Y	
Perry[45]	Prospective comparative study with historical control	Consecutive patients	Prospective with historical control	B. Age N Gender Y BMI N Pathology Y Intervention group were slightly older and had lower BMIs compared to control group	
Saha[46]	From Jan 00 to Dec 06. All patients who had oesophagectomy for AC that was limited to the mucosa and submucosa (pTi) at final pathological assessment for the resection specimen.	Patients were selected for laparoscopic TH or open at the discretion of the attending surgeon.		E Age Y Gender Y BMI ~ Pathology N All patients in the laparoscopic group had N0 disease; none received adjuvant treatment.	
Schroder[47]	Retrospective study over 12 year period		Retrospective with historical control	B Age N Gender Y BMI ~ Pathology Y Patients in HMIO group older, more likely to have AC than SCC, to have lower grade disease, and to have received adjuvant therapy.	
Shiraishi[30]	Retrospective review of patient records		Retrospective with historical control	B. Age N Gender Y BMI ~ Pathology N Open surgery group significantly older, more likely to have had surgery in 1995/99 rather than 2000/04, and to have deeper tumour	

				penetration	
Thomson[47]	Prospective comparative study with historical control		Prospective from database	C Age Y Gender Y BMI ~ Pathology N Comparable but more severe cases in open group in terms of stage	Not described
Van den Broek[32]	Prospective comparative study with historical control		Historical control – patients who underwent an open THE in previous 4 years.	B Age Y Gender Y BMI ~ Pathology Y More patients received neoadjuvant chemotherapy in the laparoscopic group. Statistically tested.	
Wang[48]	Prospective comparative analysis.	Unclear how allocated to groups.		A Age Y Gender Y BMI ~ Pathology Y	

4.2.1.2.5 Outcomes

Data on the outcomes of interest to this review are presented in Tables 14-16 below.

Five of the six studies which presented data on mean length of hospital stay found that this was shorter in patients undergoing HMIO, although in some cases the difference was small, particularly in those studies in which the patient groups were considered to have baseline comparability and which reported this outcome (Hamouda[44] and van den Broek[32]). Two studies found in-hospital mortality was higher with HMIO, whereas five found it was higher with open surgery. Of the six studies which compared the recurrence of oesophageal cancer after HMIO with that following open surgery, four found that recurrence rates were lower in patients undergoing HMIO. However, the largest of these studies, that by Thomson et al,[38] noted that there was no statistical association between operative approach and risk of cancer recurrence.

No consistent pattern was observed in relation to anastomotic leakage, or laryngeal or vocal cord damage. The majority of studies which reported infection rates found that these were lower in patients undergoing HMIO (for details, see Tables 14-16).

One study (Wang[48]) assessed quality of life in patients undergoing VATS or open oesophagectomy, using the EORTC QLQ-C30 and QLQ-OES18 preoperatively and at 2, 4, 12, and 24 weeks postoperatively. QLQ-C30 scores for global quality of life and physical functioning were similar in both groups preoperatively, but at 2 weeks postoperatively they were considerably lower (indicating poorer quality of life) in the group undergoing open surgery than in the VATS group. Both scores had virtually returned to preoperative levels at 12 weeks in the VATS group, while in the open surgery group they had not quite reached those levels at 24 weeks; the difference between the two groups at 24 weeks was said to be statistically significant. Fatigue, pain, and dyspnoea symptom scores were persistently higher (indicating worse quality of life) in the open surgery group than in the VATS group, especially in weeks 2 to 12, although little difference remained by week 24 (for details, see Table 17).

Table 14: HMIO vs open surgery: efficacy outcomes

Author	In hospital mortality (30 days) %		Duration of Follow up (Months)		Lymph node retrieval				Length of Stay (Days)				Local/regional recurrence %	
	I	C	I	C	I Mean	I SD	C Mean	C SD	I Mean	I SD	C Mean	C SD	I	C
Bernabe[18]	0	0	~	~	8.7		9.8		9.1	3.2	11.6	2.9	5.9	0
Buess[46]	10	14	12	12	~		~		~		~		~	~
Braghetto[15]	6	11	36	36	~		~		~		~		~	~
Bresadola[20]	0	0	~	~	22.23	12.02	18.61	13.4	16.38	8.35	22.28	10.6	~	~
Caputo[43]	2	0	11	11	~		~		~		~		~	~
Hamouda[44]	0	0	~	~	18		24		15.5		16		~	~
Kitagawa[22]	0	0	~	~	~		~		~		~		~	~
Law[24]	5	0	24	24	†7	range 2-13	†13	range 5-34	15		16		~	~
Osugi[28]			60	60	33.9	12	32.8	14	~		~		~	~
Perry[45]	0	5	30	30	†10	range 4-12	†3	range 0-7	†10	Range 8-14	†14	Range 10-19	4.8	9.5
Saha[46]	0	7	44	44	†15	range 4-41	†17.5	range 3-51	~		~		19	7.1
Schroder[47]	3	6	~	~	†27	Δ 25.6-28.3	†32.3	Δ 30.6-34.1	~		~		~	~
Shiriashi[30]	3	8	~	~	~		~		~		~		~	~
Thomson[47]	~	~	~	~	~		~		~		~		58	68
Van den Broek[32]	0	0	17	54	7	4.9	6.5	4.9	16		15		44	50
Wang[48]	0	0	6	6	~		~		~		~		0	3.4

†Median Value
Δ Confidence Interval
~ Not reported

Table 15: HMIO vs open surgery: safety outcomes (1)

Author	Anastomotic leakage %		Anastomotic leakage requiring reoperation %		Chyle leakage %		Tracheal perforation %		Pulmonary embolism %		Pulmonary complication %	
	I	C	I	C	I	C	I	C	I	C	I	C
Bernabe[18]	~	~	~	~	~	~	~	~	~	~	~	~
Buess[46]	19	20	19	20	~	~	~	~	~	~	~	~
Braghetto[15]	9	22	6	14	~	~	~	~	0	1	~	~
Bresadola[20]	7	14	7	14	~	~	~	~	7	0	~	~
Caputo[43]	18	8	0	0	~	~	~	~	~	~	~	~
Hamouda[44]	8	4	8	4	6	0	~	~	~	~	~	~
Kitagawa[22]	6	10	6	10	~	~	~	~	~	~	~	~
Law[24]	0	3	0	0	~	~	5	13	~	~	~	~
Osugi[28]	1	3	0	0	4	0	~	~	~	~	~	~
Perry[45]	19	29	19	76	~	~	0	5	~	~	~	~
Saha[46]	13	11	13	11	~	~	~	~	~	~	~	~
Schroder[47]	8	9	2	7	~	~	~	~	~	~	4	7
Shiriashi[30]	12	24	12	24	~	~	~	~	~	~	~	~
Thomson[30]	~	~	~	~	~	~	~	~	~	~	~	~
Van den Broek[32]	1	1	1	1	8	0	~	~	~	~	~	~
Wang[48]	~	~	~	~	7	3	~	~	~	~	4	14

Table 16: HMIO vs open surgery: safety outcomes (2)

Author	Infection %			Laryngeal nerve or vocal cord damage %		Damage to adjacent structures %		Conversion to open operation %
	Definition	I	C	I	C	I	C	I
Bernabe[18]		~	~	~	~	~	~	~
Buess[46]	Pneumonia	19	29	18	12	~	~	~
Braghetto[15]	Pneumonia	15	18	0	2	~	~	~
Bresadola[20]				21	7	~	~	~
Caputo[43]				~	~	2	15	0
Hamouda[44]	Pneumonia	8	13	~	~	~	~	~
Kitagawa[22]	Pneumonia or wound site	13	40	6	10	~	~	~
Law[24]	Pneumonia	14	17	18	13	0	0	18
Osugi[28]	Wound, pneumonia or atelectasis	16	18	14	13	~	~	~
Perry[45]	Pneumonia	10	5	5	10	0	5	4.8
Saha[46]		~	~	~	~	~	~	~
Schroder[47]		~	~	~	~	~	~	~
Shiriashi[30]				33	27	~	~	~
Thomson[47]		~	~	~	~	~	~	~
Van den Broek[32]	Wound or pneumonia	8	15	8	10	8	10	0
Wang[48]	Wound	0	3	~	~	~	~	~

Table 17: Selected quality of life scores following oesophagectomy (data from Wang[48])

QLQ-C30	HMIO					Open surgery				
	Preoperation	**Week 2**	**Week 4**	**Week 12**	**Week 24**	**Preoperation**	**Week 2**	**Week 4**	**Week 12**	**Week 24**
Global quality of life	71.9 (13.1)	57.7 (11.8)	59.3 (11.4)	71.0 (11.9)	74.7 (10.7)	71.0 (12.9)	43.4 (12.7)	42.2 (9.9)	62.9 (12.1)	68.4 (12.1)
Physical functioning	83.0 (7.2)	68.7 (12.2)	75.7 (11.9)	82.2 (10.3)	83.5 (9.0)	81.8 (6.9)	46.8 (15.7)	45.4 (15.2)	71.9 (11.3)	75.9 (10.7)
Fatigue	21.9 (12.7)	49.6 (15.3)	48.1 (13.9)	40.0 (13.0)	23.7 (12.4)	21.4 (12.5)	67.9 (18.8)	65.5 (15.7)	50.7 (13.9)	27.6 (11.5)
Pain	17.9 (11.2)	42.6 (13.4)	23.5 (11.5)	20.4 (10.7)	19.2 (11.0)	17.2 (13.7)	61.5 (18.4)	58.0 (22.2)	33.3 (19.4)	26.4 (12.2)
Dyspnoea	27.1 (20.8)	55.6 (16.0)	40.7 (19.2)	32.1 (21.7)	28.4 (20.0)	25.3 (19.2)	70.1 (20.6)	63.2 (20.6)	49.4 (30.4)	43.7 (29.7)

4.2.1.3 MIO/HMIO vs Open Surgery (three studies)

4.2.1.3.1 Participants

The studies in this group included 281 patients, of whom 109 underwent either MIO or HMIO and 172 underwent open surgery. The number of patients included in the individual studies ranged from 64 to 154. Studies were conducted in the USA, Austria, and Australia. The mean age of participants in those studies ranged from 60 to 67 years. None of the studies reported average patient BMI. Patients were being treated for oesophageal cancer and also, in the study by Fabian et al,[21] for benign disease; the reporting of pathology varied across studies. For details, see Table 18.

Table 18: MIO/HMIO vs open surgery: baseline characteristics of participants

Author	Year	Country	N	Age	BMI	Gender (%)	
						Male	Female
Fabian[21]	2008	USA	65	62	~	72	28
Schoppmann[49]	2010	Austria	62	60	~	74	26
Zingg[50]	2009	Australia	154	67	~	75	25

Author	Gender (%)		Indication for oesophagectomy (%)			Tumour size (n)				Pathologic (UICC) stage (n)						Site of tumour (n)		
	Male	Female	AC	SCC	Other	T1n	T2n	T3n	T4n	0	I	IIA	IIB	III	IV	Upper	Middle	Distal
Fabian[21]	72	28	69	17	14	~	~	~	~	9	15	15*	-	13	4	1	10	54
Schoppmann[49]	74	26	47	53	0	14	13	29	3	0	12	10	15	22	3	~	~	~
Zingg[50]	75	25	~	~	~	~	~	~	~	29	24	33	25	38	0	5	24	116**

* stage II not differentiate
d into IIA and IIB
** in a further 9 * patients, the tumour was located at the gastro-oesophageal junction
~ Not reported

4.2.1.3.2 Intervention

The three studies in this group compared pooled data relating to MIO (laparoscopic and thoracoscopic oesophagectomy) and hybrid procedures on the one hand with open surgery on the other; the latter could be two-stage, transhiatal, left thoraco-abdominal, or three-stage. Inclusion and exclusion criteria for each study are reported in Table 19.

Table 19: MIO/HMIO vs open surgery: inclusion and exclusion criteria

Author	Consecutive patients	Inclusion criteria	Exclusion criteria	Intervention	I n	Control	C n
Fabian[21]	~	All patients undergoing oesophagectomy during 4-year period were included regardless of disease, indications for intervention, type of oesophagectomy, comorbidities, and whether the procedure was undertaken in an elective or emergency operation	Implicitly none	Thoracoscopic and/or laparoscopic oesophagectomy (varied techniques)	22	Open surgery: transhiatal; transthoracic; transthoracic with cervical anastomosis; or thoraco-abdominal	43
Schoppmann[49]	Consecutive	~	~	Transthoracic thoracoscopy with either laparoscopy or laparotomy	31	Laparotomy and thoracotomy	31
Zingg[50]	~	For MIO/HMIO: oesophageal tumours not extending below the gastro-oesophageal junction and no previous thoracic, hiatal, or bariatric surgery. Controls selected by identifying the records of all patients who met the criteria for MIO/HMIO but underwent open surgery; selection was blind to perioperative or postoperative clinical outcomes.	~	Thoracoscopic/laparoscopic abdominal (n=30, 53.6%) or thoracoscopic laparotomy (n=26, 46.4%)	56	Ivor Lewis (n=88, 89.8%) or three-stage (n=10, 10.2%)	98

4.2.1.3.3 Summary of Surgical Procedures

None of the three studies explicitly stated where the gastric conduit was formed, although two stated where the specimen was removed from. One study used a sutured anastomosis, one used staple or suture, and the third said that the type of anastomosis used depended on surgeon preference. One study specified that the operations were carried out by thoracic surgeons, and one that they were performed by specialised upper-GI surgeons. The third provided some indication of the level of experience of the surgeons performing MIO. All three studies reported administering chemo/radiotherapy prior to treatment. For details, see Table 20.

Table 20: MIO/HMIO vs open surgery: summary of surgical procedure

Author	Gastric Conduit	Specimen Removal	Type of Anastomosis	Surgeon Experience	Baseline Comparability	Neoadjuvant Therapy	
						I	C
Fabian[21]	~	~	Varied depending on surgeon preference	Four thoracic surgeons: 3 performed both MIO/HMIO and open surgery; one only performed open oesophagectomy, having left the team before the adoption of minimally invasive techniques.	Comparable, except that benign conditions more common in the control group	*	*
Schoppmann[49]	~	Chest	Staple or Suture	All operations were performed by specialised upper-GI surgeons. All MIO/HMIOs were done by 2 surgeons. Although open operations were performed by 4 surgeons, 23/31(75%) were carried out by the same 2 surgeons who performed the MIO/HMIOs.	Comparable	15/31 (48.4%)	8/31 (25.8%) p=NS
Zingg[50]	~	Abdomen	Suture	All MIO/HMIOs performed by two surgeons who had each previously performed more than 20 procedures before 1999. Four different surgeons performed open surgery.	Comparable, except that neoadjuvant therapy more common in MIO/HMIO group	40/56 (71.4%)	48/98 (50.5%) p=0.016

*Study mentions the use of neoadjuvant therapy but doesn't provide further data

4.2.1.3.4 Summary of Study Design and Quality

All three studies used historical controls in the form of patient records for oesophagectomy performed at the same centre using open surgery. Schoppmann reported that intervention data were collected from consecutive patients.[49] Few details were provided of how controls were selected other than the period of time during which the operations were performed, and therefore there is potential for selection bias; however, Zingg reported that selection was blind to perioperative or postoperative clinical outcomes.[50] In the other studies, although patient data may be comparable between groups in terms of baseline characteristics, hidden criteria relating to outcome data may have determined the selection of historical controls.

In all three studies, the intervention and control groups were similar in terms of reported baseline data, although this was not tested statistically in one study (Fabian[21]). None of the studies reported blinding at outcome assessment.

Table 21: MIO/HMIO vs open surgery: summary of study quality

Author	Study Design	Methods to create groups	Baseline comparability A: tested stat and comparable B: tested stat and not comparable C: described as comparable D: described as not comparable E: not described	Blinding at outcome assessment
Fabian[21]	Retrospective analysis. First year	Described as comparable but not tested	C Age Y Gender Y BMI ~ Pathology N Benign conditions more common in the control group	None described
Schoppmann[49]	Prospective case controlled pair-matched study	Data from 55 patients treated years 2004 and 2008. Data collected into a prospective computer database and applied to this analysis.	A Age Y Gender Y BMI ~ Pathology Y	None described
Zingg[50]	Retrospective	Retrospective. Only patients who also met the selection criteria for the thoracoscopic approach were included in the OO group. Patients selected by identifying from the database all patients who met the selection criteria for MIE but who had undergone an OO. Selection was done without knowledge of the perioperative or postoperative clinical outcome.	A Age Y Gender Y BMI ~ Pathology Y Comparable, except that neoadjuvant therapy more common in MIO/HMIO group	None described

4.2.1.3.5 Outcomes

Data on the outcomes of interest to this review are presented in Tables 22-24 below.

In-hospital mortality was lower, and length of hospital stay shorter, in patients undergoing MIO/HMIO than in those undergoing open surgery. No consistent pattern was observed in relation to anastomotic leakage, chyle leakage, or laryngeal or vocal cord damage. Fabian[21] and Schoppmann[49] both found that rates of pneumonia were lower in patients undergoing MIO/HMIO, whereas Zingg[50] found that pulmonary complications were much higher in the MIO/HMIO group (for details, see Tables 22-24).

Table 22: MIO/HMIO vs open surgery: efficacy outcomes

Author	In hospital mortality (30 days) %		Duration of Follow up (Months)		Lymph node retrieval				Length of Stay (Days)			
	I	C	I	C	I Mean	I SD	C Mean	C SD	I Mean	I SD	C Mean	C SD
Fabian[21]	5	9	~	~	15	6	8	7	†9.5	-	†11	-
Schoppmann[49]	0	0	36	36	17.9	7.74	20.52	12.6	†15	range 8-46	†29	range 6-49
Zingg[50]	4	6	~	~	5.7	0.4	~	~	19.7	1.97	21.9	2

† Median value

Table 23: MIO/HMIO vs open surgery: safety outcomes (1)

Author	Anastomotic leakage %		Anastomotic leakage requiring reoperation %		Chyle leakage %		Pulmonary embolism %		Pulmonary complication %	
	I	C	I	C	I	C	I	C	I	C
Fabian[21]	14	7	5	7	0	5	5	0	~	~
Schoppmann[49]	3	26	3	26	3	6	~	~	0	6
Zingg[50]	20	11	9	9	4	2	~	~	59	17

Table 24: MIO/HMIO vs open surgery: safety outcomes (2)

Author	Infection %			Laryngeal nerve or vocal cord damage %		Damage to adjacent structures %		Conversion to open operation %
	Define	I	C	I	C	I	C	I
Fabian[21]	pneumonia	5	19	5	5	~	~	4.5
Schoppmann[49]	pneumonia	6	35	13	42	~	~	~
Zingg[50]		~	~	~	~	~	~	~

4.2.1.4 MIO vs HMIO vs Open Surgery (two studies)

4.2.1.4.1 Participants

The two studies in this group included 567 patients, of whom 64 underwent MIO, 343 underwent HMIO, and 160 underwent open surgery. A UK study included 121 patients with a mean age of 62, while an Australian study had 446 participants with a mean age of 62.5. Neither study reported average patient BMI. Patients were being treated for oesophageal cancer or high-grade dysplasia; for details of pathology, see Table 25.

Table 25: MIO vs HMIO vs open surgery: baseline characteristics of participants

Author	Year	Country	N	Age	BMI	Gender (%)	
						Male	Female
Safranek[51]	2010	UK	121	62	~	75	25
Smithers[16]	2007	Australia	446	62.5	~	88	12

Author	Indication for oesophagectomy (%)			Pathologic Stage (n)					ASA Stage (n)				Site of tumour (n)			
	Adeno	Squamous	Dysplasia	0	I	IIA	IIB	III	1	2	3	4	Upper	Middle	Distal	OG junction
Safranek[51]	79	19	2	4	15	28	14	60	~	~	~	~	1	9	73	~
Smithers[16]	71	19	6	~	~	~	~	~	21	282	142	3	10	84	262	90

~ Not reported

4.2.1.4.2 Intervention

Because these studies compare minimally invasive (laparoscopic and thoracoscopic) oesophagectomy against both hybrid and open procedures, they have two intervention groups. Inclusion and exclusion criteria were not reported (for details, see Table 26).

Table 26: MIO vs HMIO vs open surgery: inclusion and exclusion criteria

Author	Consecutive Patients	Inclusion Criteria	Exclusion Criteria	Intervention 1	I1 n	Intervention 2	I2 n	Control	C n
Safranek [49]	Consecutive	All patients undergoing oesophagectomy during a 9-yr period were included. Patients selected for MIO had tumours of the middle and lower third of the oesophagus	~	Total thoracoscopic/ laparoscopic approach	41	Thoracoscopic laparotomy or laparoscopic thoracotomy	34	Left thoracoabdominal, Ivor Lewis, or transhiatal	46
Smithers [16]	Consecutive	~	~	Total thoracoscopic/ laparoscopic approach	23	Thoracoscopic laparotomy approach	309	Open thoracotomy and laparotomy	114

~ Not reported

4.2.1.4.3 Summary of Surgical Procedures

Safranek et al[51] compared MIO (i.e. a total laparoscopic and thoracoscopic approach) with either HMIO (thoracoscopic oesophageal mobilisation plus laparotomy, or laparoscopic gastric mobilisation plus right thoracotomy) or open surgery (transhiatal or Ivor Lewis). Thus, MIO was compared with the combined results of two different hybrid procedures and the combined results of two different open procedures.

By contrast, Smithers et al compared MIO (i.e. a total laparoscopic and thoracoscopic approach) with either thoracoscopic-assisted laparotomy (HMIO) or transthoracic resection (open).[16] Thus MIO was compared with only one procedure in each group.

Table 27: MIO vs HMIO vs open surgery: surgical details

Author	Gastric conduit	Specimen removal	Type of anastomosis	Surgeon experience	Baseline Comparable	Neoadjuvant Therapy		
						I1	I2	C
Safranek[49]	Intracorporeal for first half of series, extracorporeal for second half	Neck or, if bulky, abdomen	Suture or staple + suture	~	No: AC more common in open group and SCC in MIO group	34/41 (83%)	27/34 (79%)	34/46 (74%)
Smithers[16]	~	Incision in the right upper quadrant	Suture	~	No: more patients in control group than intervention with stage III cancer, and with tumour located at OG junction; more patients in thoracoscopic-assisted group had compromised respiratory function and diabetes	8/23 (35%)	128/309 (41%)	29/114 (25%)

4.2.1.4.4 Summary of Study Design and Quality

Both studies undertook prospective data collection on all patients undergoing oesophagectomy. In one study (Safranek[51]) patients were operated on by one surgeon who carried out both the open, hybrid and minimally invasive procedures. Allocation to treatment was a subjective decision. In the other study (Smithers[16]), data was also collected prospectively and allocation to treatment was determined either by the procedure being used at that time or by a subjective decision by the surgeon.

The methods of patient allocation to treatment in these studies makes them highly likely to demonstrate selection bias. The lack of baseline comparability would suggest that the groups were not comparable and results also vulnerable to bias.

Table 28: MIO vs HMIO vs open surgery: summary of study quality

Author	Study Design	Methods to create groups	Prospective/retrospective data collection	Baseline comparability A: tested stat and comparable B: tested stat and not comparable C: described as comparable D: described as not comparable E: not described	Blinding at outcome assessment
Safranek[49]	Prospective cohort study	Based on exposure	Prospective	E Age Y Gender N*(sig more females in MIO) BMI ~ Pathology Y	None reported
Smithers[16]	Prospective cohort study	Grouped following treatment. No method of random allocation	Prospective database	B. Age Y Gender N*(sig more females in hybrid) BMI ~ Pathology Y Male predominance, open more likely to have AC, and tumour at the OG junction. The thoracoscopic-assisted group had more patients with compromised respiratory function and diabetes when compared with the other groups. More patients in the thoracoscopic-assisted group had preoperative chemotherapy or radiotherapy.	None reported

4.2.1.4.5 Outcomes

Data on the outcomes of interest to this review are presented in Tables 29-30 below.

The two studies displayed no consistent pattern in relation to in-hospital mortality. Both found length of hospital stay to be shorter in patients undergoing MIO than in those undergoing either HMIO or open surgery, but the difference was not great. Both studies found lymph node retrieval to be comparable whatever surgical method was used.

The two studies differed in relation to the incidence of anastomotic leak: Safranek found this was highest with MIO and lowest with open surgery, while Smithers found it was lowest with MIO and highest with open surgery. Safranek found that laryngeal nerve or vocal cord damage was highest with MIO and lowest with open surgery, whereas Smithers found no cases of such damage with MIO or open surgery, and a rate of only 3% with HMIO. Only Safranek reported the incidence of pneumonia, which was lowest with MIO.

Table 29: MIO vs HMIO vs open surgery: efficacy outcomes

Author	In hospital mortality (30 days) %			Duration of Follow up (Months)			Lymph node retrieval (median)						Length of Stay (median Days)					
	I1	I2	C	I1	I2	C	I 1	I 1 range	I 2	I 2 range	C	C range	I 1	I 1 range	I 2	I 2 range	C	C range
Safranek[49]	2	6	2	~	~	~	14	2-38	14	1-34	13.5	1-41	11	7-45	13	10-52	12	8-30
Smithers[16]	0	2	3	32	17	18	17	9-33	17	2-59	16	1-44	11	7-49	13	8-123	14	8-44

Table 30: MIO vs HMIO vs open surgery: safety outcomes

Author	Anastomotic Leakage %			Anastomotic Leakage requiring reoperation %			Chyle Leakage %			Tracheal Perforation %			Infection %				Laryngeal nerve or vocal cord damage %			Conversion to open operation %	
	I 1	I 2	C	I 1	I 2	I 1	I 1	I 2	C	I 1	I 2	C	Define				I 1	I 2	C	I 1	I 2
Safranek[49]	17	12	2	0	0	0	0	3	7	2	0	2	Pneumonia	15	21	20	17	9	2	4.9	0
Smithers[16]	4	6	9	4	6	8.7	8.7	5	6				~				0	3	0	8.0	3.1

4.2.1.5 MIO/HMIO vs Open Surgery – analysis of routinely-collected data

Lazzarino et al[37] undertook a retrospective analysis of routinely-collected Hospital Episode Statistics (HES) relating to all oesophagectomies performed for oesophageal cancer in all NHS Trusts in England during the period from April 1996 to March 2008.

4.2.1.5.1 Participants

The study included all patients diagnosed with oesophageal cancer (ICD-10 codes C15, C16.0, and D00.1) who underwent oesophagectomy (OPCS-4 codes G01, G02, G03) in all NHS Trusts in England during the study period. Only 699 of a total of 18,673 oesophagectomies (3.7%) were performed using minimally invasive techniques. While, overall, the patients were representative of clinical practice in England at the time, Lazzarino et al[37] suggest that those undergoing MIO or HMIO may have differed from those undergoing open surgery, especially in terms of socioeconomic status and comorbidity (see Table 31).

Table 31: selected characteristics of patients undergoing open and minimally invasive oesophagectomy for the treatment of oesophageal cancer in all NHS hospitals in England, 1996/97 to 2007/08[37]

Factor	Open (n=17974)	MIO/HMIO (n=699)	p
Mean age	~	~	
Male gender	13394 (74.5%)	530 (75.8%)	0.437
Socioeconomic class			0.001
1 (least deprived)	3428 (19.1%)	167 (23.9%)	
2	4004 (22.3%)	173 (24.7%)	
3	3996 (22.2%)	152 (21.7%)	
4	3381 (18.8%)	113 (16.2%)	
5 (most deprived)	2896 (16.1%)	89 (12.7%)	
Not known	269 (1.5%)	5 (0.7%)	
Comorbidity score			0.018
<3	11859 (66.0%)	455 (65.1%)	
3-4	2060 (11.5%)	103 (14.7%)	
5+	4055 (22.6%)	141 (20.2%)	

4.2.1.5.2 Intervention

This study compared oesophagectomy performed using minimally invasive techniques (laparoscopy, thoracoscopy, or both) with oesophagectomy performed using open surgery.

4.2.1.5.3 Summary of Study Design and Quality

OPCS codes were used to identify operations in which minimal access surgery was used: during the study period, oesophagectomies performed using laparoscopy were coded Y50.8 or Y75, and those performed using thoracoscopy were coded Y49.8 or Y74. 147 of the 699 operations which used minimally invasive techniques (21.0%) used thoracoscopy, 413 (59.1%) used laparoscopy, and only 139 (19.9%) used both thoracoscopy and laparoscopy. The data for MIO and HMIO were pooled for analysis.

The study is comprehensive in that it includes all 18,673 oesophagectomies recorded as having been performed in NHS hospitals in England during the study period. However, because of its use of routinely-collected data, it lacks details of the specific techniques used, and there is no information regarding the number of procedures initiated using minimally invasive techniques which had to be converted to open surgery. Moreover, only data relating to a limited number of outcomes were available.

Although the study appears to use contemporary controls, in that it presents data relating to both MIO/HMIO and open oesophagectomy performed throughout the 12-year study period, prior to 2004/05 very few oesophagectomies were performed using minimally invasive techniques, and therefore the data are biased in that patients undergoing open surgery have a higher probability than those undergoing MIO/HMIO of having undergone surgery in the earlier part of the study period. In addition, while the nature of the data made it possible to control for the number of comorbidities, and for socioeconomic deprivation as indicated by the patient's area of residence, no data were available regarding the degree of experience of the various hospitals in performing oesophagectomy, and thus it is impossible to exclude the possibility that the results for MIO/HMIO may reflect the standard of care available within centres of excellence rather than the nature of the intervention.

4.2.1.5.4 Outcomes

Lazzarino et al found that, although MIO/HMIO appeared to be associated with lower in-hospital, 30-day in-hospital, and 365-day total mortality than open surgery, and to show a trend towards lower 30-day total mortality (see Table 32), when multiple regression analysis was used, MIO/HMIO were only associated with a non-significant reduction in 365-day mortality relative to open procedures (OR = 0.68, 95% CI 0.46,1.01, p=0.058). Moreover, they considered that, in the absence of information relating to clinical factors (e.g. tumour stage, surgical procedure, number of lymph nodes retrieved, and completeness of resection), even if MIO/HMIO were associated with better outcomes than open surgery, it would not be clear whether this reflected the superiority of minimally invasive techniques or confounding due to the selection for MIO/HMIO of patients with better prognoses.[37] To this, one might add the possibility of additional confounding if minimally invasive techniques were used predominantly by teams with more extensive experience of oesophagectomy.

Table 32: Open oesophagectomy vs oesophagectomy using minimally invasive techniques: efficacy and safety outcomes (data from Lazzarino et al[37])

Outcome	Open	MIO/HMIO	Crude OR (95% CI)	p
Length of hospital stay (median, days)†	16	15	0.96 (0.92-1.00)	0.076
In-hospital mortality	1679/17974 (9.3%)	46/699 (6.6%)	0.68 (0.51-0.93)	0.014
30-day in-hospital mortality	1238/17974 (6.9%)	31/699 (4.4%)	0.63 (0.44-0.90)	0.012
30-day total mortality*	566/8966 (6.3%)	9/251 (3.6%)	0.55 (0.28-1.08)	0.083
365-day total mortality**	2210/7571 (29.2%)	32/153 (20.9%)	0.64 (0.43-0.95)	0.027
28-day emergency readmission†	2131/16295 (13.1%)	94/653 (14.4%)	1.12 (0.89-1.40)	0.329

† Calculated on patients who did not die in hospital
* Data available only for years 2001/02 to 2005/06
** Data available only for years 2001/02 to 2004/05

4.2.1.6 Summary of Efficacy Data

The evidence for the efficacy of MIO and HMIO relative to open oesophagectomy is not conclusive. Although some studies suggested that the use of minimally invasive techniques was associated with higher in-hospital mortality rates, more suggested that open surgery was associated with higher in-hospital mortality rates. However, in their analysis of a large database, Lazzarino et al found that, following multiple regression analysis to control for age, gender, socio-economic deprivation, comorbidity score, year, and number of emergency admissions, the use of minimally invasive techniques was not associated with lower in-hospital and 30-day in-hospital mortality rates relative to open procedures, but only with a non-significant reduction in 365-day mortality.

The evidence relating to the length of hospital stay suggests that the mean length of hospital stay may be shorter in patients undergoing MIO or HMIO than in those undergoing open surgery; however, in many cases the difference was not great.

There is no evidence for a consistent difference between MIO or HMIO and open surgery in terms of either lymph node retrieval or cancer recurrence. Although the majority of studies which reported recurrence rates found that they were lower in patients undergoing HMIO, but the largest of these studies, that by Thomson et al,[38] noted that there was no statistical association between operative approach and risk of cancer recurrence.

However, quality of life data from the study by Wang et al[48] suggest that recovery from HMIO is more rapid than recovery following open oesophagectomy.

4.2.2 Observational Studies (included for safety)

4.2.2.1 Case Series

Two publications were identified which presented uncontrolled data relating to patients with oesophageal cancer or high-grade dysplasia who underwent MIO in one university hospital or its affiliated tertiary care hospital in the USA. Luketich et al[35] reported prospectively-collected data relating to 222 patients considered suitable for cervical anastomosis, who underwent MIO between June 1996 and August 2002. Mean follow-up was 19 months (range 1-68 months). Kilic et al[40] reviewed data relating to 282 patients who underwent MIO between 1999 and 2004 in order to assess the impact of obesity (BMI $\geq$30) on perioperative outcomes. As the time periods for the two case series overlap, some patients are presumably included in both studies, making it inappropriate to pool their results.

4.2.2.1.1 Participants

Both studies stated that they analysed data relating to all eligible patients who were treated during the relevant period. Kilic et al excluded patients with a BMI of less than 18.5 kg/m^2 because poor nutritional status could have an adverse effect on operative outcomes; however, only two patients were excluded for this reason.[40] For details of baseline characteristics, see Table 33.

Table 33: Case series: baseline characteristics of participants in the case series by Luketich et al[35] and Kilic et al[40]

Characteristic	1996-2002[35] (n=222)	1999-2004[40] (n=282)	
		Obese (n=84)	Non-obese (n=198)
Male	186 (83.8%)	71 (84.5%)	166 (83.8%)
Female	36 (16.2%)	13 (15.5%)	32 (16.2%)
Median age, years (range)	66.5 (39-89)	61.6	64.9
Mean BMI	~	34.5	25.5
Indication for operation: carcinoma (tumour stage I-IV)	175 (78.8%)	58 (69.0%)	134 (67.7%)
Indication for operation: high-grade dysplasia/carcinoma in situ	46 (21.2%)	26 (31.0%)	64 (32.3%)
Tumour histology: AC	~	69 (82.1%)	158 (79.8%)
Tumour histology: SCC	~	15 (17.9%)	40 (20.2%)
Neo-adjuvant chemotherapy	78 (35.1%)	30 (35.7%)	66 (33.3%)
Neo-adjuvant radiation	36 (16.2%)	8 (9.5%)	35 (17.7%)

4.2.2.1.2 Intervention: summary of surgical techniques

Luketich et al stated that a laparoscopic transhiatal approach was initially used only for patients with smaller tumours or high-grade dysplasia (n=8). However, the procedure was soon modified by the addition of a right video-assisted thoracoscope, and this combined thoracoscopic and laparoscopic approach was used for the remaining 214 patients in their case series (96.4%). In 213 patients (95.9%), the oesophageal bed was used for the gastric conduit, while in the remaining nine the substernal route was used to allow postoperative radiation of the oesophageal bed without irradiation of the gastric pull-up. A gastric tube of 5 to 6 cm in diameter was used in most patients. However, midseries, a narrower tube (3-4 cm) was used for 58 patients (26.1%) to avoid the need for a pyloric drainage procedure, with the hope of reducing the risk of reflux; because of an increased risk of leakage, this narrow tube was later abandoned in favour of the 6 cm tube with a pyloroplasty.[35] Kilic et al[40] stated that the MIO technique used for patients in their study was similar to that described by Luketich et al;[35] further details were not provided, other than to indicate that 9 patients (3.2%) did not have a cervical anastomosis,[40] whereas Luketich et al[35] indicated that all patients included in their case series were suitable for cervical anastomosis, and that open surgery was used for those who required an intrathoracic anastomosis.

4.2.2.1.3 Summary of Study Design and Quality

Both publications took the form of analyses of prospectively-collected data. Kilic et al specified that their review was performed retrospectively.[40]

4.2.2.1.4 Outcomes

In the series by Luketich et al, MIO was successfully completed in 206 of the 222 patients (92.8%). 12 of the remaining 16 required thoracotomy, and 4 laparotomy: in 5, mini-thoracotomy was planned, while 10 required “nonemergent” conversions because of adhesions, and one because a persistent intercostal vessel could not be satisfactorily controlled by VATS. 26 patients (11.7%) suffered an anastomotic leak (see Table 34): 15 of the 58 patients who had been given a narrow tube (25.9%) compared with 10 of the 164 given a standard tube (6.1%, $p<0.001$).

Because neither report presented information on all outcomes of interest, data from both reports are presented in Table 33. For comparability, data relating to obese and non-obese patients from Kilic et al’s study have been pooled. Unsurprisingly, given that both sets of data come from the same centre and will relate to some of the same patients, the rates for the same outcomes are broadly similar, the one exception being total major complications, where, perhaps surprisingly, the rate is noticeably higher for the later period (32.3% vs 23.9%, see Table 34).

Table 34: case series by Luketich et al[35] and Kilic et al[40]: selected outcomes

Outcome	Number (%)	
	1996-2002[35] (N=222)	1999-2004[40] (N=282)
Conversion to open operation	16 (7.2%)	~
30-day operative mortality	3 (1.4%)	5 (1.8%)
90-day mortality	~	16 (5.8%)
Total major complications	53 (23.9%)	91 (32.3%)
Total minor complications	71 (32.0%)	88 (31.2%)
Anastomotic leak	26 (11.7%)	36 (12.8%)
Pulmonary embolism	3 (1.4%)	7 (2.5%)
Deep vein thrombosis	3 (1.4%)	2 (0.7%)
Vocal cord palsy	8 (3.6%)	~
Recurrent laryngeal nerve injury	~	15 (5.3%)
Minor intraoperative tracheal perforation (1-2mm)	2 (0.9%)	~
Tracheal tear	2 (0.9%)	2 (0.7%)
Chylothorax	7 (3.2%)	7 (2.5%)
Pneumonia	17 (7.7%)	27 (9.6%)
Acute respiratory disease	4 (1.8%)	~
Respiratory failure requiring intubation or tracheostomy	~	16 (5.8%)

Kilic et al noted that outcomes were generally similar in obese and non-obese patients: moreover, while complication rates and 30-day operative mortality were comparable, obese patients had a lower 90-day mortality rate (1.2% vs 7.6%, p=0.045).[40]

Summary

Luketich et al and Kilic et al report major complications in between 24% and 32% of patients undergoing MIO, with 12-13% suffering anastomotic leak, 4-5% suffering injury to the recurrent laryngeal nerve or vocal cord palsy, and 8-10% developing pneumonia. It should be noted that these results come from a centre with extensive experience in oesophageal surgery and minimally invasive surgical techniques;[35] Luketich himself is an excellent surgeon, and is supported by a technically excellent team and a superb ITU. Thus, his results are not generalisable to either a normal UK oesophageal centre or an average US teaching centre.

4.2.2.2 Case Reports

Seven case reports were identified which reported rare adverse effects associated with oesophagectomy performed using minimally invasive techniques. These related to five complications: hiatus hernia, tension capnothorax, complex tracheal lesion, injury to the thoracic aorta, and injury to an aberrant subclavian artery. Four of these complications were not reported in any of the included comparative studies; one of the included studies, that by van den Broek et al,[32] briefly mentions herniation of the small intestine into the thorax in one of 20 patients undergoing open oesophagectomy (5%).

Three case reports related to hiatus hernia presenting as a late complication of laparoscopic-assisted oesophagectomy. Lowe et al reported three cases occurring between four and seven months after laparoscopic-assisted cardio-oesophagectomy.[52] Fumagalli et al reported two cases of acute massive hiatal hernia occurring 4 to 8 months after laparoscopic gastroplasty with transthoracic oesophagectomy for cancer in a high-volume referral centre for oesophageal surgery, following an uneventful postoperative course.[53] Finally, Vallböhmer et al[54] identified hiatus hernia in 5 patients between 0.5 and 14 months after oesophagectomy with laparoscopic mobilisation of the stomach; one of the patients was asymptomatic.

Bala et al reported tension capnothorax resulting from a pleural tear made during laparoscopic mobilisation of the oesophagus within the mediastinum.[55] This adverse event had apparently not been previously reported even though Bala et al stated that pleural tears occurred in as many as 93% of laparoscopic transhiatal oesophagectomies. However, the evidence which they cite does not suggest that pleural tears are significantly more common when oesophagectomy is performed using minimally invasive techniques: the figure of 93% is taken from a small case control study by Makay et al in which pleural tears also occurred in 84% of patients undergoing open oesophagectomy.[56]

Ferreira et al reported a complex tracheal lesion in a patient undergoing minimally invasive oesophagectomy using video-assisted thoracoscopy and laparoscopy. However, while stating that air fistulae resulting from lesions of the trachea or main stem bronchi are severe and potentially fatal complications of oesophagectomy, Ferreira et al did not suggest that such lesions were more likely to occur with minimally invasive than with open oesophagectomy.[57]

Bonavina et al[58] report injury to the supradiaphragmatic aorta during the laparoscopic phase of an oesophagectomy. This necessitated immediate conversion to laparotomy, and it was then possible both to repair the injury and to complete the oesophagectomy.

Finally, Pantvaidya et al reported injury to an aberrant right subclavian artery during video-assisted thoracoscopic mobilisation of the oesophagus performed during oesophagectomy for cancer. Following repair, the patient made a complete recovery. The authors note that this anatomical anomaly is rare, occurring in at most 2% of the population. As it is also usually asymptomatic, and the most likely symptom, dysphagia, is also a symptom of oesophageal cancer, preoperative diagnosis depends on a high index of suspicion and very careful radiological investigation. Pantvaidya et al suggest that, if such an anomaly has not been identified preoperatively, the inability to palpate pulsations when performing thoracoscopic oesophagectomy would make it more difficult to identify and preserve the anomalous artery than would be the case using a transhiatal/transthoracic approach.[59]

4.2.3 Summary of Safety Evidence

The comparative studies included in the systematic review vary in terms of the adverse events which they report. The three most commonly reported adverse events were anastomotic leak, pneumonia, and laryngeal nerve or vocal cord damage. The incidence of these complications varied from study to study, both in terms of absolute rates and in terms of whether they were more commonly associated with open operations or with the use of minimally invasive techniques. The range of incidence rates is set out in Table 35; for MIO, data from the large case series by Luketich et al[35] and Kilic et al[40] are included for comparison. The rates of conversion to open operation are also summarised. However, it should be noted that such conversion may occur for any one of a number of reasons, including bleeding, adhesions, and kit failure.

Table 35: Incidence of major complications

Complication	MIO		HMIO: comparative studies	MIO/HMIO: comparative studies	Open: comparative studies
	Comparative studies	Case series			
Anastomotic leak	4-17%	12-13%	0-19%	3-20%	2-29%
Pneumonia	0-25%	8-10%	0-21%	5-6%	3-35%
Laryngeal nerve or vocal cord damage	0-20%	4-5%	0-33%	5-13%	0-42%
Conversion to open operation	5-8%	7%	0-18%	4.5%	n/a

n/a not applicable

The studies included in the current review reported rates of anastomotic leak ranging from zero in a number of studies to 20% in patients undergoing MIO or HMIO in the study by Zingg et al,[50] and 29% in patients undergoing open oesophagectomy in the study by Perry et al.[45] While some studies found the use of minimally invasive techniques to be associated with higher rates of anastomotic leak, slightly more found that rates were higher in patients undergoing open surgery. Reported rates of pneumonia ranged from zero in a number of studies to 25% in patients undergoing MIO in the study by Pham et al[41] and 35% in patients undergoing open oesophagectomy in the study by Schoppmann et al.[49] Finally, reported rates of laryngeal nerve or vocal cord injury ranged from zero in a number of studies to 33% in patients undergoing HMIO in the study by Shiraishi et al[30] and 42% in patients undergoing open oesophagectomy in the study by Schoppmann et al.[49] Some studies found the use of minimally invasive techniques to be associated with lower rates of injury to the recurrent laryngeal nerve or vocal cord, but slightly more found that rates were lower in patients undergoing open surgery. While it has been suggested that variations in reported rates may be related to the methods used to assess such injury, with the implication that rates may be particularly high in studies which use laryngoscopy to look for abnormal cord movement,[60] it should be noted that Schoppmann et al, who report the highest rate, appear simply to report hoarseness.[49]

It is noteworthy that the data from even a specialised centre such as Luketich's indicate that MIO is associated with high rates of major complications (around 23-32%), and relatively high rates of individual complications such as anastomotic leak (12-13%), pneumonia (8-10%), severe respiratory failure (6%) and vocal cord palsy or recurrent laryngeal nerve injury (4-5%). Although these rates are lower than those reported by some of the comparative studies included in this review, they suggest that the very low rates reported in others of the included studies should be viewed with caution.

Rates of conversion to open operation ranged from 5-9% for MIO and 0-18% for HMIO (for details, see section 5.3.4).

Case reports have drawn attention to the possibility of other, less common but potentially serious, adverse events: hiatus hernia, tension capnothorax, and injuries to the trachea, thoracic aorta, and subclavian artery. Generally, case reports do not provide any indication of the rate of incidence of the complications which they report. However, two of the reports of hiatus hernia summarised above attempt to do so. Fumagalli et al[53] suggest that hiatus hernia may be more common after laparoscopic oesophagectomy than after open surgery because it occurred in 4.5% (2/44) of patients who underwent laparoscopic gastroplasty in their centre between February 2003 and November 2005, while they draw attention to reported incidence rates of 0.4% to 2% for standard open oesophagectomy; however, as they also report that the rate associated with open oesophagectomy rises to 6% with longer follow-up, their case is not conclusive. Moreover, Vallböhmer et al[54] found an incidence of hiatus hernia of 2.7% (5/187) in consecutive patients who underwent oesophagectomy with laparoscopic mobilisation of the stomach in their centre, compared with 2.4% (4/168) in those who underwent open surgery, suggesting that the incidence may not be affected by the operative technique used. Similarly, the evidence cited by Bala et al in their discussion of tension capnothorax resulting from a pleural tear[55] does not indicate that pleural tears are significantly more common when oesophagectomy is performed using minimally invasive techniques than with open oesophagectomy.

5 DISCUSSION

5.1 Quantity and Quality of Available Evidence

The quantity and quality of available evidence was not as good as might have been hoped. Although 26 relevant comparative studies were identified, few of these reported total MIO, and the evidence relating specifically to MIO is derived from only 191 patients. Most studies reported results relating to a “hybrid” MIO technique where part of the surgery was video-assisted and part was performed using a thoracotomy or laparotomy; data have been reported relating to over 1000 patients undergoing HMIO. The existence of many variants of the hybrid procedure, and the use of many different combinations of technique and equipment in the included studies, limits the possibility of direct comparison between studies.

The procedure used for open surgery also varied between studies. They included two-stage, transhiatal, left thoraco-abdominal, and three-stage procedures. Frequently, the operative procedure was not described at all. As there is a debate about the efficacy of different open procedures for oesophagectomy (e.g. transhiatal versus transthoracic), the use of various types of open surgery as a comparator is not ideal.

In addition, few studies provided details about the experience or skill of the surgeon operating in either the intervention or control group. Details such as whether the surgeon was an upper gastrointestinal or thoracic surgeon, and how many procedures they had completed before the study, while important for interpreting study results, are seldom reported. Studies from centres in the early stages of introducing MIO techniques for oesophagectomy may include “learning curve” data whereas studies from more experienced centres may have more favourable results due to superior experience with MIO techniques (see section 5.2 below).

Furthermore, details of how and why different procedures were employed were rarely provided. Reasons such as hospital protocol, surgeon preference, patient preference, availability of facilities, and pathology were inconsistently and/or infrequently reported.

In terms of study design, the quality of the included studies was generally poor. No randomised controlled trials were identified. Because participants were not randomised to treatment groups, the possibility of selection bias cannot be excluded, particularly as there was seldom evidence that the intervention and control group were well matched. Moreover, sample sizes were frequently small.

The baseline comparability of the treatment groups was questionable. In some cases, this was because patients undergoing MIO had different pathology from patients undergoing open oesophagectomy. However, even when baseline comparability appeared good, the use of historical controls introduced uncertainty. As studies seldom reported details of how the controls were selected, even when they stated that the intervention data were gathered prospectively and/or consecutively, there is always a potential for selection bias in the retrospective identification of control patients. In their analysis of routinely-collected data relating to a large number of patients, Lazzarino et al observed a significant reduction over time in mortality rates following oesophagectomy, whether performed using open or minimally invasive techniques.[37] They suggested that this reduction might be related to improved patient selection for surgery, better perioperative care (which may include the increase in preoperative radiochemotherapy[47]), improved surgical care, and increasing centralisation of oesophageal cancer surgery services; but, whatever the reason for the phenomenon, the result is that studies which use historical controls are likely to favour the use of minimally invasive techniques.

Finally, outcomes were not reported consistently across studies. This is particularly true of surgical complications. For instance, anastomotic leak is a risk commonly associated with the surgery. Whilst anastomotic leaks were frequently reported, details of their management were not: many studies failed to describe whether the leak was managed conservatively or whether it required reoperation.

5.2 Discussion of Efficacy Data

The efficacy data summarised in section 4.2.1.6 above suggest that oesophagectomy performed using minimally invasive techniques may be associated with lower in-hospital mortality rates and slightly shorter lengths of stay than open oesophagectomy, with no increase in the risk of cancer recurrence. However, given the poor quality of the evidence, these findings cannot be considered conclusive.

The included studies focus primarily on short-term outcomes: Thomson et al,[38] who report 5-year cancer recurrence, provide the only evidence relating to survival beyond one year. Moreover, none of the included studies report as an outcome return to normal activity, arguably one of the most important outcome measures, and one which may differ considerably between MIO and open surgery even when the length of hospital stay is similar. However, quality of life data from the study by Wang et al[48] suggest that recovery is more rapid following HMIO than following open oesophagectomy.

A question has been raised regarding the generalisablity to the western hemisphere of efficacy data from the East, where the incidence of oesophageal cancer is considerably higher than in the West. Because the incidence does not justify the use of screening programmes in the West, tumours are generally more advanced when they are identified. In addition, adenocarcinomas are common in the West, but rarely found in the East.[61] Because of the poor reporting of many of the included studies, it has not been possible to assess the extent to which these factors may affect the efficacy data.

5.3 Discussion of Safety Data

This section focuses on the three adverse events most commonly reported in the studies included in this review - anastomotic leak, pneumonia, and laryngeal nerve or vocal cord damage - and also conversion to open operation.

5.3.1 Anastomotic Leak

Anastomotic leaks occur more frequently with cervical anastomoses than with thoracic anastomoses, affecting 10-25% of cervical anastomoses but fewer than 10% of thoracic anastomoses. Cervical anastomoses are generally used for MIO and HMIO, but may also be used for open oesophagectomy, depending on the location of the tumour and the specific procedure which is used. As noted in section 4.2.3, there is no evidence to suggest that the rate of anastomotic leak is higher when oesophagectomy is performed using minimally invasive techniques.

A recent systematic review of randomised trials found that, following oesophagectomy for cancer, cervical anastomosis was associated with significantly higher rates of recurrent laryngeal nerve trauma and anastomotic leak than was intrathoracic anastomosis; however, it was not associated with an increased risk of pulmonary infection, perioperative mortality, benign stricture, or tumour recurrence[62] (for details, see Table 36). This may reflect the fact that, although clinically apparent leaks are more common with cervical anastomoses, they are less serious than those from thoracic anastomoses: the latter are associated with a mortality rate of around 60%, compared with under 20% for clinically apparent leaks from cervical anastomoses.[63]

Table 36: Risk of complications with cervical anastomosis, compared with intrathoracic anastomosis (after Biere et al 2011[62])

Complication	Odds ratio	95% CI	p
Recurrent laryngeal nerve trauma	7.14	1.75-29.14	0.006
Anastomotic leak	3.43	1.09 -10.78	0.03
Pulmonary infection	0.86	0.13-5.59	0.87
Perioperative mortality	1.24	0.35-4.41	0.74
Stricture of anastomosis	0.79	0.17-3.87	0.79
Tumour recurrence	2.01	0.68-5.91	0.21

5.3.2 Pneumonia

Pulmonary complications form the most common source of morbidity and mortality following oesophagectomy. It was hoped that the use of thoracoscopy rather than thoracotomy would reduce pulmonary morbidity by minimising damage in that area. However, studies vary considerably in their definition of a pulmonary complication,[9] and therefore, in the hopes of increasing inter-study comparability, the current review has focused primarily on pneumonia. Most studies included in this review found that the use of minimally invasive techniques was associated with lower rates of pneumonia, although some found that rates were lower in patients undergoing open surgery.

5.3.3 Injury to the Recurrent Laryngeal Nerve or Vocal Cord

Injury to the recurrent laryngeal nerve or vocal cord forms a relatively common complication of oesophagectomy, particularly when a cervical anastomosis is used. In some cases, the symptoms may be mild and transient hoarseness with unimpaired swallowing. In other cases, problems with swallowing may be so severe that food may be aspirated, leading to potentially life-threatening pulmonary complications and requiring urgent corrective surgery.[64] Baba et al found that, in 21 out of 51 oesophagectomy patients with postoperative vocal cord paralysis, symptoms had resolved spontaneously at one year postoperatively; however, in 30 patients (59%) it persisted at one year, and the 11 of these 30 patients who complained of severe hoarseness displayed weight loss and loss of vital capacity relative to patients with normal vocal cord function, with three requiring hospitalisation for repeated aspiration pneumonia.[65] Gockel et al also found that recurrent laryngeal nerve paralysis (RLNP) following oesophagectomy for cancer was associated with a significantly increased risk of post-operative pneumonia, although the risk of 30-day or total mortality was not increased[66] (see Table 37).

Table 37: Perioperative morbidity and mortality after oesophagectomy for oesophageal cancer in patients with and without recurrent laryngeal nerve paralysis (RLNP) (data from Gockel et al 2005[66]

Outcome	Patients with RLNP (n=63)	Patients without RLNP (n=341)	p
30-day mortality	2 (3.2%)	23 (6.7%)	0.252
Total mortality	6 (9.5%)	39 (11.4%)	~
Pneumonia	33 (52.4%)	90 (26.4%)	0.027

~ not reported

While some studies included in this review found that rates of injury to the recurrent laryngeal nerve or vocal cord were higher in patients undergoing open surgery, slightly more found that the use of minimally invasive techniques was associated with higher injury rates.

5.3.4 Conversion to Open Operation

Relatively few of the comparative studies included in the current review reported conversion to open surgery as an outcome and, unfortunately, the routinely-collected data analysed by

Lazzarino et al[37] did not distinguish between procedures which were completed using minimally invasive techniques and those which were started using those techniques and then required conversion to open surgery. However, in those comparative studies which reported this outcome, conversion rates for MIO ranged from 4.9% to 8.0%, while those for HMIO ranged from 0 to 18.2%; in the large case series by Luketich et al,[35] conversion to open surgery was necessary in only 16 out of 222 patients undergoing MIO (7.2%) (for details, see Table 38).

Table 38: Conversions from minimally invasive to open surgery

Study	MIO (%)	HMIO (%)	MIO/HMIO (%)
Caputo[43]	-	0/45	-
Fabian[21]	-	-	1/22 (4.5%)
Law[24]	-	4/22 (18.2%)	-
Luketich[35]	16/222 (7.2%)	-	-
Perry[45]	-	1/21 (4.8%)	-
Safranek[51]	2/41 (4.9%)	0/34	-
Smithers[16]	2/25 (8.0%)	10/319 (3.1%)	-

It should be borne in mind that the available evidence for the rate of conversion to open surgery is drawn from a small number of procedures (288 MIOs, 441 HMIOs, and 22 MIO/HMIOs), and that 19 studies did not report conversions. Because of the frequent lack of transparency in reporting patient recruitment, it is possible that these studies only reported successful intervention procedures, either excluding cases of conversion from their intervention groups and/or reporting them as part of the open surgery group without mentioning that they had initially been intended for minimally invasive surgery. It is fruitless to speculate what the conversion rates might have been in these studies.

5.3.4.1 Reasons for Conversion to Open Surgery from MIO

Law et al could not complete oesophageal mobilisation in three patients because they had **locally advanced tumours** with infiltration to surrounding structures; in one, the oesophagus was also located on the left side of the vertebral column, out of reach of thoracoscopic instruments. In the fourth patient, thoracoscopy was stopped because of **poor single-lung ventilation**; subsequently, during laparoscopy, metastases were found and oesophagectomy was not attempted. None of the patients required urgent conversion because of bleeding or damage to mediastinal structures.[24]

Luketich et al stated that mini-thoracotomy was planned from the outset in 5 of the patients who underwent conversion to open surgery, and was non-emergency in the remaining 11, being due to **adhesions** in 10, and to the **need to oversew a persistent intercostal vessel** in the eleventh.[35]

One patient in the study by Perry et al required conversion to laparotomy because of **upper abdominal adhesions from previous abdominal surgery**.[45]

In the study by Safranek, MIO had to be converted to open surgery in two patients: one required conversion to laparotomy because of **dense adhesions following previous open cholecystectomy**, while another required rapid conversion to open surgery, with splenectomy, following **profuse bleeding from a short gastric vessel**; this patient, whose tumour was also found to be more advanced than indicated by CT scanning, died four days after surgery from multiple organ failure and disseminated intravascular coagulation. A further 5 patients undergoing MIO required a small abdominal incision to assist in passing the gastric conduit through the posterior mediastinum; in one patient in this group, the gastric conduit was inadvertently constructed with a twist.[51]

Finally, in the study by Smithers et al two patients were converted from MIO to open surgery; these were excluded from the total of 446 patients whose subsequent results were presented, and **reasons for conversion were not given**.[16]

5.3.4.2 Reasons for Conversion to Open Surgery from HMIO

Caputo[43] and Safranek[51] reported no conversions to open surgery, while Smithers et al reported 10 conversions; again, these patients were excluded from the total of 446 patients whose subsequent results were presented, and **reasons for conversion were not given**.[16]

5.3.4.3 Reasons for Conversion to Open Surgery from MIO/HMIO

In the study by Fabian et al, one patient required conversion to laparotomy because of **changes to the pancreatic bed resulting from neoadjuvant chemoradiation**.[21]

5.3.4.4 Reasons for Conversion to Open Surgery: case reports

One case report also reported **injury to the aorta** which required urgent conversion to laparotomy because of bleeding;[58] the **injury to an aberrant subclavian artery** reported by

Pantvaidya et al[59] also appears to have required conversion to open surgery. Finally, the **tension capnothorax** reported by Bala et al required the conversion of laparoscopic transhiatal oesophagectomy to open surgery.[55]

5.3.4.5 Reasons for Conversion to Open Surgery: summary

In the studies included in this review, the most frequently reported reason for conversion to open surgery was the presence of adhesions; the second most common was that the tumour was more advanced than anticipated (see Table 39). Safranek et al reported the only case from a comparative study of a patient who required urgent conversion from MIO to open surgery because of bleeding.[51]

Table 39: Summary of reasons for conversion from minimally invasive to open surgery

Study	MIO	HMIO	MIO/HMIO
Comparative studies			
Fabian[21]	-	-	Changes caused by neoadjuvant chemoradiation (n=1)
Law[24]	Tumour stage (n=3) Poor single-lung ventilation (n=1)	-	-
Luketich[35]	Adhesions (n=10) Planned mini-thoracotomy (n=5) Persistent intercostal vessel (n=1)	-	-
Perry[45]	Adhesions (n=1)	-	-
Safranek[51]	Adhesions (n=1) Bleeding (n=1)	-	-
Smithers[16]	Reason not given (n=2)	Reason not given (n=10)	-
Case series			
Bala[55]		Tension capnothorax (n=1)	
Bonavina et al[58]		Bleeding (n=1)	
Pantvaidya [59]		Injury to aberrant subclavian artery (n=1)	

5.4 Oesophagectomy: the learning curve

5.4.1 Caseloads and Outcomes: oesophagectomy of any type

There is substantial evidence to suggest that patient outcomes following open oesophagectomy are heavily influenced by experience, although there is some debate as to whether that experience pertains more to the individual surgeon or to the institution.

5.4.1.1 Mortality

In analyses of nationwide US Medicare data relating to patients aged 65 to 99, Birkmeyer et al found that, when adjusted for case mix, operative mortality rates for oesophagectomy between 1994 to 1999 were 11.9% higher in hospitals which performed fewer than 2 such procedures a year than in those which performed over 19,[67] while between 1992 and 2002 the 5-year survival rate in centres performing fewer than 4 oesophagectomies a year in elderly Medicare patients was almost half that seen in centres performing over 14 oesophagectomies in such patients (17.4% vs 33.7%). After adjusting for patient characteristics and adjuvant therapy, the hazard ratio for mortality in high-volume compared with low-volume centres was 0.71 (95% CI 0.54-0.92).[68] Because the analyses were restricted to oesophagectomies performed in elderly patients treated under Medicare, these figures underestimate the total number of oesophagectomies performed in the various hospitals, and therefore the thresholds for safer oesophagectomy; nonetheless, they strongly suggest that patient outcomes are associated with hospital caseload.

Other studies suggest that outcomes following oesophagectomy may be associated with the surgeon's annual caseload of relevant operations. Thus, in Canada, the operative mortality rate in all 74 cancer patients who underwent oesophagectomy between 1989 and 1993 was significantly lower for surgeons who performed 6 or more oesophagectomies a year for cancer than for those who performed 5 or fewer such operations a year (0 vs 22%, $p<0.0014$).[69] While that result may be related to hospital caseload, a prospective cohort study of all patients first diagnosed with oesophageal or gastric cancer in all NHS hospital trusts in the former South and West health region of England between July 1996 and July 1997 found that, after adjusting for clinical factors and the hospitals' surgical volume, operative mortality in patients who underwent any surgery (resection, bypass, or 'open and close') for oesophageal cancer declined by 40% (OR 0.60, 95% CI 0.36-0.99), and risk of death over a follow-up period of at least 2 years by 8% (HR 0.92, 95% CI 0.85-0.99), for each increase of 10 patients in doctors' annual surgical caseloads.[70] Moreover, in-hospital (operative) mortality at Papworth Hospital between January 1994 and December 2005 was significantly lower for the two surgeons who performed a mean of 11 oesophagectomies per year than for those who performed a mean of only four (4.2% vs 16.9%, $p=0.004$).[71]

In response to such data, in 2001, the NHS Executive issued guidance that "treatment for patients with oesophageal cancer should be the responsibility of Specialist Oesophago-gastric Cancer Teams based in Cancer Units or Cancer Centres which would normally serve populations of at least one million".[4] It was anticipated that these specialist teams, which would normally manage at least 100 patients with oesophageal cancer, would perform approximately 40 oesophageal resections a year.[72] The NHS Executive further stated that surgery for cancer of the oesophagus and oesophago-gastric junction should only be undertaken by specialist surgeons who carried out "a sufficiently high volume of such procedures for meaningful audit of outcomes (likely to be at least 10 per year)".[4]

Possibly as a result of this guidance, between 1997/98 and 2003/04 the total number of hospitals in England which performed total or partial oesophagectomy or oesophago-gastrectomy for cancer decreased from 180 to 111, primarily because of a reduction in the number of very low-volume hospitals undertaking the procedures. There was also a significant overall decrease in in-hospital mortality over the same period. The percentage of emergency admissions also decreased significantly, from 7.7% in 1997/98 to 3.5% in 2003/04 (p<0.001), but there was no significant change in the mean age of the patients undergoing surgery, or in the male:female ratio; data on other clinical factors such as disease severity and comorbidity were not available. As the number of resections also declined over the study period, despite an increase in the annual number of diagnoses of oesophageal cancer, the reduction in in-hospital mortality may reflect improvements in the selection of patients with resectable cancers. However, throughout the period, in-hospital mortality was consistently lowest in hospitals which performed 40 or more resections a year[72] (see Table 40).

Table 40: In-hospital mortality in patients undergoing total or partial oesophagectomy or oesophago-gastrectomy for cancer in England, by number of resections performed (data from Al-Sarira et al[72])

	1997-1999	2000-2001	2002-2003	p
Overall	627/5349 (11.7%)	323/3260 (9.9%)	246/3229 (7.6%)	<0.001
Very low-volume hospitals (≤9 resections)	187/1444 (13.0%)	97/763 (12.7%)	54/459 (11.8%)	0.801
Low-volume hospitals (10-19 resections)	227/1628 (13.9%)	92/791 (11.6%)	85/1026 (8.3%)	<0.001
Medium-volume hospitals (20-29 resections)	94/738 (12.7%)	41/445 (9.2%)	37/614 (6.0%)	<0.001
High-volume hospitals (30-39 resections)	53/587 (9.0%)	39/389 (10.0%)	38/422 (9.0%)	0.845
Very high-volume hospitals (≥40 resections)	66/952 (6.9%)	54/872 (6.2%)	32/708 (4.5%)	0.118

A study of outcomes in all 252 patients who underwent total thoracic oesophagectomy for cancer at a tertiary referral centre in Belfast between June 1994 and June 2006 found that the case volume per surgeon (which ranged from a mean of 5 to 10.5 cases/year) did not have any significant influence on operative mortality or, when adjusted for pathological staging, on overall 1-year and 5-year survival. Thus, the authors suggested that patient outcomes are influenced not so much by the single component of the surgeon's experience, measured by relevant caseload, as by the skill and experience of the multidisciplinary team working within the high-volume hospital.[73]

5.4.1.2 Morbidity

A study of specific postoperative complications recorded in routinely-collected data for all 366 patients discharged from Maryland hospitals from 1994 to 1998 following oesophagectomy found that 43% of patients had complications: 22% had one complication, 11% had 2, 4% had 3, and 5% had 4 or more. The incidence of mortality, and of several of the specified complications, was significantly higher in low-volume hospitals than in high-volume hospitals, and remained higher after adjustment for patient demographics, nature of admission, type of surgery, and comorbidities (for details, see Table 41).[74] Similarly, no significant difference was found in the rate of infection in patients who underwent oesophagectomy for cancer in Californian hospitals which performed over and under 30 oesophagectomies from 1990 to 1994. However, the mortality associated with infection was significantly lower in the high-volume hospitals (for details, see Table 42).[75] Thus, while the high-volume hospitals may have complication rates similar to the lower-volume hospitals, their management of those complications may be better.

Table 41: Incidence of mortality and specified postoperative complications after oesophagectomy at high- and low-volume hospitals* in Maryland, 1994-1998 (data from Dimick et al[74])

Complication	High-volume hospitals (204 patients)	Low-volume hospitals (162 patients)	Adjusted odds ratio (95% CI)	p value of adjusted OR
Mortality	2.5%	15.4%	5.7 (2.0, 16)	<0.001
Pulmonary failure	2.9%	11.8%	4.8 (1.6, 14)	0.002
Myocardial infarction	0.5%	1.2%	1.3 (0.7, 27)	0.8
Renal failure	0.5%	8.0%	19.0 (1.9, 178)	0.01
Aspiration	16.0%	34.0%	1.8 (1.0, 3.3)	0.04
Cardiac complications	16.0%	13.0%	0.7 (0.37, 1.3)	0.2
Pneumonia	8.8%	14.0%	1.8 (0.92, 3.5)	0.07
Postoperative infection	3.4%	6.2%	1.4 (0.5, 4.0)	0.4
Reintubation	7.8%	27.0%	2.9 (1.4, 6.1)	0.004
Surgical complications	6.9%	14.0%	3.3 (1.6, 6.9)	0.001
Septicaemia	1.5%	6.2%	4.0 (1.1, 15)	0.04

* Defined respectively as hospitals which discharged 34 or more oesophagectomy patients, and those which discharged fewer than 34 such patients, during the study period

Table 42: Incidence of postoperative complications and associated mortality in California, 1990-1994; hospitals grouped by number of oesophagectomies performed (data from Patti et al[75])

Outcome	Number of oesophagectomies performed over 5-year period					P value
	1-5	6-10	11-20	21-30	>30	
Infection						
Incidence	8%	9%	9%	7%	9%	0.8
Mortality	32%	39%	19%	40%	4%	0.008
Haemorrhage						
Incidence	4%	5%	3%	4%	7%	0.04
Mortality	25%	35%	11%	44%	6%	0.08

The only evidence which relates specifically to the effect of caseload on oesophagectomies performed using minimally invasive techniques comes from Decker et al's systematic review: in order to avoid the potentially negative impact of early learning curves, this only included studies which reported series of 10 or more such procedures. Decker et al found that centres which reported more than 50 cases had lower mortality and morbidity rates than those with less experience; they also appeared to perform a more extensive lymph node dissection which could potentially allow higher cure rates[9] (for details, see Table 43).

Table 43: MIO: outcomes in more and less experienced centres (data from Decker et al[9])

Outcome	Studies reporting 25 or fewer cases	Studies reporting 50 or more cases
Mortality rate	3.9% (21/533)	2.1% (22/1063)
Overall morbidity	60% (276/460)	44% (472/1063)
Respiratory complication rate	30.8% (150/487)	20.3% (216/1063)
Conversion rate	9.6% (48/501)	4.5% (48/1063)
Reoperation rate	6.6% (31/469)	4.7% (25/534)
Lymph node retrieval	Median 12 (range 5-17.5)	Median 22.5 (range 16-62)

5.4.2 Oesophagectomy Performed Using Minimally Invasive Techniques: the learning curve

There is some evidence that the learning curve for open oesophagectomy may be very long. So, an analysis of data from 150 consecutive patients who underwent Ivor Lewis subtotal oesophagectomy performed or supervised by a single UK surgeon between April 1990 and December 1996 found that, while there was no significant difference in the incidence of positive resection margins, 30-day or in-hospital mortality, minor or major complications, total operating time or abdominal operating time, continuing improvement was seen over the 7-year period in factors such as single-lung ventilation time, lymph node yield, blood loss, blood transfusion requirements, ITU stay, and total hospital stay. This may suggest that the surgeon's technical performance continued to improve for a considerable period of time even though he had apparently completed his superspecialist training in oesophagectomy before the study period. However, the improvement may also reflect the increased expertise of the entire healthcare team, which is likely to have improved in parallel with that of the surgeon, and may illustrate the learning curve of an evolving specialist centre rather than of an individual surgeon.[76]

Such evidence as has been identified supports the existence of a learning curve in relation to oesophagectomy performed using minimally invasive techniques. A number of studies included in this review refer to such a learning curve, predominantly in relation to the operating time, which was generally found to be longer in the earlier group of patients undergoing MIO or HMIO. However, only one study, that by Osugi et al,[28] specified that the difference was statistically significant, while Safranek et al stated that there was no significant difference between the first 20 and last 21 of the 41 patients in whom they performed MIO[51] (for details, see Table 44). Safranek et al also provided information relating to other factors: while there was no difference between the two groups in lymph node harvest (p=0.434), the last 21 patients had significantly fewer anastomotic strictures which required dilatation (2 vs 10, p=0.006) and a shorter length of hospital stay (10.5 vs 13.5 days, p=0.032).[51]

Table 44: Impact of the learning curve on operating times: data from included studies

Study	Procedure	Operating time
Bernabe 2005[18]	HMIO (transhiatal laparoscopic oesophagectomy) (n=17)	Overall mean operating time 336$\pm$53 minutes (n=17); mean operating time for the last 6/17 procedures 311$\pm$31 minutes; no p value reported
Kunisaki 2004[23]	Hand-assisted laparoscopy with video-assisted thoracoscopy and mini-thoracotomy	Mean operating time for first 10 patients 596.4$\pm$77.9 minutes; for next 5 patients 512.9$\pm$51.2 minutes; no p value reported
Osugi 2003[28]	HMIO (video-assisted thoracoscopic oesophagectomy)	Mean operating time for first 36 patients 270$\pm$96 minutes; for next 41 patients 185$\pm$25 minutes (p<0.001)
Parameswaran 2009[42]	MIO	Median operating time 442 minutes; said to have decreased consistently until now down to approximately 400 minutes; no p value reported
Perry 2009[45]	HMIO (laparoscopic inversion oesophagectomy)	Mean operating time for first 10 patients 453$\pm$83 minutes; for next 11 patients 351$\pm$56 minutes; no p value reported.
Pham 2010[41]	MIO	Overall mean operating time 543 minutes (n=44); mean operating time for the last 8/44 procedures 440 minutes; no p value reported
Safranek 2010[51]	MIO	No significant difference in duration of operation between first 20 and last 21 patients (p=0.057)

Three studies were identified which specifically analysed data relating to the learning curve in MIO/HMIO. Osugi et al compared outcomes in the first 34 and last 46 of 80 consecutive patients who underwent video-assisted thoracoscopic oesophagectomy (VATS) with extensive mediastinal lymphadenectomy for SCC of the thoracic oesophagus; this was performed by a single surgeon with substantial experience of open oesophagectomy. Overall morbidity was similar in the two groups but operative time, blood loss, and pulmonary infection were significantly lower, and the number of retrieved mediastinal nodes significantly higher, in the second group (for details, see Table 45). Multivariate analysis indicated that the only risk factor for pulmonary infection was the surgeon's experience of performing VATS (p=0.0331). Data on operative time and blood loss suggest that the surgeon acquired the basic skills during the first 17 procedures.[77]

Table 45: Selected outcomes in 80 patients undergoing VATS performed by a single surgeon in Osaka City University, Japan (data from Osugi et al 2003[77;77])

Outcome	Group 1 (n=34)	Group 2 (n=46)	p
Time of operation (minutes)	277.7±93.5	182.8±28.1	<0.0001
Operative blood loss (g)	427.8±439.1	160.8±95.8	<0.0001
Number of retrieved mediastinal nodes	28.8±12.0	36.0±11.2	0.0076
Any complication	16 (47.1%)	12 (26.1%)	NS
Recurrent laryngeal nerve palsy	5 (14.7%)	7 (15.2%)	NS
Pulmonary infection*	10 (29.4%)	3 (6.5%)	0.0127

* defined as radiological evidence of pulmonary consolidation with leukocytosis and pyrexia, regardless of whether pathogenic bacteria were cultured

Subsequently, the procedure used by Osugi was introduced to two other Japanese centres, at each of which it was performed by a single surgeon with prior experience of open oesophagectomy but little experience of scopic surgery. The duration of the thoracic procedure was significantly shorter in the proficient period at Kanazawa than in the instruction phase at either centre (for details, see Table 46). No other significant differences were observed, and the absence of a learning curve in terms of clinical outcomes was attributed to the fact that, unlike Osugi, the surgeons at both hospitals were given adequate instruction; they concluded that a surgeon with substantial experience of open oesophagectomy could safely master the basic skills of VATS in a relatively short period of time given adequate instruction by an surgeon who was experienced in the procedure.[78]

Table 46: Outcomes: patients who underwent curative VATS by a single operator (data from Ninomiya et al 2010[78])

	Kanazawa			Maebashi	p
	Jan 2003-Aug 2004 (Instruction period)	Sept 2004-Aug 2005 (Post-instruction period)	Sept 2005-Dec 2007 (Proficient period)	Sept 2005-Dec 2007 (Instruction period)	
Number of cases	9	8	29	13	
Median number of dissected mediastinal nodes (range)	35 (22-52)	41 (26-53)	32 (17-69)	29 (17-42)	0.139
Median duration of thoracic procedure (minutes) (range)	350 (280-448)	300 (230-455)	266 (199-555) p vs group A = 0.005 p vs group D = 0.002	345 (270-420)	0.003
Median thoracic blood loss (g) (range)	170 (90-380)	275 (130-550)	220 (10-660)	210 (75-543)	0.373
Surgery-related deaths	0	0	0	0	NR
Pneumonia and atelectasis	3 (33.3%)	1 (12.5%)	5 (17.2%)	4 (30.7%)	0.688
Recurrent nerve palsy	4 (44.4%)	1 (12.5%)	16 (55.2%)	5 (38.4%)	0.183
Chylothorax	1 (11.1%)	0	0	0	0.130
Anastomotic leak	0	1 (12.5%)	2 (6.9%)	0	0.515

In a smaller study, Song el al reported outcomes in 28 South Korean patients who underwent MIO or HMIO performed between September 2004 and December 2007 by a single surgeon with substantial previous experience of oesophageal surgery. The total operating time was significantly shorter in the 14 patients operated on in the second 17 months (396 ± 60 vs 538 ± 65 minutes, $p<0.001$). The reductions in total hospital stay (10.6 ± 1.8 vs 12.5 ± 3.2 days, $p=0.085$) and numbers of patients with complications (21% vs 64%, $p=0.054$) in the second 27 months were not statistically significant,[79] but the study may have been underpowered for these outcomes.

5.4.3 The Learning Curve: summary

There is evidence to suggest that higher relevant caseload, whether of the individual surgeon or of the institution is associated with better patient outcomes following oesophagectomy. Although the bulk of this evidence is not specific to oesophagectomy performed using minimally invasive techniques, there is no reason to believe that it is not applicable to it.

There is also evidence of a learning curve in relation to oesophagectomy performed using minimally invasive techniques. This evidence generally relates to operating times, which may reduce with experience. The only study which reported clinical outcomes, that by Safranek et al, found a significant reduction length of hospital stay, and in the number of anastomotic strictures requiring dilatation, but did not observe a significant difference in operating time.[51]

6 CONCLUSIONS

This review has highlighted the problems which exist in relation to the data comparing oesophagectomy performed using minimally invasive techniques with open oesophagectomy. There are no randomised controlled trials, and it is impossible to exclude the possibility of selection bias in the non-randomised studies from which the evidence for efficacy is drawn. It is likely that, in many cases, patient inclusion criteria will have been favourable to MIO/HMIO, even if this is not apparent from the published data; thus, there may be selection bias even if contemporary controls are used. However, many of the included studies used historical controls, and few reported in adequate detail how those controls were selected. Thus, these studies may incorporate bias in terms of patient characteristics and, even if baseline comparability between groups appears good, they may incorporate bias, favouring MIO/HMIO, derived from the fact that outcomes in patients undergoing oesophagectomy have improved over time. Finally, very few of the included studies provide any information relating to the surgeons who performed the procedures, and their levels of competence, and this makes it difficult, in most cases, to exclude the possibility of performance bias.

In addition, it is difficult to compare studies because of variations in the techniques and equipment used in MIO/HMIO, shortcomings in the reporting of the procedures used in the open surgery, and failure to report details relating to the surgeons involved (notably their specialism, and their levels of experience and skill in the procedures under study). Furthermore, the included studies were not consistent either in the outcomes which they reported or in the way in which they defined some of those outcomes (particularly adverse events) which they did report.

As a consequence of the poor quality of the included studies, and their heterogeneity, it was not considered appropriate to perform meta-analyses. The evidence relating to the efficacy of MIO/HMIO is therefore not easy to summarise. Some studies suggested that the use of minimally invasive techniques was associated with higher in-hospital mortality rates than open surgery, but more suggested that in-hospital mortality was higher with open surgery;

however, this outcome is susceptible to bias arising from both patient selection and the use of historic controls; following multiple regression analysis, Lazzarino et al found no significant difference between MIO/HMIO and open surgery.[37] Mean hospital stays may be shorter in patients undergoing MIO/HMIO than in those undergoing open surgery, but in many cases the difference was not great. None of the studies provided data relating to time to return to normal activity, although this is arguably one of the most important outcome measures, and one which may differ considerably between MIO and open surgery even when the length of hospital stay is similar. However, quality of life data from the study by Wang et al[48] suggest that recovery from HMIO is more rapid than recovery following open oesophagectomy. No evidence was found of a statistically significant difference in the risk of cancer recurrence between patients undergoing MIO/HMIO and open surgery.

Because of the nature of the evidence, it is also difficult to assess the relative safety of MIO/HMIO. In a very specialised centre, Luketich et al reported major complication rates of 23-32% with MIO;[35] unfortunately, comparable figures are not available for open surgery. The most commonly reported adverse events were anastomotic leak, pneumonia, and injury to the laryngeal nerve or vocal cord. Although widely varying rates have been reported in the included studies, the rates reported by Luketich et al perhaps provide the best indication of what can be achieved in a centre of excellence: rates of 12-13% for anastomotic leak, 8-10% for pneumonia, and 4-5% for laryngeal nerve or vocal cord damage, with a rate of conversion to open operation of around 7%.[35]

There is evidence that patient outcomes following open oesophagectomy are heavily influenced by the extent of the surgeon's experience, or that of the institution in which he or she works, as measured by relevant caseload. There is also evidence from a systematic review by Decker et al to suggest that the same is true of oesophagectomy performed using minimally invasive techniques.[9] Moreover, there is evidence to suggest the existence of a learning curve in relation to MIO/HMIO. All of this evidence supports the NHS Executive's guidance that surgery for cancer of the oesophagus should only be performed in specialist centres by specialist surgeons who perform a relatively high volume of such procedures a year.[4]

7 RECOMMENDATIONS FOR FURTHER RESEARCH

Ideally, the evidence for the efficacy and safety of MIO and HMIO relative to open oesophagectomy would be derived from adequately powered randomised controlled trials which compared long-term as well as short-come outcomes in patients randomised to open or minimally invasive oesophagectomy, with full detailed reporting of the surgical procedures used and patient characteristics at baseline. However, it is not feasible to recommend the performance of such studies not only because of the difficulty and cost of undertaking trials of adequate power but also because it may be particularly difficult, and potentially unethical, to undertake such trials because of surgeons' preferences for particular operative techniques, and also because they may have decided views about the technique which they feel to be most suitable for a given patient.

It therefore seems more appropriate to recommend the performance of better-designed nonrandomised studies to compare MIO and HMIO with open surgery. Where possible, these should be prospective and should use contemporary controls. If this is not possible, thought should be given to devising studies which minimise the amount of bias in using retrospective data. Whether retrospective or prospective, studies should incorporate transparency in relation to the reasons for patient allocation to treatment, and should provide full details of patient characteristics at baseline (including tumour characteristics, co-morbidity etc), the surgical procedures used, the use of neoadjuvant therapy, the surgeon's experience, and the resources available to the surgical team. Any prospective studies should include quality of life among their outcome measures.

Because of time constraints, the current review only includes studies which compared oesophagectomy performed using minimally invasive techniques with open surgery. Consideration might therefore be given to performing a systematic review which also included studies which only compared the different types of oesophagectomy performed using minimally invasive techniques, as this would allow a fuller assessment of the relative merits of the different kinds of hybrid procedures or MIO techniques than was possible in the current review.

Qualitative research may also be of value in exploring the reasons underlying surgeons' decisions to use open or minimally invasive techniques in particular patients. Qualitative data may also yield important information about patients' experience of recovery which is poorly elicited in the study designs included in this review.

8 REFERENCES

(1) National Institute for Health and Clinical Excellence. Thoracoscopically assisted oesophagectomy. IPG 189. Internet [2006 [cited 2011 Jan. 4]; Available from: URL:http://guidance.nice.org.uk/nicemedia/live/11260/31575/31575.pdf

(2) National Institute for Health and Clinical Excellence. Interventional procedure overview of thoracoscopically assisted oesophagectomy. Internet 2005 Available from: URL:http://www.nice.org.uk/nicemedia/live/11260/31574/31574.pdf

(3) Cancer Research UK. Oesophageal cancer - UK incidence statistics. Internet 2010; Available from: URL:http://info.cancerresearchuk.org/cancerstats/types/oesophagus/incidence/

(4) NHS Executive. Guidance on Commissioning Cancer Services. Improving Outcomes in Upper Gastro-intestinal Cancers. The Manual. 2001. 11-3-2011.

(5) Lagergren J, Lagergren P. Oesophageal cancer. *BMJ* 2010; 341:1207-1211.

(6) Cancer Research UK. Oesophageal cancer survival statistics. Internet 2009; Available from: URL:http://info.cancerresearchuk.org/cancerstats/types/oesophagus/survival/#five

(7) Biere SS, Cuesta MA, van der Peet DL. Minimally invasive versus open esophagectomy for cancer: a systematic review and meta-analysis. *Minerva Chirurgica* 2009; 64(2):121-133.

(8) Blazeby JM, Farndon JR, Donovan J, Alderson D. A prospective longitudinal study examining the quality of life of patients with esophageal cancer. *Cancer* 2000; 88(8):1781-1787.

(9) Decker G, Coosemans W, De LP, Decaluwe H, Nafteux P, Van RD et al. Minimally invasive esophagectomy for cancer. *European Journal of Cardio-Thoracic Surgery* 2009; 35(1):13-20.

(10) Cuschieri A, Shimi S, Banting S. Endoscopic oesophagectomy through a right thoracoscopic approach. *Journal of the Royal College of Surgeons of Edinburgh* 1992; 37:7-11.

(11) Gemmill EH, McCulloch P. Systematic review of minimally invasive resection for gastro-oesophageal cancer. *British Journal of Surgery* 2007; 94(12):1461-1467.

(12) Nagpal K, Ahmed K, Vats A, Yakoub D, James D, Ashrafian H et al. Is minimally invasive surgery beneficial in the management of esophageal cancer? A meta-analysis. *Surgical Endoscopy* 2010; 24(7):1621-1629.

(13) Verhage RJ, Hazebroek EJ, Boone J, van HR. Minimally invasive surgery compared to open procedures in esophagectomy for cancer: a systematic review of the literature. *Minerva Chirurgica* 2009; 64(2):135-146.

(14) Sgourakis G, Gockel I, Radtke A, Musholt TJ, Timm S, Rink A et al. Minimally invasive versus open esophagectomy: meta-analysis of outcomes. *Digestive Diseases & Sciences* 2010; 55(11):3031-3040.

(15) Braghetto I, Csendes A, Cardemil G, Burdiles P, Korn O, Valladares H. Open transthoracic or transhiatal esophagectomy versus minimally invasive esophagectomy in terms of morbidity, mortality and survival. *Surgical Endoscopy* 2006; 20(11):1681-1686.

(16) Smithers BM, Gotley DC, Martin I, Thomas JM. Comparison of the outcomes between open and minimally invasive esophagectomy. *Annals of Surgery* 2007; 245(2):232-240.

(17) Benzoni E, Bresadola V, Terrosu G, Uzzau A, Cedolini C, Intini S et al. Minimally invasive esophagectomy: a comparative study of transhiatal laparoscopic approach versus laparoscopic right transthoracic esophagectomy. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques* 2008; 18(2):178-187.

(18) Bernabe KQ, Bolton JS, Richardson WS. Laparoscopic hand-assisted versus open transhiatal esophagectomy: a case-control study. *Surgical Endoscopy* 2005; 19(3):334-337.

(19) Bonavina L, Bona D, Binyom PR, Peracchia A. A laparoscopy-assisted surgical approach to esophageal cancer. *Journal of Surgical Research* 2004; 1171(152):57.

(20) Bresadola V, Terrosu G, Cojutti A, Benzoni E, Baracchini E, Bresadola F. Laparoscopic versus open gastroplasty in esophagectomy for esophageal cancer: a comparative study. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques* 2006; 16(2):63-67.

(21) Fabian T, Martin JT, McKelvey AA, Federico JA. Minimally invasive esophagectomy: a teaching hospital's first year experience. *Diseases of the Esophagus* 2008; 21(3):220-225.

(22) Kitagawa H, Akimori T, Okabayashi T, Namikawa T, Sugimoto T, Kobayashi M et al. Total laparoscopic gastric mobilization for esophagectomy. *Langenbecks Archives of Surgery* 2009; 394(4):617-621.

(23) Kunisaki C, Hatori S, Imada T, Akiyama H, Ono H, Otsuka Y et al. Video-assisted thoracoscopic esophagectomy with a voice-controlled robot: The AESOP system. *Surgical Laparoscopy, Endoscopy and Percutaneous Techniques* 2004; 14(6):323-327.

(24) Law S, Fok M, Chu KM, Wong J. Thoracic esophagectomy for esophageal cancer. *Surgery* 1997; 122(1):8-14.

(25) Martin DJ, Bessell JR, Chew A, Watson DI. Thoracoscopic and laparoscopic esophagectomy: initial experience and outcomes. *Surgical Endoscopy* 2005; 19(12):1597-1601.

(26) Morris LGT, Tran TN, DeLacure MD. Early experience with minimally invasive esophagectomy in head and neck surgical patients. *Otolaryngology - Head and Neck Surgery* 2007; 137(6):947-949.

(27) Nguyen NT, Follette DM, Wolfe BM, Schneider PD, Roberts P, Goodnight JEJ. Comparison of minimally invasive esophagectomy with transthoracic and transhiatal esophagectomy. *Archives of Surgery* 2000; 135(8):920-925.

(28) Osugi H, Takemura M, Higashino M, Takada N, Lee S, Kinoshita H. A comparison of video-assisted thoracoscopic oesophagectomy and radical lymph node dissection for squamous cell cancer of the oesophagus with open operation [erratum appears in Br J Surg 2003 90(6):764]. *British Journal of Surgery* 2003; 90(1):108-113.

(29) Scheepers JJ, van der Peet DL, Veenhof AA, Cuesta MA. Influence of circumferential resection margin on prognosis in distal esophageal and gastroesophageal cancer approached through the transhiatal route. *Diseases of the Esophagus* 2009; 22(1):42-48.

(30) Shiraishi T, Kawahara K, Shirakusa T, Yamamoto S, Maekawa T. Risk analysis in resection of thoracic esophageal cancer in the era of endoscopic surgery. *Annals of Thoracic Surgery* 2006; 81(3):1083-1089.

(31) Taguchi S, Osugi H, Higashino M, Tokuhara T, Takada N, Takemura M et al. Comparison of three-field esophagectomy for esophageal cancer incorporating open or thoracoscopic thoracotomy. *Surgical Endoscopy* 2003; 17(9):1445-1450.

(32) van den Broek WT, Makay O, Berends FJ, Yuan JZ, Houdijk AP, Meijer S et al. Laparoscopically assisted transhiatal resection for malignancies of the distal esophagus. *Surgical Endoscopy* 2004; 18(5):812-817.

(33) Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F et al. Evaluating non-randomised intervention studies. *Health Technology Assessment* 2003; 7(27):1-173.

(34) Buess G, Kayser J, Manncke K, Walter DJ, Bessell JR, Becker HD. Endoscopic microsurgical dissection of the esophagus. *International Surgery* 1997; 82(2):109-112.

(35) Luketich JD, Alvelo-Rivera M, Buenaventura PO, Christie NA, McCaughan JS, Litle VR et al. Minimally invasive esophagectomy. Outcomes in 222 patients. *Annals of Surgery* 2003; 238(4):486-495.

(36) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339:332-339.

(37) Lazzarino AI, Nagpal K, Bottle A, Faiz O, Moorthy K, Aylin P. Open versus minimally invasive esophagectomy: trends of utilization and associated outcomes in England. *Annals of Surgery* 2010; 252(2):292-298.

(38) Thomson IG, Smithers BM, Gotley DC, Martin I, Thomas JM, O'Rourke P et al. Thoracoscopic-assisted esophagectomy for esophageal cancer: analysis of patterns and prognostic factors for recurrence. *Annals of Surgery* 2010; 252(2):281-291.

(39) Dupont WD. Randomized vs. historical clinical trials. Are the benefits worth the cost? *American Journal of Epidemiology* 1985; 122(6):940-946.

(40) Kilic A, Schuchert MJ, Pennathur A, Yaeger K, Prasanna V, Luketich JD et al. Impact of obesity on perioperative outcomes of minimally invasive esophagectomy. *Annals of Thoracic Surgery* 2009; 87(2):412-415.

(41) Pham TH, Perry KA, Dolan JP, Schipper P, Sukumar M, Sheppard BC et al. Comparison of perioperative outcomes after combined thoracoscopic-laparoscopic

esophagectomy and open Ivor-Lewis esophagectomy. *American Journal of Surgery* 2010; 199(5):594-598.

(42) Parameswaran R, Veeramootoo D, Krishnadas R, Cooper M, Berrisford R, Wajed S. Comparative experience of open and minimally invasive esophagogastric resection. *World Journal of Surgery* 2009; 33(9):1868-1875.

(43) Caputo M, Fumagalli RU, Bona S, Rosati R, Peracchia A. Laparoscopic gastroplasty for esophagectomy. *Rays* 2005; 30(4):315-318.

(44) Hamouda AH, Forshaw MJ, Tsigritis K, Jones GE, Noorani AS, Rohatgi A et al. Perioperative outcomes after transition from conventional to minimally invasive Ivor-Lewis esophagectomy in a specialized center. *Surgical Endoscopy* 2010; 24(4):865-869.

(45) Perry KA, Enestvedt CK, Pham T, Welker M, Jobe BA, Hunter JG et al. Comparison of laparoscopic inversion esophagectomy and open transhiatal esophagectomy for high-grade dysplasia and stage I esophageal adenocarcinoma. *Archives of Surgery* 2009; 144(7):679-684.

(46) Saha AK, Sutton CD, Sue-Ling H, Dexter SP, Sarela AI. Comparison of oncological outcomes after laparoscopic transhiatal and open esophagectomy for T1 esophageal adenocarcinoma. *Surgical Endoscopy* 2009; 23(1):119-124.

(47) Schroder W, Holscher AH, Bludau M, Vallbohmer D, Bollschweiler E, Gutschow C. Ivor-Lewis esophagectomy with and without laparoscopic conditioning of the gastric conduit. *World Journal of Surgery* 2010; 34(4):738-743.

(48) Wang H, Feng M, Tan L, Wang Q. Comparison of the short-term quality of life in patients with esophageal cancer after subtotal esophagectomy via video-assisted thoracoscopic or open surgery. *Diseases of the Esophagus* 2010; 23(5):408-414.

(49) Schoppmann SF, Prager G, Langer FB, Riegler FM, Kabon B, Fleischmann E et al. Open versus minimally invasive esophagectomy: A single-center case controlled study. *Surgical Endoscopy and Other Interventional Techniques* 2010; 24(12):3044-3053.

(50) Zingg U, McQuinn A, DiValentino D, Esterman AJ, Bessell JR, Thompson SK et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer. *Annals of Thoracic Surgery* 2009; 87(3):911-919.

(51) Safranek PM, Cubitt J, Booth MI, Dehn T. Review of open and minimal access approaches to oesophagectomy for cancer. *British Journal of Surgery* 2010; 97(12):1845-1853.

(52) Lowe C, Subar D, Hall C, Kumpavat J, Decadt B, Agwunobi A. Hiatal hernias presenting as a late complication of laparoscopic-assisted cardio-oesophagectomy. *Hernia* 2010; 14(2):211-213.

(53) Fumagalli U, Rosati R, Caputo M, Bona S, Zago M, Lutmann F et al. Diaphragmatic acute massive herniation after laparoscopic gastroplasty for esophagectomy. *Diseases of the Esophagus* 2006; 19(1):40-43.

(54) Vallböhmer D, Hölscher AH, Herbold T, Gutschow C, Schröder W. Diaphragmatic hernia after conventional or laparoscopic-assisted transthoracic esophagectomy. *Annals of Thoracic Surgery* 2007; 84(6):1847-1852.

(55) Bala R, Saini S, Dureja JC, Kad N, Thakur A, Kiran S et al. Tension capnothorax during laparoscopic transhiatal oesophagectomy - A case report. *Southern African Journal of Anaesthesia and Analgesia* 2008; 14(5):45-46.

(56) Makay Ö, van den Broek WT, Yuan JZ, Veerman DP, Helfferich DWH, Cuesta MA. Anesthesiological hazards during laparoscopic transhiatal esophageal reconstruction. A case control study of the laparoscopic-assisted vs the conventional approach. *Surgical Endoscopy* 2004; 18:1263-1267.

(57) Ferreira HP, Araujo CA, Cavalcante JF, Lima RP. Complex tracheal lesion: correction with an intercostal muscle pedicle flap. *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia* 2009; 35(12):1250-1253.

(58) Bonavina L, Bona D, Saino G, Nencioni M. Injury of the thoracic aorta during laparoscopic esophagectomy. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques* 2009; 19(2):e55-e56.

(59) Pantvaidya GH, Mistry RC, Ghanekar VR, Upasani VV, Pramesh CS. Injury of an aberrant subclavian artery: a rare complication of video assisted thoracoscopic esophagectomy. *Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia* 2005; 11(1):35-37.

(60) Force S. The "innocent bystander" complications following esophagectomy: atrial fibrillation, recurrent laryngeal nerve injury, chylothorax, and pulmonary complications. *Seminars in Thoracic & Cardiovascular Surgery* 2004; 16(2):117-123.

(61) Watson A. Operable esophageal cancer: results from the West. *World Journal of Surgery* 1994; 18:361-366.

(62) Biere SSAY, Maas KW, Cuesta MA, van der Peet DL. Cervical or thoracic anastomosis after esophagectomy for cancer: a systematic review and meta-analysis. *Digestive Surgery* 2011; 28:29-35.

(63) Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: a review. *American Journal of Surgery* 1995; 169:634-640.

(64) Parekh K, Iannettoni MD. Complications of esophageal resection and reconstruction. *Seminars in Thoracic and Cardiovascular Surgery* 2007; 19(1):79-88.

(65) Baba M, Natsugoe S, Shimada M, Nakano S, Noguchi Y, Kawachi K et al. Does hoarseness of voice from recurrent nerve paralysis after esophagectomy for carcinoma influence patient quality of life? *Journal of the American College of Surgeons* 1999; 188(3):231-236.

(66) Gockel I, Kneist W, Keilmann A, Junginger Th. Recurrent laryngeal nerve paralysis (RLNP) following esophagectomy for carcinoma. *European Journal of Surgical Oncology* 2005; 31:277-281.

(67) Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I et al. Hospital volume and surgical mortality in the United States. *New England Journal of Medicine* 2002; 346(15):1128-1137.

(68) Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. *Annals of Surgery* 2007; 245(5):777-783.

(69) Miller JD, Jain MK, de Gara CJ, Morgan D, Urschel JD. Effect of surgical experience on results of esophagectomy for esophageal carcinoma. *Journal of Surgical Oncology* 1997; 65:20-21.

(70) Bachmann MO, Alderson D, Edwards D, Wotton S, Bedford C, Peters TJ et al. Cohort study in South and West England of the influence of specialization on the management and outcomes of patients with oesophageal and gastric cancers. *British Journal of Surgery* 2002; 89:914-922.

(71) Migliore M, Choong CK, Lim E, Goldsmith KA, Ritchie A, Wells FC. A surgeon's case volume of oesophagectomy for cancer strongly influences the operative mortality rate. *European Journal of Cardio-Thoracic Surgery* 2007; 32(2):375-380.

(72) Al-Sarira AA, David G, Willmott S, Slavin JP, Deakin M, Corless DJ. Oesophagectomy practice and outcomes in England. *British Journal of Surgery* 2007; 94:585-591.

(73) Jeganathan R, Kinnear H, Campbell J, Jordan S, Graham A, Gavin A et al. A surgeon's case volume of oesophagectomy for cancer does not influence patient outcome in a high volume hospital. *Interactive Cardiovascular & Thoracic Surgery* 2009; 9:66-69.

(74) Dimick JB, Pronovost PJ, Cowan JA, Lipsett PA. Surgical volume and quality of care for esophageal resection: do high-volume hospitals have fewer complications? *Annals of Thoracic Surgery* 2003; 75:337-341.

(75) Patti MG, Corvera CU, Glasgow RE, Way LW. A hospital's annual rate of esophagectomy influences the operative mortality rate. *Journal of Gastrointestinal Surgery* 1998; 2:186-192.

(76) Sutton DN, Wayman J, Griffin SM. Learning curve for oesophageal cancer surgery. *British Journal of Surgery* 1998; 85:1399-1402.

(77) Osugi H, Takemura M, Higashino M, Takada N, Lee S, Ueno M et al. Learning curve of video-assisted thoracoscopic esophagectomy and extensive lymphadenectomy for squamous cell cancer of the thoracic esophagus and results. *Surgical Endoscopy* 2003; 17:515-519.

(78) Ninomiya I, Osugi H, Tomizawa N, Fujimura T, Kayahara M, Takamura H et al. Learning of thoracoscopic radical esophagectomy: how can the learning curve be made short and flat? *Diseases of the Esophagus* 2010; 23(8):618-626.

(79) Song SY, Na KJ, Oh SG, Ahn BH. Learning curves of minimally invasive esophageal cancer surgery. *European Journal of Cardio-Thoracic Surgery* 2009; 35(4):689-693.

(80) Benzoni E, Terrosu G, Bresadola V, Uzzau A, Intini S, Noce L et al. A comparative study of the transhiatal laparoscopic approach versus laparoscopic gastric

mobilisation and right open transthoracic esophagectomy for esophageal cancer management. *Journal of Gastrointestinal & Liver Diseases* 2007; 16(4):395-401.

(81) Campos GM, Jablons D, Brown LM, Ramirez RM, Rabl C, Theodore P. A safe and reproducible anastomotic technique for minimally invasive Ivor Lewis oesophagectomy: the circular-stapled anastomosis with the trans-oral anvil. *European Journal of Cardio-Thoracic Surgery* 2010; 37(6):1421-1426.

(82) Dapri G, Himpens J, Cadiere GB. Minimally invasive esophagectomy for cancer: laparoscopic transhiatal procedure or thoracoscopy in prone position followed by laparoscopy? *Surgical Endoscopy* 2008; 22(4):1060-1069.

(83) Law SY, Fok M, Wei WI, Lam LK, Tung PH, Chu KM et al. Thoracoscopic esphageal mobilization for pharyngolaryngoesophagectomy. *Annals of Thoracic Surgery* 2000; 70(2):418-422.

(84) Levy RM, Wizorek J, Shende M, Luketich JD. Laparoscopic and thoracoscopic esophagectomy. *Advances in Surgery* 2010; 44:101-116.

(85) Nakatsuchi T, Otani M, Osugi H, Ito Y, Koike T. The necessity of chest physical therapy for thoracoscopic oesophagectomy. *Journal of International Medical Research* 2005; 33(4):434-441.

(86) Narumiya K, Nakamura T, Ide H, Takasaki K. Comparison of extended esophagectomy through mini-thoracotomy/laparotomy with conventional thoracotomy/laparotomy for esophageal cancer. *Japanese Journal of Thoracic & Cardiovascular Surgery* 2005; 53(8):413-419.

(87) Perry KA, Enestvedt CK, Diggs BS, Jobe BA, Hunter JG. Perioperative outcomes of laparoscopic transhiatal inversion esophagectomy compare favorably with those of combined thoracoscopic-laparoscopic esophagectomy. *Surgical Endoscopy* 2009; 23(9):2147-2154.

(88) Scheepers JJ, Sietses C, Bos DG, Boelens PG, Teunissen CM, Ligthart-Melis GC et al. Immunological consequences of laparoscopic versus open transhiatal resection for malignancies of the distal esophagus and gastroesophageal junction. *Digestive Surgery* 2008; 25(2):140-147.

(89) Schoppmann SF, Prager G, Langer F, Riegler M, Fleischman E, Zacherl J. Fifty-five minimally invasive esophagectomies: a single centre experience. *Anticancer Research* 2009; 29(7):2719-2725.

APPENDICES

Appendix 1: IP search history and checklist template: Update search (IP: 326_2: Minimally invasive oesophagectomy)

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	4.01.2011	Issue 12 of 12, December 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	4.01.2011	n/a
HTA database (CRD website)	4.01.2011	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	4.01.2011	Issue 12 of 12, December 2010
MEDLINE (Ovid)	4.01.2011	1950 to December Week 3 2010
MEDLINE In-Process (Ovid)	4.01.2011	December 30, 2010
EMBASE (Ovid)	4.01.2011	1980 to 2010 Week 51
CINAHL (NLH Search 2.0 or EBSCOhost)	4.01.2011	n/a
Zetoc	4.01.2011	n/a

Search strategies
Database: Medline

1	exp Thoracoscopy/ and exp Laparoscopy/ and exp Esophagectomy/	71
2	(thoracoscop* adj3 assist* adj3 (esophagectom* or oesophagectom*)).tw.	36
3	((laparoscop* or thoracoscop*) adj3 (oesophagectom* or esophagectom*)).tw.	182
4	Surgical Procedures, Minimally Invasive/	12376
5	(mini* adj3 (invas* or access*) adj3 (esophagectom* or oesophagectom*)).tw.	125
6	TLE.tw.	1784
7	(ivor adj3 lewis).tw.	183
8	or/1-7	14518
9	exp Esophageal Neoplasms/	31682
10	((oesophag* or esophag* or gullet*) adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan*)).tw.	25356
11	Barrett Esophagus/	4906
12	(barrett* adj3 (esophagus or oesophagus or syndrome* or epithelium*)).tw.	4881
13	11 or 12	5903
14	(((high adj3 grade) or high-grade) adj3 dysplasia*).tw.	2078
15	13 and 14	863
16	9 or 10 or 15	36025
17	8 and 16	509
18	Animals/ not Humans/	3391613
19	17 not 18	505
20	limit 19 to ed=20100805-20110131	31

Database: Medline in Process

1	exp Thoracoscopy/ and exp Laparoscopy/ and exp Esophagectomy/	0
2	(thoracoscop* adj3 assist* adj3 (esophagectom* or oesophagectom*)).tw.	1
3	((laparoscop* or thoracoscop*) adj3 (oesophagectom* or esophagectom*)).tw.	5
4	Surgical Procedures, Minimally Invasive/	0
5	(mini* adj3 (invas* or access*) adj3 (esophagectom* or oesophagectom*)).tw.	16
6	TLE.tw.	66
7	(ivor adj3 lewis).tw.	13
8	or/1-7	94
9	exp Esophageal Neoplasms/	0
10	((oesophag* or esophag* or gullet*) adj3 (neoplasm* or cancer* or carcinoma* or adenomcarcinom* or tumour* or tumor* or malignan*)).tw.	752
11	Barrett Esophagus/	0
12	(barrett* adj3 (esophagus or oesophagus or syndrome* or epithelium*)).tw.	200
13	11 or 12	200
14	(((high adj3 grade) or high-grade) adj3 dysplasia*).tw.	86
15	13 and 14	35
16	9 or 10 or 15	762
17	8 and 16	21
18	Animals/ not Humans/	0
19	17 not 18	21

Database: Embase

1	exp Thoracoscopy/ and exp Laparoscopy/ and exp Esophagectomy/	76
2	(thoracoscop* adj3 assist* adj3 (esophagectom* or oesophagectom*)).tw.	42
3	((laparoscop* or thoracoscop*) adj3 (oesophagectom* or esophagectom*)).tw.	230
4	Surgical Procedures, Minimally Invasive/	16719
5	(mini* adj3 (invas* or access*) adj3 (esophagectom* or oesophagectom*)).tw.	170
6	TLE.tw.	2508
7	(ivor adj3 lewis).tw.	231
8	or/1-7	19665
9	exp Esophageal Neoplasms/	40054
10	((oesophag* or esophag* or gullet*) adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan*)).tw.	30459
11	Barrett Esophagus/	8200
12	(barrett* adj3 (esophagus or oesophagus or syndrome* or epithelium*)).tw.	6365
13	11 or 12	8913
14	(((high adj3 grade) or high-grade) adj3 dysplasia*).tw.	2714
15	13 and 14	1119
16	9 or 10 or 15	44764
17	8 and 16	677
18	nonhuman/ not human/	2925901
19	17 not 18	673
20	limit 19 to em=201030-201051	55

Database: Cochrane

#1	MeSH descriptor **Thoracoscopy** explode all trees	197
#2	MeSH descriptor **Laparoscopy** explode all trees	3696
#3	MeSH descriptor **Esophagectomy** explode all trees	208
#4	(#1 AND #2 AND #3)	0
#5	(thoracoscop* near/3 assist* near/3 (esophagectom* or oesophagectom*))	2
#6	((laparoscop* or thoracoscop*) near/3 (oesophagectom* or esophagectom*))	6
#7	MeSH descriptor **Surgical Procedures, Minimally Invasive** explode all trees	11955
#8	(mini* near/3 (invas* or access*) near/3 (esophagectom* or oesophagectom*))	6
#9	TLE	43
#10	(ivor near/3 lewis)	11
#11	(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)	12008
#12	MeSH descriptor **Esophageal Neoplasms** explode all trees	746
#13	((oesophag* or esophag* or gullet*) near/3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan*))	1440
#14	(barrett* near/3 (esophagus or oesophagus or syndrome* or epithelium*))	249
#15	((high near/3 grade) or (high-grade) near/3 dysplasia*)	2069
#16	(#14 AND #15)	62
#17	(#11 AND #16)	32

Database: CRD

1	MeSH Thoracoscopy EXPLODE 1 2 3	67
2	MeSH Laparoscopy EXPLODE 1 2	952
3	MeSH Esophagectomy EXPLODE 1	36
4	#1 and #2 and #3	0
5	thoracoscop* NEAR assist* NEAR esophagectom*	0
6	thoracoscop* NEAR assist* NEAR oesophagectom*	1
7	laparoscop* NEAR oesophagectom*	2
8	laparoscop* NEAR esophagectom*	1
9	thoracoscop* NEAR oesophagectom*	2
10	thoracoscop* NEAR esophagectom*	1
11	MeSH Surgical Procedures, Minimally Invasive EXPLODE 1	2366
12	mini* NEAR invas* NEAR esophagectom*	2
13	mini* NEAR invas* NEAR oesophagectom*	3
14	mini* NEAR access* NEAR esophagectom*	0
15	mini* NEAR access* NEAR oesophagectom*	0
16	TLE	3
17	ivor NEAR lewis	1
18	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17	2369
19	MeSH Esophageal Neoplasms EXPLODE 1 2 3 4 5	162
20	oesophag* NEAR neoplasm*	24
21	oesophag* NEAR cancer*	130
22	oesophag* NEAR carcinoma*	34
23	oesophag* NEAR adenocarcinoma*	41
24	oesophag* NEAR tumour*	26

25	oesophag* NEAR tumor*	0
26	oesophag* NEAR malignan*	25
27	esophag* NEAR malignan*	13
28	esophag* NEAR tumor*	7
29	esophag* NEAR tumour*	4
30	esophag* NEAR adenocarcinoma*	11
31	esophag* NEAR carcinom*	22
32	esophag* NEAR cancer*	70
33	esophag* NEAR neoplasm*	7
34	gullet* NEAR neoplasm*	0
35	gullet* NEAR cancer*	3
36	gullet* NEAR carcinoma*	1
37	gullet* NEAR adenocarcinom*	1
38	gullet* NEAR tumour*	1
39	gullet* NEAR tumor*	0
40	gullet* NEAR malignan*	0
41	MeSH Barrett Esophagus EXPLODE 1 2	61
42	barrett* NEAR esophagus*	41
43	barrett* NEAR oesophagus*	52
44	barrett* NEAR syndrome*	1
45	barrett* NEAR epithelium*	2
46	#41 or #42 or #43 or #44 or #45	79
47	high NEAR grade NEAR dysplasia*	40
48	high-grade NEAR dysplasia*	41
49	#47 or #48	41
50	#46 and #49	28
51	#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40	250
52	#18 and #50 and #51	16
53	#52 RESTRICT YR 2010 2011	1

Database: CINAHL

1	THORACOSCOPY/	290
2	LAPAROSCOPY/	1958
3	(thoracoscop* ADJ3 assist* ADJ3 esophagectom*).ti,ab	1
4	(thoracoscop* ADJ3 assist* ADJ3 oesophagectom*).ti,ab	0
5	(laparoscop* ADJ3 oesophagectom*).ti,ab	1
6	(laparoscop* ADJ3 esophagectom*).ti,ab	6
7	((thoracoscop* ADJ3 oesophagectom*)).ti,ab	0
8	((thoracoscop* ADJ3 esophagectom*)).ti,ab	3
9	MINIMALLY INVASIVE PROCEDURES/	2285
10	((mini* ADJ3 invas* ADJ3 esophagectom*)).ti,ab	9
11	((mini* ADJ3 invas* ADJ3 oesophagectom*)).ti,ab	1
12	((mini* ADJ3 access* ADJ3 esophagectom*)).ti,ab	0
13	((mini* ADJ3 access* ADJ3 oesophagectom*)).ti,ab	0
14	TLE.ti,ab	85
15	((ivor ADJ3 lewis)).ti,ab	4
16	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	4494
17	ESOPHAGEAL NEOPLASMS/	1340
18	(oesophag* ADJ3 neoplasm*).ti,ab	0
19	(oesophag* ADJ3 cancer*).ti,ab	195

20	(oesophag* ADJ3 carcinoma*).ti,ab	51
21	(oesophag* ADJ3 adenocarcinoma*).ti,ab	50
22	(oesophag* ADJ3 tumour*).ti,ab	21
23	(oesophag* ADJ3 tumor*).ti,ab	0
24	(oesophag* ADJ3 malignan*).ti,ab	12
25	(esophag* ADJ3 malignan*).ti,ab	49
26	(esophag* ADJ3 tumor*).ti,ab	51
27	(esophag* ADJ3 tumour*).ti,ab	0
28	(esophag* ADJ3 adenocarcinoma*).ti,ab	180
29	(esophag* ADJ3 carcinom*).ti,ab	200
30	(esophag* ADJ3 cancer*).ti,ab	539
31	(esophag* ADJ3 neoplasm*).ti,ab	12
32	(gullet* ADJ3 neoplasm*).ti,ab	0
33	(gullet* ADJ3 cancer*).ti,ab	2
34	(gullet* ADJ3 carcinoma*).ti,ab	0
35	(gullet* ADJ3 adenocarcinom*).ti,ab	0
36	(gullet* ADJ3 tumour*).ti,ab	0
37	(gullet* ADJ3 tumor*).ti,ab	0
38	(gullet* ADJ3 malignan*).ti,ab	0
39	BARRETT ESOPHAGUS/	465
40	(barrett* ADJ3 esophagus*).ti,ab	291
41	(barrett* ADJ3 oesophagus*).ti,ab	79
42	(barrett* ADJ3 syndrome*).ti,ab	3
43	(barrett* ADJ3 epithelium*).ti,ab	25
44	39 OR 40 OR 41 OR 42 OR 43	561
45	(high ADJ3 grade ADJ3 dysplasia*).ti,ab	125
46	(high-grade ADJ3 dysplasia*).ti,ab	124
47	45 OR 46	125
48	44 AND 47	68
49	17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38	1622
50	16 AND 48 AND 49	1
51	50 [Limit to: Publication Year 2010-2011]	0

Appendix 2: Details of searches undertaken for Procedure Number 326 (Thoracoscopic assisted oesophagectomy)

Action	Comments	Version searched (if applicable)	Date searched
Search for similar NICE topics	No information of relevance found.	N/A	8/7/2005
Consult notification and specialist advisors questionnaires for additional papers	Not yet available	N/A	8/7/2005
Conduct general internet search for background	No information of relevance found.	N/A	8/7/2005
Search for Cochrane systematic review	No Cochrane reviews. 1 Cochrane Protocol on Transthoracic esophagectomy vs transhiatal esophagectomy for the surgical treatment of esophageal carcinoma.	2005 Issue 2	8/7/2005
ASERNIP website	No information of relevance found.	N/A	8/7/2005
FDA website	No information of relevance found.	N/A	8/7/2005
Search conferences websites	No information of relevance found.	N/A	8/7/2005
Search Databases:			
The Cochrane Library	5 hits	2005 Issue 2	5/7/2005
CRD Databases	13 hits	June 2005	6/7/2005
Embase	159 hits See also further break-down of searches	1980 to 2005 Week 27	5/7/2005
Medline	177 hits See also further break-down of searches	1966 to June Week 4 2005	5/7/2005
Premedline	7 hits See also further break-down of searches	July 01, 2005	5/7/2005
CINAHL	4 hits	1982 to July Week 1 2005	8/7/2005
BLIC (limit to current year only)	0 hit	Current year	8/7/2005
National Research Register	9 hits	2005 Issue 2	8/7/2005
Controlled Trials Registry	0 hit	N/A	8/7/2005

Database: Cochrane 2005 Issue 2: Date searched 5/7/2005

#1	thoracoscop* in All Fields in all products	153
#2	MeSH descriptor Thoracoscopy explode all trees in MeSH products	95

#3	minimal* near/2 surg* in All Fields in all products	381
#4	minimal* near/2 invasive in All Fields in all products	620
#5	minimal* near/2 access in All Fields in all products	46
#6	"MIS" in All Fields in all products	112
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)	948
#8	oesophagectomy or esophagectomy in All Fields in all products	214
#9	MeSH descriptor Esophagectomy explode all trees in MeSH products	117
#10	oesophag* near/2 (incis* or dissect*) in All Fields in all products	2
#11	esophag* near/2 (incis* or dissect*) in All Fields in all products	7
#12	(#8 OR #9 OR #10 OR #11)	214
#13	"GIA 30" in All Fields in all products	1
#14	GIA next stapler in All Fields in all products	7
#15	endoscopic near/2 stapler in All Fields in all products	11
#16	autosuture in All Fields in all products	9
#17	(#13 OR #14 OR #15 OR #16)	25
#18	MeSH descriptor Esophageal Neoplasms explode all trees in MeSH products	479
#19	oesophag* near/3 (cancer* or neoplasm* or carcinoma* or tumo?r* or malignant) in All Fields in all products	235
#20	esophag* near/3 (cancer* or neoplasm* or carcinoma* or tumo?r* or malignant) in All Fields in all products	889
#21	MeSH descriptor Barrett Esophagus explode all trees in MeSH products	72
#22	barrett* next oesophagus in All Fields in all products	104
#23	barrett* next esophagus in All Fields in all products	104
#24	MeSH descriptor Esophageal Achalasia explode all trees in MeSH products	67
#25	achalasia in All Fields in all products	99
#26	(#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)	1144
#27	(#7 AND #12 AND #26)	5
#28	(#12 AND #17)	0
#29	(#17 AND #26)	0
#30	(#27 OR #28 OR #29)	5

CRD Databases: Date searched: 6/7/2005

- thoracoscop/All fields AND oesophagectomy or esophagectomy/All fields
- thoracoscopy/Subject Headings Exploded AND esophagectomy/Subject Headings Exploded
- minimal(s)surg/All fields AND esophagectomy or oesophagectomy/All fields
- minimal(s)invasive/All fields AND esophagectomy or oesophagectomy/All fields
- minimal(s)access/All fields AND esophagectomy or oesophagectomy/All fields
- endoscop/All fields AND oesophagectomy or esophagectomy/All fields
- laparo/All fields AND esophagectomy or oesophagectomy/All fields

Embase 1980 to 2005 Week 27: Date searched: 5/7/2005

0 thoracoscop$.tw. (3711)
2 exp THORACOSCOPY/ (3912)
3 (minimal$ adj2 surg$).tw. (3478)
4 (minimal$ adj2 invasive).tw. (10436)
5 (minimal$ adj2 access).tw. (669)
6 MIS.tw. (2021)
7 or/1-6 (17916)
8 (oesophagectomy or esophagectomy).tw. (2568)
9 exp esophagus resection/ (3726)

10 (oesophag$ adj2 (incis$ or dissect$)).tw. (50)
11 (esophag$ adj2 (incis$ or dissect$)).tw. (242)
12 or/8-11 (4474)
13 GIA 30.tw. (21)
14 GIA stapler.tw. (69)
15 (endoscopic adj2 stapler).tw. (99)
16 autosuture.tw. (74)
17 or/13-16 (248)
18 exp Esophagus tumor/ (16750)
19 (oesophag$ adj3 (cancer$ or neoplasm$ or carcinoma$ or tumo?r$ or malignant)).tw. (3036)
20 (esophag$ adj3 (cancer$ or neoplasm$ or carcinoma$ or tumo?r$ or malignant)).tw. (11290)
21 exp Barrett Esophagus/ (3821)
22 Barrett$ oesophagus.tw. (643)
23 barrett$ esophagus.tw. (2193)
24 exp ESOPHAGEAL ACHALASIA/ (2457)
25 achalasia.tw. (2101)
26 or/18-25 (23743)
27 7 and 12 and 26 (159)
28 12 and 17 (6)
29 17 and 26 (8)
30 27 or 28 or 29 (169)
31 limit 30 to humans (159)
32 from 31 keep 1-159 (159)

Database: MEDLINE(R) 1966 to June Week 4 2005: Date searched: 5/7/2005

1 thoracoscop$.tw. (4586)
2 exp THORACOSCOPY/ (4767)
3 (minimal$ adj2 surg$).tw. (3838)
4 (minimal$ adj2 invasive).tw. (10982)
5 (minimal$ adj2 access).tw. (689)
6 MIS.tw. (2368)
7 or/1-6 (20153)
8 (oesophagectomy or esophagectomy).tw. (3017)
9 exp ESOPHAGECTOMY/ (2626)
10 (oesophag$ adj2 (incis$ or dissect$)).tw. (62)
11 (esophag$ adj2 (incis$ or dissect$)).tw. (300)
12 or/8-11 (4288)
13 GIA 30.tw. (30)
14 GIA stapler.tw. (73)
15 (endoscopic adj2 stapler).tw. (115)
16 autosuture.tw. (112)
17 or/13-16 (315)
18 exp Esophageal Neoplasms/ (22813)
19 (oesophag$ adj3 (cancer$ or neoplasm$ or carcinoma$ or tumo?r$ or malignant)).tw. (3460)
20 (esophag$ adj3 (cancer$ or neoplasm$ or carcinoma$ or tumo?r$ or malignant)).tw. (14972)
21 exp Barrett Esophagus/ (3033)
22 Barrett$ oesophagus.tw. (603)
23 barrett$ esophagus.tw. (2304)
24 exp ESOPHAGEAL ACHALASIA/ (3514)
25 achalasia.tw. (2769)

26 or/18-25 (31200)
27 7 and 12 and 26 (167)
28 12 and 17 (9)
29 17 and 26 (11)
30 27 or 28 or 29 (181)
31 limit 30 to humans (177)

Database: Premedline 01 July 2005: Date searched: 5/7/2005

1 thoracoscop$.tw. (147)
2 (minimal$ adj2 surg$).tw. (159)
3 (minimal$ adj2 invasive).tw. (561)
4 (minimal$ adj2 access).tw. (37)
5 MIS.tw. (100)
6 or/1-5 (818)
7 (oesophagectomy or esophagectomy).tw. (75)
8 (oesophag$ adj2 (incis$ or dissect$)).tw. (1)
9 (esophag$ adj2 (incis$ or dissect$)).tw. (8)
10 or/7-9 (80)
11 GIA 30.tw. (0)
12 GIA stapler.tw. (0)
13 (endoscopic adj2 stapler).tw. (1)
14 autosuture.tw. (0)
15 or/11-14 (1)
16 (oesophag$ adj3 (cancer$ or neoplasm$ or carcinoma$ or tumo?r$ or malignant)).tw. (42)
17 (esophag$ adj3 (cancer$ or neoplasm$ or carcinoma$ or tumo?r$ or malignant)).tw. (298)
18 Barrett$ oesophagus.tw. (15)
19 barrett$ esophagus.tw. (83)
20 achalasia.tw. (52)
21 or/16-20 (456)
22 6 and 10 and 21 (7)
23 10 and 15 (0)
24 15 and 21 (0)
25 or/22-24 (7)
26 from 25 keep 1-7 (7)

Database: CINAHL: Date searched: 8/7/2005

1 thoracoscop$.tw. (131)
2 exp THORACOSCOPY/ (117)
3 (minimal$ adj2 surg$).tw. (203)
4 (minimal$ adj2 invasive).tw. (523)
5 (minimal$ adj2 access).tw. (46)
6 MIS.tw. (186)
7 or/1-6 (928)
8 (oesophagectomy or esophagectomy).tw. (28)
9 exp ESOPHAGECTOMY/ (0)
10 (oesophag$ adj2 (incis$ or dissect$)).tw. (0)
11 (esophag$ adj2 (incis$ or dissect$)).tw. (4)
12 or/8-11 (32)
13 GIA 30.tw. (0)
14 GIA stapler.tw. (0)
15 (endoscopic adj2 stapler).tw. (2)
16 autosuture.tw. (0)

17 or/13-16 (2) 18 exp Esophageal Neoplasms/ (359) 19 (oesophag$ adj3 (cancer$ or neoplasm$ or carcinoma$ or tumo?r$ or malignant)).tw. (64) 20 (esophag$ adj3 (cancer$ or neoplasm$ or carcinoma$ or tumo?r$ or malignant)).tw. (195) 21 exp Barrett Esophagus/ (57) 22 Barrett$ oesophagus.tw. (17) 23 barrett$ esophagus.tw. (69) 24 exp ESOPHAGEAL ACHALASIA/ (42) 25 achalasia.tw. (42) 26 or/18-25 (535) 27 7 and 12 and 26 (4) 28 12 and 17 (0) 29 17 and 26 (0) 30 27 or 28 or 29 (4) 31 from 30 keep 1-4 (4)

Database: BLIC: Date searched: 8/7/2005

No	Search term	Results
1	thoracoscop$	9
2	laparo$6	153
3	endoscop$5	119
4	1 OR 2 OR 3	277
5	esophagectomy OR oesophagectomy	3
6	4 AND 5	0

Database: National Research Register Date searched: 8/7/2005

#1.	thoracoscop* or endoscop* or laparo*	1586
#2.	THORACOSCOPY explode all trees (MeSH)	11
#3.	(minimal* near invasive)	148
#4.	(minimal* near access)	66
#5.	(minimal* near surg*)	131
#6.	mis	58
#7.	(#1 or #2 or #3 or #4 or #5 or #6)	1800
#8.	(oesophagectomy or esophagectomy)	38
#9.	ESOPHAGECTOMY explode all trees (MeSH)	15
#10.	((oesophag* near incis*) or (oesophag* near dissect*))	2
#11.	((esophag* near incis*) or (esophag* near dissect*))	0
#12.	(#8 or #9 or #10 or #11)	39
#13.	(gia next 30)	0
#14.	(gia next stapler)	0
#15.	(endoscopic near stapler)	0
#16.	autosuture	5
#17.	(#13 or #14 or #15 or #16)	5
#18.	(#7 and #12)	9
#19.	(#12 and #17)	0
#20.	(#18 or #19)	9

Database: Controlled Trials Registry: Date searched: 8/7/2005

thoracoscop% and oesophagectomy thoracoscop% and esophagectomy laparo% and esophagectomy laparo% and oesophagectomy endoscop% and esophagectomy endoscop% and oesophagectomy

Appendix 3: Tabulation of excluded studies

Study	Reason for exclusion
Benzoni 2007[80]	No open control
Benzoni 2008[17]	Same data as Benzoni 2007[80]
Bonavina 2004[19]	No open control
Campos 2010[81]	No open control
Dapri 2008[82]	No open control
Law 2000[83]	No open control
Levy 2010[84]	Refers to experience of performing laparoscopic and thoracoscopic oesophagectomy in >500 patients, but does not quantify outcome data
Martin 2005[25]	Unclear reporting of results (36 patients included but results only reported for 21)
Morris 2007[26]	Includes thyroid, head and neck cancers
Nakatsuchi 2005[85]	Does not report relevant outcomes, only those related to chest physical therapy.
Narumiya 2005[86]	Does not utilise any minimally invasive techniques
Perry 2009[87]	No open control
Scheepers 2008[88]	Does not report relevant outcomes
Scheepers 2009[29]	Does not report relevant outcomes (focuses on circumferential margins only).
Schoppmann 2009[89]	Same data as Schoppmann et al 2010,[49] which is included in this review
Song 2009[79]	Unclear reporting of results. MIO planned for all patients, and the authors attempt to use as controls the 14 patients who had to be converted to open surgery.
Taguchi 2003[31]	Same data as presented in Osugi et al 2003,[28] which is included in this review.