New and Emerging Techniques - Surgical

Horizon Scanning Report

Minimally Invasive Oesophagectomy

August 2004

ASERNIP/S

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical

New and Emerging Techniques – Surgical

Horizon scanning reports are for information only

Royal Australasian College of Surgeons

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Introduction

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) in conjunction with the Royal Australasian College of Surgeons has undertaken a Horizon Scanning Report to provide advice on the state of play of the introduction and use of minimally invasive oesophagectomy (MIO); (alternatively known as minimally invasive esophagectomy (MIE)).

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of minimally invasive oesophagectomy, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with minimally invasive oesophagectomy.

Background

Background to the Condition

Barrett's oesophagus is characterised by atypical changes to cell nuclei in oesophageal cells which result in abnormal cell growth patterns. The presence of Barrett's oesophagus has shown to be associated with an increased risk of developing squamous carcinoma or adenocarcinoma of the oesophagus (National Cancer Institute 2004). Barrett's oesophagus is believed to occur as a consequence of chronic mucosal exposure to gastroesophageal reflux (Nguyen *et al.* 2000b). Patients with Barrett's oesophagus may progress to high-grade dysplasia (Nguyen *et al.* 2000b) with up to 50% of resected high-grade dysplasia shown to contain carcinoma in situ or invasive carcinoma (Nguyen *et al.* 2000b). Most people who are diagnosed with oesophageal cancer die from the disease, with surgery the only hope of a cure (Swanstrom 2002). Oesophagectomy has been the recommended treatment for both benign and malignant disease but it is associated with high morbidity and mortality rates (Nguyen *et al.* 2000b).

Patients tend to seek medical advice with the increased inability to swallow, a symptom developed with late-stage disease. Since cure rates are seen predominately with early-stage disease, late presentation lessens the chance of survival (Swanstrom 2002, Australia Cancer Study 2003). Generally, oesophagectomy is only recommended as a treatment for high-grade dysplasia or cancer in Barrett's oesophagus (Nguyen *et al.* 2000b), as the risk of complications from surgery is too great to justify removing the oesophagus of all patients who have Barrett's oesophagus. Development of a MIO, with potentially decreased morbidity and mortality rates, would allow the treatment of patients where (due to the risks for open surgery) only surveillance would be recommended.

Description of the Technology

The Procedure

Minimally invasive oesophagectomy can be performed in a variety of ways, with the combined thoracoscopic and laparoscopic oesophagectomy approach being well documented. This approach can be divided into three stages (Swanstrom 2002, Nguyen *et al.* 2000a). In the first stage, thoracoscopic dissection is done with the patient in the left lateral decubitus position. Four thoracic trocars are introduced into the right chest. The mediastinal pleura, overlying the oesophagus, is divided to expose the intrathoracic oesophagus. The azygous vein is divided, and a Penrose drain is placed around the oesophagus to facilitate oesophageal retraction. The oesophagus is mobilised from the oesophageal hiatus up to the thoracic inlet. A 28F chest tube is then inserted through the camera port for postoperative chest drainage (Swanstrom 2002, Nguyen *et al.* 2000b).

In the second stage, the patient is moved into the supine position. Five abdominal ports are placed into the anterior abdominal wall. The stomach is mobilised, preserving the right gastroepiploic vessels. The left gastric vessel is isolated and divided. Stapling of the stomach creates a gastric conduit, which is sutured to the mobilised oesophagus for tunnelling to the neck. The stomach is used as an oesophageal substitute. A feeding tube is then placed laparoscopically in the proximal jejunum (Swanstrom 2002, Nguyen *et al.* 2000a).

In the third stage, a horizontal neck incision is made and the cervical oesophagus is mobilised until the dissection plane in the right chest is achieved. The entire oesophagheal specimen with the attached gastric conduit is delivered through the cervical incision (Swanstrom 2002, Nguyen *et al.* 2000a).

Intended Purpose

Currently this procedure is being used as an alternative to conventional open oesophagectomy in patients with high-grade dysplasia/cancer, in an attempt to reduce intra- and post-surgical complications along with morbidity and mortality rates. Potentially, not only could patients with high-grade dysplasia and cancer be recommended for the procedure but so could patients with other complex oesophageal disorders, such as achalasia and giant paraoesophageal hernia (Luketich *et al.* 2003). However, postoperative morbidity after MIO has been shown to be related to the stage of the cancer. Therefore only patients meeting stringent criteria through intensive preoperative patient evaluation by minimally invasive surgical staging or endoscopic ultrasound are currently eligible for MIO.

Due to the surgical complexity of the procedure it is found that surgeons who are experienced with the open oesophagectomy procedure have reduced postoperative complications and morbidities when they perform minimally invasive oesophagectomy. It has been reported that surgeons at institutions performing more than 30 operations during a 5-year period have the lowest mortality rates (Nguyen *et al.* 2000b) compared to those surgeons with less experience.

Contraindications

The MIO procedure is unsuitable for cancers that have metastasised as associated morbidity has been shown to be associated with the stage of the cancer. According to studies by the Pittsburgh Medical Centre at a mean follow-up of 13.4 months, 90% of stage I, 65% of stage II and 25% of stage III patients had survived. Stage I cancer is where the tumour involves the lamina propria or submucosa; stage II, the tumour invades the muscularis propria/adventitia or invades the lamina propria/submucosa or muscle propria with regional lymph node metastasis; stage III, the tumour invades the adventitia or adjacent structures with regional lymph node metastasis; and stage IV, where any degree of tumour and lymph node involvement is accompanied with distant metastasis.

Clinical Need and Burden of Disease

In Australia, it is estimated that 1000 people per year will develop oesophageal cancer (Australian Cancer Study 2003). In 2001/02, there were 1240 hospital separations for stomach, oesophageal and duodenal procedures involving malignancies, with separate figures for oesophageal cancer not available (AIHW 2004). New Zealand reported a total of 663 separations from public hospitals for malignant neoplasms of the oesophagus in 2000/01 with 187 deaths reported in 2000 (2.9 deaths per 100 000 people, age standardised) (New Zealand Health Information Service 2004).

International statistics suggest that mortality rates are high. In 2000, 7364 people were diagnosed with oesophageal cancer in the United Kingdom and in 2002, 7245 people died from the disease (8.9 deaths per 100 000 people, age standardised) (Cancer Research UK). In the United States it is estimated that 14 250 people will be diagnosed with oesophageal cancer in 2004, and 13 300 will die from the disease (American Cancer Society 2004). Patients are often elderly, may have comorbid disease and may be malnourished from malignant dysphagia. The five-year survival rate (5 to 30% after surgery) is worse than many other cancers. Oesophagectomies are associated with significant morbidity and mortality rates; in the United States mortality rates range from 8% to 23% (Birkmeyer et al. 2002).

Stage of Development

Minimally invasive oesophagectomy has been offered to the majority of patients with resectable cancers at the University of Pittsburgh Medical Centre, USA since 2000 (Fernando et al. 2000). In addition, a multi-centre study with 125 patients in five different centres experienced with MIE, will be performed in the United States to assess whether MIE can be developed in other centres with similar positive outcomes (Luketich et al.

2003). Comparative studies of MIO have also been conducted in the United Kingdom since January 1993 (Ganesh 2003 and Wastell 1997).

With the high morbidity and mortality rates associated with conventional oesophagectomy, the minimally invasive technique has the potential to be widely adopted by surgeons as a replacement for invasive thoracotomy and laparotomy (Luketich 2003). Potentially the MIO technique could decrease the incidence of oesophageal cancer by allowing the treatment of dysplasia before its progression to adenocarcinoma of the oesophagus (Barrett's oesophagus).

Treatment Alternatives

Existing Comparators

Oesophagectomy has a variety of approaches: transthoracic (Ivor-Lewis), left thoracoabdominal, left thoracoabdominal with left neck anastomosis and transhiatal. Photodynamic therapy is also used as a non-surgical procedure (National Cancer Institute 2004). With 30-day oesophagectomy mortality rates ranging from 8% in experienced centres to 23% in low-volume centres (Birkmeyer *et al.* 2002), many patients with oesophageal cancer are not even referred for surgery at all (Luketich *et al.* 2003). Older patients and those with comorbid conditions may be referred for photodynamic therapy which has a morbidity rate that approaches zero, but it has yet to be proven to be as beneficial as surgical resection (Luketich *et al.* 2003). Photodynamic therapy is not currently available in Australia but it has been approved by the United States Food and Drug Administration for the treatment of Barrett's oesophagus. The MIO procedure has the potential for lower morbidity compared with open operation and to allow quicker return to normal function, therefore a greater number of patients may be referred to this alternative technique (Luketich et al. 2003).

Clinical Outcomes

Evidence on the efficacy and safety of the MIO procedure exists from one non-randomised comparative study (Nguyen *et al.* 2000a) and four case series (Fernando *et al.* 2002, Luketich *et al.* 2003, Nguyen *et al.* 2000b and Nguyen *et al.* 2003). Data were taken from the latest most complete report. Fernando *et al.* (2002) included 28 patients, Luketich *et al.* (2003) included 222 patients, Nguyen *et al.* (2000a) included 54 patients, Nguyen *et al.* (2000b) included 12 patients, Nguyen *et al.* (2003) included 46 patients. The 12 patients reported in Nguyen *et al.* (2000b), were also reported in Nguyen *et al.* (2003). Most procedures used a combined thoracoscopic and laparoscopic approach. The summary of the study findings are summarised in tables in Appendix A.

Effectiveness

Survival

In Nguyen *et al.* (2003), 38/45 (84.4%) patients had cancer, and the survival rate at three years for those 38 was 57%. In Nguyen *et al.* (2000b), all 12 patients were alive and free of metastatic disease at mean follow-up of 12.6 months. In Fernando *et al.* (2002), 27/28 (96.4%) patients were alive and free of disease at median follow-up of 13 months (range 2 to 41 months).

Procedure Time

A non-randomised comparative study between MIO, transthoracic oesophagectomy (TT) and blunt transhiatal oesophagectomy (THE) conducted by Nguyen *et al.* (2000a), reported that operating times were shorter in the MIO group (mean 364 standard deviation [73] minutes) compared with both the TT (437 [65] minutes) and THE (391 [144] minutes) groups, $p<0.001$.

Across three case series (Fernando *et al.* 2002, Nguyen *et al.* 2000b, Nguyen *et al.* 2003), the median procedure time was 468 minutes (range 350 to 480 minutes).

Duration of Hospital Stay

The non-randomised comparative study (Nguyen *et al.* 2000a) reported that the mean duration of hospital stay was shorter in the MIO group (11.3 [14.2] days) compared to the TT (23.0 [22.3] days) and THE (22.3 [16.1] days) groups, $p<0.05$.

The median duration of hospital stay based on all four case series studies was 7.5 days (range 5 to 8.3 days). This compares favourably with that of open procedures, which almost universally exceeds a hospital stay of 10 days (Luketich *et al.* 2000).

Duration of Intensive Care Unit Stay

Nguyen *et al.* (2000a) found that the mean overall duration of intensive care unit stay was shorter in the MIO group (6.1 [11.3] days), compared with the TT (9.9 [16.3] days) and THE (11.1 [15.7] days) groups, $p<0.004$.

The median duration of time patients were required to stay in intensive care between the four case series was 1.5 days (range 1 to 2.6 days).

Margin Clearance

As the majority of patients undergoing invasive oesophagectomy have cancer, the adequacy of surgical margins is critical. In the study conducted by Nguyen et al. (2000b) all 12 patients had surgical resection margins which were found to be free of tumour or Barrett's dysplasia.

Recurrence

Nguyen *et al.* (2003) reported no recurrent local or metastatic disease in the MIO group (n=45). Nguyen *et al.* (2000b) and Fernando *et al.* (2002) both reported no recurrence of disease. Nguyen *et al.* (2000a) reported that no patients developed recurrent local or metastatic disease and there had been no tumour recurrence at the thoracoscopic or laparoscopic cannula sites.

Lymph Node Collection

Nguyen et al. (2000b) reported a mean number of lymph nodes obtained at surgical resection to be 11.5 [6.9] (range 0 to 23).

Safety

Mortality Rate

The non-randomised comparative study (Nguyen *et al.* 2000a) reported a zero 30-day mortality rate for MIO, TT and THE. However, one in-hospital death due to multiple organ failure occurred in the THE group on day 70 and one MIO patient who developed tracheogastric fistula died of bronchopneumonia six months later.

In case series studies by Nguyen *et al.* (2000b) and Luketich *et al.* (2003), the 30-day mortality rate was reported to be 0% and 1.4% (3/222), respectively. Nguyen *et al.* (2003) reported an overall mortality rate of 4.3% (2/46). Fernando *et al.* (2002) reported 1/28 (3.6%) patient death due to sepsis, pneumonia and multi-system organ failure. It was not reported how long post-procedure the death occurred.

Complications

In Nguyen *et al.* (2000a), MIO resulted in 7/18 (38.8%) postoperative complications compared to TT 8/16 (50%) and THE 11/20 (55%). There was no significant difference in the incidence of respiratory complications (e.g. pneumonia, respiratory failure and pulmonary embolism) and anastomotic leaks among the three different groups. Nguyen *et al.* (2003) reported major complications in 8/46 (17.4%) patients and Nguyen *et al.* (2000b) reported six major complications in 5/12 (42%) patients.

The main complications arising in the case series, which may be linked to the MIO procedure, included delayed gastric emptying 3/12 (25%) (Nguyen *et al.* 2000b), pneumonia 17/222 (7.7%) (Luketich *et al.* 2003), pleural effusion requiring a tube 14/222 (6.3%) (Luketich *et al.* 2003) and tracheal gastric fistula 1/18 (5.5%) (Nguyen *et al.* 2000b). Anastomotic leak rate in Luketich *et al.* (2003) was reported to be affected by the size of the gastric tube. Overall they reported an anastomotic leak rate of 26/222 (11.7%), showing an increased incidence when narrow gastric tubing was used 16/222 (25.9%) compared with normal gastric tubing 10/222 (6.1%).

Blood Loss

Blood loss was significantly decreased in the MIO group (297 [233] mL) compared to the TT (1046 [792] mL) and THE (1142 [785] mL) groups in Nguyen *et al.* (2000a), $p<0.0001$. Consequently, this resulted in significantly fewer transfusions required in the MIO group (3/18, 16.7%) compared to the TT (8/16, 50%) and THE (15/20, 75%) groups, $p<0.05$. Nguyen *et al.* (2003) reported the MIO procedure to have a mean blood loss of 279 [184] mL.

Potential Cost Impact

Cost Analysis

Minimally invasive oesophagectomy is performed under the same conditions as for open oesophagectomy but reportedly requires less operative time and a decreased duration of ICU and overall hospital stay, potentially making the procedure more cost effective than open oesophagectomy. However, the costs associated with the MIO procedure were not available.

Ethical Considerations

Informed Consent

It is not apparent in the included studies if patients were informed of the 'newness of the technology' prior to providing informed consent.

Access Issues

Access is limited to major metropolitan areas, as with conventional open oesophagectomy, due to the complexity of the MIO procedure.

Training and Accreditation

Training

No information could be found in regard to the training required in addition to the standard training for oesophagectomy and laparoscopy.

Clinical Guidelines

No clinical guidelines could be found for minimally invasive oesophagectomy.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of minimally invasive oesophagectomy, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Search Strategy Used for Report

A systematic search of MEDLINE, EMBASE, PubMed, Cochrane Library and Science Citation Index using Boolean search terms was conducted, from the inception of the databases until February 2004. Clinicaltrials.gov, National Research Register, relevant online journals and the internet were also searched in February 2004. Searches were conducted without language restrictions.

Articles were obtained on the basis of the abstract containing safety and efficacy data on the MIO procedure in the form of randomised controlled trials (RCTs), other controlled or comparative studies, case series and case reports. Conference abstracts and manufacturers information were included if they contained relevant safety and efficacy data. In the case of duplicate publications, the latest, most complete study was included. Articles were rejected for reporting no clinical outcomes, being review articles without data or involving techniques other than the MIO procedure.

Availability and Level of Evidence

Total number of studies:	5
Non-randomised comparative studies	1
Case series	4

Published evidence on the safety and efficacy of the MIO procedure exists from one non-randomised comparative study and four case series, of which two (ie. one non-randomised comparative study and one case series) probably report on an overlap of patients.

Sources of Further Information

Luketich *et al*. (2003) mentions that a multicentre study involving the MIO procedure is being planned.

According to the UK National Research Register two trials have been completed using the MIO procedure.

1. TITLE: Comparing postoperative outcome of laparoscopic oesophagectomy and open oesophagectomy
   END DATE: 01/08/2003
   CONTACT: Mr Radhakrishnan Ganesh
   Bedford Hospital
   South Wing
   Brittannia Road
   Beds
   MK42 9DJ
   UK
   Phone: 01234 355122
2. TITLE: Total oesophagectomy employing minimally invasive technique
   END DATE: 13/10/1997
   CONTACT: Professor C Wastell
   Department of Surgery
   Chelsea and Westminster Hospital
   369 Fulham Road
   London
   SW10 9NH
   Telephone: +44 181 746 8463

It should be noted publications of this data could not be located.

Impact Summary

Reduced blood loss and shorter hospital stay make MIO a more attractive and less costly option than the open procedure, which is associated with significant morbidity and mortality.

Conclusions

MIO may enable effective oesophageal resection whilst resulting in decreased procedure time, duration of ICU and overall hospital stay, blood loss and hence need for transfusions. However, more studies comparing MIO and the open procedure are required to determine the relative safety an efficacy of MIO.

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Luketich JD, Schauer PR, Christie NA, Weigel TL, Raja S, Fernando HC, Keenan RJ, Nguyen NT. Minimally Invasive Esophagectomy. *Annals of Thoracic Surgery* 2000; **70**: 906-12.

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Appendix A: Table of Key Efficacy and Safety Findings - Comparative Study

Author, Date, Location, Number of Patients, Length of Follow-up, Selection Criteria

Nguyen *et al.* 2000a, USA
Retrospective comparative study
Evidence level III-3

54 patients
Follow-up: mean 6.3 months

Comparison:
Group 1- minimally invasive oesophagectomy (MIO): 18 patients
Follow-up: mean 6.3 months (range 2-14)
Group 2- Transthoracic (TT): 16 patients
Group 3- blunt transhiatal (THE): 20 patients

Selection criteria:
Inclusion criteria not stated

For groups 2 & 3, 19 patients were excluded for the following reasons: emergency oesophagectomy for oesophageal perforation (8 patients), subtotal gastrectomy and primary colonic interposition (5 patients) and combined pharyngolaryngectomy with oesophagectomy (6 patients).

Group 1 patients appear to also be reported in Nguyen *et al.* 2003.

Key Efficacy Findings

<u>Procedure time (min):</u>

	MIO (n=18)	TT (n=16)	THE (n=20)
Mean min [SD]	364 [73]	437 [65]	391 [144]

Procedure time was less in MIO group than in other two groups (p<0.001)

<u>Duration of hospital stay:</u>

	MIO (n=18)	TT (n=16)	THE (n=20)
Mean days [SD]	11.3 [14.2]	23.0 [22.3]	22.3 [16.1]

The duration of hospital stay was 50% shorter in MIO patients compared to TT (p<0.004) and THE patients (p<0.001).

<u>Duration of hospital stay:</u>

	MIO (n=18)	TT (n=16)	THE (n=20)
Mean days [SD]	6.1 [11.3]	9.9 [16.3]	11.1 [15.7]

MIO patients had a shorter ICU stay than TT (p<0.03) and THE (p<0.04) patients.

Key Safety Findings

<u>Complications:</u>
No intraoperative complications were reported in MIO or TT patients, 4/20 (20%) patients in the THE group, had complications:

- tracheal tear (1 patient)
- incidental splenectomy (2 patients)
- torn azygous vein (1 patient)

<u>Postoperative complications:</u>

	Incidence of complication		
Complication type	MIO (n=18)	TT (n=16)	THE (n=20)
GI bleeding	0	1/16 **(6%)**	0
Anastomotic leaks	2/18 **(11.1%)**	2/16 **(12.5%)**	2/20 **(10%)**
Gastric conduit Ischaemia	0	1/16 **(6%)**	0
Pulmonary embolism	1/18 **(5.5%)**	0	1/20 **(5%)**
Respiratory failure	2/18 **(11.1%)**	3/16 **(18.8%)**	3/20 **(15%)**
Delayed gastric emptying	1/18 **(5.5%)**	0	0
Chylous ascites	0	0	1/20 **(5%)**
Hoarseness	0	0	4/20 **(20%)**
Intra-abdominal	0	1/16 **(6%)**	0

Appraisal/Comments

Patient selection:
Not clear how patients were selected. Consecutive patient selection occurred in MIO group. Historical comparison using retrospective chart review was used for other two groups.

Other:
There were no significant differences among the 3 groups in terms of age, history of abdominal surgery, American Society of Anesthesiology classification and indications.

Short follow-up in MIO group. No follow-up in TT and THE groups.

Number of nodes removed:

	MIO (n=18)	TT (n=16)	THE (n=20)
No. of nodes	10.8 [8.4]	6.3 [6.0]	6.9 [5.4]

The mean number of lymph nodes removed during MIO was similar to the number removed during TT and THE procedures.

Margins:
All surgical margins were free from tumour in the (0/18) MIO group. 1/16 (6.3%) patients in TT group had a positive margin for Barrett's metaplasia, and 1/20 (5%) of patients in the THE group had a positive margin for carcinoma.

At 6 months follow-up none of the patients in the MIO group with oesophageal cancer, had developed local, recurrent local or metastatic disease.

abscess			
Tracheal-gastric fistula	1/18 **(5.5%)**	0	0

Blood loss:

	MIO (n=18)	TT (n=16)	THE (n=20)
Mean mL [SD]	297 [233]	1046 [792]	1142 [785]

The operative blood loss was significantly less in MIO patients compared to patients in other groups ($p<0.001$)

Intraoperative transfusion:

	MIO (n=18)	TT (n=16)	THE (n=20)
Mean units [SD]	0.3 [0.7]	1.8 [2.2]	2.9 [3.1]

Fewer transfusions were needed in MIO patients compared to patients in other groups ($p<0.05$).

Fewer transfusions were needed in the MIO group (3/18, 16.7%) than in TT (8/16, 50%) and THE group (15/20, 75%) ($p<0.05$).

Mortality rate:
30 day mortality was zero in all groups.

One in-hospital death due to multiple organ failure occurred in the THE group on day 70. One MIO patient who developed tracheal-gastric fistula died of bronchopneumonia six months later.

Appendix A: Table of Key Efficacy and Safety Findings - Case Series

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Nguyen *et al.* 2003, USA 46 patients Follow-up: mean 26 months *Selection Criteria:* Patients with carcinoma, Barrett's oesophagus with high-grade dysplasia and recalcitrant stricture.	MIO was successfully completed in 45/46 (97.8%) patients. Procedure time: Mean operative time was 5.8 hours {1.25} hours. Duration of ICU stay: Median 2 days. Duration of hospital stay: Median 8 days. Among 38 patients with cancer who received MIO, the survival rate at 3 years was 57%.	Complications: Major complications occurred in 8/46 (17.4%) patients and minor complications occurred in 10.8%. Late complications were seen in 26.1% of patients. Blood loss: The mean blood loss was 279 [184] mL. Mortality rate: The overall mortality was 2/46 (4.3%).	Retrospective chart review of 46 consecutive patients.

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr>
<td>Nguyen et al. 2000b, USA

12 patients
Mean age: 64 years (range 40 to 78 years)
Follow-up: mean 12.6 months

Selection criteria:
Patients with Barrett's oesophagus with high-grade dysplasia (all but one underwent a combined thoracoscopic and laparoscopic procedure).

Inclusions & Exclusions:
Although complete details are unavailable in source; preoperative evaluations consisted of pulmonary function tests, cardiac evaluations and endoscopic ultrasounds.
Patients had at least a 50% predicted force expiratory volume in one second and vital capacities > 60%.

No patient had previous chemotherapy or radiotherapy. Patients who had undergone prior abdominal surgery were not excluded.</td>
<td><u>Procedure time:</u>
Mean operative time was 7.8 {2.1} hours.

<u>Duration of Intensive Care Unit stay:</u>
Mean intensive care stay was 2.6 {2.2} days (range 1 to 8 days).

<u>Duration of hospital stay:</u>
Mean length of hospital stay was 8.3 {4.7} days (range 4 to 21 days)

<u>Lymph node collection:</u>
Mean number of lymph nodes obtained at surgical resection was 11.5 {6.9} (range 0 to 23).

<u>Margins:</u>
All surgical resection margins were free of tumour or Barrett's dysplasia.

All patients were alive without evidence of metastatic disease at mean follow-up of 12.6 months.</td>
<td>There were no anastomotic leaks or strictures reported.

<u>Complications:</u>
5/12 (41.7%) patients had complications - one single minor complication and 6 major complications in 5 patients.

<u>Postoperative complications:</u>
<table>
<tr><th>Type of complication</th><th>No. of complications (%)</th></tr>
<tr><td>Major</td><td></td></tr>
<tr><td>Small bowel perforation</td><td>1/12 (8%)</td></tr>
<tr><td>Respiratory insufficiency</td><td>2/12 (17%)</td></tr>
<tr><td>Delayed gastric emptying requiring pyloroplasty</td><td>3/12 (25%)</td></tr>
<tr><td>Anastomotic leak</td><td>0/12 (0%)</td></tr>
<tr><td>Minor</td><td></td></tr>
<tr><td>J-tube site infection</td><td>1/12 (8%)</td></tr>
<tr><td>Hoarseness</td><td>0/12 (0%)</td></tr>
</table>

<u>Mortality:</u>
30-day mortality 0/12 (0%)</td>
<td>Patient selection:
Consecutive patient selection occurred.

Other:
All 12 patients underwent successful minimally invasive oesophagectomy however an additional patient was treated non-surgically due to advanced age and poor performance status.

The first patient underwent laparoscopic transhiatal oesophagectomy without thoracoscopy or thoracotomy, all subsequent patients underwent combined laparoscopic and thoracoscopic oesophagectomy. The transhiatal oesophagectomy approach seemed limited by the difficulty in mobilizing the midoesophagus region due to poor optical visualization and inadequate length of laparoscopic instrumentation.</td>
</tr>
</table>

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr>
<td>Luketich et al. 2003, USA

222 patients
Median age: 66.5 years (range, 39 to 89)
Follow-up: mean 19 months

Selection criteria:
Patients with high-grade dysplasia or carcinoma.

Inclusion & exclusion criteria:
Initial patient selection included only small T1 tumours or high-grade dysplasia. As experience was gained T2 and T3 tumours were included. Due to the reterospective nature of the study, more specific selection criteria are not applied.

Inclusion & exclusion criteria:
The primary inclusion criteria in patients with oesophageal cancer was the presence of a respectable lesion after evaluation by endoscopic ultrasound and computerized topography (CT).</td>
<td>MIO was successfully completed in 206/222 (92.8%) patients.

<u>Duration of ICU stay:</u>
The median intensive care unit stay was 1 day (range, 1 to 30 days).

<u>Duration of hospital stay:</u>
The median hospital stay was 7 days (range, 3 to 75).

Median time to oral intake was 4 days (range, 1 to 40 days).

Anastomic leak rate was affected by the size of the gastric tube, the leak rate was significantly increased when the narrow tube was used (P<0.001).

Mean gastroesophageal reflux disease-health related quality of life scale (HRQOL) scores were 4.6, which represents normal / no reflux. 4% of patients complained of significant reflux (HRQOL >15).</td>
<td><u>Complications:</u>
Postoperative complications include:
<table>
<tr><th>Type of complications</th><th>No. of complications</th></tr>
<tr><td>Major
Anastomotic leak –
Narrow gastric tube (3-4cm)
Normal gastric tube (6cm)
Myocardial infarction
Gastric tip necrosis
Delayed gastric emptying
Pancreatitis
Chylothorax
Tracheal tear
Deep vein thrombosis
Pulmonary embolous
Pneumonia
Acute respiratory disease
Vocal cord palsy
Renal failure
Miscellaneous
Minor
Atrial fibrillation
Atelectasis with mucus plug requiring bronchoscopy
Pleural effusion requiring tube
J-tube infection
Clostridium difficile colitis
Wound infection
Minor intraoperative tracheal perforation (1-2mm)
Miscellaneous</td>
<td>

16/222 (25.9%)
10/222 (6.1%)
4/222 (1.8%)
7/222 (3.2%)
4/222 (1.8%)
3/222 (1.4%)
7/222 (3.2%)
2/222 (0.9%)
3/222 (1.4%)
3/222 (1.4%)
17/222 (7.7%)
4/222 (1.8%)
8/222 (3.6%)
2/222 (0.9%)

4/222 (1.8%)
26/222 (11.7%)
10/222 (4.5%)
14/222 (6.3%)
1/222 (0.5%)
2/222 (0.9%)
2/222 (0.9%)
2/222 (0.9%)

5/222 (2.25%)</td></tr>
</table>
<u>Mortality rate:</u>
The 30-day operative mortality rate was 3/222 (1.4%).</td>
<td>Patient selection:
Unable to determine how patient selection was done.
Retrospective database review

Other:
Initially used a laparoscopic transhiatal approach for patients with smaller tumors or high-grade dysplasia (n=8), this evolved to VATS approach to mobilize the intrathoracic esophagus and to allow more complete lymph node dissection (n=214).
Combined thoracoscopic and laporoscopic approach remains procedure of choice.

Midseries a narrower gastric tube of 3-4cm in diameter was used (n=58) to avoid the need for a pyloric drainage procedure and in the hope of subsequent less reflux. This was abandoned due to increased leak rate.

MIO was successfully completed in 206 (92.8%) patients. Thoracotomy was required in 12/222 (5.4%) patients and laparotomy in 4/222 (1.8%) patients.

Luketich et al. (2000) patient group included in Luketich et al. (2003).</td>
</tr>
</table>

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Fernando et al. 2002, USA **(**patients included in Luketich *et al.* 2003) 28 patients Median age: 61 years (range 40 to 78 years) Follow-up: median 13 months (range 2 to 41 months) Selection Criteria: Patients with high-grade dysplasia	<u>Procedure time:</u> Median operating time was 8 hours (range 5.8 to 13 hours). <u>Duration of ICU stay:</u> Median intensive care unit stay was 1 day (range 1 to 20 days). <u>Duration of hospital stay:</u> Median hospital stay was 5 days (range 3 to 20 days). All hospital survivors (27/28) were alive and free of disease at follow-up.	<u>Complications:</u> Complications occurred in 15/27 (55.5%) patients. In addition to a patient who died, five reoperations were required (5/28: 7.9%). Complications involving reoperation included: Small bowel perforation - 1/27 (3.7%) Jejunostomy leak – 1/27 (3.7%) Pyloric dilation for gastric outlet obstruction – 1/27 (3.7%) Cholecystectomy – 1/27 (3.7%)	*Patient selection:* Unable to determine how patient selection occurred. Retrospective review. *Other:* MIO initially involved a laparoscopic transhiatal approach (n=1) but subsequently evolved to laparoscopy with video-assisted thoracoscopic (VATS) mobilization of the oesophagus. One patient was converted to laparotomy due to dense adhesions (1/28: 3.6%).