Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial

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Summary

Background **Surgical resection is regarded as the only curative option for resectable oesophageal cancer, but pulmonary complications occurring in more than half of patients after open oesophagectomy are a great concern. We assessed whether minimally invasive oesophagectomy reduces morbidity compared with open oesophagectomy.**

Methods **We did a multicentre, open-label, randomised controlled trial at five study centres in three countries between June 1, 2009, and March 31, 2011. Patients aged 18–75 years with resectable cancer of the oesophagus or gastro-oesophageal junction were randomly assigned via a computer-generated randomisation sequence to receive either open transthoracic or minimally invasive transthoracic oesophagectomy. Randomisation was stratified by centre. Patients, and investigators undertaking interventions, assessing outcomes, and analysing data, were not masked to group assignment. The primary outcome was pulmonary infection within the first 2 weeks after surgery and during the whole stay in hospital. Analysis was by intention to treat. This trial is registered with the Netherlands Trial Register, NTR TC 2452.**

Findings **We randomly assigned 56 patients to the open oesophagectomy group and 59 to the minimally invasive oesophagectomy group. 16 (29%) patients in the open oesophagectomy group had pulmonary infection in the first 2 weeks compared with five (9%) in the minimally invasive group (relative risk [RR] 0·30, 95% CI 0·12–0·76; p=0·005). 19 (34%) patients in the open oesophagectomy group had pulmonary infection in-hospital compared with seven (12%) in the minimally invasive group (0·35, 0·16–0·78; p=0·005). For in-hospital mortality, one patient in the open oesophagectomy group died from anastomotic leakage and two in the minimally invasive group from aspiration and mediastinitis after anastomotic leakage.**

Interpretation **These findings provide evidence for the short-term benefits of minimally invasive oesophagectomy for patients with resectable oesophageal cancer.**

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Introduction

The global incidence of oesophageal cancer has increased by 50% in the past two decades, from 316 000 people diagnosed in 1990 to 482 300 new cases recorded in 2008.[1,2] Surgical resection with radical lymphadenectomy, usually after neoadjuvant chemotherapy or chemoradiotherapy, is regarded as the only curative option for resectable oesophageal cancer.[3–5]

Mortality rates in oesophageal resection are less than 5%.[6] However, at least half the patients who have open oesophagectomy, performed through a right thoracotomy and laparotomy, are at risk for developing pulmonary complications that need protracted stay in intensive-care units and hospitals, with subsequent consequences for quality of life during convalescence.[6] Minimally invasive oesophagectomy, avoiding thoracotomy and laparotomy, can reduce the rate of pulmonary infections, thus reducing stay in hospital.[7,8] Because of these potential advantages, minimally invasive oesophagectomy is being increasingly implemented; however, no randomised trials have investigated the benefits of this technique.[9,10] We compared open with minimally invasive oesophagectomy in patients with oesophageal cancer to assess the rate of pulmonary infections and quality of life associated with the minimally invasive procedure.

Methods

Study design and participants

We undertook a multicentre, open-label, randomised trial between June 1, 2009, and March 31, 2011 at five centres: two in Amsterdam (Netherlands), and one in Nijmegen (Netherlands), Girona (Spain), and Milan (Italy). Eligible participants had resectable oesophageal cancer (cT1–3, N0–1, M0), histologically proven adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma of the intrathoracic oesophagus and gastro-oesophageal junction. Patients were aged 18–75 years and had a WHO performance status of 2 or less. We excluded patients with cervical oesophageal cancer or another malignancy.

For quality assurance, the principal investigator visited all centres interested in trial participation. Minimally invasive oesophagectomies were observed in person by

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the principal investigator. To prevent surgeon bias, both procedures were done by surgeons experienced in open oesophageal resection, and with extensive experience in minimally invasive procedures, who had done at least ten minimally invasive oesophagectomies. To prevent institution bias, only hospitals with more than 30 oesophagectomies per year participated. We discussed operative technique and standard instructions to the pathologists, and included them in the protocol. The medical ethics board of all participating hospitals approved the trial. Diagnosis and staging was established before neoadjuvant treatment by oesophagoscopy and biopsies; CT scans of the neck, thorax, and abdomen; and endoultrasonography. Surgeons at the outpatient clinic informed eligible patients of the treatment regimen. Written informed consent was obtained from included patients.

Randomisation and masking

We used a computer-generated randomisation sequence to randomly assign patients, in a 1:1 ratio, to undergo either open or minimally invasive oesophagectomy. Randomisation was stratified by study centre. All participating centres compiled an exclusion list to analyse the quality of the randomisation rate. Patients, and investigators undertaking interventions, assessing outcomes, and analysing data were not masked to group assignment.

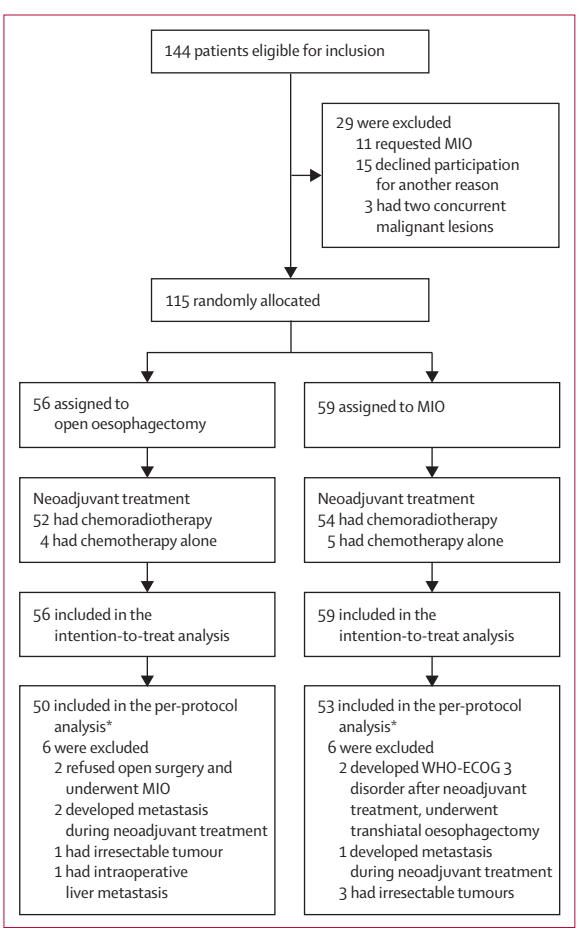

Figure: **Trial profile**
MIO=minimally invasive oesophagectomy. ECOG=Eastern Cooperative Oncology Group. *See appendix for per-protocol analysis of primary and secondary outcome parameters.

See Online for appendix

Procedures

Patients in both groups received similar preoperative treatment, including regular consultations by a dietitian for assessment of supplemental feeding and by a physiotherapist, especially during periods of neoadjuvant treatment. For most patients, neoadjuvant treatment consisted of weekly administrations of 50 mg/m² paclitaxel plus carboplatin (Calvert's formula for dosing; area under the concentration-time curve 2 for 5 weeks) and concurrent radiotherapy (41·4 Gy in 23 fractions for 5 days per week). After 6–8 weeks, neoadjuvant treatment was followed by surgery by open or minimally invasive oesophagectomy. Patients received perioperative intravenous antibiotics (second-generation cephalosporin and metronidazole), an epidural catheter, a central venous pressure line, and an arterial line. Open oesophagectomy involved a right posterolateral thoracotomy in the lateral decubitus position with double tracheal intubation and lung block, midline laparotomy, and cervical incision. No cervical incision was used for patients in this treatment group with an intrathoracic anastomosis. Minimally invasive oesophagectomy was performed through a right thoracoscopy in the prone position with single-lumen tracheal intubation, upper abdominal laparoscopy, and cervical incision.

To maintain partial collapse of the right lung during thoracoscopy, the thoracic cavity was insufflated with carbon dioxide at 8 mm Hg. Both procedures included a two-field oesophageal resection with 3–4 cm wide gastric tube formation followed by a cervical or intrathoracic anastomosis. For patients undergoing minimally invasive oesophagectomy with an intrathoracic anastomosis, a bronchus blocker was placed in the right bronchus to help with one-lung ventilation during anastomosis. Details of the surgical techniques for open and minimally invasive oesophagectomy have been published elsewhere.[11]

After surgery, all patients were admitted to the intensive-care unit for stabilisation and detubation, and were discharged the next day to a general surgical ward or medium-care unit. In the first 3 days after surgery, patients received epidural analgesia. If epidural analgesia was unsuccessful, patient-controlled analgesia with intravenous opioids was given. To regain early mobilisation from the first day after surgery, patients were encouraged to move out of bed after detubation. Enteral feeding was started on day 1 after surgery through a percutaneous jejunostomy catheter. Patients progressively resumed normal diet while jejunostomy feeding

was decreased. Patients were discharged when they could eat solid food, were mobile, and were comfortable with oral analgesia. Feeding via jejunostomy could be continued as supplemental feeding after discharge. Follow-up was scheduled at 6 weeks; 3, 6, and 12 months; and twice a year thereafter.

Study outcomes

We postulated that minimally invasive oesophagectomy would significantly decrease the rate of postoperative pulmonary infections compared with open oesophagectomy. The primary outcome was postoperative pulmonary infection, defined as clinical manifestation of pneumonia or bronchopneumonia confirmed by thoracic radiographs or CT scan (assessed by independent radiologists) and a positive sputum culture, within the first 2 weeks of surgery and during the whole stay in hospital.

Secondary outcomes were length of hospital stay; quality of life (assessed by short form 36 [SF 36] Health Survey [version 2] and European Organization for Research and Treatment of Cancer [EORTC] quality of life questionnaires C30 and OES18 module) measured 6 weeks after surgery;[12,13] pathological parameters of the resected specimen, including pathological tumour-node-metastasis classification, resection and circumferential margins (R0 defined as >1 mm from a resection margin), number of lymph nodes retrieved, and response rate according to the Mandard score;[14] intraoperative data, such as operating time (min) calculated from skin incision to skin closure, estimated blood loss (mL), and conversion of thoracoscopy or laparoscopy to an open procedure; postoperative complications other than pulmonary infections (postoperative bleeding, anastomotic leakage, thoracic complications not related to leakage [including empyema, mediastinitis, chylous leakage needing reoperation, and hiatal herniation], vocal-cord paralysis confirmed by laryngoscopy, pulmonary embolism, and reoperations); stay in intensive-care unit; postoperative mortality (30-day and in-hospital), defined as death from any cause; and the visual analogue scale pain score, measured preoperatively and every day after surgery until day 10 after surgery.

Statistical analysis

We used Power and Precision (version 2) for sample size calculation. Previous data indicated a 28% difference in pulmonary infections between minimally invasive (29%)[7–9,15,16] and open (57%) oesophagectomy.[6] To show a difference of this magnitude, two groups of 48 patients would be needed (α 0·05, β 0·80). With an estimation that about 20% of the eligible patients might not undergo the allocated intervention (eg, owing to metastases during neoadjuvant treatment or unresectable tumours), we enrolled 60 patients per group. We expressed data as median and range for continuous variables, or mean and SDs when appropriate. We expressed distributions of dichotomous data in percentages. We calculated relative risk (RR) for the primary endpoint with 95% CIs. When appropriate, we compared groups with an independent samples *t* test, otherwise a Mann-Whitney U test, or χ^2 test. We analysed pain scores with a linear mixed model. We did statistical analysis with SPSS (version 17). We analysed the conversion rate of patients in the minimally invasive group to either thoracotomy or laparotomy by intention to treat.

This trial is registered with the Netherlands Trial Register, NTR TC 2452.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SSAYB, KWM, ESMdL, DLvdP, and MAC had full access to all data in the study and had final responsibility for the decision to submit for publication. All other authors could request examination of any of the data elements.

Results

The figure shows the trial profile. We randomly assigned 115 of 144 eligible patients to receive either open oesophagectomy or minimally invasive oesophagectomy.

	OO (N=56)	MIO (N=59)
Sex		
Male	46 (82%)	43 (73%)
Female	10 (18%)	16 (27%)
Age (years)*	62 (42–75)	62 (34–75)
BMI (kg/m²)†	24 (3·7)	25 (3·6)
ASA classification		
1	15 (27%)	10 (17%)
2	32 (57%)	34 (58%)
3	8 (14%)	14 (24%)
4	1 (2%)	1 (2%)
Type of carcinoma		
Adenocarcinoma	36 (64%)	35 (59%)
Squamous cell carcinoma	19 (34%)	24 (41%)
Other	1 (2%)	0 (0%)
Location of tumour‡		
Upper third	3 (5%)	1 (2%)
Middle third	22 (39%)	26 (44%)
Lower third or gastro-oesophageal junction	31 (55%)	32 (54%)
Neoadjuvant treatment		
Chemoradiotherapy	52 (93%)	54 (92%)
Chemotherapy alone	4 (7%)	5 (8%)

Data are n (%), median (range), and mean (SD). OO=open oesophagectomy. MIO=minimally invasive oesophagectomy. BMI=body-mass index. ASA=American Association of Anesthesiologist. *Skewed distribution, Mann-Whitney test applied. †Normal distribution, Independent Samples *t* test applied. ‡American Joint Committee on Cancer site classification of thoracic and abdominal oesophagus.

Table 1: **Baseline demographic and clinical characteristics of the intention-to-treat population**

Four crossovers occurred: two patients assigned to the open oesophagectomy group underwent minimally invasive oesophagectomy, and two assigned to minimally invasive oesophagectomy developed a WHO-ECOG score of 3 during neoadjuvant treatment and thus had transhiatal oesophagectomy (appendix). Eight patients did not undergo a resection (figure); we included these patients in the analysis of the allocated group. 56 patients were analysed in the open oesophagectomy group and 59 in the minimally invasive group. The demographic and clinical characteristics of the two groups were similar at baseline (table 1). In the first 2 weeks after surgery, significantly fewer patients had pulmonary infections in the minimally invasive oesophagectomy group than in the open oesophagectomy group (table 2; RR 0·30 95% CI 0·12–0·76). Furthermore, fewer patients in the minimally invasive oesophagectomy group had pulmonary infection in-hospital than did those in the open oesophagectomy group (table 2; 0·35, 0·16–0·78). Hospital stay in the minimally invasive group was significantly shorter than that in the open group (table 2).

The physical component summary of the SF 36, EORTC C30, and quality-of-life domains of talking and pain in the OES 18 questionnaire (representative of short-term [6 weeks] postoperative quality of life) were significantly better for patients in the minimally invasive group than for those in the open oesophagectomy group (table 2). Pathological examination of the resected specimens showed that the number of retrieved lymph nodes and the completeness of resection (ie, resection margin [R0]) were similar between both groups (table 2). Seven patients in the open oesophagectomy group and nine in the minimally invasive group had no residual cancer in the oesophagus and lymph nodes. One patient in the open oesophagectomy group, and two in the minimally invasive group, had a complete response in the oesophagus with lymph node metastasis and were staged accordingly as pIIb. 30-day and in-hospital mortality did not differ significantly between the groups (table 2). For 30-day mortality, one patient in the minimally invasive group died from mediastinitis after anastomotic leakage

	OO (N=56)	MIO (N=59)	p value
Primary outcomes			
Pulmonary infection within 2 weeks	16 (29%)	5 (9%)	0·005
Pulmonary infection in-hospital	19 (34%)	7 (12%)	0·005
Secondary outcomes			
Hospital stay (days)*	14 (1–120)	11 (7–80)	0·044
Short-term quality of life†			
SF 36†			
Physical component summary	36 (6; 34–39)	42 (8; 39–46)	0·007
Mental component summary	45 (11; 40–50)	46 (10; 41–50)	0·806
EORTC C30†			
Global health	51 (21; 44–58)	61 (18; 56–67)	0·020
OES 18‡			
Talking	37 (39; 25–49)	18 (26; 10–26)	0·008
Pain	19 (21; 13–26)	8 (11; 5–11)	0·002
Total lymph nodes retrieved*	21 (7–47)	20 (3–44)	0·852
Resection margin§			0·080
R0	47 (84%)	54 (92%)	..
R1	5 (9%)	1 (2%)	..
pStage¶			0·943
0	0 (0%)	1 (2%)	..
I	4 (7%)	4 (7%)	..
IIa	16 (29%)	17 (29%)	..
IIb	6 (11%)	9 (15%)	..
III	14 (25%)	11 (19%)	..
IV	5 (9%)	4 (7%)	..
No residual tumour or lymph-node metastasis	7 (13%)	9 (15%)	..
Mortality‖			0·590
30-day mortality	0 (0%)	1 (2%)	..
In-hospital mortality	1 (2%)	2 (3%)	..

Data are n (%), median (range), or mean (SD, 95% CI), unless otherwise indicated. OO=open oesophagectomy. MIO=minimally invasive oesophagectomy. SF 36=Short Form 36 Health Survey (version 2). EORTC=European Organization for Research and Treatment of Cancer Quality of Life Questionnaires. *Skewed distribution, Mann-Whitney test applied. †Measures general aspects of health; scores range from 0 to 100, with higher scores representing better well-being. ‡Assesses several aspects of oesophageal function; scores range from 0 to 100, with lower scores indicating better function. Only statistically significant domains presented. §Defined as >1 mm from a resection margin. ¶Staging based on the American Joint Committee on Cancer, 6th edn; four patients in each group did not undergo resection due to metastasis or irresectability of the tumour. ‖Death from any cause.

Table 2: **Primary and secondary outcomes for the intention-to-treat population**

	OO (N=56)	MIO (N=59)	p value
Intraoperative data			
Operative time (min)*†	299 (66–570)	329 (90–559)	0·002
Blood loss (mL)†	475 (50–3000)	200 (20–1200)	<0·001
Conversions‡	NA	8 (14%)	..
Level of anastomosis§			0·970
Cervical	37 (66%)	38 (64%)	
Thoracic	15 (27%)	17 (29%)	
Postoperative data			
ICU stay (days)†	1 (0–106)	1 (0–50)	0·706
VAS (10 days)¶	3 (2)	2 (2)	0·001
Epidural failure‖	11 (20%)	10 (17%)	0·734
Other complications			
Anastomotic leakage	4 (7%)	7 (12%)	0·390
Thoracic complications without anastomotic leakage**	2 (4%)	2 (3%)	0·958
Vocal-cord paralysis††	8 (14%)	1 (2%)	0·012
Pulmonary embolism	0 (0%)	1 (2%)	0·328
Reoperations	6 (11%)	8 (14%)	0·641

Data are median (range), n (%), or mean (SD), unless otherwise indicated. OO=open oesophagectomy. MIO=minimally invasive oesophagectomy. NA=not applicable. ICU=intensive-care unit. VAS= Visual Analogue Scale pain score. *Time from skin incision to skin closure. †Skewed distribution, Mann-Whitney test applied. ‡Six patients were converted to thoracotomy and two to laparotomy. §Four patients in the OO group and four in the MIO group did not undergo resection with subsequent anastomosis because of metastasis or irresectability of the tumour. ¶Linear mixed model. ‖In the first 2 days after surgery. **Thoracic complications not related to leakage were mediastinitis, empyema, chylous leakage needing reoperation, and hiatal herniation. ††Confirmed by laryngoscopy.

Table 3: **Other outcomes of the intention-to-treat population**

on day 15 after surgery; for in-hospital mortality, one patient in the open oesophagectomy group died from anastomotic leakage and two patients in the minimally invasive group died from aspiration and mediastinitis after anastomotic leakage, respectively.

Although operating time was significantly longer in the minimally invasive group than in the open oesophagectomy group, blood loss was lower for patients undergoing the minimally invasive procedure (table 3). Eight patients converted: six to thoracotomy and two to laparotomy. We noted no difference in stay in intensive-care unit between the groups (table 3). According to the VAS pain score, patients in the minimally invasive group had significantly less pain in the first 10 days after surgery than did those in the open group (table 3). Other postoperative complications did not differ significantly between groups; however, significantly more patients had vocal-cord paralysis in the open group than in the minimally invasive group (table 3). Furthermore, the number of reoperations between the groups did not differ significantly (table 3). Six patients in the open oesophagectomy group underwent reoperation: two for anastomotic leakage, one for empyema not related to leakage, one had splenic bleeding, one had a hiatal herniation, and one had a tracheal lesion. Eight patients underwent reoperation in the minimally-invasive group: four because of an anastomotic leakage, one for control of a persistent chylous leakage, one had a suspected torsion of the gastric tube, one had a tracheogastric conduit fistula, and one because of suspected mesenteric ischaemia.

Panel: **Research in context**

Systematic review

We searched Medline, Embase, and Cochrane Library, and did a manual cross-reference search in Sept, 2008, to assess the outcome after minimally invasive oesophagectomy compared with open oesophagectomy.[9] We included all studies written in English that compared both techniques. We used the following search terms: "oesophageal cancer", "cardia cancer", "minimally invasive", "laparoscopy", "thoracoscopy". We used logical combinations of these and related terms—eg, oesophagus, neoplasms, carcinoma—to maximise sensitivity. Furthermore, we used a truncation symbol in each database to allow retrieval of all suffix variations of a root word. We used a critical review checklist of the Cochrane Center to appraise the included studies.

Interpretation

Our study is the first randomised trial to compare open with minimally invasive oesophagectomy in patients with oesophageal cancer. Our results show that patients undergoing the minimally invasive procedure have an improved short-term outcome for pulmonary infections, hospital stay, and quality of life than do those undergoing open oesophagectomy, with no compromise of the quality of the resected specimen. These findings provide evidence for the short-term benefits of minimally invasive oesophagectomy for patients with resectable oesophageal cancer.

Discussion

In this trial, minimally invasive oesophagectomy resulted in a lower incidence of pulmonary infections 2 weeks after surgery and during stay in hospital, a shorter hospital stay, and better short-term quality of life than did open oesophagectomy, with no compromise in the quality of the resected specimen. The reduced frequency of pulmonary infections in the minimally invasive group could be explained by several factors, all of which might reduce the development of atelectasis.

Use of the prone position with the minimally invasive procedure compared with the lateral position with the open procedure could be a beneficial factor of this surgical technique. By contrast with the lateral decubitus position, in prone position the mediastinum lies in its usual midposition and the chest and abdomen are free of compression.[17] Cuschieri[18] did the first minimally invasive oesophagectomy in the prone position to reduce the incidence of pulmonary infections noted after lateral thoracoscopy. A second advantage might be the avoidance of total lung collapse during minimally invasive oesophagectomy in prone position. This advantage could explain why, in a large series of non-randomised studies, minimally invasive oesophagectomy in the prone positition had a slightly lower pulmonary infection rate than when the technique was done in the lateral decubitus position (1·5% *vs* 7·7%).[7,8,19] During minimally invasive oesophagectomy in the prone position, the right lung is partially collapsed by gravity and by insufflation with carbon dioxide to a maximum pressure of 8 mm Hg. This technique allows for optimum visualisation of the mediastinum with preserved ventilation and oxygenation by contrast with the one-lung ventilation needed for open oesophagectomy.[19,20] Absence of one-lung ventilation reduces arteriovenous shunt with better preserved oxygenation.[7] Another possible factor for the increased rate of infection in the open group might be the thoracotomy wound itself. In addition to development of atelectasis due to the collapsed lung, postoperative discomfort caused by the wound has a role, and increases the rate of infections.[21]

The incidence of pulmonary infections in the minimally invasive group in our trial was higher than in published series;[7,8] however, selection bias could be a factor in the published findings from non-randomised series. The rate of pulmonary infection in the open oesophagectomy group was clearly lower than the rate used for our sample size calculation. Preoperative programmes, including physiotherapy and adequate nutrition, and the standard postoperative administration of epidural anesthesia could explain the substantial decrease in the open oesophagectomy group. Additionally, minimally invasive oesophagectomy preserved quality of life better than open oesophagectomy did. After 6 weeks, the SF 36 questionnaire and global health experience in the EORTC C30 module were better for patients in the minimally invasive oesophagectomy group than for those in the open oesophagectomy group. In the oesophageal-specific OES 18 questionnaire, pain and talking were adversely affected in patients in the open oesophagectomy group as compared with those in the minimally invasive group. After open

oesophagectomy, quality of life typically returns to normal after 1 year.[22] In future analysis at 1 year, we aim to assess whether the recovery rate after minimally invasive oesophagectomy will be faster than after open oesophagectomy, as has already been noted in a non-randomised study.[23]

A shorter hospital stay in the minimally invasive group in our trial indicates a faster postoperative recovery than in the open oesophagectomy group. Luketich and colleagues,[8] with lateral thoracoscopy, and Palanivelu and colleagues[7] with prone thoracoscopy, reported a hospital stay of 7 days in both groups, which is shorter than for the groups in our study. However, these results are based on non-randomised series, which could be affected by selection bias. Furthermore, the discharge criteria were not specified in these studies. Importantly, we noted no compromise in the quality of the resected specimen and no significant differences in the number of lymph nodes retrieved. Long-term outcome measurements, including survival analyses, are planned for the future. We noted no significant differences in complication rate between the two groups, which accords with published work.[24,25] However, we observed increased vocal-cord paralysis in the open oesophagectomy group. Pneumatic dissection by carbon dioxide from the thoracic cavity into the neck can simplify the neck dissection and reduce recurrent nerve lesions.[20] Furthermore, use of the double lumen tube in the open oesophagectomy group could be an important factor for the incidence of vocal-cord paralysis in this group.[26,27]

In conclusion, our findings provide evidence for the short-term benefits of minimally invasive compared with open oesophagectomy for patients with resectable oesophageal cancer (panel).

Contributors

SSAYB and KWM obtained and analysed data. SSAYB and MAC drafted the paper. MAC, DLvdP, and SSAYB designed the protocol. MAC, DLvdP, and MlvBH were the main investigators. ESMdL contributed to design of the protocol and calculation of the study's power. All other authors participated in study design and were local investigators in participating centres. All authors were involved in editing the paper and approved the final text.

Conflicts of interest

We declare that we have no conflicts of interest.

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