Minimally invasive esophagectomy for cancer; beyond techniques

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2014

Chapter 6

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

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The Lancet, 2012; 12:60516-9

ABSTRACT

Background

Surgical resection is the cornerstone of curing patients with esophageal cancer. Pulmonary complications occurring in more than 50% of the patients after open esophagectomy remains a great concern. This randomised trial was performed to determine whether minimally invasive esophagectomy (MIE) is associated with a reduced morbidity than with open esophagectomy (OE).

Methods

A multicentre, randomised controlled trial comparing open transthoracic with minimally invasive esophagectomy for resectable cancer of the esophagus or gastro-esophageal junction was performed. The primary outcome was post-operative pulmonary infection. Secondary outcomes included hospital stay, short-term quality of life, completeness of resection, and mortality.

Results

Fifty-six patients were allocated to the open esophagectomy (OE) group and 59 to the MIE group. The pulmonary infection rate within the first two weeks was 29% (16 patients) in the OE group and 9% (5 patients) in the MIE group (relative risk (RR) for the MIE group 0.30 95% confidential interval [CI] 0.12-0.76; p =0.005). The overall in- hospital incidence of pulmonary infections was 34% (19 patients) in the OE group and12% (7 patients) in the MIE group (RR for the MIE group 0.35 95% CI 0.16-0.78; p=0.005). Hospital stay was significantly shorter in the MIE group (14 versus 11 days, p=0.044). At six weeks, the post-operative quality of life was significantly better in the MIE group. Other post-operative data including pathology parameters and mortality rate (1.8% vs. 3.4%) were not significantly different.

Conclusions

MIE is associated with fewer pulmonary infections, shorter hospital stay and an improved quality of life than OE.

INTRODUCTION

The global incidence of esophageal cancer has increased by 50% in the past two decades: in 1990, 316,000 people were diagnosed with esophageal cancer while 482,300 new cases of esophageal cancer were recorded in 2008.[1,2] Surgical resection with radical lymphadenectomy, usually after neoadjuvant chemotherapy or chemoradiotherapy, is considered the only curative option for resectable esophageal cancer.[3,4,5]

Open esophagectomy (OE), performed through a right thoracotomy and laparotomy, puts at least half the patients at risk for developing pulmonary complications necessitating protracted stay in intensive care units (ICU) and hospital with subsequent consequences for quality of life during convalescence.[6] Current mortality rates of esophageal resection is less than 5%.[6] Minimally invasive esophagectomy (MIE), avoiding thoracotomy and laparotomy, may reduce the rate of pulmonary infections resulting in a shorter hospital stay.[7,8]

Because of these potential advantages, MIE is currently increasingly implemented. However, no randomised trials have been performed in order to investigate the benefits of MIE.[9,10] To assess the reduction of pulmonary infections and improved quality of life associated with MIE, we conducted a multicentre, randomised trial comparing open with minimally invasive esophagectomy in patients with esophageal cancer.

PATIENTS AND METHODS

Study Design and Patients

The tested hypothesis was that MIE would be associated with a significantly decreased rate of post-operative pulmonary infections as compared to OE. All patients presenting at the five participating centres with a resectable esophageal cancer (cT1-3, N0-1, M0), histological proven adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma of the intrathoracic esophagus, and gastro-esophageal (GE) junction were eligible for inclusion in the study. The minimal age of included patients was 18 years with a maximum of 75 years, with a WHO performance status ≤ 2. Patients with cervical esophageal cancer or with another malignancy were excluded.

Quality assurance of this trial was established by the following criteria: the principal investigator visited all centres that expressed interest to participate in the trial. Minimally invasive esophagectomies were observed in person by the principal investigator. To prevent surgeon bias, either MIE or OE had to be performed by experienced surgeons in open esophageal resections with an experience of at least 10 minimally invasive esophagectomies. In order to prevent institution bias, only hospitals with high volume (> 30 esophagectomies/ year) participated in this trial. Operative technique and standard instructions to the pathologists were discussed and included in the protocol. The Medical Ethics Board of all participating hospitals approved the trial.

Diagnosis and staging was established before neoadjuvant therapy by esophagoscopy and biopsies, Computed Tomography (CT)-scan of neck, thorax, and abdomen and by endo-ultrasonography (EUS).

The surgeon at the outpatient clinic informed eligible patients about the whole trajectory of treatment consisting of neoadjuvant therapy followed by surgery of one of the two modalities, OE or MIE. Written informed consent was obtained from included patients.

Randomization and Masking

When patients were eligible for inclusion, they were individually assigned to undergo either open esophagectomy (OE) or minimally invasive esophagectomy (MIE). A computer-generated randomisation was used at the coordinating centre to create an allocation sequence to assign patients to the study arms. Randomisation was stratified for each study centre. All participating centres compiled an exclusion list in order to analyse the quality of the randomisation rate. Patients, and investigators giving interventions, assessing outcomes, and analyzing data were not masked.

Study Interventions

Patients in both groups received similar pre-operative treatment. This included regular consultations by a dietician for evaluation of supplemental feeding and physiotherapist especially during the periods of neoadjuvant therapy. Neoadjuvant therapy consisted of weekly administrations of paclitaxel (50 mg/m2 and carboplatin AUC= 2 for 5 weeks) and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week). The interval between neoadjuvant therapy and operation was 6-8 weeks.

Patients received peri-operative intravenous antibiotics (second generation cephalosporine and Metronidazole), an epidural catheter, a central venous pressure line, and arterial line.

The OE implied a right postero-lateral thoracotomy in lateral decubitus position with double tracheal intubation and lung block, midline laparotomy and cervical incision. No cervical incision was used for patients in the OE group with an intrathoracic anastomosis. Whereas the MIE was performed through a right thoracoscopy in prone position with single lumen tracheal intubation and upper abdominal laparoscopy and cervical incision. To maintain a partial collapse of the right lung during thoracoscopy, the thoracic cavity was insufflated with CO2 at 8 mm Hg. The OE as well as the MIE included a two-field esophageal resection with 3-4 cm wide gastric tube formation followed by a cervical or intrathoracic anastomosis. For patients scheduled to undergo a MIE with an intrathoracic anastomosis a bronchus blocker was placed in the right bronchus to facilitate one lung ventilation during the anastomotic phase. Details of the surgical techniques for OE and MIE esophagectomy have been published elsewhere.[11]

After surgery, all patients were admitted to the intensive care unit (ICU) for stabilization and detubation, and were discharged the following day to the general surgical ward or to the medium care unit (MCU). In the first three days after surgery, analgesics were administered by the epidural route. If there was failure of the epidural anesthesia, Patient Controlled Anesthesia (PCA) with intravenous opioids was administered. To regain early mobilization starting day 1, patients were encouraged to mobilize out of bed after detubation. Enteral feeding was started on day 1 after operation through a percutaneous jejunostomy catheter. Normal diet is progressively resumed while jejunostomy feeding was decreased. Patients were discharged when they were able to eat solid food, were mobile and were comfortable with oral analgesia. Completion of the feeding via jejunostomy could be continued in a small portion after discharge. Follow-up was scheduled at 6 weeks, 3, 6 and 12 months, and thereafter twice a year.

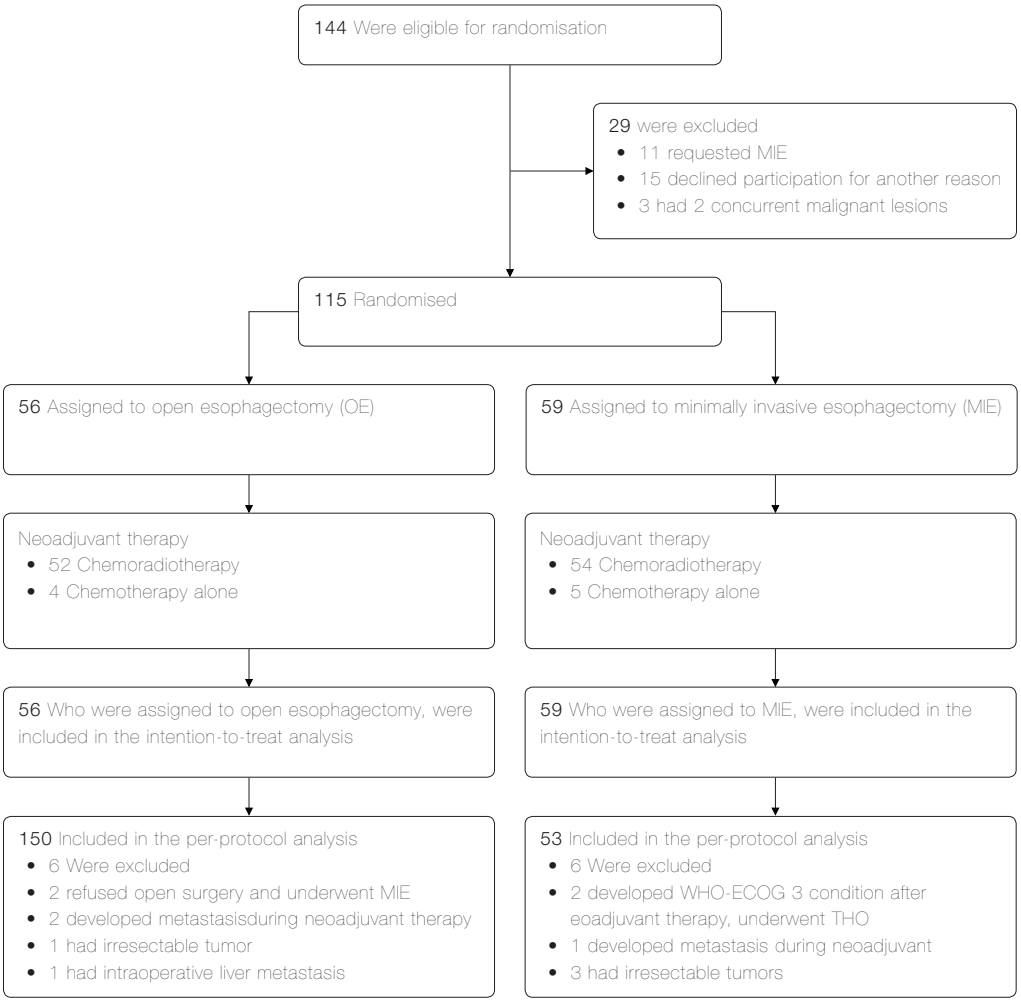
Outcomes

The primary outcome of the study was post-operative pulmonary infection, defined as clinical manifestation of (broncho-) pneumonia confirmed by thorax X-ray and/ or CT-scan (assessed by independent radiologists) and a positive sputum culture, occurring within the first two weeks and during the whole in-hospital stay.
The secondary outcome included: 1) length of hospital stay; 2) quality of life (questionnaires Short Form (SF)-36, version 2 and European Organization for Research and Treatment of Cancer (EORTC) C30 + OES18 module) measured 6 weeks after surgery[12,13]; 3) pathology parameters of the resected specimen including pTNM classification, resection and circumferential margins (R0 defined as >1mm distance from a margin), number of lymph nodes retrieved, and response rate according to the Mandard score[14]; 4) intra-operative data such as operating time (minutes) calculated from skin incision to skin closure, estimated blood loss (ml), and conversion of thoracoscopy or laparoscopy to an open procedure; 5) post-operative complications, other than pulmonary infections, including re-operations. Post-operative bleeding, anastomotic leakage, thoracic complications not related to leakage (including empyema, mediastinitis, chylous leakage requiring re-operation, hiatal herniation), vocal cord paralysis (confirmed by laryngoscopy), pulmonary embolism, and re-operations were recorded; 6) intensive care unit stay; 7) post-operative mortality (30-day mortality and in-hospital)— defined as death from any cause; 8) the Visual Analogue Score (VAS)-pain-score measured pre-operatively and daily after surgery up to the 10th post-operative day.

Statistical Analysis and Power Calculation

Software (Power and Precision, Biostat, Englewood, NJ) was used for sample size calculation. The aim was to test for superiority of MIE, as compared to OE, with respect to the incidence of pulmonary infections within 2 weeks after operation. The available data from the literature suggested a 28% difference in pulmonary infections between MIE (29%)[7-9,15,16] and open esophagectomy (57%).[6] To demonstrate a 0.28 difference, 2 groups of 48 patients were required (alpha=0.05 and beta=0.80). Estimating that approximately 20% of the eligible patients may not undergo the allocated intervention (e.g. metastases during neoadjuvant therapy, irresectable tumors), approximately 60 patients per group were asked to participate.
Data were expressed as median and range for continuous variables or mean and standard deviations where appropriate. The distributions of dichotomous data were given in percentages. Relative risk (RR) was calculated for the primary endpoint with a 95% confidence interval (CI). Where appropriate, groups were compared using an Independent Samples T-test, otherwise a Mann Whitney U test, or Chi-square test. Pain scores were also analysed using a linear mixed model. Statistical analysis was performed with SPSS version 17 (SPSS Inc., Chicago, Il). Converted patients were analysed in the MIE arm in accordance with the intention-to-treat principle.

Figure 1. Trial profile
MIE, minimally invasive esophagectomy
THO, transhiatal esophagectomy



RESULTS

Patients and Study Interventions

Between June 2009 and March 2011, 144 patients were eligible for randomisation. Of these, 29 were excluded for various reasons (Figure 1). A total of 115 patients underwent randomisation in 5 centres. There were four crossovers: two patients who were randomly assigned to undergo open esophagectomy underwent MIE and two patients assigned to MIE, developed a WHO-ECOG score of 3 during neoadjuvant therapy and underwent a transhiatal esophagectomy. Of the 115 patients, eight patients did not undergo a resection: three patients developed metastasis during neoadjuvant therapy, four had an irresectable tumor during surgery, and one patient had liver metastasis that was diagnosed intra-operatively. These patients, based on intention to treat principle, are consequently included in the analysis of the allocated group. Fifty-six patients were analysed in the open group and 59 patients in the minimally invasive group. The demographic and clinical characteristics of the two groups were similar at baseline (Table 1).

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

		OE (n= 56)	MIE (n= 59)
Gender			
Male		46	43
Female		10	16
Age^ (years)		62 (42-75)	62 (34-75)
BMI* (kg/m2)		24 (±3.7)	25 (±3.6)
ASA-classification			
1		15	10
2		32	34
3		8	14
4		1	1
Type carcinoma			
Adenocarcinoma		36	35
Squamous cell	carcinoma	19	24
Other			
		1	0
Location of tumor¶			
Upper third		3	1
Middle third		22	26
Lower third/ junction		31	32
Neoadjuvant therapy			
Chemoradiotherapy		52	54
Chemotherapy alone		4	5

OE, Open Esophagectomy.

MIE, Minimally Invasive Esophagectomy.

^, Skewed distribution, median (range), Mann Whitney U test applied.

*, Normal distribution, mean (standard deviation), Independent samples t test applied.

BMI, Body Mass Index.

ASA, American Association of Anesthesiologist classification system.

¶, American Joint Committee on Cancer (AJCC) site classification of thoracic and abdominal esophagus.

Outcomes

Table 2 depicts the primary and secondary outcome. Within the first two weeks pulmonary infections occurred in 29% (16 patients) in the OE group and 9% (5 patients) in the MIE group (RR in the MIE group 0.30 95% CI 0.12-0.76; p=0.005). The overall in-hospital incidence of pulmonary infections was 34% (19 patients) in the OE group and 12% (7 patients) in the MIE group (RR in the MIE group 0.35 95% CI 0.16-0.78; p=0.005).

A significantly shorter hospital stay was observed in the MIE group (14 vs. 11 days, p=0.044).
The physical component summary of the SF 36 (version 2), EORTC C30, and the quality of life domains of talking and pain found in the OES 18 questionnaire — as representing short-term (6 weeks) post-operative quality of life — were significantly better for patients who underwent MIE.
Pathological examination of the resected specimens showed that the completeness of resection (i.e. resection margin (R0)) and the number of retrieved lymph nodes was comparable between the OE group and MIE group. Complete response (no residual cancer in the esophagus and lymph nodes) was found in 7 and 9 patients respectively. One patient in the OE group and two in the MIE group, had a complete response in the esophagus with lymph node metastasis and were staged accordingly as stage pIIb.
There were no significant differences between the groups with regard to 30-day and in-hospital mortality, (OE versus MIE) 0 versus 1.7% (one patient) and 1.8% (one patient: anastomotic leakage) versus 3.4% (two patients: aspiration; mediastinitis after anastomotic leakage) respectively.

Other Data

Other general outcomes are depicted in Table 3. The operating time was significantly longer in MIE. However, blood loss was lower in MIE. Conversion rate was 14% (8 patients): six patients were converted to thoracotomy and two to laparotomy. There was no difference in ICU stay between the groups. MIE patients experienced significant less pain in the first 10 days post-operatively (mean VAS 3 vs. 2, p= 0.001). There were no significant differences between the groups with regard to epidural failure within 2 days (10 vs. 11 patients, p=0.734).
Other post-operative complications were not significantly different. However, there were significantly more patients with vocal cord paralysis in the OE group compared to the MIE group (8 (15%) vs. 1 (2%), p=0.012). Furthermore, there was no significant difference in re-operations between the groups. Six patients in the OE group underwent re-operation: two for anastomotic leakage; one due to empyema not related to leakage; one had a splenic bleeding; another had a hiatal herniation; and the last had a tracheal lesion. In the MIE group, eight patients underwent re-operation: four because of an anastomotic leakage; one for control of a persistent chylous leakage; one had a suspected torsion of the gastric tube; another had a tracheo-gastric conduit fistula; and the last was suspected having mesenteric ischemia.

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

			OE (n= 56)	MIE (n= 59)	P value
Primary outcome‡					
	Pulmonary infection within 2 weeks		16 (29%)	5 (9%)	0.005
	Pulmonary infection (in-hospital)		19 (34%)	7 (12%)	0.005
Secondary outcome					
	Hospital stay (days) ^		14 (1-120)	11 (7-80)	0.044
	Short-term quality of life (mean scores (95%CI))				
		SF-36*			
		Physical component summary	36 (34-39)	42 (39-46)	0.007
		Mental component summary	45 (40-50)	46 (41-50)	0.806
		EORTC C30*			
		Global health	51 (44-58)	61 (56-67)	0.020
		OES 18†			
		Talking	37 (25-49)	18 (10-26)	0.008
		Pain	19 (13-26)	8 (5-11)	0.002
	Total LN retrieved ^		21 (7-47)	20 (3-44)	0.852
	Resection margin¶				0.080
		R0	47 (90%)	54 (98%)	
		R1	5 (10%)	1 (2%)	
	pStage~				0.943
		0	0	1	
		I	4	4	
		IIa	16	17	
		IIb	6	9	
		III	14	11	
		IV	5	4	
		No residual tumor/no LN metastasis	7	9	
	Mortalityfi				0.590
		30-day mortality	0	1 (1.7%)	
		In-hospital mortality	1 (1.8%)	2 (3.4%)	

OE, Open Esophagectomy.

MIE, Minimally Invasive Esophagectomy.

‡, Defined as clinical manifestation of (broncho-) pneumonia confirmed by thorax X-ray and/ or CT-scan (assessed by independent radiologists) and a positive sputum culture.

^, Skewed distribution, median (range), Mann Whitney U test applied. Patient were discharged if they were able to eat solid food, were mobile and were comfortable with oral analgesia.

*, The SF-36 physical and mental component summaries and EORTC C30 'global health domain' measures general aspects of health quality of life. Scores range from 0 to 100, with higher scores representing better well-being. Assessment at 6 weeks post-operatively.

†, OES 18 assesses several items of esophageal function. Scores range from 0 to 100, with lower scores indicating better function. Only domains which were statistically significant are presented here. Assessment at 6 weeks post-operatively.

¶, R0 resection margin defined as > 1mm distance from a margin.

~, Staging based on the American Joint Committee on Cancer (AJCC) 6th Edition. Four patients in each group did not undergo resection due to metastasis or irresectability of the tumor.

LN, Lymph Node.

fi, Defined as death from any cause (30-day and in-hospital mortality).

Table 3. Other outcomes of the intention-to-treat population

	OE (n= 56)	MIE (n= 59)	P value
Intra-operative data			
Operative time (min) †	299 (66-570)	329 (90-559)	0.002
Blood loss (mL)^	475 (50-3000)	200 (20-1200)	<0.001
Conversions‡	N/A	8 (14%)	
Level of anastomosis¶			0.970
cervical	37	38	
thoracic	15	17	
Post-operative 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 leakagefi	2 (3%)	2 (3%)	0.958
Vocal cord paralysis∞	8 (14%)	1 (2%)	0.012
Pulmonary embolism	0	1 (2%)	0.328
Re-operations	6 (10%)	8 (14%)	0.641

OE, Open Esophagectomy.

MIE, Minimally Invasive Esophagectomy.

†, Defined as time in minutes from skin incision to skin closure. Skewed distribution, median (range), Mann Whitney U test applied.

^, Skewed distribution, median (range), Mann Whitney U test applied.

‡, Six patients were converted to thoracotomy and two to laparotomy.

N/A, not applicable.

¶, Four patients in the OE and 4 in the MIE group did not undergo a resection with subsequent anastomosis due to metastasis or irresectability of the tumor.

ICU, Intensive Care Unit.

*, Visual Analogue Score for pain, linear mixed model, mean (standard deviation).

§, in the first 2 days after surgery

fi, Thoracic complications not related to leakage included mediastinitis, empyema, chylous leakage requiring re-operation and hiatal herniation.

∞, Confirmed by laryngoscopy.

DISCUSSION

This multicentre, randomised trial examined whether minimally invasive esophageal resection for cancer would lead to a lower incidence of post-operative pulmonary infections as compared to an open transthoracic esophagectomy.

In this trial, a reduction of pulmonary infection within 2 weeks and during the in-hospital period of 20% and 22% respectively were observed in favour of MIE. We hypothesize that the lower incidence of pulmonary infections found in the MIE group could be explained by several factors, which all might reduce the development of atelectasis.

Use of the prone position in comparison with the open thoracotomy in lateral position could be one of the underlying beneficial factors. In contrast with the lateral decubitus position, in prone position the mediastinum hangs in its usual midposition and the chest and abdomen are free of compression.[17] A second advantage may be the avoidance of a total collapse of the lung during MIE in prone position. The right lung is partially collapsed by gravity and by the employed insufflation of CO2 to a maximum pressure of 8 mmHg. This permits an optimal visualization of the mediastinum with preserved ventilation and oxygenation in contrast to the required one-lung ventilation for OE.[18,19] Absence of one-lung ventilation reduces arterio-venous shunt with better preserved oxygenation.[7] Another possible underlying factor for the higher rate of pulmonary infection in OE may be the thoracotomy wound itself. Not only the development of atelectasis as result of the totally collapsed lung plays a role but also the post-operative discomfort, produced by the wound, causes an increased rate of pulmonary infections.[20] All these factors together could explain the important advantages of thoracoscopy in prone position in comparison with the standard posterolateral right thoracotomy.

Furthermore, thoracoscopy in prone position may have advantages over the thoracoscopy performed in lateral position due to the use of one-lung ventilation in the latter. Cuschieri performed the first MIE in prone position in order to reduce the

incidence of pulmonary infections observed after thoracoscopy in lateral position.[21] In large series of nonrandomised studies, MIE in prone position seems to show a slightly better outcome regarding pulmonary infection rate compared to MIE in the lateral decubitus position (1.5% versus 7.7%).[7,8] This difference may again be explained by the absence of total lung collapse in prone position.[19] We encountered an incidence of pulmonary infections of 12% in the MIE group. As compared to the before mentioned series, this is higher. However, these results are based on analysis of nonrandomised series. Selection bias could therefore be present. The rate of pulmonary infection in the OE group is clearly lower than the rate used for the sample size calculation. Current pre-operative programs including physiotherapy and adequate nutritional and the standard post-operative administration of epidural anesthesia may explain this substantial decrease in the OE group.

In addition, MIE preserved the quality of life better than OE. After 6 weeks, the physical component summary of the SF 36 questionnaire and global health experience in the EORTC C30 were better for patient in the MIE group. In the esophageal specific OES 18 questionnaire, pain and talking were significant hampered in patients randomised to the OE group. After OE, the quality of life returns to normal after one year.[22] Future analysis at one year to be performed in this study will reveal whether the recovery rate after

MIE will be faster than after OE — as already had been observed in a nonrandomised study.[23]

A shorter hospital stay of 14 versus 11 days, in favour of the patient operated with MIE, reflects a faster post-operative recovery. Luketich and colleagues using the lateral thoracoscopy and Palanivelu and colleagues the prone position, reported both a hospital stay of 7 days.[7,8] However, these results are based on analysis of nonrandomised series. Selection bias could therefore be present. Furthermore, the discharge criteria were not specified in these studies.

Importantly, there was no compromise in the quality of the resected specimen. Pathology parameters showed no significant differences, with a R0 resection of 90% after OE versus 98% after MIE. Moreover, the number of lymph nodes retrieved, median of 21 versus 20 was not different. Long-term outcome including survival analyses are planned for this study.

Concerning the complication rate, there were no statistical differences between the two groups and this is in concordance with current literature.[24,25] However, there was significantly more vocal cord paralysis observed in the OE group. Pneumatic dissection by CO2 from the thoracic cavity into the neck can simplify the neck dissection and reduce the recurrent nerve lesions.[19] In addition, the use of the double lumen tube in the OE group could also be an important factor for the higher incidence in this group.[26,27]

In conclusion, this randomised trial comparing open esophagectomy for cancer with minimally invasive esophagectomy shows that MIE results in a lower incidence of pulmonary infections, a shorter hospital stay, and better short-term quality of life without compromise of the quality of the resected specimen.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: Cancer J Clin* 2011; 61: 69-90.
2. Parkin DM, Pisani P, Ferlay J. Global cancer statistics. *CA: Cancer J Clin* 1999; 49: 33-64.
3. Enzinger PC, Mayer RJ. Esophageal Cancer. *N Engl J Med* 2003; 349: 2241-2252
4. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, Gebski V. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable esophageal carcinoma: an updated meta-analysis. *Lancet oncolog* 2011; 12: 681-692.
5. Scheepers JJ, Mulder CJ, van der Peet DL, Meijer S, Cuesta MA. Minimally invasive esophageal resection for distal esophageal cancer; a review of literature. *Scand J Gastroentero* 2006; 41 suppl.: 123-134.
6. Hulscher JBF, van Sandwick JW, de Boer AG et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002; 347: 1662-1669.
7. Palanivelu C, Prakash A, Senthilkumar R, Senthilnathan P, Parthasarthi R, Rajan S, Venkatachlam S. Minimally invasive esophagectomy: thoracoscopic mobilization of the esophagus and mediastinal lymphadenectomy in prone position--experience of 130 patients. *J Am Coll Surg* 2006; 203: 7-16.
8. Luketich JD, Alvelo-Rivera M, Bunaventura PO et al. Minimally invasive esophagectomy: outcomes in 222 patients. *Ann Surg* 2003; 238: 486-494.
9. Biere SSAY, Cuesta MA, van der Peet DL. Minimally invasive versus open esophagectomy for cancer: a systematic review and meta-analysis. *Minerva Chir* 2009; 64: 121-133.
10. Biere SS, van Weyenberg SJ, Verheul HM, Mulder CJ, Cuesta MA, van der Peet DL. Non-metastasized esophageal cancer. *Nederlands Tijdschr Geneeskd* 2010; 154: A820.
11. Biere SSAY, Maas KW, Bonavina L et al. Traditional invasive vs. minimally invasive esophagectomy: a multi-center, randomized trial. *BMC Surg* 2011; 11: 2.
12. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85: 365-376.
13. Blazeby JM, Conroy T, Hammerlid E et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES 18 to assess quality of life in patients with esophageal cancer. *Eur J Cancer* 2003; 39:1384-1394.
14. Mandard AM, Dalibard F, Mandard JC et al. Pathological assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathological correlations. *Cancer*. 1994; 73: 2680-2686.
15. Zingg U, McQuinn A, DiValentino D et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer. *Ann Thorac Surg* 2009; 87: 911-919.
16. Nguyen NT, Hinojosa MW, Smith BR, Chang KJ, Gray J, Hoyt D. Minimally invasive esophagectomy: lessons learned from 104 operations. *Ann Surg* 2008; 248: 1081-1091.
17. Overholt RA, Woods FM. The prone position in thoracic surgery. *J Internat Coll Surg* 1946; 10: 216-222.
18. Yatabe T, Kitagawa H, Yamashita K, Akimori T, Hanazaki K, Yokoyama M. Better postoperative oxygenation in thoracoscopic esophagectomy in prone positioning. *J Anesth* 2010; 24: 803-806.

19. Fabian T, Martin J, Katigbak M, McKelvey AA, Federico JA. Thoracoscopic esophageal mobilization during minimally invasive esophagectomy: a head-tohead comparison of prone versus lateral decubitus positions. *Surg Endosc* 2008; 22: 2485-2491.
20. Grogan EL, Jones DR. VATS lobectomy is better than open thoracotomy: what is the evidence for short-term outcomes? *Thorac Surg Clin* 2008; 18: 249-258.
21. Cuschieri A. Thoracoscopic subtotal esophagectomy. *Endosc Surg Allied Technol* 1994; 2: 21-25.
22. De Boer AG, van Lanschot JJ, van Sandwick JW et al. Quality of life after transhiatal compared with extended transthoracic resection for adenocarcinoma of the esophagus. *J Clin Oncol* 2004; 22: 4202-4208.
23. Parameswaran R, Blazeby JM, Hughes R, Mitchell K, Berrisford RG, Wajed SA. Health-related quality of life after minimally invasive esophagectomy. *Br J Surg* 2010; 97: 525-531.
24. Portale G, Hagen JA, Peters JH, Chan LS, DeMeester SR, Gandamihardja TA, DeMeester TR. Modern 5-year survival of resectable esophageal adenocarcinoma: single institution experience with 263 patients. *J Am Coll Surg* 2006; 202: 588-596.
25. Ruol A, Castoro C, Portale G et al. Trends in management and prognosis for esophageal cancer surgery: twenty-five years of experience at a single institution. *Arch Surg* 2009; 144: 247-254.
26. Knoll H, Ziegeler S, Schreiber JU et al. Airway injuries after one-lung ventilation: a comparison between double lumen tube and endotrachial blocker: a randomized, prospective, controlled trial. *Anesthesiology* 2006; 105: 471-477.
27. Zhong T, Wang W, Chen K, Ran L, Story DA. Sore throat or hoarse voice with bronchial blockers or double-lumen tubes for lung isolation: a randomised, prospective trial. *Anaesth Intensive Care* 2009; 37: 441-446.