Chapter 7

Quality of life after minimally invasive versus open esophagectomy: results of a randomized controlled trial

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ABSTRACT

Background

The minimally invasive esophagectomy (MIE) is being implemented widely for treating esophageal cancer in order to reduce morbidity and improve quality of life. Non-randomized studies investigating long-term quality of life after MIE show conflicting results at one year follow-up. Therefore, we investigated whether MIE brings about an enduring better long-term one-year quality of life than does open esophagectomy (OE) indicating both a faster recovery and less procedure-related symptoms.

Methods

A one year follow-up analysis of the quality of life was conducted for patients participating in the randomized trial in which MIE was compared with OE. Late complications and survival data were also reported. This trial is registered with the Netherlands Trial Register as NTR TC 2452.

Results

Quality of life at one year was better in the MIE group than in the OE group for the physical component summary SF36 (50 (6; 48-53) versus 45 (9; 42-48) p=.003); global health C30 (79 (10; 76-83) versus 67 (21; 60-75) p=.004); and pain OES18 module (6 (9; 2-8) versus 16 (16; 10-22) p=.001), respectively. Overall survival at one year post-surgery was 76% and 68% for MIE and OE respectively (p=0.314). Twenty-six patients (44%) in the MIE and 22 patients (39%) in the OE group were diagnosed and treated for symptomatic stenosis of the anastomosis

Conclusions

This first randomized trial shows that MIE is associated with a better long-term one year quality of life as compared to OE.

INTRODUCTION

Esophagectomy with lymphadenectomy after neoadjuvant chemoradiotherapy or chemotherapy is regarded as the only curative option for patients with resectable esophageal cancer.[1-3] This operative procedure has a high incidence of postoperative complications, especially pulmonary infections and is also associated with an impaired quality of life.[4] Minimally invasive procedures are increasingly implemented for reducing such complications and improving postoperative quality of life.

To date, the short-term results of only one randomized trial have been published. This multicenter, randomized trial provides evidence for certain short-term benefits of the minimally invasive approach for patients with resectable esophageal cancer. It reported significantly less pulmonary infections after the minimally invasive esophagectomy (MIE) as well as better pain scores, less blood loss and a shorter hospital stay. Importantly, this trial showed a better short-term quality of life at six weeks after surgery for the patients who underwent a MIE procedure.[5]

The quality of life after open transthoracic esophagectomy usually improves within one year.[6] However, studies investigating the long-term quality of life after MIE show conflicting results at one year follow-up.[7, 8-13] Furthermore, these results are based on analysis of patient series and non-randomized study design.

Therefore a one-year follow-up analysis of the quality of life was conducted for patients participating in the randomized trial in which MIE was compared with open esophagectomy (OE).[5] We investigated if MIE has a continuing better long-term one year quality of life than OE indicating both a faster recovery and less procedure-related symptoms. Additionally, late complications and one-year follow-up survival data are also reported.

METHODS

Study design and patients

This study at one year follow-up is an analysis of a multicenter, randomized trial that was carried out between June 1, 2009, and March 31, 2011 at five centers: two in Amsterdam (Netherlands), and the others in Nijmegen (Netherlands), Girona (Spain), and Milan (Italy).[5] Eligible participants had resectable esophageal cancer (cT1–3,N0–1, M0), histologically proven adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma of the intrathoracic esophagus and gastro-esophageal junction. Patients were aged 18–75 years and had a WHO performance status of 2 or less. We excluded patients with cervical esophageal cancer or another malignancy.

For quality assurance, the principal investigator visited all centers interested in trial participation. Minimally invasive esophagectomies were observed in person by the principal investigator. Both procedures were done by surgeons experienced in open esophageal resection, and with extensive experience in minimally invasive procedures, who had done at least ten minimally invasive esophagectomies. Only hospitals with more than 30 esophagectomies per year participated and their medical ethics boards approved the trial. Diagnosis and staging was established before neoadjuvant treatment by esophagoscopy and biopsies; CT

scans of the neck, thorax, and abdomen; and endo-ultrasonography were performed.

Surgeons at the outpatient clinic informed eligible patients of the treatment regimen. Written informed consent was obtained from included patients. We used a computer-generated randomisation sequence to randomly assign patients, in a 1:1 ratio, to undergo either open or minimally invasive esophagectomy. Randomisation was stratified by study center. All participating centers compiled an exclusion list to analyze the quality of the randomisation rate. Patients, and investigators undertaking interventions, assessing outcomes, and analyzing data were not masked to group assignment.

Operative procedure

Patients in both groups received identical pre-and postoperative 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 five weeks) and concurrent radiotherapy (41,4 Gy in 23 fractions for five days per week). After six–eight weeks, neoadjuvant treatment was followed by surgery by open- or minimally invasive esophagectomy.

Open esophagectomy involved a right posterolateral thoracotomy in the lateral decubitus position with double tracheal intubation and lung block, midline laparotomy, and cervical or intrathoracic anastomosis. Minimally invasive esophagectomy was performed through a right thoracoscopy in the prone position with single-lumen tracheal intubation, upper abdominal laparoscopy, and cervical incision. For patients undergoing minimally invasive esophagectomy with an intrathoracic anastomosis, a bronchus blocker was placed in the right bronchus to help with one-lung ventilation during anastomosis.

Both procedures included a two-field esophageal resection with 3–4 cm wide gastric tube formation followed by a cervical or intrathoracic anastomosis. Further details of the surgical techniques for open and minimally invasive esophagectomy have been published elsewhere.[15]

In the first three days after surgery, patients received epidural analgesia. If epidural analgesia was unsuccessful, patient-controlled analgesia with intravenous opioids was given. Enteral feeding was started on day 1 after surgery through a percutaneous jejunostomy catheter.

Study endpoints

The primary short-term endpoint of the study 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 short-term endpoints included among others postoperative complications other than pulmonary infections (e.g. anastomotic leakage, vocal-cord paralysis confirmed by laryngoscopy), 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).

Long-term secondary endpoints included quality of life at one year (assessed by SF 36 and EORTC C30 and OES18 module), incidence of late complications (e.g. anastomotic stenosis) and overall and disease-free survival. Data were collected prospectively during outpatient visits every three months during the first year. Radiological and/or endoscopic assessment (for recurrence or metastasis) was performed only by indication if the history and physical examination of the patient lead to suspicion.

Statistical analysis

We used Power and Precision (version 2) for sample size calculation in the short-term study. Previous data indicated a 28% difference in rates of pulmonary infections between minimally invasive (29%) [7, 15-18] and open (57%) esophagectomy.[19] To show a difference of this magnitude, two groups of 48 patients would be needed (α=005, β=080). With an estimation that about 20% of the eligible patients might not undergo the allocated intervention (e.g. due to metastases during neoadjuvant treatment or unresectable tumors), 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. When appropriate, we compared groups with an independent samples *t*-test, else a Mann-Whitney U test, or Chi-square test. We calculated relative risk (RR) for the primary endpoint with 95% CIs. Data was analyzed according to the intention to treat principle. We did statistical analysis with SPSS (version 17).

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

RESULTS

Subjects

We randomly assigned 115 of 144 eligible patients to receive either OE or MIE. Four crossovers occurred: two patients assigned to the OE group underwent MIE, and two assigned to MIE developed a WHO-ECOG score of 3 during neoadjuvant treatment and were treated by transhiatal esophagectomy. Eight patients did not undergo a resection (Figure 1); we included these patients in the analysis of the allocated group according to the intention-to-treat principle. Fifty-six patients were analyzed in the OE group and 59 in the MIE group. The demographic and clinical characteristics of the two groups were similar at baseline (Table 1). The short-term results are reported elsewhere.[5]

Quality of life

Quality of life questionnaires were obtained at one year postoperatively. A response compliance of 82% by patients was obtained. Under the non-responders were nine patients with recurrence; these patients were equally distributed between both groups. Moreover, six patients did not complete the questionnaires for unknown reasons, also equally distributed between both groups.

Quality of life questionnaire results are shown in Table 2. Overall the quality of life scores at one year were better for both groups compared at six weeks and preoperatively when using the SF-36 and EORTC C-30 Global health domain and the EORTC OES-18 domains. Importantly, there were significantly better scores after one year follow-up for the MIE group as compared to the OE group. These differences are present in three domains: physical activity (SF36: 50 (6; 48-53) versus 45 (9; 42-48) p=.003); global health (C30: 79 (10; 76-83) versus 67 (21; 60-75) p=.004); and pain (OES18: 6 (9; 2-8) versus 16 (16; 10-22) p= .001).

Not only compared to postoperative levels, but also compared to preoperative levels we see that after one year the patients in both groups improved their scores, without significant differences of improvement between the groups (Table 3).

Late complications

Late complications observed during the first year are depicted in Table 4.

After one year, 26 patients (44%) in the MIE and 22 patients (39%) in the OE group were diagnosed and treated for symptomatic stenosis of the anastomosis. Endoscopic dilatations were performed with a median number of five dilatations (2 to 20). One patient in the MIE group was re-admitted at two months postoperatively because of herniation of colon and small bowel in the thoracic cavity, necessitating reposition of viable bowels through median laparotomy.

Recurrence, distant metastasis and survival.

Data about local recurrence and distant metastases are shown in Table 5. Thirty-two patients died during the first year, 18 (32%) in the OE group and 14 (23%) in the MIE group (p=0.314). Death was related principally to distant metastases (19 patients), without significant differences between the two groups (p=0.167). Local recurrence was observed in three patients in the OE group (p=0.072).

A Kaplan-Meier analysis of the overall survival and disease-free survival at one year postoperatively is

shown in Figure 2. At one year follow-up, overall survival was 68% in the OE and 76% in the MIE group
(p=0.314). The disease-free survival was 59% and 69% respectively (p=0.237).

Figure. 1. Trial profile

MIE = minimally invasive esophagectomy. WHO-ECOG= World Health Organization- Eastern Cooperative Oncology Group. QoL= Quality of Life.
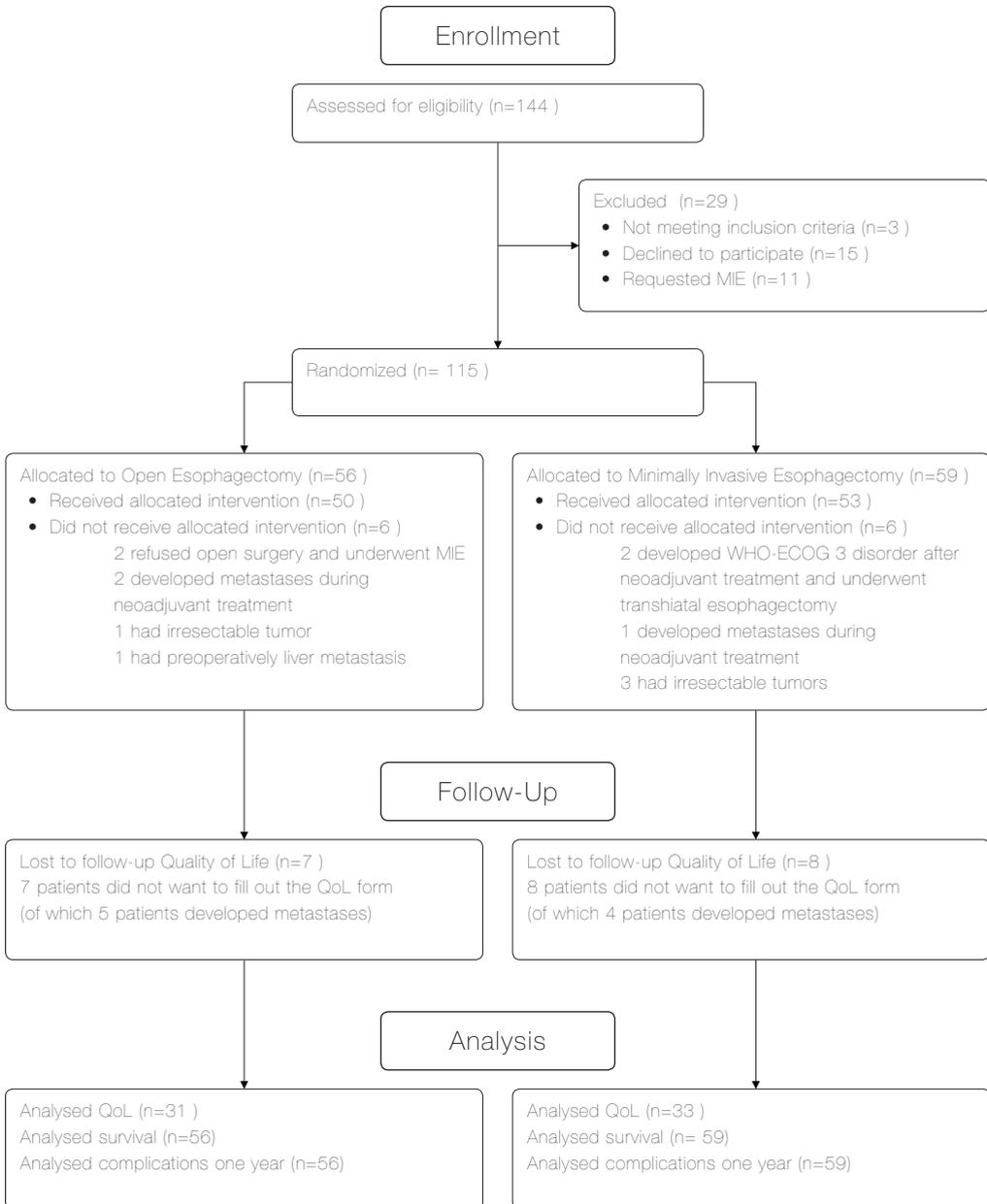Analysis: intention-to-treat.

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

	OE (N=56)	MIE (N-59)
Gender		
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%)
Neoadjuvant treatment		
Chemoradiotherapy	52 (93%)	54 (92%)
Chemotherapy alone	4 (7%)	5 (8%)
Location of tumor††		
Upper third	3 (5%)	1 (2%)
Middle third	22 (39%)	26 (44%)
Lower third or gastro-esophageal junction	31 (55%)	32 (54%)
Level of anastomosis		
Cervical	37 (66%)	38 (64%)
Thoracic	15 (27%)	17 (29%)
Total lymph nodes retrieved*	21 (7-47)	20 (3-44)
Resection margin¶		
R0	47 (84%)	54 (92%)
R1	5 (9%)	1 (2%)
pStage§		
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 tumor of lymph-node metastasis	7 (13%)	9 (15%)

Data are n (%), median (range), and mean (SD). OE=open esophagectomy. MIE=minimally invasive esophagectomy. BMI=body-mass index. ASA=American Association of Anesthesiologists. *Skewed distribution, Mann-Whitney test applied. †Normal distribution, Independent Samples t test applied. ††American Joint Committee on cancer site classification of thoracic and abdominal esophagus. ¶Defined as >1mm from a resection marge. §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.

Table 2. Quality of life domains

	OE	MIE	P-value
SF 36†			
Mental component summary			
- preoperatively	45 (9; 43-48)	46 (12; 43-49)	.955
- 6 wk	45 (11; 40-50)	46 (10; 41-50)	.806
- 1 yr	50 (10; 47-53)	53 (10; 49-56)	.317
Physical component summary			
- preoperatively			
- 6 wk	43 (9; 40-46)	46 (8; 44-48)	.072
- 1 yr	36 (6; 34-39)	42 (8; 39-46)	.007
	45 (9; 42-48)	50 (6; 48-53)	.003
EORTC C30†			
Global health			
- preoperatively	63 (23; 56-70)	66 (22; 60-72)	.631
- 6 wk	51 (21; 44-58)	61 (18; 56-67)	.020
- 1yr	67 (21; 60-75)	79 (10; 76-83)	.042
EORTC OES 18‡			
Pain			
- preoperatively	23 (22; 17-30)	17 (24; 11-24)	.187
- 6 wk	19 (21; 13-26)	8 (11; 5-11)	.002
- 1 yr	16 (16; 10-22)	6 (9; 3-10)	.003
Talking			
- preoperatively	12 (25; 4-19)	10 (23; 4-17)	.745
- 6 wk	37 (39; 25-49)	18 (26; 10-26)	.008
- 1 yr	10 (21; 3-18)	5 (14; 0-11)	.288

Data are mean (SD, 95% CI). OE=open esophagectomy. MIE=minimally invasive esophagectomy. EORTC=European Organization for Research and Treatment of Cancer Quality of Life Questionnaires. SF 36=Short Form 36 Health Survey (version 2). †Measures general aspects of health; scores range from 0 to 100, with higher scores representing better well-being. ‡Assesses several aspects of esophageal function; scores range from 0 to 100, with lower scores indicating better function.

Table 3. Improvement (delta) of Quality of life in time.

	OE	MIE	P-value
SF36			
- Mental component summary	10 (0.499)	10 (0.514)	0.546
- Physical component summary	10 (0.327)	9 (0.406)	0.465
EORTC C30			
- Global health	14 (0.518)	16 (0.498)	0.080
EORTC OES18			
- Pain	-7 (0.366)	0 (-0.041)	0.065
- Talking	-28 (0.256)	-18 (-0.083)	0.091

Data are mean difference between six weeks postoperatively and one year postoperatively (correlationcoefficient) OE=open esophagectomy. MIE=minimally invasive esophagectomy. EORTC=European Organization for Research and Treatment of Cancer Quality of Life Questionnaires. SF 36=Short Form 36 Health Survey (version 2).

Table 4. Late complications one year postoperatively

|	OE (56)	MIE (59)	P-value
Stenosis anastomosis	22 (39%)	26 (44%)	0.603
Intrathoracic herniation	1 (2%)	0 (0%)	0.303

Data are n (%). OE=open esophagectomy. MIE=minimally invasive esophagectomy

Table 5. Overall and disease free survival at one year

	OE (56)	MIE (59)	P- value
Overall survival	38 (68%)	45 (76%)	0.314
Disease free survival	33 (59%)	41 (69%)	0.237
Causes of death	18 (32%)	14 (24%)	0.314
- metastases	12 (21%)	7 (12%)	0.167
- recurrence	3 (5%)	0 (0%)	0.072
- in hospital mortality	1 (2%)	2 (3%)	0.590
- irresectable tumor	1 (2%)	3 (5%)	0.335
- other causes	1 (2%)	2 (3%)	0.590

Data are n (%). OE=open esophagectomy. MIE=minimally invasive esophagectomy

igure 2. Kaplan-Meier analysis of the overall survival and disease-free survival at one year postoperatively
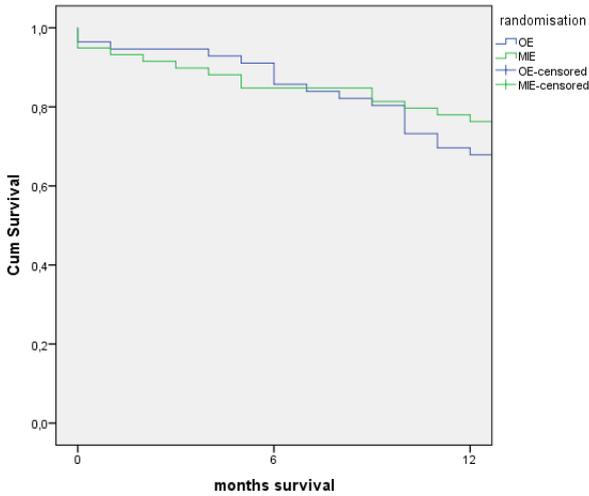
	Baseline	6 months	12 months
Total no. survived	115 (100%)	98 (85%)	83 (72%)
OE	56 (100%)	48 (86%)	38 (68%)
MIE	59 (100%)	50 (85%)	45 (76%)
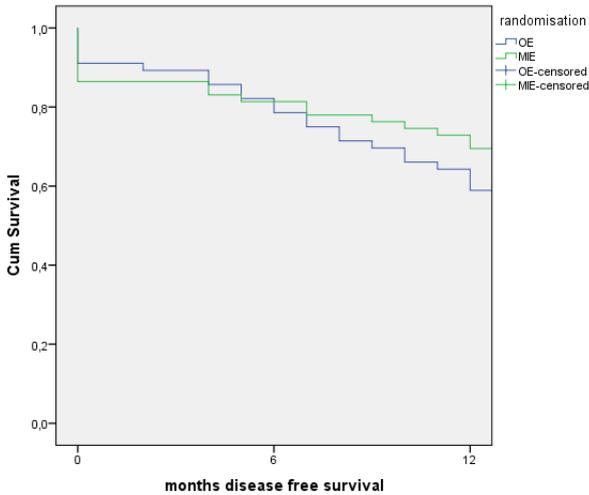
	Baseline	6 months	12 months
Total no. survived	115 (100%)	92 (80%)	74 (65%)
OE	56 (100%)	44 (79%)	33 (59%)
MIE	59 (100%)	48 (81%)	41 (69%)

DISCUSSION

In this trial, minimally invasive esophagectomy resulted in a better long-term one year quality of life for the physical component summary of the SF-36 questionnaire, EORTC C30 global health domain and OES 18 pain domain compared to open esophagectomy. In addition, there were no differences in survival and late complications at one year between the groups.

The impact of the surgical procedure is apparently of influence even after one year. The better physical domains of the SF-36 and pain of the OES 18 module for the MIE group indicate fewer limitations for the patients probably due to less surgical trauma by the smaller incisions which are used for MIE. Post-thoracotomy-related pain is well known and widely reported.[20, 21] It is probably a combination of intercostal nerve damage and myofascial pain.[22] It has been reported that up to 50% of patients describe post-thoracotomy pain one year after the procedure.[23] A recent study on the type of thoracotomy found an inverse relationship between the incision length and post-thoracotomy pain.[24] With MIE both incision length and myofascial damage is limited. This could explain the better outcome at one year after MIE. In addition, the abdominal incision is also smaller in MIE compared to OE. However, the influence of abdominal wall pain after laparotomy at one year is probably marginal compared to the influence of post thoracotomy pain on quality of life.

Postoperative health-related quality of life is impaired in patients with esophageal cancer in comparison to preoperative levels [8, 9] and to that of healthy reference populations.[25-27] The recovery after esophagectomy to preoperative levels was present for both groups at one year. Quality of life data after minimally invasive esophagectomy is limited. Parameswaran et al. studied 97 patients undergoing either OE, laparoscopic assisted esophagectomy (LAE), or MIE for high-grade dysplasia or cancer.[9] Patients completed validated questionnaires before, after six weeks, at three months and at six months after surgery. Following surgery, the fatigue levels increased dramatically and activity levels reduced in all groups after six weeks. These gradually recovered to baseline levels following MIE and LAE within six months, but the scores regarding ability to perform activities of daily living and most indicators of fatigue had not returned to baseline levels in the OE group. Although the studied questionnaires in the above mentioned study differ from those used in our protocol and have a non-randomized design, nonetheless it is clear that the trend is comparable. In our study we also see a drop at six weeks after surgery and even better results than baseline after one year.

In this trial, overall survival and disease-free survival rates after one year were not different between the groups. This data are in concordance with recent literature of patients treated by neoadjuvant therapy followed by esophageal resection.[2,3] Local recurrence and distal metastases were also not different between the groups and comparable with other reports.[3,28] However, reliable survival analysis is usually performed at five years postoperatively. This will be reported in the future.

The rate of late complications—as defined between the discharge and one year follow-up—does not differ between the two groups. Almost 40% of the patients necessitated dilatations because of symptomatic benign stenosis of the gastric tube anastomosis. The median average of dilatations was five per patient. This outcome corresponds with other prospective studies.[29,30]

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This study has some limitations. This trial was powered for short-term pulmonary infections and not for long-term quality of life. However, considering the impaired physical domains of the quality of life, which is probably related to post-thoracotomy pain, it is likely that this difference with the MIE group would still be present. Other trials, powered for quality of life, however are needed to confirm our results. In addition, the quality of life questionnaires at one year was not completed by all patients (82% completion). Some patients with cancer recurrence did not complete the questionnaires. Given their equal distribution in both groups the influence of the non-responders is small in the final outcome.

In conclusion, this first randomized trial shows that minimally invasive esophagectomy for esophageal cancer is associated with a better long-term one year quality of life as compared to open esophagectomy.

REFERENCES

1. Enzinger PC, Mayer RJ. Esophageal Cancer. N Engl J Med 2003; 349: 2241-2252

2. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, Gebski V. Survival after neoadjuvant chemotherapy or chemoradiotherapy for respectable esophageal carcinoma: an updated meta-analysis. Lancet oncolog 2011; 12:681-692.

3. van Hagen P, Hulshof MCCM, van Lanschot JJB et al. Preoperative Chemoradiotherapy for Esophageal or Esophagogastric Junction Cancer Improves Survival. N Engl J Med 2012;366:2074-84.

4. Scarpa M, Valente S, Alfieri R, Cagol M, Diamantis G, Ancona E, Castoro C. Systematic review of health related quality of life after esophagectomy for esophageal cancer. World J Gastroenterology 2011; 17(42):4660-74.

5. Biere SS, van Berge Henegouwen MI, Maas KW et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer: a multicenter, open label, randomised controlled trial. Lancet 2012;379:1887-92.

6. 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.

7. Luketich JD, Alvelo-Rivera M, Bunaventura PO et al. Minimally invasive esophagectomy: outcomes in 222 patients. Ann Surg 2003; 238: 486-494.

8. 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.

9. 9- Parameswaran R, Titcomb DR, Blencowe NS et al. Assessment and Comparison of Recovery after Open and Minimally Invasive Esophagectomy for Cancer: An Exploratory Study in Two Centers. Ann surg Oncol 2013 Jan 11. Epub ahead of print.

10. Nafteux P, MOEns J, COEsemans W, Decaluwé H, Decker G, De Leyn P, Van Raemdonck D, Lerut T. Minimally invasive esophagectomy: a valuable alternative to open esophagectomy for the treatment of early esophageal and gastro-esophageal junction carcinoma. Eur J Cardiothoracic Surg 2011; 40(6):1455-63.

11. Sundaram A, Geronimo JC, Willer BL, Hoshino M, Torgersen Z, Juhasz A, Lee TH, Mittal SK. Survival and quality of life after minimally invasive esophagectomy: a single surgeon experience. Surg Endosc 2012; 26(1):168-76.

12. Kim T, Hochwald SN, Sarosi GA, Caban AM, Rossidis G, Ben-David K. Review of minimally invasive esophagectomy and current controversies. Gastroenterol Res Pract 2012; 2012:683213.

13. Mehran R, Rice D, El-Zein R, Huang JL, Vaporciyan A, GOEdyear A, Mehta A, Correa A, Walsh G, Roth J, Swisher S, Hofstetter W. Minimally invasive esophagectomy versus open esophagectomy, a symptom assessment study. Dis Esophagus 2011; 24(3):147-52.

14. Biere SSAY, Maas KW, Bonavina L, et al. Traditional invasive vs minimally invasive esophagectomy: a multi-center, randomized trial. BMC Surg 2011; 11:2.

15. Palanivelu C, Prakash A, Senthilkumar R, et al. 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.

16. Biere SS, Cuesta MA, van der Peet DL. Minimally invasive versus open esophagectomy for cancer: a systematic review and meta-analysis. Minerva Chir 2009;64:121-33

17. Zingg U, McQuinn A, DiValentino D, et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer. Ann Thor Surg 2009; 87:911-19

18. Nguyen NT, Hinojosa MW, Smith BR, Chang KJ, Gray J, Hoyt D. Minimally invasive esophagectomy: lessons learned from 104 operations. Ann Surg 2008; 248: 1081-91.

19. Hulscher JBF, van Sandwick JW, de Boer AG, et al. Extended thoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Eng J Med 2002; 347: 1662-69.

20. Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. Eur J Cardiothorac Surg 2009; 36: 170-80

21. Gottschalk A, Cohen SP, Yang A, Ochroch A. Preventing and treating pain after thoracic surgery. Anesthesiol 2006;104:594-600

22. Karmakar MK, Ho AM. Postthoracotomy pain syndrome. Thorac Surg Clin 2004; 14: 345-52

23. Maguire MF, Ravenscroft A, Beggs D, et al. A questionnaire study investigating the prevalence of the neuropathic component of chronic pain after thoracic surgery. Eur J Cardiothoracic Surg 2006; 29:800-805

24. Elshiekh MA, Lo TT, Shipolini AR, McCormack DJ. Does muscle-sparing thoracotomy as opposed to posterolateral thoracotomy result in better recovery? Interact Cardiovasc Thorac Surg 2013; 16: 60-7

25. Rutegard M, Lagergren P, Rouvelas I et al. Population-based study of surgical factors in relation to health-related quality of life after esophageal cancer resection. Br J Surg 2008; 95:592-601.

26. Blazeby JM, Farndon JR, Donovan J et al. A prospective longitudinal study examining the quality of life of patients with esophageal carcinoma. Cancer 2000; 88:1781-1787.

27. Gutschow AC, Holschner AH, Leers J, Fuchs, Bludau M, Prenzel KL, Bollschweiler E, Schroder W. Health-related quality of life after Ivor Lewis esophagectomy. Langenbecks Arch Surg 2013; 398:231-237

28. Li CL, Zhang FL, Wang YD et al. Characteristics of recurrence after radical esophagectomy with two field lymph node dissection for thoracic esophageal cancer. Oncol Lett 2013;5:355-359.

29. Nederlof N, Tilanus HW, Tran TC et al. End-to-end versus end-t-side esophagogastrostomy after esophageal cancer resection. A prospective randomized study. Ann Surg 2011;254:226-33.

30. van Heijl M, GOEszen JA, Fockens P et al. Risk factors for development of benign cervical structures after esophagectomy. Ann Surg 2010;251:1064-9.