

# Chapter 9

The cost-effectiveness of minimally invasive esophagectomy for esophageal cancer, a cost analysis of a randomized controlled trial.

**Kirsten W. Maas**

Veerle M.H. Coupé

Surya S.A.Y. Biere

Miguel A. Cuesta

Donald L. van der Peet

# ABSTRACT

## Introduction

Minimally invasive esophagectomy (MIE) is associated with less pulmonary complications, shorter hospital stay, and better quality of life as compared to open esophagectomy (OE). However, there are concerns about the likely higher costs for this procedure. Therefore, we carried out an economic evaluation of the randomized controlled TIME trial in MIE was compared to OE in patients with curable esophageal cancer.

## Methods

The economic evaluation combined a cost-effectiveness analysis and a cost-benefit analysis in the comparison of MIE with OE within a time-period of 30 days postoperatively. Cost data was prospectively measured by registration of detailed intervention units per patient, thereby obtaining the actual resource-use scores per individual patient. The cost-benefit analysis entailed comparing the difference between MIE and OE in operation-related costs with their difference in post operative costs during the 30-days post operative period. The cost-effectiveness analysis entailed comparing differences in total costs with differences in quality of life domains. Uncertainties regarding the cost and effect differences were estimated by bootstrapping and graphically represented on planes.

## Results

The difference in total healthcare costs between MIE and OE was small and not statistically significant. The cost-effectiveness plane indicated that improvements in quality of life could be achieved at limited or no costs.

## Conclusion

Total healthcare costs holding for MIE or OE procedures are similar. Minimally invasive esophagectomy is favored over the open procedure because of better quality of life effects and less post operative complications.

## INTRODUCTION

In the past two decades, the global incidence of esophageal cancer increased rapidly (+30%), from 316.000 people diagnosed in 1990 to 482.300 new cases recorded in 2008.<sup>1,2</sup> Surgical resection with radical lymphadenectomy is the only curative treatment for patients with resectable esophageal cancer after neoadjuvant chemotherapy or radio chemotherapy.<sup>3-5</sup> Esophagectomy can be performed through a transthoracic approach by combining thoracotomy with laparotomy involving intrathoracic or cervical anastomosis; or it can be done by a transhiatal route using only laparotomy with cervical approach for anastomosis. These procedures have a high complication rate, mostly due to postoperative pulmonary infections and resulting in poor quality of life.<sup>6,7</sup>

In a multicenter randomized trial, the TIME-trial, MIE by thoracoscopy and laparoscopy has been proven to decrease post operative pulmonary infections; from 29% to 9% in the first two postoperative weeks and from 34% to 12% during the in-hospital period. Moreover in the appraisal of MIE versus OE a significant difference was observed in the quality of life six weeks post surgery and such held for various domains such as the physical component of SF-36, the Global health EORTC-C30 score, and the talking and pain domains of the EORTC-OES 18.<sup>8</sup>

Concerns do remain regarding the possible higher healthcare costs associated with the implementation of MIE in comparison with OE, not only because of the longer operative time for MIE but also because of the associated wide use of disposable products. To date there are few cost-analyses comparing open versus minimally invasive esophagectomy for cancer. Parameswaran et al. reported higher operative costs and lower inpatient care costs for MIE versus OE, with no difference in total costs.<sup>9</sup> Lee et al. recently analysed the cost-effectiveness of MIE versus OE and concluded that MIE is cost-effective as compared to OE, as long as MIE is oncologically found to be equivalent in short- and long-term health outcomes.<sup>10</sup>

This study is a substudy of the TIME-trial and compared direct healthcare costs of patients with resectable esophageal cancer randomized for either MIE or OE resection. Furthermore, a cost-benefit and cost-effectiveness analysis of MIE in comparison with OE is presented.

# METHODS

## Study design

This study involves an economic evaluation of the TIME-trial, comparing minimally MIE to OE in patients with esophageal cancer. The TIME-trial was a prospective, multicenter, randomized, controlled study, carried out from June 2009 to March 2011. Eligible patients were randomized to either MIE or OE. In the present study only patients from the VU University Medical Center were included.

Primary clinical endpoint was incidence of postoperative pulmonary infection within two weeks and during the in-hospital stay. Secondary endpoints included quality of life assessment by the Short Form-36 version 2 (SF-36) questionnaire, EORTC-C30 and EORTC-OES18 measured six weeks after surgery. Written informed consent was obtained from eligible patients. Data were analysed according to the intention to treat principle.

## Cost data

The economic evaluation was conducted from a hospital perspective. As such, only direct health care costs were considered.

Since no uniformity or transparency exists for cost registration in the different participating clinics and countries of the TIME\_trial, only patients who were treated in the VU University Medical Center were included. Data on resource-use were aggregated from the 'TOREN'-software program (iSOFT<sup>®</sup>, Leiden, The Netherlands). This program enables prospective registration of detailed intervention units per patient, such as materials (sutures and disposables), medical equipment, personnel costs and specialist fees. Procedures consisting of operations, admission days or diagnostic tools comprise several intervention units, resulting in actual resource use per individual patient. Different procedures are grouped into seven categories as shown in Table 1.

The actual costs per individual patient holding for the seven categories are also shown in Table 1. The costs were calculated and summed to obtain the total direct costs for the period from operation until 30 days after surgery.

Table 1 Resources per category

Category	Resource examples
1. Hospitalization	Admission days, laboratory testing, medication, nurses fee
2. Operation	Operating room per hour, sterilization costs, disposable materials, specialist fee
3. Imaging	CT-scan, ultrasound, radiograph
4. Diagnostic procedures	Endoscopy, EKG
5. Blood products	Packed Cells, Fresh Frozen Plasma
6. Consulting specialists	Cardiology, Internal Medicine, Dermatology
7. Paramedical services	Physiotherapy, dietician, social worker

## Cost-benefit and cost-effectiveness analysis

Regarding the cost-benefit analysis, the difference between MIE and OE in operation-related costs was compared to the difference in post-operative costs during the 30 days post-operative period. As cost data are typically skewed, 95% confidence intervals for differences in mean costs cannot be estimated with conventional methods that assume normality. To avoid distributional assumptions, the non-parametric bootstrap was applied.<sup>11-13</sup> Basically, in the non-parametric bootstrap, samples of the same size as the original dataset are drawn by sampling with replacement from the observed data. These bootstrap samples can be used to estimate standard errors and confidence intervals. To obtain 95% confidence intervals for cost differences, we performed a non-parametric bootstrap with a number of 2000 replications.<sup>12</sup>

Regarding the cost-effectiveness analysis, the difference in total costs between MIE and OE was compared to the difference in SF-36 values for general health, and to the difference in EORTC-C30 and EORTC-OES18 scores six weeks post-surgery. Uncertainty about the differences in total costs and effectiveness was estimated using the bias corrected and accelerated bootstrapping method (5000 replications). The results are presented on a cost-effectiveness plane.<sup>14</sup>

Table 2. Clinical outcomes

	OE (n=21)	MIE (n=22)	P value
Operative time (min)	258	321	0.017
Blood loss mL	460	363	0.056
Pneumonia (<2w)	8	2	0.034
Pneumonia in hospital	10	3	0.023
Hospital stay*	18 (11.5-31.5)	12.5 (9-28.8)	0.545
ICU stay*	2 (1-12)	1 (1-2.5)	0.291
QoL 6 wk post-op**			
C30	51 (5; 40-61)	61 (5; 51-71)	0.140
SF36			
MCS	40 (3; 34-46)	43 (3; 36-50)	0.548
PCSOES18	33 (2; 29-37)	42 (2; 37-46)	0.006
Pain	24 (6; 11-36)	7 (2; 2-12)	0.011
Talking	31 (11; 7-55)	18 (6; 4-31)	0.303

\* median (interquartile range Q1-Q3)

\*\* Standard deviation and 95% confidence interval

**Table 3.** Mean (SD) costs (€) per treatment group within 30 days

Category	OE (n=21)	MIE (n=22)	Difference (95% CI)*
1. Hospitalization	6243 (5287)	6090 (6563)	-153 (-3300 to 3579)
2. Operation	9097 (5130)	9359 (2804)	262 (-2436 to 2433)
3. Imaging	703 (728)	795 (1051)	92 (-334.33 to 801.01)
4. Diagnostic procedures	545 (393)	759 (1407)	214 (-175 to 1342)
5. Blood products	243 (611)	0.00 (0.00)	-243 (-621 to -81)^
6. Consulting specialists	216 (465)	293 (616)	77 (-199 to 474)
7. Paramedical services	697 (416)	723 (667)	26 (-220 to 436)
<b>Total costs</b>	<b>17744 (10828)</b>	<b>18018 (10666.60)</b>	<b>275 (-5986 to 6689)</b>

\* Difference with 95% CI obtained from a non-parametric bootstrap method with 2000 replications

^ statistically significant

## RESULTS

### Clinical outcomes

A total of 115 patients were included in the TIME- trial, of which 43 patients were treated at the VU Medical Center: 22 of these were randomized to the MIE group and 21 to the OE group. At baseline, no differences in clinical characteristics were found between the MIE and OE groups. Results are shown in Table 2. The short-term analysis for the group of patients treated at the VU Medical Center showed significant differences in operating time and pulmonary infections. For the physical component of the quality of life questionnaire SF36 as well as for the pain domain of the EORTC-OES18, significant differences within the subgroup was reached as was also the case in the complete trial. The differences in quality of life for SF36 mental, EORTC-C30 and EORTC-OES 18 talking were not statistically significant in the group of the VU Medical Center patients only (n=43), but did reach significance in the complete trial (n=115).<sup>8</sup>

### Costs differences and cost-benefit

Table 3 shows the mean costs for the two groups, MIE and OE, per category. The total healthcare costs within 30 days were €17743 for the OE group and €18018 for the MIE group. The difference (€275) between the groups was small and not statistically significant (95% CI -€5986 to €6689). The only significant difference between the two groups was seen for blood products; OE €243 vs MIE €0 (p .047), which is in agreement with the results in Table 2, where the difference in blood loss was close to being significant (p .056) in favor of the MIE group.

Figure 1 shows the results of the cost-benefit analysis on a cost-benefit plane. That is, the difference in operation-related costs (y-axis) is plotted against the difference in post-operative costs (benefits, x-axis). Neither differences in costs nor benefits are seen between the two groups. Due to the small number of patients, the uncertainty about the point estimates for the cost differences is large.

### Cost-effectiveness

The cost-effectiveness planes (Fig. 2, Fig. 3) show that most of the cost-effect pairs are positioned on the right side of the y-axis, but centered around the x-axis. This indicates better quality of life for SF36 and EORTC-C30, without a difference in costs. For EORTC-OES18, most of the cost-effectiveness pairs in the plane are positioned on the left side of the y-axis (Fig. 3), but on this scale lower scores relate to better outcome. Hence, Figure 3 also indicates better quality of life for the MIE group, without a difference in costs.

Fig 1. Cost-benefit plane

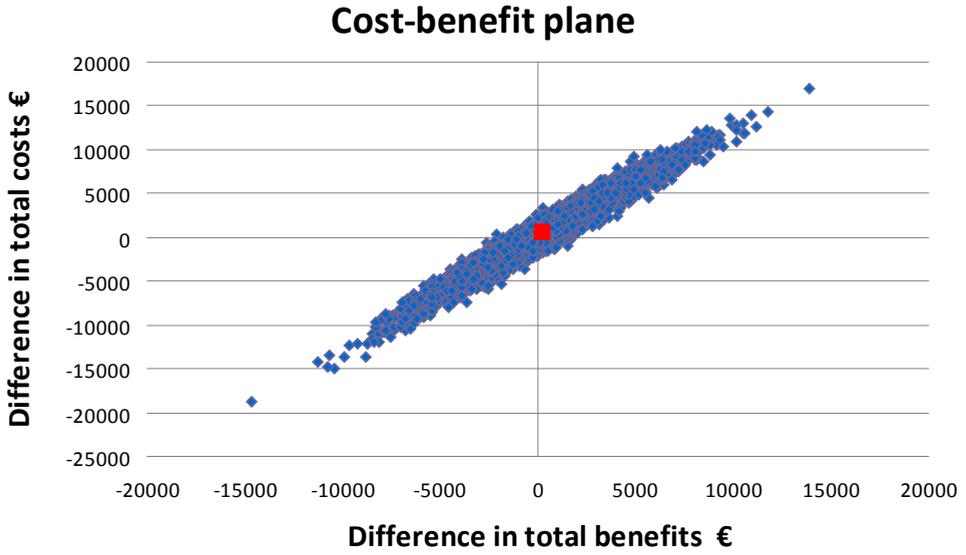


Fig 2. Cost-effectiveness plane SF36PCS

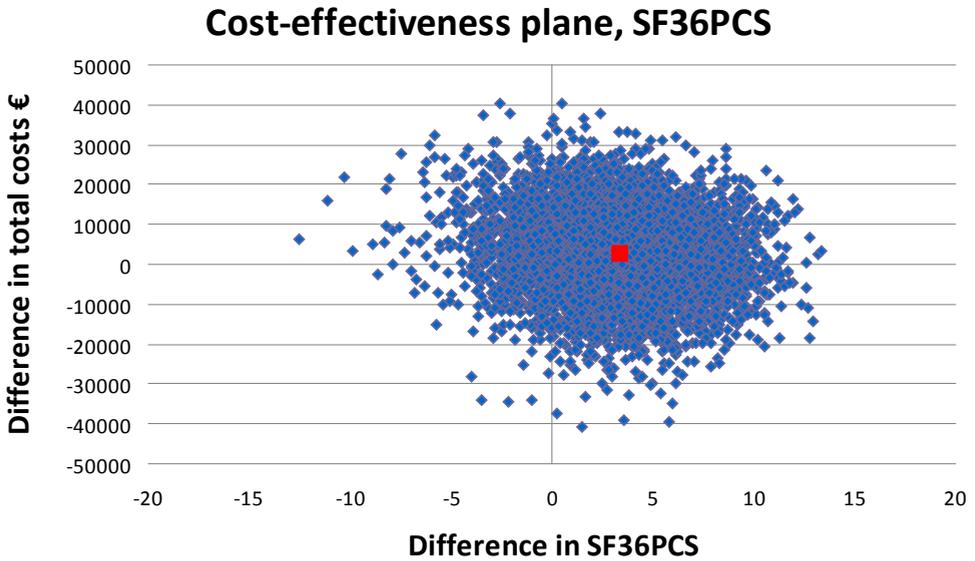


Fig 3. Cost-effectiveness plane C30

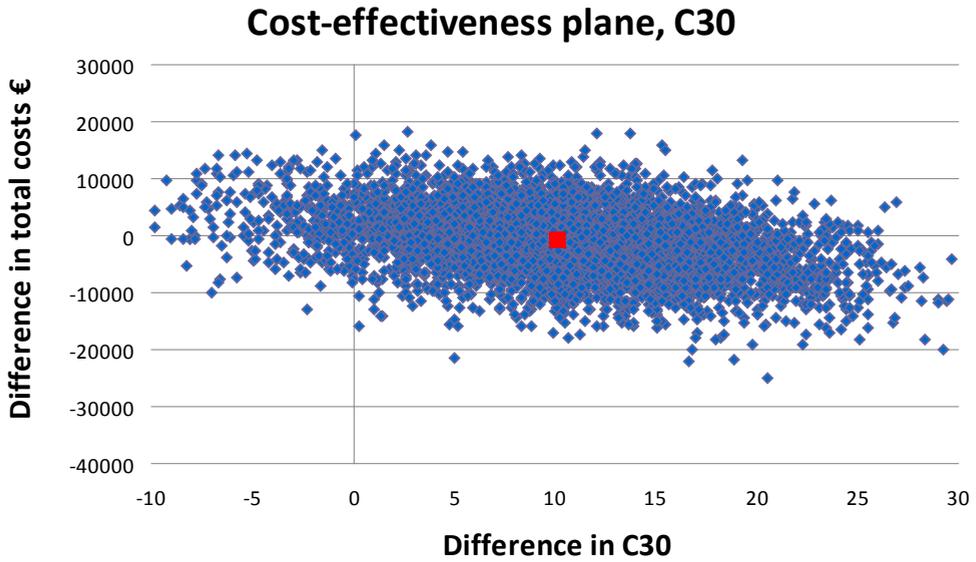
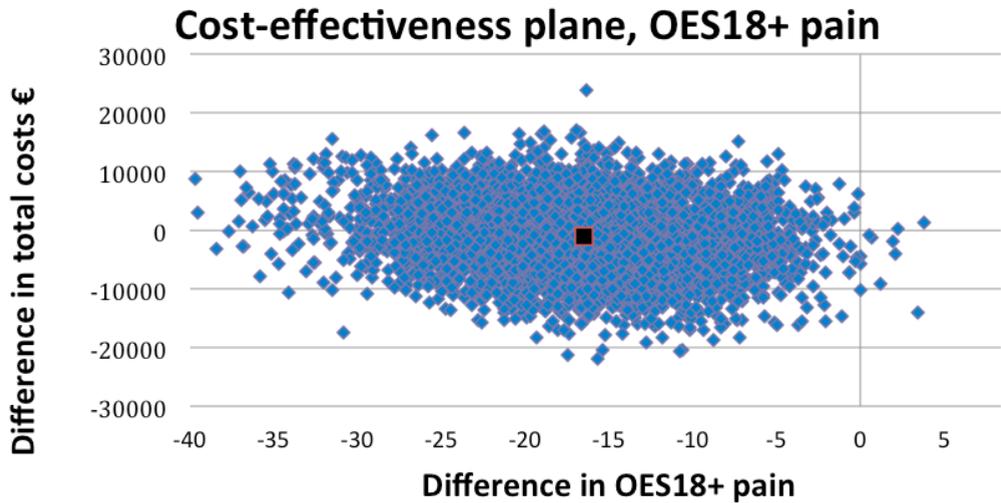


Fig 4. Cost-effectiveness plane OES18+ pain



## DISCUSSION

Minimally invasive esophagectomy for esophageal cancer is not more expensive than the traditional open procedure. Moreover, MIE leads to better quality of life six weeks after the procedure on several quality of life scales as compared to OE.

In treatment of esophageal cancer, the highest costs are made for doing surgery together with the combination of chemo- and radiotherapy.<sup>15</sup> The greater part of the surgical costs are related to the initial three days of hospital stay, which includes the stay in the intensive care unit, ventilation time and intra-operative time.<sup>16</sup> Additional costs are mainly related to complications occurring in the post-operative period.<sup>15</sup>

In this study, a significant difference in operating time between MIE and OE was established, leading to the higher operation costs of €260 holding for MIE in this substudy. The costs of diagnostic procedures were also somewhat higher in the minimally invasive group. However, again these costs were offset by a decrease in the costs of hospitalization and blood products. This is in line with the observed decrease in complications occurring in the post-operative period in the minimally invasive group. Overall, the difference in total costs between the two groups, MIE and OE, within a 30-day period, was small and the difference was not significant.

The cost-effectiveness planes showed that MIE led to increased quality of life as measured by the SF36 physical scale, the EORTC-C30, and the EORTC-OES18 talking scale at similar costs as hold for OE. It should be noted, however, that the uncertainty reflected by display of the plane is large due to the small sample size. Similarly, the cost-benefit plane demonstrated a balance between the (operation-related) costs of MIE and the benefits (postoperative costs) compared to OE. Here again, the uncertainty was large.

This study is the first randomized study where the costs of MIE and OE for esophageal cancer have been compared and analysed for cost-effectiveness. The results are in concordance with earlier non-randomized analyses.<sup>9,10</sup>

In this study only patients from a single center were analysed. Because of the small sample size most differences in quality of life were no longer significant comparing to the main data.<sup>8</sup> Nevertheless a trend is seen in favor for the MIE group, with no differences in costs. We only analysed the costs in the first 30 days postoperatively, whereas the measuring time-point for the quality of life was at six weeks. This means that an assessment of costs at a period of two weeks, week five and week six postoperatively was not conducted. From a social point of view it is to be expected that a potential difference in costs in this period would be in favor of the MIE group. We used the resource utilization results from prospective registration of detailed resource items per patient, which enables an accurate calculation of actual costs per individual patient. From a more social perspective, also indices regarding productivity losses and caregiver burden should also be included. Given the fact that quality of life after six weeks is better for the MIE group, patients in the MIE group are expected to return to work faster. Studies comparing open and minimally invasive procedures for colorectal, bariatric and other abdominal surgery, have reported favorable outcomes for the minimally invasive groups.<sup>17-21</sup>

Overall, we conclude that total healthcare costs at 30 days postoperative are similar for minimally invasive esophagectomy and for open esophagectomy. As differences in clinical outcomes favor the MIE group, this procedure should become standard for resectable esophageal cancer. Future long-term analyses including productivity costs are needed to obtain a more accurate assessment of the cost-effectiveness of MIE.

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