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Minimally Invasive *Versus* Open Ivor-Lewis Esophagectomy for Esophageal Cancer or Cancer of the Gastroesophageal Junction: Comparison of Postoperative Outcomes and Long-term Survival Using Propensity Score Matching Analysis

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Abstract. *Background/Aim: Esophagectomy is crucial for achieving long-term survival in patients with esophageal cancer, while being associated with a significant risk of complications. Aiming to reduce invasiveness and morbidity, total minimal-invasive esophagectomy (MIE) has been gradually implemented worldwide. The aim of the study was to compare MIE to open Ivor-Lewis esophagectomy (OE) for esophageal cancer or cancer of the gastroesophageal junction (GEJ), in terms of postoperative and oncological outcomes. Patients and Methods: Clinicopathological data of patients undergoing oncologic transthoracic esophagectomy (Ivor Lewis procedure) between 2010 and 2019 were assessed. Postoperative outcomes and long-term survival of patients undergoing OE were compared to those after MIE using 1:1 propensity score matching. Results: After excluding hybrid and robotic procedures, 90 patients who underwent MIE were compared with a matched cohort of 90 patients who underwent OE. MIE was associated with lower major postoperative morbidity (31% vs. 46%, p=0.046) and lower 90-day mortality (2% vs. 12%, p=0.010) compared to OE. MIE showed non-inferior 3-year overall (65% vs. 52%, p=0.019) and comparable disease-free survival rates (49% vs. 51%, p=0.851) in comparison to OE. Conclusion: Our data suggest that MIE should be preferably performed in patients with esophageal cancer or cancer of the GEJ.*

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Key Words: Esophageal cancer, minimal-invasive esophagectomy, cancer of the gastroesophageal junction.

The incidence of esophageal cancer and cancer of the gastroesophageal junction (GEJ) is steadily increasing in the Western population (1). For locally advanced esophageal cancer or cancer of the GEJ, radical surgical resection performing transthoracic esophagectomy (Ivor Lewis procedure) with lymphadenectomy remains the mainstay of multimodal treatment including either preoperative chemotherapy or combined radiochemotherapy, increasing the 5-year survival rate to up to 40% (2-4). However, esophagectomy poses a demanding procedure with significantly high risk for postoperative morbidity and mortality. Postoperative complications occur in up to 75% of cases (5), with pulmonary complications being the most common (6, 7), while 90-day mortality rate can be as high as 13% (8, 9).

Minimal-invasive approaches for esophagectomy were introduced in the 1990s in an effort to reduce postoperative morbidity and subsequent mortality (10). The benefits of minimal-invasive resections for malignant lesions have been well reported for several cancer types including hepatectomy for hepatocellular carcinoma (11, 12) or colorectal liver metastases (12, 13), and gastrectomy for gastric cancer (14, 15). Since the 2000s, minimal-invasive esophagectomy (MIE) has gained importance for patients with esophageal cancer (16, 17). Several retrospective studies as well as prospective trials comparing hybrid esophagectomy (18), robotic resection with cervical anastomoses (19) or MIE with mainly cervical anastomoses (20) reported the advantages of minimal-invasive techniques compared to open esophagectomy (OE) including lower blood loss, shorter hospital stay, reduced postoperative overall morbidity and pulmonary complications (21-26).

Additionally, a minimal-invasive approach was proven equivalent in terms of oncologic outcomes with increased numbers of harvested lymph nodes (27), higher rates of R0 resections (28), and comparable overall (OS) and disease-free survival (DFS) (27, 29). Previously, two randomized controlled trials (RCT) were conducted including a multi-center study in Europe (20, 30) and another in the Netherlands (19) that confirmed the benefits of MIE over OE regarding postoperative outcomes and underlined non-inferiority of the minimal-invasive technique regarding oncologic outcomes. However, different minimal-invasive laparoscopic (20, 30) or robotic (19) techniques as well as hybrid techniques (18) are in use, with relevant differences in surgical approach and levels of esophagogastric anastomosis. To date, no RCT comparing total minimal-invasive with open transthoracic Ivor-Lewis esophagectomy has been published.

Nowadays, modern statistical methods have been increasingly applied in surgical research to compare different techniques, since randomized controlled trials are often faced with methodological challenges (31, 32). In this regard, propensity-score matching (PSM) analysis may help reduce the impact of treatment-selection bias of retrospectively collected observational data (33). To date, only few studies implemented PSM for the evaluation of MIE in comparison to OE (34, 35).

The objective of this study was to review the institutional experience of a high-volume center by comparing postoperative and long-term outcomes of patients with esophageal or GEJ cancer undergoing MIE with those pf patients undergoing OE using PSM analysis.

Patients and Methods

Patient inclusion criteria. After approval from the local Institutional Review Board, clinicopathological data of 284 consecutive patients undergoing resection for esophageal cancer or cancer of the GEJ were evaluated. Inclusion criteria comprised curatively intended surgery and patient age ≥18 years. Patients undergoing palliative surgery or presenting with a second malignant disease at time of surgery were excluded.

Preoperative assessment. Preoperatively, all patients underwent routine evaluation including medical history, physical examination, laboratory studies, imaging studies, and pre-anesthesia evaluation. Diagnosis and staging of cancer were obtained via esophagogastroduodenoscopy with multiple biopsies and endosonography. Staging was completed with cross-sectional imaging (computer tomography or magnetic resonance imaging) and diagnostic laparoscopy for adenocarcinomas. In borderline cases, fluorodeoxyglucose–positron emission tomography was performed to rule out metastatic disease. For each patient, treatment was recommended by a multidisciplinary tumor board. Preoperative treatment consisted of chemotherapy alone or combined radiochemotherapy, to some extent as part of ongoing trials (36-38). In some cases, patients did not receive any preoperative treatment due to severe comorbidities.

Surgical procedure and postoperative management. All patients underwent transthoracic esophagectomy (Ivor Lewis procedure) with gastric pull-up and 2-field lymphadenectomy. Procedures were performed as previously reported (39). At the beginning of either laparotomy or laparoscopy, metastatic cancer spread was ruled out. Stapled circular end-to-side anastomoses were created in all cases. In case of MIE, an incision at the distal end of the gastric sleeve was made to guide the stapler. All anastomoses were secured with 4-0 PDS sutures. A chest tube and a Jackson-Pratt perianastomotic drain were routinely placed. Additional abdominal drains were placed only at the surgeon's discretion.

After surgery, all patients were admitted to a specialized intensive care unit. Postoperative complications including bleeding, anastomotic leak, intraabdominal or wound infections, pneumonia, and organ failure were recorded. Any complication or mortality within 90 days after resection was defined as postoperative morbidity and mortality, respectively. Postoperative complications were graded according to the Clavien-Dindo classification of surgical complications (40). Major morbidity was defined as grade ≥3a.

In the light of minimal-invasive surgery and enhanced recovery after surgery protocols, our current practice includes the removal of nasogastric tubes on the first or second postoperative day, along with early mobilization, and early oral fluid intake. Before 2015, all patients underwent gastrointestinal decompression for five days postoperatively, with an oral contrast swallow on the fifth postoperative day to rule out anastomotic leak and to allow the nasogastric tube to be removed (39). Perianastomotic drains were removed on postoperative day 5, all others after postoperative day 3, if discharge was unremarkable and less than 200 cc per day.

Histological evaluation. Histopathological evaluation of resected specimen included the confirmation of the diagnosis of squamous cell carcinoma or adenocarcinoma of the esophagus or GEJ. Furthermore, the tumor stage according to the TNM classification was defined and the surgical margins were examined for malignant cells.

Statistical analysis. After stratification of patients according to the type of surgical procedure, propensity scores were used to match patients who underwent MIE for esophageal cancer or cancer of the GEJ with a cohort of patients who were treated with OE. Patients who underwent resection via hybrid or robotic procedures were excluded from matching. A 1:1 PSM using a logistic regression model with a match tolerance of 0.1 was performed based on the following matching parameters: patient age, sex, body mass index, American Society of Anesthesiologists (ASA) status, comorbidities, tumor location (esophagus or GEJ), Union for International Cancer Control (UICC) tumor stage, preoperative therapy (no preoperative therapy, chemotherapy alone or combined radiochemotherapy). Adenocarcinoma of the GEJ was defined and classified according to Siewert *et al*. (41). Standardized difference was calculated for all covariates to assess imbalance after matching, and values <0.1 were considered balanced (42).

Quantitative and qualitative variables were expressed as medians (range) and frequencies. The Chi-square or Fisher's exact test, and the Mann-Whitney *U*-test were used to compare categorical and continuous variables between the MIE and OE cohorts, as appropriate. Using the Kaplan-Meier method, OS was calculated from the date of resection to the date of death or last follow-up and DFS was calculated from the date of resection to the date of diagnosis of recurrent disease or last follow-up. OS and DFS rates were compared between the MIE and OE patient cohorts using log-rank tests. *p*-Values <0.05 were considered statistically significant. SPSS software package, version 25, by IBM (Armonk, NY) was used for statistical analyses.

Results

Patient and tumor characteristics. During the study period, 284 consecutive patients undergoing resection for cancer of the esophagus or GEJ were included in this study. OE, hybrid esophagectomy (HE), MIE, and robot-assisted MIE (RAMIE) were performed in 126 (44%), 39 (14%), 90 (32%), and 29 (10%) patients, respectively. MIE was introduced in our clinic in 2014 and has been predominantly performed since 2015. Since then, OE was rarely performed from the beginning of the operation, but rather as a switch from MIE in case of severe adhesions, or if one-lung ventilation was not feasible (*e.g.*, because of pre-existing lung diseases). Patient baseline characteristics differed significantly in median age at resection (*p*<0.0001) and UICC stage (*p*=0.024). For the homogeneous comparison of laparoscopic MIE with OE we excluded patients undergoing HE (n=39) and RAMIE (n=29). Before matching, groups differed significantly in terms of median age at resection (*p*<0.0001), age >65 years (*p*=0.017), tumor location (esophagus/GEJ, *p*=0.011; Siewert classification, *p*=0.039), and preexisting pulmonary diseases (*p*=0.046). Afterwards, 90 patients who underwent MIE were matched with 90 patients who were treated with OE using PSM. After matching, both cohorts were comparable regarding patient characteristics and health status (Table I). No significant differences were found regarding sex (male: 81% *vs*. 82%, *p*=0.847), BMI (26 *vs*. 24.98 kg/m^2, *p*=0.340), comorbidities or ASA physical status (*p*=0.271). The median age at resection was still significantly different between the groups (65 *vs*. 61.5 years, *p*=0.009). The kind of preoperative therapy was equivalent between OE and MIE (*p*=0.147). However, significant differences regarding the administered regimens could be found between the groups (see Table I). Comparison of tumor-related characteristics revealed no significant differences concerning T category (*p*=0.512), N category (*p*=0.188), UICC stage (*p*=0.266), tumor grading (*p*=0.371), invasion of lymph vessels (17% *vs*. 15%, *p*=0.689) or veins (2% *vs*. 4%, *p*=0.673), and the histologic type between the MIE and OE groups (*p*=0.360). Standardized differences were <0.1 for all clinicopathological parameters after PSM with the exception of age at resection (d=0.551).

The median duration of resection was shorter after OE than after MIE (365.5 *vs*. 414 minutes, *p*<0.0001; Table II). MIE facilitated a significantly higher median number of harvested lymph nodes than OE (29 *vs*. 16, *p*<0.0001). Histopathological evaluation revealed surgical resection margins positive for tumor cells in 4% of the cases in each group (*p*=1).

Postoperative morbidity and mortality. Overall postoperative morbidity was lower after MIE in comparison to OE but failed to reach statistical significance (56% *vs*. 68%, *p*=0.092). Major postoperative morbidity was lower after MIE than after OE (31% *vs*. 46%, *p*=0.046). Wound infections (1% *vs*. 11%, *p*=0.005), pulmonary (46% *vs*. 56%, *p*=0.180), and cardiovascular complications (7% *vs*. 22%, *p*=0.003), occurred less often after MIE than after OE. Red blood cell transfusions were required in 3% and 38% of the cases after MIE and OE, respectively (*p*<0.0001). The length of hospital stay was comparable between MIE and OE (15 *vs*. 17.5 days, *p*=0.112). Postoperative 90-day mortality rate was lower after MIE than after OE (2% *vs*. 12%, *p*=0.010; Table II).

Long-term survival and disease-free survival. Median follow-up periods were 70 months (95% CI=61.5-78.5 months) in the OE group, and 10 months (95% CI, 7.2-12.8 months) in the MIE group, respectively. Three-year OS rates were higher in the MIE group than in the OE group (65% *vs*. 52%, *p*=0.019; Figure 1). Three-year DFS rates were comparable between the two groups (49% *vs*. 51%, *p*=0.851; Figure 2).

Discussion

In this study, we compared the postoperative and long-term outcomes of patients with esophageal cancer or adenocarcinoma of the GEJ who underwent MIE with those of patients treated with conventional OE. After MIE, we found significantly lower major morbidity and 90-day mortality rates in comparison to OE. In addition, MIE was associated with a higher median number of resected lymph nodes, a lower need for postoperative transfusions, reduced cardiovascular complications, and a reduced incidence of postoperative wound infections. Three-year OS was superior after MIE than after OE while DFS was equivalent.

Table I. *Clinicopathological characteristics of patients who underwent esophagectomy for esophageal cancer or cancer of the gastroesophageal junction after propensity-score matching (n=180).*

Characteristics	OE (N=90)	MIE (N=90)	*p*-Value
Male gender, n (%)	74 (82)	73 (81)	0.847
Median age at resection, years (range)	61.5 (36-82)	65 (44-83)	0.009
Age >65 years, n (%)	36 (40)	43 (48)	0.293
Median BMI, kg/m^2 (range)	24.98 (15-40)	26 (16-51)	0.340
BMI >30 kg/m^2, n (%)	12 (13)	16 (18)	0.411
Tumor location, n (%)			0.233
Esophagus	51 (57)	43 (48)	
Gastroesophageal junction	39 (43)	47 (52)	
Siewert classification of GEJ tumors, n (%)			0.087
Type I	30 (77)	28 (60)	
Type II	9 (23)	19 (40)	
Comorbidities, n (%)			
Diabetes	15 (17)	10 (11)	0.281
Cardiovascular disease	61 (68)	63 (70)	0.747
Pulmonary disease	23 (26)	17 (19)	0.282
Liver cirrhosis	3 (3)	4 (4)	1
Renal insufficiency	8 (9)	10 (11)	0.619
ASA physical status, n (%)			0.271
I	4 (5)	5 (6)	
II	28 (33)	40 (47)	
III	50 (60)	39 (46)	
IV	2 (2)	1 (1)	
Preoperative therapy, n (%)			0.147
No preoperative therapy	19 (21)	11 (12)	
Chemotherapy alone	33 (37)	44 (49)	
Combined radiochemotherapy	38 (42)	35 (39)	
Regimen if chemotherapy alone*, n (%)			
5-FU + cisplatin/oxaliplatin	2 (2)	1 (1)	1
FLO(T)	11 (12)	33 (37)	<0.0001
FLOT + trastuzumab	1 (1)	3 (3)	0.621
FLOT + atezolizumab	0 (0)	3 (3)	0.246
ECF/DCF	8 (9)	2 (2)	0.051
ECX/EOX	5 (6)	0 (0)	0.059
Paclitaxel/docetaxel + cisplatin/carboplatin	2 (2)	1 (1)	1
Other/Unknown	4 (4)	2 (2)	0.682
Chemotherapy regimen for combined radiochemotherapy*, n (%)			
5-FU + cisplatin	12 (13)	2 (2)	0.005
Carboplatin/cisplatin + paclitaxel/docetaxel	16 (18)	29 (32)	0.038
Docetaxel + cisplatin + cetuximab	10 (11)	0 (0)	0.001
Other/Unknown	5 (6)	4 (4)	1
T category, n (%)			0.512
T0	0 (0)	1 (1)	
T1	11 (13)	6 (7)	
T2	12 (14)	9 (11)	
T3	59 (68)	65 (76)	
T4	5 (5)	4 (5)	
N category, n (%)			0.188
N0	35 (40)	26 (31)	
N1	19 (22)	29 (35)	
N2	23 (26)	23 (27)	
N3	11 (12)	6 (7)	
UICC stage, n (%)			0.266
I	15 (17)	9 (11)	
II	21 (25)	18 (21)	
III	39 (45)	50 (60)	
IV	11 (13)	7 (8)	
Lymphangiosis carcinomatosa, n (%)	12 (15)	15 (17)	0.689

Table I. *Continued*

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Characteristics	OE (N=90)	MIE (N=90)	*p*-Value
Venous invasion, n (%)	3 (4)	2 (2)	0.673
Tumor grading (G), n (%)			0.371
G1	3 (4)	6 (9)	
G2	37 (53)	30 (43)	
G3	30 (43)	34 (49)	
Histologic type, n (%)			0.360
Adenocarcinoma	57 (66)	64 (72)	
Squamous cell carcinoma	30 (34)	25 (28)	

*Cumulated numbers may differ due to changed regimen during therapy. OE, Open esophagectomy; MIE, minimal-invasive esophagectomy; BMI, body-mass index; ASA, American Society of Anesthesiologists; 5-FU, 5-fluorouracil; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; ECF, epirubicin, cisplatin and 5-fluorouracil; DCF, docetaxel, cisplatin, and 5-fluorouracil; ECX, epirubicin, cisplatin and capecitabine; EOX, epirubicin, oxaliplatin and capecitabine; UICC, Union internationale contre le cancer.

Table II. *Operative outcomes of 180 propensity-score matched patients who underwent esophagectomy for esophageal cancer or cancer of the gastroesophageal junction.*

Characteristics	OE (N=90)	MIE (N=90)	*p*-Value
Median duration of resection (range), min	365.5 (156-592)	414 (254-572)	<0.0001
Median number of lymph nodes removed (range)	16 (1-45)	29 (6-60)	<0.0001
Positive resection margins, n (%)	4 (4)	4 (4)	1
Median highest postoperative CRP (range), mg/dl	174.55 (12-320)	196.5 (54-509)	0.080
Median duration of hospital stay (range), days	17.5 (10-136)	15 (9-101)	0.112
Need for transfusions, n (%)	34 (38)	3 (3)	<0.0001
Postoperative morbidity (grade 1-2), n (%)	61 (68)	50 (56)	0.092
Major postoperative morbidity (grade ≥3a), n (%)	41 (46)	28 (31)	0.046
Anastomotic leak, n (%)	19 (21)	15 (17)	0.446
Pulmonary complications, n (%)	50 (56)	41 (46)	0.180
Postoperative pneumonia, n (%)	28 (31)	29 (32)	0.873
Cardiovascular complications, n (%)	20 (22)	6 (7)	0.003
Wound infection, n (%)	10 (11)	1 (1)	0.005
30-day mortality, n (%)	5 (6)	0 (0)	0.059
90-day mortality, n (%)	11 (12)	2 (2)	0.010

OE, Open esophagectomy; MIE, minimal-invasive esophagectomy; CRP, C-reactive protein.

Resection remains the mainstay of curatively intended therapy for patients with esophageal cancer of adenocarcinoma of the GEJ, although only approximately 20-30% of all cases present as localized disease (43). Combined treatment with perioperative systemic therapy has prolonged 5-year OS rates of up to 47% (36). However, the complexity of the surgical procedure and high postoperative morbidity rates of up to 59% hamper the prospects of successful surgery, ultimately resulting in a negative impact on long-term survival (44, 45). The most commonly performed surgical approach in many centers is still OE, but in an effort to reduce postoperative complications and improve patient recovery, MIE was introduced in the 1990s (10). Before the implementation of total MIE, hybrid approaches have been used as a first step to reduce the invasiveness of esophagectomy, usually combining a laparoscopic abdominal phase with open thoracotomy. Reports about improved morbidity, such as reduced pulmonary complications, without compromising long-term outcomes advocated the implantation of MIE (18, 46). Davakis *et al*. have recently showed respiratory complication and anastomotic leak rates after hybrid esophagectomy of 17% and 9%, respectively (46), highlighting the safety and feasibility of this approach. However, controversial reports concerning the superiority of MIE over OE in terms of postoperative morbidity have been published since. One randomized controlled trial (RCT) from the Netherlands suggested improved short-term outcomes after MIE; Biere *et al*. randomly assigned 115 patients to undergo either OE or MIE

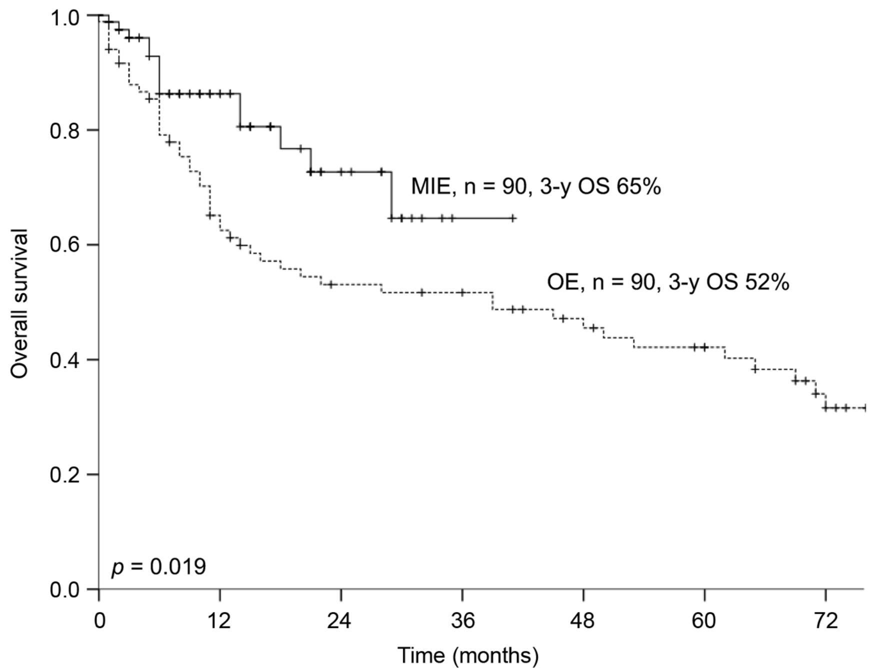

Figure 1. *Overall survival of 180 propensity-score matched patients who underwent esophagectomy for esophageal cancer or cancer of the gastroesophageal junction.*

and found a significantly lower rate of pulmonary infections and a shorter length of hospital stay after MIE (30). Two other RCTs in Japan (47) and the UK (48, 49) are still ongoing. Worth mentioning is another recent RCT that compared 207 patients who randomly underwent hybrid MIE or OE and found significantly less major postoperative complications after hybrid MIE than after OE (18). Meta-analyses confirmed these favorable short-term outcomes after MIE (50, 51). In contrast, several studies using PSM reported equivalent or partially worse outcomes after MIE than after OE (35, 52, 53). Similarly, retrospective studies with large patient cohorts described sobering postoperative results following minimal-invasive resection. In 2014, Takeuchi *et al.* provided data of over 5,000 patients originating from the Japanese nationwide database. They found a significantly higher rate of postoperative morbidity after MIE than after OE (54). In a large cohort from the United Kingdom analyzed by Mamidanna *et al.*, postoperative morbidity was equivalent between MIE and OE, however, MIE necessitated an increased re-intervention rate (25). In addition, some authors reported increased anastomotic leak rates after MIE (18, 30). Ninety-day mortality rate following MIE in our study was 2% and was comparable to the mortality rate of this technique reported in previous studies (26, 30).

In our study, MIE was associated with comparable overall postoperative morbidity (56% *vs.* 68%, p=0.092) and improved major postoperative morbidity (31% *vs.* 46%, p=0.046) after MIE in comparison to OE. Pulmonary complications such as pneumonia and respiratory insufficiency remain the most common type of adverse event after esophagectomy. Respiratory events represent also the main cause of postoperative mortality (6, 55, 56) and significantly influence long-term survival after surgery (57). In our study, pulmonary complications (46% *vs.* 56%, p=0.180) and the incidence of postoperative pneumonia (32% *vs.* 31%, p=0.873) were comparable between MIE and OE. Of note, both cohorts were equivalent regarding patient- and tumor-related characteristics after PSM, and especially the prevalence of comorbidities including pulmonary diseases did not differ between the two groups. MIE also resulted in less wound infections than OE (1% *vs.* 11%, p=0.010) due to the prevention of large incisions for thoracotomy and laparotomy.

Unlike previously reported in other experiences (54), the rate of anastomotic leak after surgery was equivalent between MIE and OE (17% *vs.* 21%, p=0.446). Of note, this rate is higher than expected in this propensity score matched cohort. The explanation for the rather high leak rate in the MIE cohort may be related to the anastomotic technique itself as well as the rather early MIC experience. The overall leak rate in our entire OE cohort (n=126) was 14%, which is comparable with the leak rate of 11.4% reported as an international benchmark in a large multicenter analysis of 2,704 OE patients (45). Therefore, it is interesting to see the higher leak rate in the 90 propensity matched OE patients. Interestingly, the overall leak rate in 118

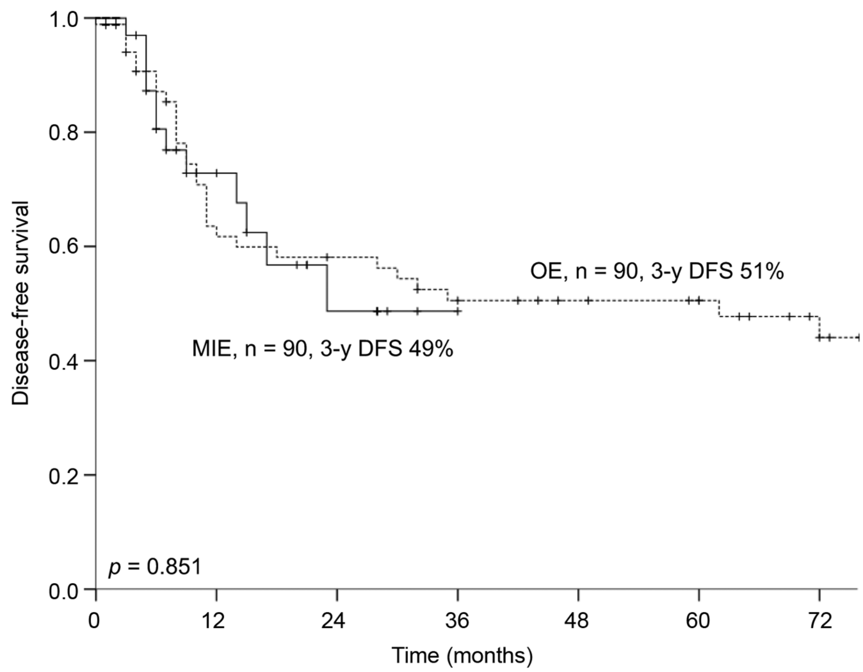

Figure 2. *Disease-free survival of 180 propensity-score matched patients who underwent esophagectomy for esophageal cancer or cancer of the gastroesophageal junction.*

minimal-invasive or hybrid cases in our series with only intrathoracic anastomosis was 11.9% (14/118), while cervical anastomoses are still burdened with leak rates of up to 25% in a recent multicenter analysis of high-volume centers in Europe (58). Furthermore, the initial 55 intrathoracic anastomoses in our cohort were performed by 25 mm circular end-to-side double stapling, before we switched to a 29 mm purse-string technique for end-to-side anastomosis. The end-to-side double stapling technique was reported to be burdened by leak rates of up to 23% in the analysis by Schröder *et al*. (58). Also, the 2019 published Dutch RAMIE trial comparing open and robotic resection with hand-sewn cervical anastomoses reported a 24% leak rate for the robotic and a 20% leak rate for the open cohort (19). In conclusion, the gastroesophageal anastomosis remains a significant hurdle in the advancement of the surgical technique in esophageal cancer surgery.

Postoperative morbidity may diminish long-term survival (59, 60). Accordingly, we found improved three-year OS rates after MIE in comparison to OE (65% *vs*. 52%, p=0.019). The only two RCTs comparing MIE and OE showed comparable OS and DFS rates (18, 20). The first meta-analysis, that was published in 2012 and summarized four previous studies, also stated no differences in 5-year OS after MIE and OE (27). A recent meta-analysis by Gottlieb-Vedi *et al*. analyzed the long-term survival of 14,592 patients in 55 studies who underwent MIE or OE for esophageal cancer (61). Patients receiving either technique were evenly distributed with 50% of patients in each group. The authors found a significantly lower 5-year all-cause and disease-specific OS after MIE than after OE. However, a common problem of meta-analyses concerning the outcomes following MIE and OE was that different surgical procedures were often summarized within the term of MIE. This inhomogeneity of MIE techniques may have significantly influenced the results. Therefore, a clear definition of the surgical procedures performed in our practice is crucial (62). Furthermore, median follow-up in our study was 13 months with a notable difference between the groups, which was mainly influenced by the fact that MIE was newly introduced in our clinic and has ben predominantly performed since 2015. Survival data was therefore limited and further restricted by patients who were lost to follow-up especially in the MIE group. Nevertheless, conclusive three-year survival rates could be reported.

A long-known factor proven to be essential for achieving improved long-term survival is a thorough and extensive lymph node dissection (63, 64). During MIE, a significantly higher median number of lymph nodes could be resected in comparison to OE (29 *vs*. 16, p<0.0001). This finding may contribute to prolonged survival rates for patients after MIE. The difference between OE and MIE may be attributed to improved histopathological evaluation and surgical technique after the German guidelines on the diagnostic and therapy of esophageal cancer were published in 2015 (65) and updated in 2018 (66). Our study period began a few years prior in 2010 when OE was still the standard surgical procedure. In contrast, MIE was predominantly performed since 2015 that may have contributed to different lymph node harvest numbers.

Another factor associated with OS is the administration of perioperative transfusions (67). A recent meta-analysis found a significantly reduced OS in patients who received allogenic blood transfusions compared to those who did not receive transfusions (68). In addition, perioperative morbidity is improved when restricting transfusions (69). In our cohort, MIE have made significantly less perioperative transfusions necessary compared to OE (3% *vs*. 38%, $p<0.0001$), and this may have improved short- and long-term outcomes. By performing MIE, intraoperative blood loss may be reduced due to laparoscopic magnification of the operative field in case of bleeding, improved haemostatic devices, and less traumatic impact on the tissue. In contrast, this study comprised a rather long study period starting in 2010 when transfusions were still ordered more liberally. Over the course of the study period, our institution's policy on the administration of blood products changed to a more restrictive position which may have contributed to the lower number after MIE.

All in all, current evidence regarding the advantages of MIE over OE involves improved postoperative outcomes, most notably with less pulmonary complications (30) and reduced need for intraoperative blood transfusions (59), and at least equivalent oncological outcomes (20). Possible disadvantages include a steep learning curve that is associated with the implementation of MIE possibly leading to learning-associated morbidity (70, 71). In addition, the cost-effectiveness of MIE remains unclear. In theory, reduced morbidity rates and shorter ICU and hospital stay after MIE may compensate for higher expenses that are required for new surgical devices and longer operative times. However, recent literature reported conflicting results and most studies failed to show cost-effectiveness of MIE compared to OE (72-75).

Best scientific evidence may be generated by RCTs. However, establishing RCTs in surgical research is often faced with methodical challenges (31). Therefore, PSM analysis could be alternatively performed to evaluate MIE and OE cohorts aiming to create a comparison with minimal differences regarding patient- and tumor-related characteristics and thereby reduce confounding bias (76-78). With general guidelines regarding the use of PSM in surgical studies still lacking, we have chosen to include all parameters related to the patients' general status and health, as well as tumor-related parameters, and the administration of preoperative chemoradiation therapy into the PSM procedure.

Nevertheless, this study has several limitations. Firstly, data was collected retrospectively and non-randomized in a rather small cohort of patients. Therefore, general conclusions drawn from our results should be carefully interpreted. By performing PSM, we aimed to reduce selection bias in order to create a meaningful statistical comparison. However, PSM failed to create groups with comparable median age although patients aged >65 years were equally distributed between the groups. Therefore, age needs to be acknowledged as a possible confounder. Previous studies showed that the risk for postoperative complications is increased for elderly patients after esophagectomy (79, 80). In our study, median age at resection was lower in the matched OE group in comparison to the MIE group (61.5 *vs*. 65 years, $p=0.009$). Interestingly, MIE was able to achieve better postoperative outcomes despite the higher median patient age. Furthermore, preoperatively applied radiochemotherapy was equally distributed between the groups, however, significant differences regarding specific regimens were found. These differences may be due to the rather long study period from 2010 to 2019 resulting in a wide variety of different regimens being included in our study. However, PSM was conducted on basis of applied radio-/chemotherapy in order to consider its effects as a confounder while allowing for the composition of equally sized cohorts.

Still, unrecorded and unknown covariates may have influenced our results. In addition, the implementation of MIE is associated with a considerable learning curve, which may have had an influence on the outcomes (70, 71). Therefore, our results can be evaluated as an early experience. In the near future, we expect outcome parameters to be further improved. Nevertheless, all procedures were performed by experienced upper GI surgeons and resulted in superior outcomes compared to the conventional OE.

Conclusion

MIE for esophageal cancer or adenocarcinoma of the GEJ is associated with lower major postoperative morbidity and non-inferior OS rates compared to conventional OE. Therefore, we consider MIE as the preferred oncologic procedure in our Center.

Conflicts of Interest

The Authors declare the following conflicts of interest unrelated to this work: M.S. – Merck, Bayer, Erbe, Ethicon, Takeda, Olympus, Medtronic, Intuitive; J.P. – Merck, Medtronic, Intuitive, Verb Surgical.

Authors' Contributions

Conceptualization, M.B. (Matthias Biebl), S.K., and A.A.; methodology: M.B. (Matthias Biebl), S.K., and A.A.; formal analysis: S.K. and A.A.; investigation: S.K., A.A., and T.H.; data curation: S.K., A.A., and T.H.; writing: S.K. and A.A.; visualization: S.K.; supervision: S.C., C.D., P.C.T.-P., D.K., M.B. (Marcus Bahra), M.S., J.P., M.B. (Matthias Biebl); project administration: J.P. and M.B. (Matthias Biebl). All Authors have read and agreed to the published version of the manuscript.

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