Esophageal resection in Austria—preparing a national registry

Matthias Paireder · Reza Asari · Wolfgang Radlspöck · Anna Fabbri · Andreas Tschoner · Reinhold Függer · Johannes Zacherl · Sebastian F. Schoppmann

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Summary

Background Esophageal resection is a technically challenging procedure. Despite improvements in perioperative management and outcome, it is still associated with considerably high morbidity and mortality rates even if performed in high-volume centers. This study aimed to shed light on the results of routine patient care in three representative referral centers concerning caseload and surgical and oncological outcomes.

Methods This study is a retrospective, multicenter, national-wide analysis of a newly established database including perioperative and long-term outcome data from three referral centers in Austria.

Results In a 6-year study period (2013–2018), 411 patients were eligible for analysis. The indication for esophageal resection was esophageal adenocarcinoma in 299 (72.7%) patients and esophageal squamous cell carcinoma in 90 (21.9%) patients. The abdominothoracic approach (70.1%) was the most common operation, followed by transhiatal extended gastrectomy (14.8%) and a thoracic-abdominal-cervical approach (8.5%). Most patients (77.9%) underwent neoadjuvant therapy (chemotherapy 45.3%, radiochemotherapy in 32.6%). A minimally invasive approach was chosen in 25.3%. Major complications and mortality were seen in 21.7% and 2.9%, respectively. The 1-year survival rate was 84%, 3-year survival 60%, and 5-year survival was 52%. The pooled overall median survival was 110 months (95% CI 33.97–186.03).

Conclusion This first publication of the Austrian Society of Esophageal Surgery shows that the outcome of esophageal surgery for cancer in Austria compares well with that of renowned international centers. However, a more comprehensive approach including as many national centers as possible will improve outcome research, offer quality management, and improve patient safety. The study group invites all Austrian institutions performing esophagectomy to participate in the initiative.

Keywords Outcome · Morbidity · Esophageal carcinoma · Clinical database · Esophagectomy

Main novel aspects

1. This is the most extensive study so far demonstrating multicenter results of esophageal surgery in Austria.
2. The authors show that the current treatment and surgical approach, morbidity, and oncological results are comparable to international registries.

M. Paireder · R. Asari · S. F. Schoppmann (✉)
 Department of General Surgery, Upper-GI-Service
 Comprehensive Cancer Center, Gastroesophageal
 Tumor Unit, Medical University of Vienna,
 Spitalgasse 23, 1090 Vienna, Austria
sebastian.schoppmann@meduniwien.ac.at

W. Radlspöck · J. Zacherl (✉)
 Department of Surgery, St. Josef Hospital of Vienna,
 Auhofstraße 189, 1130 Vienna, Austria
johannes.zacherl@sjk-wien.at

A. Fabbri · A. Tschoner · R. Függer (✉)
 Department of General, Visceral, Thoracic, Vascular and
 Transplantation Surgery, Ordensklinikum Linz, Johannes
 Kepler University Linz, Sailerstaette 4, 4010 Linz, Austria
reinhold.fuegger@ordensklinikum.at

R. Függer
 Johannes Kepler University Linz,
 Altenbergerstraße 69, 4040 Linz, Austria

J. Zacherl
 Fakultät für Medizin, Sigmund Freud Privatuniversität Wien,
 Sigmund Freud Platz 3, 1020 Wien, Austria

3. This work should be a basis for creating a more significant, more comprehensive registry for esophageal surgery in Austria.

Introduction

Surgery is still the mainstay for curative treatment of esophageal cancers [1]. Notably, for locally advanced stages, multimodal therapy has gained significant importance [2, 3]. Although perioperative therapy does not impair morbidity after surgery, esophageal resection is still associated with high morbidity and mortality rates [4–6].

To improve morbidity and oncological outcome, esophageal surgery was suggested to be preferably performed in high-volume centers [7]. Implementation of such caseload requirements reduced the number of hospitals performing esophageal resections, expecting to improve outcomes [8]. In 2013 a caseload threshold of at least five esophagectomies per year was introduced in Austria, and elevated to a minimum of 10 procedures 1 year later on. Currently, there are ten Austrian centers performing esophagectomies regularly.

A minimally invasive approach in esophageal surgery was introduced to reduce the incisional trauma, improve the postoperative pulmonary condition, and allow faster recovery and possibly better quality of life at an equal oncological outcome [9–11]. Multiple trials demonstrated that minimally invasive esophagectomy (MIE) showed comparable oncological results with reduced postoperative morbidity and improved functional recovery [10, 12, 13]. Despite the beneficial aspects of MIE, many cases are required to overcome the learning curve [14].

This study aimed to assess the treatment numbers and the surgical and oncological outcome in three high-volume referral centers representative for esophageal cancer surgery in Austria. Moreover, implementation of MIE and centralization of surgery is assessed and compared with current evidence.

Materials and methods

Registry

This study is a retrospective, multicenter, national analysis of a newly established database including patient data of three high-volume referral centers in Austria. The data were prospectively collected in each center and entered into the registry after pseudonymization. All consecutive patients who received esophageal surgery in the 6 years between 2013 to 2018 were included. One center started in 2014 and did not include transhiatal extended gastrectomies. The indication for surgery was either an esophageal malignancy (adenocarcinoma [AC], esophageal squamous cell carcinoma [ESCC], gastrointestinal stromal tumor [GIST], sarcoma, neuroendocrine carcinoma)

or a benign indication such as leiomyoma or complex GERD. The tumor location of adenocarcinomas was classified following the Siewert classification of adenocarcinoma of the esophagogastric junction (AEG) [15]. All other tumors were classified into suprabifurcal, infrabifurcal, and cervical locations.

Surgery

An esophageal surgery was defined as either abdominothoracic resection (Ivor–Lewis procedure), thoracic-abdominal-cervical approach (McKeown procedure), transhiatal esophagectomy (Orringer procedure), jejunal interposition operation (Merendino procedure), transhiatal extended gastrectomy for AEG II tumors, or anastomotic resection with esophagojejunostomy. Hybrid minimally invasive esophagectomy (MIE) was defined as a laparoscopic formation of the gastric tube combined with an open thoracic approach. Total MIE was defined as laparoscopic gastric tube formation and thoracoscopy for the thoracic phase. Morbidity was classified according to the Clavien–Dindo (C/D) classification [16]. According to recent publications a Clavien–Dindo grade IIIb or higher was classified as a major complication [11]. For more details, see Table 2.

Patients were followed up on a 3-monthly basis for the first 2 years and then every 6 months until year 5 after surgery, followed by yearly visits. In order to optimize data accuracy and reduce the number of patients lost to follow-up, patients were contacted to evaluate the current status if the information was missing. Overall survival (OS) and recurrence-free interval (RFI) were defined as the period from the operation until death or recurrence of disease, respectively. For analysis of OS and RFI, only malignant indications were used.

The study was approved by the ethics committee (EK 1310/2018) of the Medical University of Vienna. Individual informed consent was not acquired due to the study design and national regulations.

Statistics

Age is described as mean and standard deviation (SD). Other continuous variables are described as medians and quartiles due to non-normal distributions. Interquartile range (IQR) was stated when applicable. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Categorical variables are described as counts and percentages. Overall survival and the recurrence-free interval were estimated using the Kaplan–Meier method. For comparison, the log-rank test was used. A p -value < 0.05 is considered statistically significant. A 95% confidence interval (95% CI) is reported if computable. SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Macintosh, version 27.0. Armonk, NY, USA) was used for statistical analysis.

Table 1 Demographic and preoperative details

Variable	All (n= 411)
Age, years ^a	63.1 (11.4)
Gender	
Male	338 (82.2)
Female	73 (17.8)
Body mass index, kg/m ^{2b}	25.3 (22.7–28.7)
Stent before operation	31 (7.5)
Dysphagia before operation	206 (50.1)
Weight loss before operation ^c	125 (30.4)

Values in parentheses are percentages unless indicated otherwise
^avalues are mean (standard deviation)
^bvalues are median (interquartile range)
^cany involuntary weight loss reported by the patient

Table 2 Perioperative details and morbidity

Variable	All (n= 411)
Operation type	
Ivor–Lewis	288 (70.1)
McKeown	35 (8.5)
Orringer	17 (4.1)
Transhiatal extended gastrectomy	61 (14.8)
Merendino	4 (1)
Other (e.g., anastomotic resection)	6 (1.5)
Surgical approach	
Open	304 (74.0)
Hybrid MIE	100 (24.3)
Total MIE	4 (1)
Laparoscopic assisted other	3 (0.7)
Number of examined lymph nodes ^a	25 (17–34)
Clavien–Dindo classification	
0	224 (54.5)
1	21 (5.1)
2	44 (10.7)
3a	33 (8.0)
3b	64 (15.6)
4a	9 (2.2)
4b	4 (1)
5	12 (2.9)
Anastomotic leakage	58 (14.1)
Pulmonary complication	56 (13.6)
ICU stay (days) ^a	6 (4–8)
Hospital stay (days) ^a	17 (11–21)

Values in parentheses are percentages unless indicated otherwise
MIE minimally invasive esophagectomy, ICU intensive care unit
^avalues are median (interquartile range)

Results

Patients

Between 2013 and 2018, 411 patients were eligible for this analysis. The mean age was 63.1 (SD 11.4) years, and 338 (82.2%) patients were male. The median body mass index at the time of surgery was 25.3 (IQR 22.7–28.7) kg/m². The most frequent in-

dication for esophageal resection was an esophageal malignancy: adenocarcinoma in 299 (72.7%) patients and esophageal squamous cell carcinoma in 90 (21.9%) patients. Beyond that, other indications ($n=22$, 5.2%) were neuroendocrine carcinoma, high-grade dysplasia, gastrointestinal stromal tumor, and complex gastroesophageal reflux disease (GERD). The majority of patients (77.9%) received multimodal therapy before surgery. Chemotherapy was indicated in 186 (45.3%) patients, and 134 (32.6%) patients received radiochemotherapy before surgery. For more details, see Table 1.

Operation

The abdominothoracic esophageal resection (Ivor–Lewis procedure: $n=288$, 70.1%) was the most common operation, followed by transhiatal extended gastrectomy ($n=61$, 14.8%) and the thoracic-abdominal-cervical approach (McKeown procedure: $n=35$, 8.5%). Other operations were transhiatal esophagectomy (Orringer procedure), jejunal interposition operation (Merendino procedure), and other (local) resections for non-malignancies in 17 (4.1%), 4 (1%), and 6 (1.5%) patients, respectively. In total, 304 (74%) of the operations were performed in an open technique, whereas 100 (24.3%) and 4 (1%) procedures were performed in a hybrid or total minimally invasive approach, respectively.

A histologically confirmed clear resection margin was achieved in 374 (91%) patients. The median number of lymph nodes removed was 25 (IQR 17–34).

Major complications (Clavien–Dindo > IIIa) were documented in 89 (21.7%) patients. Fifty-eight patients (14.1%) developed anastomotic leakage (AL), 56 (13.6%) patients presented pulmonary complications. The median hospital stay was 17 days (IQR 11–21), and the median stay at the intensive care unit was 6 days (IQR 4–8). Overall hospital mortality was 2.9%. For more perioperative details, see Table 2.

Survival

At a median follow-up of 24 (IQR 11–49) months, 1-year survival was 84%, 3-year survival 60%, and 5-year survival was 52%. The pooled median overall survival was 110 (95% CI 33.97–186.03) months, and the median recurrence-free interval was not reached. There was no significant difference in overall survival and recurrence-free interval regarding histology, surgical approach, or extent of lymph node yield (Figs. 1, 2, 3, 4, 5 and 6).

Regarding non-TNM categories, there were significant differences in long-term survival: median overall survival and recurrence-free interval decreased significantly if a vascular, lymphatic, or perineural invasion was present (Fig. 7). For more tumor-related details, see Table 3.

Fig. 1 Kaplan–Meier analysis of overall survival according to tumor histology. A p -value < 0.05 is considered statistically significant. *n.s.* non significant

Fig. 2 Kaplan–Meier analysis of recurrence-free interval according to tumor histology. A p -value < 0.05 is considered statistically significant. *n.s.* non significant

Discussion

First and foremost, this study is the largest to demonstrate multicenter results of esophageal surgery in Austria. We show that the current treatment and surgical approach, morbidity, and oncological results are tantamount to international registries.

Ivor–Lewis esophagectomy ($n = 70.1\%$) was the most commonly performed operation, in line with the recent development towards the abdominal-thoracic approach. There is still an ongoing debate about the best surgical approach to resect and reconstruct the esophagus [17]. A randomized trial showed favorable survival results after a transthoracic approach in patients with lymph node involvement compared to the Orringer procedure [18]. After growing evidence that an intrathoracic anastomotic leakage was no longer associated with increased mortality, the transtho-

racic Ivor–Lewis approach was increasingly suggested for carcinoma localized in the distal esophagus [19]. However, transhiatal esophagectomy seemed to lead to less pulmonary morbidity and this without survival disadvantages [20]. New evidence, again, favors the transthoracic approach in a large retrospective cohort [21].

Addressing the highly relevant benchmarks of morbidity and mortality, the major complication rate (C/D $>$ IIIa) in this study was 21.7%. This rate lies within published rates, which range from around 10% to up 34.9% [11, 22]. In general, the definition of morbidity (major/minor) and the use of the classification is very inhomogeneous throughout the literature [23]. This also applies to reporting and classification of anastomotic leakage (AL). The participating centers did not use the Esophageal Complications Consensus Group definition for AL in this study [24]. However,

Fig. 3 Kaplan–Meier analysis of overall survival according to the surgical approach. A p -value < 0.05 is considered statistically significant. *n.s.* non significant, *OE* open esophagectomy, *MIE* minimally invasive esophagectomy

Fig. 4 Kaplan–Meier analysis of recurrence-free interval according to the surgical approach. A p -value < 0.05 is considered statistically significant. *n.s.* non significant, *OE* open esophagectomy, *MIE* minimally invasive esophagectomy

the reported AL rate of 14.1% lies within the published rates from 5–25% for cervical anastomosis and 5–16% for thoracic anastomosis [23]. Still, the low rates published by Luketich et al. of 8.6% should be strived for [25]. Historically, esophageal resection was associated with a high mortality rate. Improvement of surgical technique as well as perioperative management could reduce mortality. However, the low rate of 2.9% is again comparable with other national data [26].

Centralization of esophageal surgery improves outcome [26, 27]. In many European countries like Sweden, the Netherlands, or Switzerland, centralization has already taken place [8, 26]. There is still an

ongoing debate about caseload requirements in Austria, which led to different regional regulations. Nevertheless, current level 2a evidence showing the impact of centralization of cancer surgery on postoperative mortality supports this development towards caseload requirements [28].

In this study, around 25% of the esophagectomies were done with a minimally invasive approach. As there is growing evidence about the clear benefit of MIE, it is to expect that this number will rise. Still, it is crucial to implement new surgical techniques in a well-structured manner, without jeopardizing patient safety. Experts advise having adequate support, proctoring, and the appropriate infrastructure to over-

Fig. 5 Kaplan–Meier analysis of overall survival regarding lymph node yield > median number of 25. A p -value < 0.05 is considered statistically significant. *n.s.* non significant, *LN* lymph node

Fig. 6 Kaplan–Meier analysis of recurrence-free interval regarding lymph node yield > median number of 25. A p -value < 0.05 is considered statistically significant. *n.s.* non significant, *LN* lymph node

come a particular learning curve [14]. A recent multicenter study identified a substantial learning curve of 119 cases regarding anastomotic leakage in MIE [29].

The strength of this study is the multicenter approach and high treatment numbers. Furthermore, this work includes registry data exceeding the classical TNM categories. Such expanded oncological information like vascular, lymphatic, and perineural invasion and number of lymph nodes involved was also suggested for registries [30]. This will potentially refine prognostication and may direct future adjuvant therapy [30].

There are several limitations to address. First of all, this work is of a retrospective nature. The data extraction was performed locally in the particular centers and, therefore, challenging to standardize. Moreover, there are different approaches to classifying “soft” categories such as morbidity. To minimize this limitation, the centers used the Clavien–Dindo classification to categorize morbidity. A possible comprehensive registry should prospectively establish consensual reporting standards like those offered by the Esophageal Complications Consensus Group to overcome these limitations.

Fig. 7 Kaplan-Meier survival analysis for non-TNM categories: **a** overall survival (OS) for vascular invasion; **b** recurrence-free interval (RFI) for vascular invasion; **c** OS for lymphatic invasion; **d** RFI for lymphatic invasion; **e** RFI for perineural invasion; **f** OS for perineural invasion. A p -value < 0.05 is considered statistically significant

phatic invasion; **d** RFI for lymphatic invasion; **e** RFI for perineural invasion; **f** OS for perineural invasion. A p -value < 0.05 is considered statistically significant

Table 3 Tumor-related details

Variable	All (n= 411)
<i>Tumor location</i>	
ESCC above level of tracheal bifurcation	40 (9.7)
ESCC below level of tracheal bifurcation	54 (13.1)
Siewert type I	197 (47.9)
Siewert type II	73 (17.8)
Siewert type III	26 (6.3)
Non-malignancies or GIST	21 (5.1)
<i>Tumor histology, no. (%)</i>	
Adenocarcinoma	299 (72.7)
Squamous cell carcinoma	90 (21.9)
Neuroendocrine carcinoma	1 (0.2)
High-grade dysplasia	10 (2.4)
Gastrointestinal reflux disease	9 (2.1)
Gastrointestinal stromal tumor	2 (0.5)
<i>Neoadjuvant treatment^a</i>	
Chemotherapy	186 (47.7)
Radiochemotherapy	134 (34.4)
<i>Tumor grading^a</i>	
Well differentiated (G1)	12 (3.1)
Moderately differentiated (G2)	126 (32.3)
Poorly differentiated (G3)	199 (51.0)
Undifferentiated (G4)	1 (0.3)
Gx	7 (1.8)
<i>Pathologic tumor stage^a</i>	
T0	68 (17.4)
Tis (HGD)	2 (0.5)
T1a	26 (6.7)
T1b	55 (14.1)
T2	65 (16.7)
T3	161 (41.3)
T4a	11 (2.8)
T4b	2 (0.5)
<i>Pathologic nodal stage^a</i>	
N0	222 (56.9)
N1	70 (17.9)
N2	58 (14.9)
N3	36 (9.2)
Missing information	4 (1.0)
<i>Pathological distant site^a</i>	
M0	378 (96.7)
M1	12 (3.1)
<i>Surgical margin status^a</i>	
Clear	364 (93.3)
Microscopically involved (R1)	24 (6.2)
Macroscopically involved (R2)	2 (0.5)
<i>Lymphatic invasion^a</i>	
L0	249 (63.8)
L1	135 (34.6)
Missing information	6 (1.5)
<i>Vascular invasion^a</i>	
V0	359 (92.1)
V1	25 (6.4)

Table 3 (Continued)

Variable	All (n= 411)
Missing information	6 (1.5)
<i>Perineural invasion^a</i>	
Pn0	299 (76.7)
Pn1	65 (16.7)
Missing information	26 (6.7)
Values in parentheses are percentages. ESCC esophageal squamous cell carcinoma, HGD high grade dysplasia, GIST gastrointestinal stromal tumor ^a non-malignancies and GIST excluded	

Conclusion

This first publication of this multicenter study group shows the current status of esophageal surgery in three high-volume centers in Austria. The outcome of esophageal surgery in this study is comparable with international benchmarks. However, a more comprehensive approach including as many national centers as possible will improve outcome research, offer quality management, and improve patient safety. Therefore, the study group aims to include all possible centers for esophageal surgery.

Author Contribution All authors contributed to the study's conception and design. Material preparation and data collection were performed by Matthias Paireder, Anna Fabbri, Andreas Tschoner, Reza Asari, Johannes Zacherl, and Wolfgang Radlspöck. Data analysis and interpretation were done by Matthias Paireder, Johannes Zacherl, Reinhold Függer, and Sebastian F. Schoppmann. Matthias Paireder wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest M. Paireder, R. Asari, W. Radlspöck, A. Fabbri, A. Tschoner, R. Függer, J. Zacherl, and S.F. Schoppmann declare that they have no competing interests.

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