As time goes by–developments in surgery for esophageal cancer in the new millennium

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Summary

Background In the last two decades, both treatment options and epidemiological features of cancer have changed. We studied the influence of related parameters on the outcome of patients undergoing resection for esophageal carcinoma.

Methods We analyzed 499 consecutive patients who underwent esophagectomy for carcinoma since January 2000, comparing 2000–2010 with 2011–2021 and examining changes over time.

Results The percentage of men (87.9 vs. 86.9%; \( p = 0.74 \)) in the two groups was unchanged, whereas mean age increased significantly from 60.8 to 65.2 years \( (p = 0.000) \). There was a trend towards an increase of adenocarcinoma \( (\gamma = 0.120, \text{ASE} = 0.055) \). Despite significantly increasing use of induction chemoradiotherapy \( (p = 0.000) \) from 7.14% in 2000 to 68.9% in 2021 the distribution of \( pT \), \( pN \) stage, grading and the rate of positive lateral resection margins remained unchanged. When comparing the two periods, the overall 30-day mortality was 4.4 vs. 4.2% \( (\gamma = 0.56) \), recurrence-free survival was 36.9 vs. 38% at 60 months and 33.9 vs. 36.4% at 120 months \( (p = 0.93) \). Tumor-associated survival was 41.1 vs. 45% at 60 months and 35.5 vs. 38.7% at 120 months \( (p = 0.78) \). None of the survival rates differed significantly. A multivariable analysis of year of surgery, age, sex, histological subtype, grading, \( pT \), \( pN \), lateral resection margin, and induction therapy showed that only higher \( pT \) \( (p = 0.01) \), positive \( pN \) \( (p = 0.000) \), positive lateral margin \( (p = 0.003) \), squamous cell carcinoma \( (p = 0.04) \) and higher grading \( (p = 0.026) \) had a statistically significant, independent, negative influence on prognosis.

Conclusion Optimized noninvasive and invasive therapeutic modalities have produced only marginal improvement in the prognosis of esophageal cancer within the last two decades.

Keywords Esophageal cancer · Epidemiology · Treatment · Resection · Prognosis

Main novel aspects

- Increasing use of induction treatment in esophageal cancer had no impact on the distribution of \( pT \), \( pN \) stages and lateral resection margin when comparing two time periods since the year 2000.
- The only factors independently influencing prognosis were \( pT \), \( pN \), grading, histological subtype and lateral resection margin, while age, sex, surgical approach and induction therapy had no effect.

Introduction

Since the turn of the millennium, the epidemiological features of many types of cancer have changed. Whereas an increasing number of elderly patients develop cancer owing to the rise of life expectancy, changes in lifestyle and eating habits bring about tumor development in younger individuals \([1, 2]\). In addition, new substances and comedication have improved the tolerance of chemotherapy, and refinement in planning and application of radiotherapy have reduced side effects \([3, 4]\). Constant developments in surgical and anesthesiologic techniques have
enabled compromised or elderly patients to undergo major surgery at an acceptable risk [5]. These factors add up to more patients being eligible for multimodal or surgical treatment of malignant disease.

Considering esophageal cancer, various treatment options have evolved. Endoscopic mucosal resection and definitive chemoradiotherapy on the one hand and minimally invasive resection on the other have optimized therapy for a collective of patients who often present in a compromised general condition with marked comorbidity [6]. The improvements notwithstanding, surgery for esophageal carcinoma, especially in a multimodal setting, is stressful for the patients although the long-term results are superior to nonsurgical options especially in advanced cases [7, 8].

In a retrospective study, we evaluated the development of epidemiological, tumor- and treatment-related factors and outcome parameters in patients resected for esophageal carcinoma in our own collective.

Materials and methods

Patients We analyzed 499 consecutive patients who underwent esophagectomy for esophageal carcinoma between 01 January 2000 and 13 December 2021.

Staging Staging involved esophago- and bronchoscopy, endoscopic ultrasound (EUS), positron-emission tomography-computed tomography (PET-CT) scan and in case of adenocarcinoma in the distal third diagnostic laparoscopy.

Treatment All patients had treatment planning based upon the decision of an interdisciplinary tumor board. Depending on stage (>cT2; and/or >N0) and the histological features, induction therapy according to the “CROSS”- or “FLOT”- protocol was scheduled once neoadjuvant treatment had been internationally established.

We performed esophagectomy and regional lymph node dissection as well as reconstruction by gastric pull-up and cervical esophagogastrostomy according to McKeown [9]. Depending on local tumor extent and lymph node involvement, thoracolaparotomy, transhiatal access and minimally invasive hybrid technique (h-MIC; minimally invasive esophagectomy via right thoracotomy in prone position followed by minilaparotomy) were used as access for resection, whereas esophagogastrostomy was done via cervical incision along the anterior border of the left sternocleidomastoid muscle. The repositioning of the patients as required for thoracolaparotomy and h-MIC was included when reporting the operating time.

Free margins at the site of anastomosis were verified by intraoperative frozen section histology.

All patients had a transperitoneal jejunal feeding tube enabling early enteral feeding starting six hours after the end of the operation.

Statistics Statistical analysis was performed using STATA statistical program package version 15 (Stata Corporation, College Station, TX, USA). Besides descriptive statistics, we used the χ² test, Goodman and Kruskal’s gamma, and t-test where appropriate. Survival analysis was performed using life tables, log rank test, and Cox’ proportional hazard model in a univariable and multivariable approach. P<0.05 was considered to indicate statistical significance.

Ethics The study was approved by the Ethics Committee of the Medical University of Graz (Nr. 30-367 ex 17/18).

Results

Overall results

There were 436 men (87.3%) and 63 women (12.6%), mean age was 63.2 years (range 22–88), and mean body mass index (BMI) was 25.2 (range 13.6–40.9).

Biopsy specimens showed adenocarcinoma in 311 and squamous cell carcinoma in 184 cases. 6.4% lesions were located in the upper, 23.3% in the middle and 70.2% in the lower third of the esophagus. There was a statistically significant male prevalence for adenocarcinoma (p=0.008). Adenocarcinoma was also associated with a significantly higher mean BMI than squamous cell carcinoma (26 vs. 23.9; p=0.000).

A total 173 patients (34.7%) had induction chemo-/radiotherapy, while 326 had upfront resection.

The transhiatal approach was used in 278 (55.8%) cases, right thoracotomy and midline laparotomy in 171 (34.3%) and hybrid minimally invasive resection (h-MIC) in 50 (9.8%) patients.

Mean overall duration of operation was 187.6 min (range 83–426; median 171 min). For the transhiatal approach it was 156.2 min (range 81–317; median 136 min), for thoracolaparotomy 234.7 min (range 89–464; median 217 min) and for h-MIC 192 min (range 92–369; median 165 min).

The surgical specimens revealed 33 pT0, 112 pT1, 105 pT2, 223 pT3 and 26 pT4, 255 pN0, 146 pN1, 61 pN2 and 37 pN3. Twenty-eight patients had T0N0. In all, 28 tumors were G1, 221 G2 and 241 G3. In 61 pN2 and 37 pN3. Twenty-eight patients had T0N0. In all, 28 tumors were G1, 221 G2 and 241 G3. In 11% of specimens, the tumor extended to the lateral circumference of the esophagus suggesting a positive lateral margin. In 9 lesions, there was no preoperative grading available because the postinduction situation no longer allowed for postoperative grading.

The overall postoperative 30-day mortality rate was 4.2%.

The overall recurrence-free survival rate was 36.3% at 60 months and 33.7% at 120 months. Patients who died of esophageal carcinoma had a 60-month...
survival rate of 42.7%, and a 120-month survival rate of 36.6%. Overall survival—also including death from causes other than esophageal carcinoma—was 29% at 60 months and 20% at 120 months. In the presence of T0N0, survival rate was significantly higher \((p=0.03)\) with 59% at 60 months and 46% at 120 months, whereas induction chemotherapy as such had no statistically significant impact on survival. There was a trend, however, towards poorer prognosis following induction treatment.

Analysis over time

During the two 11-year periods, the number of patients undergoing resection increased by 23% from 223 to 276. There was no change in the percentages of men and women with 87.9% males in the first and 86.9% males in the second period \((p=0.74)\).

Patients’ age at the time of operation increased significantly over time with a mean of 60.8 years in the first and a mean of 65.2 years during the second period \((p=0.000)\; \text{Fig. 1}\).

Mean BMI at the time of operation was almost identical in the first \((25.6)\) and second periods \((25.03; \ p=0.16)\). Though significantly higher in patients with adenocarcinoma (see above), BMI did not increase significantly in this subgroup \((p=0.25)\).

The use of induction chemoradiotherapy increased significantly over the past 22 years \((p=0.000, \text{gamma} = 0.5; \text{ASE} = 0.047)\) from 7.14% in 2000 to 68.9% in 2021.

In the observation period, the rate of adenocarcinoma showed an increasing trend \((59 \text{ vs. } 65\%)\), which was not statistically significant, whereas the rate of squamous cell carcinoma declined \((\text{Pearson } \chi^2: 43.1; \ p = 0.424, \text{gamma} = 0.1248; \text{ASE} = 0.055)\). The same trend was reflected by the increasing rate of lesions in the lower third of the esophagus which also lacked significance \((p=0.21)\).

Whereas transhiatal access was predominant during the first period, the method was widely replaced by h-MIC in the second period. The difference is statistically significant \((p=0.000)\).

The overall mean duration of operation remained unchanged over time with 189.6 min during the first and 186.6 min during the second period \((p=0.72)\). The same applied to the length of the operation via transhiatal approach, whereas the duration when using thoracoabdominal approach \((p=0.03)\) and h-MIC \((p=0.0001)\) shortened significantly.

The distribution of pT stage, pN stage, grading and the rate of positive lateral resection margins remained unchanged throughout the 22 years \((\text{all } p>0.05)\).

Comparing the intervals 2000–2010 vs. 2011–2021, overall 30-day mortality rate was 4.4 vs. 4.2% \((p=0.56)\), recurrence-free survival was 36.9 vs. 38% at 60 months and 33.9 vs. 36.4% at 120 months \((p=0.93)\). Tumor-associated survival was 41.1 vs. 45% at 60 months and 35.5 vs. 38.7% at 120 months \((p=0.78; \text{Fig. 2})\). Overall survival including death from causes unrelated to the tumor was 31.8 vs. 32% at 60 months and 23.3 vs. 23.1% at 120 months.
Fig. 4 Pathological N-stage (pN) has significant impact on tumor-associated overall survival ($p=0.000$).

Fig. 5 Lateral resection margin (R) has significant impact on survival ($p=0.003$).

Fig. 6 Adenocarcinoma (adeno) has significantly higher survival rate than squamous cell carcinoma ($p=0.04$).

vs. 20.1% at 120 months ($p=0.77$). None of the differences was statistically significant.

When year of operation, age, sex, histological subtype, grading, pT, pN, lateral resection margin, induction therapy and surgical approach were included in a multivariable analysis defining their independent impact on tumor-associated survival, only higher pT ($p=0.01$; Fig. 3), positive pN ($p=0.000$; Fig. 4), positive lateral margin ($p=0.003$; Fig. 5), squamous cell carcinoma ($p=0.04$; Fig. 6) and higher grading ($p=0.026$) had a statistically significant negative influence on prognosis. For recurrence-free survival, the same parameters retained their statistically significant predictive value.

Discussion

Since the turn of the millennium, treatment of esophageal cancer has evolved considerably. Whereas tumors confined to the superficial epithelial layer are successfully treated by endoscopic mucosal resection [10], definitive chemoradiotherapy has become established for early stages predominantly in functionally impaired patients, whereas resection is reserved for patients in sufficiently good general condition either as an upfront procedure or as part of a multimodal protocol [11, 12].

These developments are deemed essential considering the hitherto modest long-term treatment results and the epidemiological change [13, 14] which also applies to Austria. Although still a rare tumor, the national incidence of esophageal carcinoma has increased by 40% from 321 per year in 2000 to 451 in 2019 [15]. In the same interval the number of resections in our collective increased by 23%. Though not directly matchable, the rise may be considered to mirror this development.

In the present retrospective analysis, the ratio of male and female patients remained constant throughout the 22 years examined. This finding contrasts studies documenting an isolated increase of male patients [14, 16–19]. On the other hand, our data with a trend towards an increasing incidence rate of adenocarcinoma were in accordance with other publications [14, 16–18]. Although higher BMI was significantly linked to adenocarcinoma [18, 20], mean BMI remained constant throughout the observation period. Other investigators analyzing western populations documented an increase of BMI, paralleling a rise in incidence of esophageal adenocarcinoma, corroborating the concept that the prevalence of gastroesophageal reflux increases along with BMI. There may be, however, other causative, possibly environmental factors contributing to the rising prevalence of esophageal adenocarcinoma [18, 21, 22].

There was a marked and statistically highly significant rise in patients’ age at the time of operation by a mean of almost 5 years within the 22-year period. It exceeds the increase of life expectancy in Austria be-
between 2000 and 2020, which was 3 years for men and 4 years for women [23]. The improvements in non-surgical and surgical management, allowing for treatment of patients formerly deemed unfit for strenuous therapies could explain the increase in age. Because the 30-day mortality rate did not differ significantly although older patients underwent surgery in the second period, resection seems to have been well tolerated.

In the context of developments in surgical techniques, transhiatal access, which prevailed in our collective during the first period, was largely replaced by h-MIC in the last years of the second period. Despite the change of access, the mean overall operation time of 187 min and the median time of 171 min remained unchanged. The length of the operation via transhiatal approach also remained constant at a mean of 156 min and a median of 136 min. The significant shortening of the operation time for the thoracoabdominal approach (p=0.03) can be explained by improved management of patient repositioning from lateral decubitus to supine position, whereas the reduced duration of h-MIC (p=0.0001) reflects a learning curve. Our data compare favorably to values from the literature where operative times between 252 min and 333 min for transhiatal access [24, 25], 146–330 min for MIC or h-MIC [18, 26–29] and 240 to 321 min for open interventions have been reported [26, 30].

The rate of induction chemoradiotherapy as indicated for >cT2 and/or >cN0 by the interdisciplinary tumor board rose significantly from 7.14% in 2000 to 68.9% in 2021, reflecting the developments of international treatment standards for esophageal cancer [12, 31–33]. However, despite the significantly increasing use of induction treatment, the distribution of pT and pN stages and the rate of positive lateral resection margins did not change over time. This implies that inaccuracy of preoperative staging notwithstanding [33] and despite optimistic appraisal of response in the literature, tumor regression actually resulting in downstaging of T and N is still rare following induction treatment [34, 35].

In accordance with other investigators, we found the best survival rate in the few patients with complete pathological response [35], whereas induction treatment had no independent, statistically significant impact on prognosis. Although both recurrence-free survival and tumor-associated survival showed a trend to increase when comparing the two periods, the difference was not significant. The same was true for overall survival, which includes death from causes other than tumor. Multivariable analysis showed that only few factors—all of them tumor-related—had an independent influence on survival rates. Since the distribution of the relevant parameters cell-type, grading, pT, pN, lateral resection margin did not change in the observation time, the lack of significant improvement of survival rates is not surprising.

**Conclusion**

Optimized noninvasive and invasive therapeutic modalities have produced only marginal improvement in the prognosis of esophageal carcinoma in the last two decades. Since only tumor stage, lateral resection margin and grading had independent prognostic influence on survival, development of novel antineoplastic drugs should be an eminent objective.

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