Original Research

Bagcilar Medical Bulletin 2017;2(1):1-8
DOI: 10.5350/BMB20170303091014

Changing Trends and Experience with Esophageal Cancer Surgery in a Single University Hospital: Are The Results Similar or Not?

Sebahattin Celik[1], Erkan Dogan[2], Harun Arslan[3], Abdussamed Batur[3], Remzi Kiziltan[1], Osman Toktas[1], Ozkan Yilmaz[1], M. Cetin Kotan[1]

ABSTRACT

Objective: The main treatment modality for esophageal cancer remains to be surgery. Over the last decades, surgical strategies have evolved remarkably. When neoadjuvant chemoradiotherapy became standard, discussions about the role, type, and timing of surgery began. In this study, we share results we obtained after operating our patients using various surgical techniques.

Material and Methods: Reliable data from 51 esophageal cancer patients were evaluated retrospectively. Of the 51 cases, 31 were operable. These operable cases were further classified according to surgical method and neoadjuvant therapy status. Median survival time in months, complications, hospital mortality, length of hospital stay, and pathology results (total lymph nodes harvested and pathologic tumor node metastasis stage [p_TNM]) were documented for the different surgical approaches.

Results: Open surgical methods were performed in 21 cases, while in 10 cases the Minimally Invasive Surgery (MIS) method was used. The MIS group received neoadjuvant therapy more frequently than the open surgical methods group (p=0.013). Although more complications were observed in the MIS group, the difference to the open esophagectomy methods group was not significant. Patients in the MIS group also had longer hospital stays, but again the difference was not significant. Although a pathologic complete response was seen in 8 of the 11 (72.7%) patients in our study who received chemoradiotherapy as neoadjuvant treatment, the surgical results of patients who received chemoradiotherapy were worse, although not to a statistically significant extent.

Conclusion: Despite changing trends and treatment options in esophageal cancer surgery, we have yet to see the expected improved results.

Keywords: esophagus cancer, minimally invasive surgery, neoadjuvant therapy

ÖZET

Özofagus kanser cerrahisinde tek üniversite hastanesi deneyimleri ve değişen trendler; sonuçlar değişti mi?

Amaç: Özofagus kanserinin temel tedavi yöntemi cerrahi olarak devam etmektedir. Son dekatlarda cerrahi yöntemlerde ciddi ilerlemeler olmuştur. Neoadjuvan kemoradioterapinin stantdart hale gelmesi ile beraber, cerrahinin tedavideki yeri, cerrahi yöntemin tipi ve zamanlaması tartışılmaya başlanmıştır. Bu çalışmada, farklı cerrahi yöntemler ile tedavi edilen vakalarımızın sonuçları paylaşıldı.

Yöntem: Özofagus kanserli 51 vakanın verileri retrospektif olarak değerlendirildi. Bu 51 vakanın 31 tanesi operable idi. Ameliyat edilen 31 vaka, ayrıca cerrahi yönteme ve neoadjuvant kemoradioterapiye göre alt gruplara ayrıldı. Ay olarak median sağ-kalım süreleri, komplikasyonlar, hastane mortaliteleri, yatış süreleri ve patoloji sonuçları (toplam çıkarılan lenf nodu sayısı, TNM sınıflaması) farklı cerrahi tekniklere göre yorumlandı.

Bulgular: Açık cerrahi teknikler ile 21 vaka ameliyat edilirken, 10 vaka minimal invazif yöntemler (MİY) ile ameliyat edildi. Açık cerrahi yöntemlere göre MİY ile ameliyat olanlar daha sıklıkla neoadjuvant tedavi almış idi (p=0.013). MİY ile ameliyat olan grupta daha fazla komplikasyon gözlendi ancak açık tekniklere göre bu fark istatiksel olarak anlamalı değildi. Aynı şekilde, hastanede yatış süresi açık tekniklere göre MİY ile ameliyat olanlarda daha fazla idi ancak istatiksel anlamlılık yoktu. Neoadjuvant tedavi alan 11 vakanın 8 tanesinde patolojik tam yanıt (%72.7) gözlenmesine rağmen, cerrahi sonuçlar neoadjuvant tedavi alanlarda istatiksel olarak anlamlı olmasa da, daha kötüydü.

Sonuç: Özofagus kanseri cerrahisinde, değişen trendlere ve tedavi seçeneklerine rağmen, istenilen iyi sonuçlara ulaşılamamıştır.

Anahtar kelimeler: özofagus kanseri, minimal invazif cerrahi, neoadjuvant tedavi

[1]Yuzuncu Yil University, Faculty of Medicine, Department of General Surgery, Van-Turkey
[2]Yuzuncu Yil University, Faculty of Medicine, Department of Medical Oncology, Van-Turkey
[3]Yuzuncu Yil University, Faculty of Medicine, Department of Radiology, Van-Turkey

Corresponding author:
Sebahattin Celik,
Yuzuncu Yil University, Faculty of Medicine, Department of General Surgery, 65080, Van-Turkey
Phone: +90-432-216-4705/6099
Fax: +90-432-216-8352
E-mail address: drsebahattincelik@hotmail.com

Date of submission: February 9, 2017
Date of acceptance: March 3, 2017

Introduction

In Western countries (e.g., the United States and various European countries), incidence of esophageal adenocarcinoma continues to increase and survival remains poor in comparison to other stage-matched malignancies, despite improvements in techniques and patient care (1,2). The situation is nearly the same for Middle Eastern countries (3). Although multimodal therapies are accepted as standard treatment, there are still controversies surrounding both surgical and chemoradiotherapy strategies (4). The advantages and disadvantages of different surgical approaches have become more complex since the introduction of minimally invasive surgery (MIS) to be used in esophageal cancer (5,6). There has been a tendency to use minimally invasive surgical methods to reduce morbidity and mortality from esophagectomy (first with transhiatal esophagectomy [THE], then by minimally invasive surgery). In a meta-analysis comparing THE and transthoracic esophagectomy (TTE), Hulscher et al. (7) concluded that there was no difference between the two types of resection in terms of 3- and 5-year survival rates. Another large-volume multicenter study that compared outcomes following TTE and THE found the two to be equivalent, although higher-volume centers had lower morbidity and mortality rates (8). Nonetheless, open esophagectomy has the highest mortality and morbidity rate within the field of elective gastrointestinal surgery (9). Therefore, early reports of MIS for esophageal cancer have been received with interest (10). Gemmill et al. (9), who systematically reviewed 46 studies on minimally invasive resection for esophageal and gastric cancer, concluded that MIS is feasible, but randomized studies are needed before a definite conclusion can be drawn. There are also comparisons of the results in Western and Eastern countries, finding that the latter had better results. The latest version of the NCCN Guideline recommends Neoadjuvant Therapy (chemotherapy or chemoradiotherapy) for patients whose esophageal cancer is staged at T1b N + (Stage 2B) or more advanced (11), although the level of evidence is low (generally level 2A) (12). There are conflicting results in meta-analyses of survival advantages and morbidity associated with neoadjuvant therapies (13-15). However, there is a trend towards using neoadjuvant chemoradiotherapy in the treatment of esophageal cancer. In particular, new agents (such as Taxane-based protocols, Irinotecan, and targeted therapy) have garnered interest in recent decades (16).

As doctors at a university hospital surgical clinic, we have had experience with all of these surgical methods, as well as with neoadjuvant and adjuvant therapies, throughout these changes in surgical methods and treatment recommendations. Here we aim to analyze the effects of these various surgical and medical approaches on esophageal cancer surgery outcomes in our institution, and to situate our results in the context of findings in the literature.

Methods

Specific aims and endpoints

Our primary objective was to compare the outcomes (median survival time in months, complications, hospital mortality, and length of hospital stay) and pathological results (total lymph nodes harvested and p_TNM) of different surgical approaches. Secondly, we sought to evaluate the effects of neoadjuvant therapy on surgical results.

Our outcome criteria were: overall patient survival, postoperative complications, length of hospital stay, and differences in pathology reports (harvested lymph nodes, pathological lymph nodes, pathological TNM) between the surgical methods.

Patient eligibility

Our study enrolled all esophageal cancer patients who were diagnosed with ICD codes 15.1 to 15.9 between 2009 and 2014 in the hospital registry. Written informed consent was obtained from all living patients and from the primary relatives of deceased patients. Patients for whom reliable data could not be obtained were excluded from the study. Cases miscoded as esophageal cancer which in fact were benign esophageal disease or gastric or other malignancies were excluded (Figure 1).

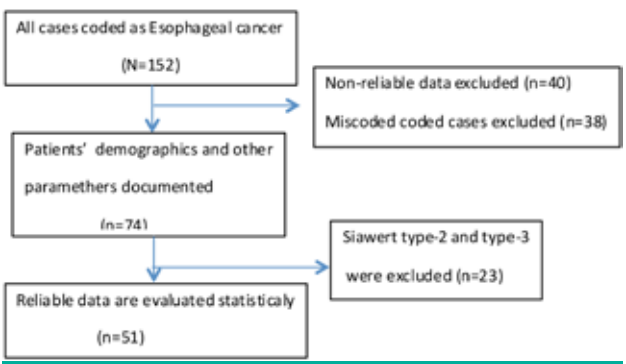

Figure 1: The algorithm for case selection, study design.

Proximal, middle, and lower (including Siewert-type 1) esophageal cancer cases were included in the study. During the 6 year period, all patient data recorded in the hospital computer records system were retrieved and evaluated retrospectively.

We measured the overall median survival time in months. Overall survival times were calculated by subtracting the date of cancer diagnosis from the date of death. Dates of death were obtained from the Provincial Civil Registry Office of Van.

Complications that occurred during hospitalization were categorized in one of the following categories: pulmonary (pulmonary problems such as pneumonia, pleural effusion, etc.), cardiac (cardiac problems such as myocardial infarction, atrial fibrillation, etc.), anastomotic leak, neurologic, hemorrhage, surgical wound infection, and other complications not mentioned above.

Criteria used to measure specific endpoints

Hospital mortality was defined as death occurring during hospitalization following surgery. Length of hospital stay was calculated as the number of days between surgery and discharge date. Harvested lymph node number and number of metastatic lymph nodes were documented according to the pathology reports. Staging was performed according to TNM classification (11). Patient performance status was documented as per the ASA (American Society of Anesthesiologists) score, which was recorded in the preoperative anesthesiology notes.

In our hospital, neoadjuvant therapy decisions are made by the oncologic committee, which meets weekly, consisting of a medical oncologist, radiologist, oncological surgeon, gastroenterologists, radiation oncologist, and nuclear medicine specialists. All esophageal cancer patients were discussed, and according to NCCN Guidelines, cases with clinical and radiological diagnosis of T2-3 with any N status and any T but N1-3 were referred for neoadjuvant therapy. Patients unwilling to undergo chemotherapy were referred for surgery. Chemotherapy and simultaneous radiotherapy were performed in our Oncology Clinic: Paclitaxel (50 mg/m^2), carboplatin (target AUC =2 mg/mL/min) plus radiotherapy (41.4 Gy in 23 fractions, 5 days per week). This protocol was given on the first day of radiotherapy and once a week thereafter for 5 weeks. Other chemotherapy protocols given (6 cycles) without radiotherapy were: cisplatin (50 mg/m^2), folinic acid (400 mg/m^2), fluorouracil in bolus form (400 mg/m^2), and fluorouracil infusion (2400 mg/m^2). Patients receiving these therapies were further categorized as: chemotherapy only, chemoradiotherapy, or radiotherapy only.

Tumor localization was established after examination of both pathology and endoscopy reports. If the tumor was 20-25 cm from the incisors, it was recorded as “upper thoracic”, between 25-30 cm “middle thoracic”, and “lower thoracic” if between 30-40 cm. If the tumor was at the esophagogastric junction, it was further categorized according to the Siewert Classification (17). Siewert type 2 and type 3 were excluded from the study.

In this study, various surgical approaches applied thus far in our General Surgery clinic were categorized as: transthoracic esophagectomy (Iwor-Lewis), transhiatal esophagectomy (Orringer approach, THE), 3-field approach (McKeown method = laparatomy, thoracotomy, then cervical anastomosis), and minimally invasive surgery (thoracoscopic esophageal mobilization plus laparoscopic gastric dissection and gastric tube formation, followed by cervical anastomose). After a defined surgical approach, we further categorized these operations as either MIS or a conventional approach. The traditional methods (THE, Ivor-Lewis and McKeown) were considered open approaches while MIS was considered a closed method.

Before patients were discharged from the hospital, their general condition was evaluated and categorized as follows: those who died in the hospital, those discharged with some kind of surgical problem (such as an open wound, surgical side infection, pulmonary complaints), those discharged without a problem, and those who had developed an anastomotic stricture. This categorization is referred to as “prognosis”. All patients were categorized according to one of two histologic types, adenocarcinoma or squamous cell carcinoma, based on the pathology reports.

Statistical Analysis

Statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) For normally distributed variables, the Independent Sample T-test was used and for non-normally distributed variables the Mann-Whitney U-Test. Comparisons of proportions between groups were performed by Chi-Square Test or Fisher’s exact test, where appropriate. A p-value of less than 0.05 was considered a statistically significant result.

Results

We examined all reliable data for 51 cases and found, surprisingly, that most of the patients were women (62.7%). Of 51 patients, 20 cases (39.2% inoperable) were metastatic and 31 were operable (60.8%). Age distribution, ASA score distribution, surgical technique, neoadjuvant treatment type, tumor localization, and histological type are summarized according to gender in Table 1. When we evaluated all patients (inoperable and operable), the mean age was 56, which was nearly the same for both sexes. The performance of most of patients was good (according to ASA, mostly 1 and 2) , and there was no significant difference between genders (χ^2, p=0.616).

Of the 51 patients, only 15 had neoadjuvant chemoradiotherapy (CRT). None of the patients were given solely radiotherapy or chemotherapy. Of these 15 cases, 11 were operated on. Three of 4 cases who did not undergo surgery died, while 1 case was alive at the end of the study. Adjuvant treatment was given to 10 patients, 5 of whom were operated on (all with open techniques). The others were inoperable. THE was the most frequently performed operation (13 cases), followed by MIS (10 cases). Almost all anatomic localizations had an equal tumor number. When we evaluated for histologic type, SCC was clearly the prominent one (86%).

Results of the 31 cases undergoing surgery are shown Table 2. According to the pathology reports, there were no stages 0, 1A, 3B, or 3C among the cases operated on. There were 8 cases that gave a pathologic complete response (72.7%) to neoadjuvant CRT among the 11 cases who underwent surgery. Although more complications were seen in the MIS group, it was not significantly different from the open esophagectomy methods group (p=0.087). Cases who underwent MIS stayed in the hospital longer, but this was not significant (p=0.096).

Total lymph nodes harvested were similar in both groups. Analyzing patient prognoses, we found that anastomotic stenosis occurred in 6 patients (19.4%), while a total of 18 patients were discharged without any problems. There was no difference between surgical methods in terms of prognosis (p=0.553). Table 3 shows the results based on classifying patients into two groups, those who received neoadjuvant therapy and those who did not. There was no statistical difference between these two groups in any of the surgical results (p=0.0966).

Table 1: Distribution of demographics, surgical techniques, neoadjuvant modalities and tumor characteristics (in all cases[a]).

	Female (n= 32)	Male (n=19)	Total
Age (mean±sd)	55.9±14.0	57.7±14.6	56.0±14.13
ASA n (%)			
1	14 (70%)	6 (30%)	20
2	11 (55%)	9 (45%)	20
3	7 (63.6%)	4 (36.4%)	11
Neoadjuvant n (%)			
Not taken	21 (58.3%)	15 (41.7%)	36
CRT[b]	11 (73.3%)	4 (26.7%)	15
Adjuvant n (%)			
No	25 (78.1%)	7 (21.9%)	32
Yes	6 (60.0%)	4 (40.0%)	10
Surgical Technique n (%)			
Inoperable	7 (35%)	13 (65%)	20
Ivor-Lewis	1 (50%)	1 (50%)	2
THE	12 (92.7%)	1 (7.7%)	13
McKeown	3 (50%)	3 (50%)	6
MIS[c]	9 (90%)	1 (10%)	10
Tumor location n (%)			
Upper thoracic	6 (66.7%)	3 (33.3%)	9
Middle thoracic	8 (57.1%)	6 (42.9%)	14
Lower thoracic	10 (76.9%)	3 (23.1%)	13
Gastroesophageal Junction (Siewart-1)	8 (57.1%)	6 (42.9%)	14
Histology n (%)			
SCC[d]	26 (70.3%)	11 (29.7%)	37
Adenocarcinoma	3 (50%)	3 (50%)	6

a: Both metastatic and operable patients, b: CRT, Chemoradiotherapy, c: Minimally Invasive Surgery (thoracoscopic and laparoscopic), d: SCC, Squamous Cell Carcinoma, CT: Chemotherapy, ASA: American Society of Anesthesiology

Table 2: Outcomes and demographics in operated patients according to surgical methods.

		Conservative approaches (Ivor Lewis, THE, McKeown)	MIS	Total	P
Gender n (%)	Female	16 (64.0%)	9 (36.0%)	25	0.634
	Male	5 (83.3%)	1 (16.7%)	6	
Age (Mean ± Std. deviation)		55.7±16.1	54.0±10.8	55.2±14.5	0.757
ASA n (%)	1	10 (71.4%)	4 (28.6%)	14	0.366
	2	9 (75.0%)	3 (25.0%)	12	
	3	2 (40.0%)	3 (60.0%)	5	
Neoadjuvant n (%)	No	17 (85.0%)	3 (15.0%)	20	0.013
	CRT	4 (36.4%)	7 (63.6%)	11	
Histology n (%)	Adenocarcinoma	2 (66.7%)	1 (33.3%)	3	1.00
	SCC	19 (67.9%)	9 (32.1%)	28	
p_TNM n (%)	Stage 1B	4 (80.0%)	1 (20.0%)	5	0.099
	Stage 2A	4 (80.0%)	1 (20.0%)	5	
	Stage 2B	5 (100.0%)	0 (0.0%)	5	
	Stage 3A	5 (62.5%)	3 (37.5%)	8	
Pathologic Complete response	Yes	3 (37.5%)	5 (62.5%)	8	0.087
	No	12 (66.7%)	6 (33.3%)	18	
Complications n (%)	Anastomotic leak	2 (40.0%)	3 (60.0%)	5	
	Pulmonary complications	6 (100.0%)	0 (0.0%)	6	
	Hemorrhage	1 (50.0%)	1 (50.0%)	2	
Total Lymph Node Harvested (Median, range)		14.0 (5-51)	9.50 (6-25)	14.0 (5-51)	0.393
Hospital Mortality	No	18 (69.2%)	8 (30.8%)	26	1.00
	Yes	3 (60.0%)	2 (40.0%)	5	
Length of hospital stay (Days) Median (range)		15.0 (5-71)	22.0 (13-42)	15.0 (5-71)	0.096

THE: Transhiatal esophagectomy, MIS: Minimally invasive surgery, ASA: American Society of Anesthesiologists, CRT: Chemoradiotherapy, SCC: Squamous cell carcinoma, p_TNM: pathologic TNM, p<0.005 is statistically significant.

Table 3: Comparison of surgical outcomes between patients who received neoadjuvant therapy and those who did not.

		No CRT	CRT	Total	p
Complications	None	12 (66.7%)	6 (33.3%)	18	0.966
	Pulmonary	4 (66.7%)	2 (33.3%)	6	
	Anastomotic Leak	3 (60.0%)	2 (40.0%)	5	
	Hemorrhage	1 (50.0%)	1 (50.0%)	2	
	Without problems	12 (66.7%)	6 (33.3%)	18	
Prognosis	With problems	1 (50.0%)	1 (50.0%)	2	0.966
	Anastomotic stenosis	4 (66.7%)	2 (33.3%)	6	
	Exitus in Hospital	3 (60.0%)	2 (40.0%)	5	
Total Lymph Nodes Harvested Median (range)		14.50 (5-51)	9.0 (6-39)	14.0 (5-51)	0.244
Metastatic Lymph Node Median (range)		0.50 (0-17)	0.00 (0-4)	0.00 (0-17)	0.145
Length of Hospital Stay (Days) Median (range)		15.0 (5-71)	19.0 (13-42)	15.0 (5-71)	0.244

CRT: Chemotherapy, p<0.005: statistically significant

The median survival time for operated cases was 14 months, ranging from 0 months to 58 months. At the end date (31.12.2014) of the study, 10 patients had died and 21 patients were still alive. The median survival time was 18.25 months (range: 0-58.5) for those patients who did not receive neoadjuvant therapy. In the CRT group, the median survival time was 11.5 months (range: 4-23.5). This difference was not statistically significant (p=0.197) (Figure 2).

When we evaluated the survival times according to various surgical procedures, in open approaches the median survival time was found to be 19.0 months (range: 0-58.5). In the MIS group, the time was 11.5 months (range: 4-22). This difference was also not significant (p=0.105). As shown in Table 2, most of the patients who received neoadjuvant therapy were

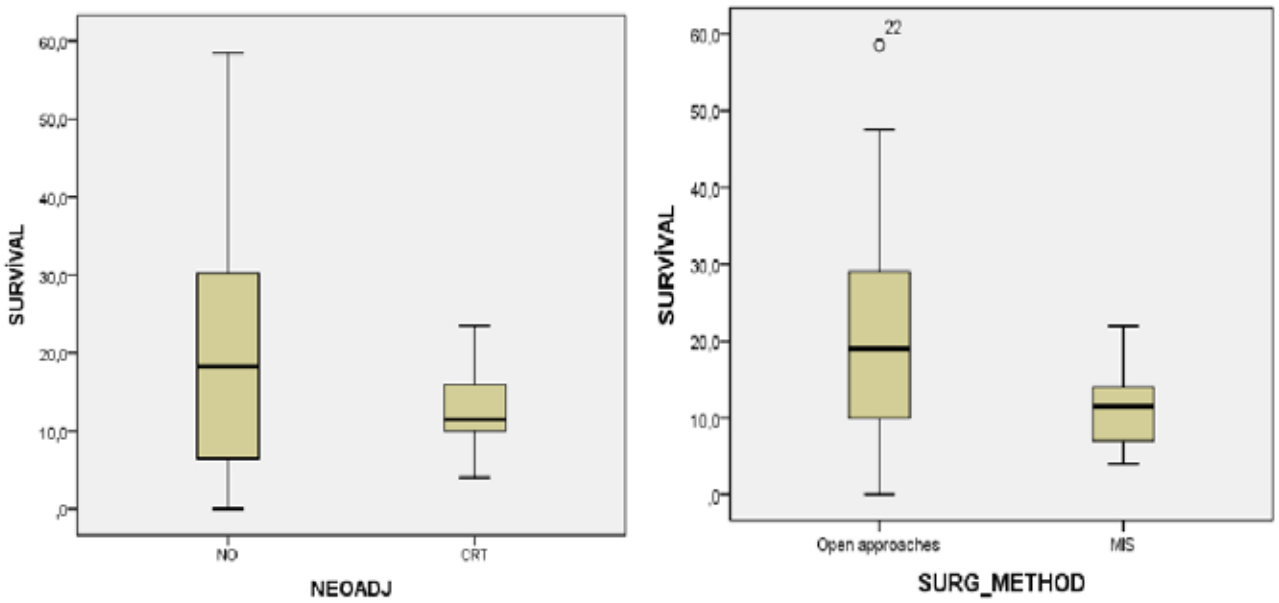

Figure 2: Median survival time of patients who underwent surgery, according to neoadjuvant therapy status and surgical methods.

operated on with MIS techniques, while the majority of patients undergoing surgery with open approaches did not receive neoadjuvant therapy. As seen in Figure 2, the mean survival times of the neoadjuvant and MIS groups were similar, as expected.

Discussion

In this study, we evaluated our own clinical experience in terms of changing trends in esophageal cancer surgery and the results of different surgical and medical approaches. In contrast to the situation in other parts of the world, esophageal cancer was found to be more common in women than men, as shown both in this and other studies conducted in the same region (the Lake Van region, in eastern Turkey) (1,2,18). The average age in this study was lower (56 years old) than the mean age reported in other studies from Eastern and Western countries (3,19). Most of our patients' performance scores were good (the ASA scores of 78.4% of all patients were ASA-1 or ASA-2). In summary, our patients were younger and healthier than other esophageal cancer patients reported in different regions of the world. It is well known that there is an increasing incidence of adenocarcinoma of the gastroesophageal junction, especially in Western countries (2). However, in this study the predominant histologic type was squamous cell cancer.

When we only compared the results of traditional methods with those of innovative methods, we did not observe significant differences between the groups in terms of surgical outcomes and survival times. Because the majority of patients operated on with the MIS method (7 out of 10 patients) also received neoadjuvant therapy, it is difficult to draw a clear conclusion regarding whether surgical outcomes were affected by neoadjuvant therapy. However, we can conclude in general that for those of our patients given neoadjuvant therapy and operated on with MIS approaches, the results were worse than for those who were operated using traditional methods, although the difference was not statistically significant. This situation may be due to our limited experience using MIS. In a study by Braghetto et al. (20), for the 47 patients who submitted to MIS, complications and mortality rates were significantly reduced (38.2% and 6.4%, respectively) compared to classical open methods. Our complication and mortality rates in the MIS group were 40% and 20%, respectively. Using open approaches, the group complication and mortality rates were 42.85%, and 14.3%, respectively. Although the number of patients who received MIS in our study was smaller (10 patients) than the number of patients in the study by Braghetto at al. (47 patients), nonetheless there were more deaths in our study. At this point, it is important to clarify that in the aforementioned study, patients receiving MIS manifested early stages of disease and none of the patients received neoadjuvant therapy. By contrast, in our study, the majority of patients who received neoadjuvant therapy were generally at stage 2B and

3A preoperatively. Unfortunately, in rural parts of Turkey, access to health services is often limited and the quality of healthcare is much worse than in Western countries.

In a systematic review by Gemmill and McCulloch (9) analyzing minimally invasive surgery results in esophageal cancer, the mean duration of hospital stay was 11 days. In our study, the median length of hospital stay was 22 days in the MIS group and 15 days for open approaches. We link this prolonged hospitalization time in both groups to delays in diagnosis and management of complications in our hospital. Another important factor in our long hospitalization periods is that inhabitants of this region tend to insist on staying in the hospital longer, until they are certain that they will not experience any negative health events. This is due to the fact that in case of an emergent medical issue while a patient is recovering at home, they know that they may experience difficulty in reaching a hospital in a timely manner.

In the aforementioned review, the mean number of retrieved lymph nodes per operation was 17.6 for esophagectomy. In our study, this number was 9.5 in the MIS group and 14 for the open approaches group. However, this difference between the groups is not the important point; rather, the adequacy of oncological resection should be questioned.

Unfortunately, endoscopic ultrasound (EUS) is not performed in our hospital for esophageal cancer staging. Thus, when patients are reviewed for neoadjuvant therapy modalities in the oncologic committee, the stage of disease is determined using computed tomography (CT), positron emission tomography (PET/CT), and magnetic resonance imaging (MRI) scans, where indicated. EUS is considered superior to CT and PET/CT in the T staging of tumors, but not in N and M staging when compared to CT and PET/CT (21). Therefore, in regard to multimodality therapy decisions, we believe that we are consistent with the literature.

Although a pathologic complete response was seen in 8 of the 11 (72.7%) patients who received CRT as neoadjuvant in our study, the surgical results of patients who received CRT were worse. In a meta-analysis conducted by Urschel et al. (14), the pathologic complete response to neoadjuvant was 21%. The high rate of pathologic complete response found in our study may be a result of the inadequacy of pathological specimen assessment, a consequence of differences present in the biology of our patients' tumors, or a consequence of the neoadjuvant treatment protocol.

Urschel et al. (14) observed that there was a non-significant trend toward increased treatment mortality with neoadjuvant chemoradiation, as also found in our study. In addition to increased mortality, this study also showed an increased complication rate with neoadjuvant therapy, although this was not significant.

The median survival time was 11.5 months both in patients with neoadjuvant therapy and in those being operated using an MIS approach. Our survival results were worse than the results reported in the literature (6,14). This may be due to inappropriate patient selection and/or inappropriate preoperative staging. Another possible explanation is our low number of operated cases, compared to other studies.

As indicated in the review by Gemmill and McCulloch (9), the quality of data in studies that investigate MIS approaches has generally been poor, with many potential sources of bias. We agree with this conclusion in terms of study design and patient follow-up strategy.

Conclusion

Because we live in a region with a high incidence of esophageal cancer, more controlled, well-designed prospective studies should be performed. Despite changing trends and treatment options in esophageal cancer surgery, we have not yet seen the expected improved results.

Contribution Categories	Name of Author
Development of study idea	S.C., E.D., M.C.K., A.B.
Methodological design of the study	S.C., H.A., R.K., O.Y.
Data acquisition and process	R.K., O.Y., H.A., E.D., S.C.
Data analysis and interpretation	S.C., H.A., O.Y., E.D., A.B.
Literature review	M.C.K., E.D., S.C., A.B.
Manuscript writing	S.C., E.D., M.C.K., R.K., O.Y.
Manuscript review and revisation	S.C., E.D., M.C.K., R.K., O.Y, A.B.

Conflict of Interest: There are no financial or other relations that could lead to a conflict of interest.

Financial Disclosure: Authors declared no financial support.

Ethical Statement: This study was conducted in accordance with the Helsinki Declaration of the World Medical Association. As this study was an observational retrospective and therefore did not involve any medical intervention, ethical approval was not sought.

References

1. International Agency for Research on Cancer. GLOBOCAN-2012. Estimated cancer incidence, mortality and prevalence in 2012. http://globocan.iarc.fr/Pages/fact_sheets.population.aspx. Access date; 02.04.2015
2. Botterweck AA, Schouten LJ, Volovics A, Dorant E, van Den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. Int J Epidemiol 2000;29(4):645-654. [CrossRef]
3. Harirchi I, Kolahdoozan S, Hajizadeh S, Safari F, Sedighi Z, Nahvijou A, et al. Esophageal cancer in Iran; a population-based study regarding adequacy of cancer surgery and overall survival. Eur J Surg Oncol 2014;40(3):352-357. [CrossRef]
4. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996 15;335(7):462-467. Erratum in: N Engl J Med 1999 29;341(5):384.
5. Maloney JD, Weigel TL. Minimally invasive esophagectomy for malignant and premalignant diseases of the esophagus. Surg Clin North Am 2008;88(5):979-990. [CrossRef]
6. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg 1999;230(3):392-400; discussion: 400-403. [CrossRef]
7. Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. Ann Thorac Surg. 2001;72(1):306-313. [CrossRef]
8. Connors RC, Reuben BC, Neumayer LA, Bull DA. Comparing outcomes after transthoracic and transhiatal esophagectomy: a 5-year prospective cohort of 17,395 patients. J Am Coll Surg 2007;205(6):735-740. [CrossRef]
9. Gemmill EH, McCulloch P. Systematic review of minimally invasive resection for gastro-oesophageal cancer. Br J Surg 2007;94(12):1461-1467. [CrossRef]
10. Cuschieri A, Shimi S, Banting S. Endoscopic oesophagectomy through a right thoracoscopic approach. J R Coll Surg Edinb 1992;37:7-11.
11. Ajani JA, D'Amico TA, Almhanna K, et al. Esophageal and esophagogastric junction cancers, version 1.2015. J Natl Compr Canc Netw. 2015;13(2):194-227.
12. Poonacha TK, Go RS. Level of evidence underlying recommendations arising from the National Comprehensive Cancer Network clinical practice guidelines. J Clin Oncol 2011;29(2):186-191. [CrossRef]
13. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002 18;359(9319):1727-1733.
14. Urschel JD and Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2003;185(6):538-543. [CrossRef]
15. Greer SE, Goodney PP, Sutton JE, Birkmeyer JD. Neoadjuvant chemoradiotherapy for esophageal carcinoma: a meta-analysis. Surgery 2005;137(2):172-177. [CrossRef]
16. Ilson DH. Oesophageal cancer: new developments in systemic therapy. Cancer Treat Rev 2003;29(6):525-532. [CrossRef]
17. Rudiger Siewert J, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. Ann Surg. 2000;232(3):353-361. [CrossRef]
18. Celik S, Yılmaz EM, Ozden F, Kotan C, Okut H. The Relationship between Eating and Lifestyle Habits and Cancer in Van Lake Region: Another Endemic Region for Esophageal and Gastric Cancers. J Cancer Epidemiol 2015;2015:254823. [CrossRef]
19. Daly JM, Fry WA, Little AG, Winchester DP, McKee RF, Stewart AK, et al. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. J Am Coll Surg 2000;190(5):562-572; discussion: 572-573. [CrossRef]
20. Braghetto I, Csendes A, Cardemil G, Burdiles P, Korn O, Valladares H. Open transthoracic or transhiatal esophagectomy versus minimally invasive esophagectomy in terms of morbidity, mortality and survival. Surg Endosc 2006;20(11):1681-1686. [CrossRef]
21. Choi J, Kim SG, Kim JS, Jung HC, Song IS. Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET/CT), and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer. Surg Endosc 2010;24(6):1380-1386. [CrossRef]