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Original Article / *Özgün Makale*

What are the independent prognostic factors in patients undergoing esophagectomy for esophageal cancer?

Özofagus kanseri nedeniyle özofajektomi yapılan hastalarda bağımsız prognostik faktörler nelerdir?

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ABSTRACT

Background: This study aims to investigate the prognostic factors affecting survival in patients undergoing surgical treatment for esophageal cancer.

Methods: A total of 50 patients (33 males, 17 females; mean age: 57.8±11.8 years; range, 28 to 80 years) who underwent esophagectomy for esophageal cancer in our clinic between January 2008 and March 2018 were retrospectively analyzed. Prognostic factors affecting survival were investigated. Data including age, sex, tumor size, histological and macroscopic type, tumor stage, T and N categories, the total number of resected lymph nodes and metastatic lymph node ratio, differentiation degree, vascular and perineural invasion, proximal surgical margin distance, adjuvant therapy, and the presence of postoperative complications were recorded.

Results: The patients after radical surgery with a tumor size of <3 cm, macroscopic type non-ulcerative-infiltrative squamous cell carcinoma pathology, Stage 1 disease, pT1-2, pN0, well-differentiated groups, no perineural invasion, a metastatic lymph node ratio of <0.2, proximal surgery margin length of 5 to 10 cm, and no postoperative complications had higher five-year survival rates. However, when the effects of these factors on overall survival were examined independently, none of them had a statistically significant effect (p>0.05). The main factors affecting the prognosis were Stage ≥2 disease, postoperative complications, and proximal surgical margin less than 5 cm.

Conclusion: Our study results suggest that Stage 1 disease, a proximal surgical margin length of more than 5 cm, and the absence of complications are associated with longer survival times and these patients are greatly benefited from surgical treatment.

Keywords: Esophageal cancer, esophagectomy, prognostic factors, surgery.

ÖZ

Amaç: Bu çalışmada özofagus kanseri nedeni ile cerrahi tedavi yapılan hastalarda sağkalımı etkileyen prognostik faktörler araştırıldı.

Çalışma planı: Ocak 2008 - Mart 2018 tarihleri arasında kliniğimizde özofagus kanseri nedeni ile özofajektomi uygulanan toplam 50 hasta (33 erkek, 17 kadın; ort. yaş: 57.8±11.8 yıl; dağılım, 28-80 yıl) retrospektif olarak incelendi. Sağkalımı etkileyen prognostik faktörler araştırıldı. Yaş, cinsiyet, tümör boyutu, histolojik ve makroskobik tipi, tümör evresi, T ve N kategorileri, total rezeke edilen lenf nodu sayısı ve metastatik lenf nodu oranı, diferansiasyon derecesi, vasküler ve perinöral invazyon, proksimal cerrahi sınır uzunluğu, adjuvan tedavi ve ameliyat sonrası komplikasyon varlığı kaydedildi.

Bulgular: Radikal cerrahi sonrasında tümör boyutu <3 cm olanlar, makroskobik tipi ülseratif-infiltratif olmayan skuamöz hücreli karsinom patolojisindeki olgular, Evre 1 hastalık, pT1-2, pN0 olan olgular, iyi diferansiye gruplar, perinöral invazyon olmayan hastalar, metastatik lenf nodu oranı <0.2, proksimal cerrahi sınır uzunluğu 5-10 cm olan olgular ve ameliyat sonrası komplikasyon gelişmeyen olguların beş yıllık sağkalım oranları daha yüksek idi. Ancak bu faktörlerin bağımsız olarak genel sağkalım üzerindeki etkileri incelendiğinde, hiçbirinin istatistiksel olarak anlamlı bir etkisi olmadığı görüldü (p>0.05). Prognozu etkileyen başlıca faktörler Evre ≥2 hastalık, ameliyat sonrası komplikasyonlar ve 5 cm'den küçük proksimal cerrahi sınır idi.

Sonuç: Çalışma sonuçlarımız Evre 1 hastalık, 5 cm'den fazla proksimal cerrahi sınır uzunluğu ve komplikasyon olmamasının daha uzun sağkalım süreleri ile ilişkili olduğunu ve bu hastaların büyük ölçüde cerrahi tedaviden fayda gördüklerini göstermektedir.

Anahtar sözcükler: Özofagus kanseri, özofajektomi, prognostik faktörler, cerrahi.

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Esophageal cancer is caused by an extremely aggressive tumor. It has a rapidly increasing incidence worldwide and currently ranks the sixth among cancer-related causes of death.[1,2] Despite advances achieved in relevant diagnostic and therapeutic methods, it remains as a disease with one of the worst prognoses among malignancies. The five-year survival rates associated with esophageal cancer are still below 20%.[2,3] Surgery continues to be considered as a curative method in the treatment of esophageal cancer. Surgical treatment is considered the primary treatment option, unless the cancer becomes metastatic or there is a medical contraindication.[4-6]

In the present study, we aimed to investigate the prognostic factors affecting survival in patients who underwent surgical treatment for esophageal cancer.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Akdeniz University, Faculty of Medicine, Thoracic Surgery Clinic between January 2008 and March 2018. A total of 106 patients who underwent esophagectomy in our clinic were reviewed. No distinction between benign and malignant cases was made. Inclusion criteria were as follows: having a diagnosis of esophageal malignancy confirmed by the pathological examination and having complete pathology report details including the tumor size, tumor type, tumor length, surgical stage, number of lymph nodes dissected, and surgical margins. Patients who did not regularly attend to their follow-up visits and whose survival follow-up could not be performed were excluded from the study. Accordingly, 16 patients who were operated for benign esophageal diseases and 40 patients who were found to have esophageal cancer, but had missing data in their files, or who were unable to be followed were excluded from the study. Finally, a total of 50 patients (33 males, 17 females; mean age: 57.8±11.8 years; range, 28 to 80 years) who underwent esophagectomy for esophageal cancer were included in the study. A written informed consent was obtained from each patient. The study protocol was approved by the Akdeniz University Hospital Ethics Committee (Date: 11.04.2018, No: 267). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Prognostic parameters such as, age, sex, tumor size, macroscopic/histological type of the tumor, tumor stage (Tumor, Node, Metastasis [TNM] classification of malignant tumors), T/N (primary tumor [T]; regional lymph node [N]) staging, lymph node involvement (total number of resected lymph nodes and lymph node ratio [LNR]), degree of differentiation, vascular and perineural invasion (PNI), proximal surgical margin length, adjuvant therapy, presence of any complications were reviewed in these patients who underwent surgery. The effects of these parameters at one-, three-, and five-year survival were investigated.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The log-rang test was used to check normality distribution. The Kaplan-Meier analysis was used for survival analysis, whereas log-rank test was used to determine whether there was any difference between the groups in terms of survival rates. Multivariate Cox regression analysis was used to examine the effects of study parameters, which were determined to be statistically significant as a result of the univariate analysis, on overall survival independently. The results obtained were reported as risk ratios (hazard ratio [HR]) and within 95% confidence interval (CI). A p value of <0.05 was considered statistically significant.

RESULTS

Of the patients, 62% were in the 50 to 70 age range, while 22% of them were below 50 years old and 16% of them were above 70 years old.

The tumor characteristics of the patients and the results of their survival analyses are shown in Table 1. Accordingly, the median survival times of patients with a tumor size that is less than 3 cm, between 3 and 5 cm, more than 5 cm were calculated as 103 (range, 15.49 to 190.51) months, 20 (range, 2.56 to 37.44) months, and seven (range, 0 to 16.11) months, respectively. An analysis of the survival times based on the locations of tumors revealed that the median survival times of the patients, whose tumors were located in the middle zone, who had distal tumors, were 21 (range, 0 to 42.51) months and 27 (range, 11.99 to 42.01) months, respectively. The median survival time of the patients who had exophytic tumors macroscopically could not be calculated. On the other hand, the median survival time of the patients who had ulcerative tumors was calculated as 20 (range, 8.22 and 31.78) months. Additionally, the median survival time of the patients who had esophageal squamous cell carcinoma (ESCC) or esophageal adenocarcinoma (EAC) histologically were calculated as 32 (range, 23.89 to 40.11) months and nine (range, 3.95 to 14.05) months, respectively.

Survival analysis according to the disease stage revealed that the median survival times of Stage 1, Stage 2, and Stage 3 and 4 patients were 120 months, 20 months, and 15 months, respectively. The median survival time was calculated as 10 (range, 3.43 to 16.57) months in the patients with vascular invasion and 15 (range, 0.27 to 29.73) months in the patients with PNI. The median survival time of the patients with good, moderate, and poor differentiation were calculated as 120 months, 20 months, and nine months, respectively.

Survival analysis according to the T categories revealed that the median survival times of T2, T3, and T4 patients were 37 (range, 7.78 to 66.22) months, 20 (range, 5.14 to 34.86) months, and nine (range, 0 to 21.8) months, respectively. The median survival time of T1 patients could not be calculated. Survival

Table 1. Survival analysis according to tumor characteristics

Survival time (%)	n	1 year	3 years	5 years	*p*
Tumor size (cm)					
<3	20	85	65	55	
3-5	20	55	10	10	0.002
>5	10	30	20	10	
Localization					
Middle	17	52.9	35.3	35.3	0.727
Distal	33	66.7	33.3	24.2	
Macroscopic type					
Exophytic	8	87.5	87.5	87.5	0.001
Ulcerative	42	57.1	23.8	16.7	
Histological type					
SCC	35	71.4	42.9	34.3	0.022
Adenocarcinoma	15	40	13.3	13.3	
Stage					
1	9	88.9	88.9	77.8	
2	15	60	40	26.7	0.003
>3	26	53.8	11.5	11.5	
Vascular invasion					
No	30	73.3	43.3	36.7	0.069
Yes	20	45	20	15	
Perineural invasion					
No	20	75	60	55	0.001
Yes	30	53.3	16.7	10	
Differentiation degree					
Good	9	88.9	88.9	55.6	
Moderate	30	63.3	23.3	23.3	0.047
Poor	11	36.4	18.2	18.2	
T category					
1	4	75	75	75	
2	9	77.8	55.6	44.4	0.043
3	34	58.8	26.5	20.6	
4	3	33.3	0	0	
N category					
0	21	81	66.7	57.1	
1	15	53.3	20	13.3	<0.001
2	6	66.7	0	0	
3	8	25	0	0	

SCC: Squamous cell carcinoma.

analysis according to the N category revealed that the median survival times of N0, N1, N2, and N3 patients were 120 months, 15 months, 21 months, and seven months, respectively. Number of patients with less than a total of 15 resected lymph nodes, 15 to 25 resected lymph nodes, and more than 25 resected lymph nodes were found to be 29 (58%), 11 (22%), and 10 (20%), respectively. The ratio of the number of metastatic lymph nodes to the number of resected lymph nodes was found to be less than 0.2 in 32 (64%) patients and more than 0.2 in 18 (36%) patients. The proximal surgical margin was found to be less than 5 cm in 64% of the patients and between 5 and 10 cm in 36% of the patients.

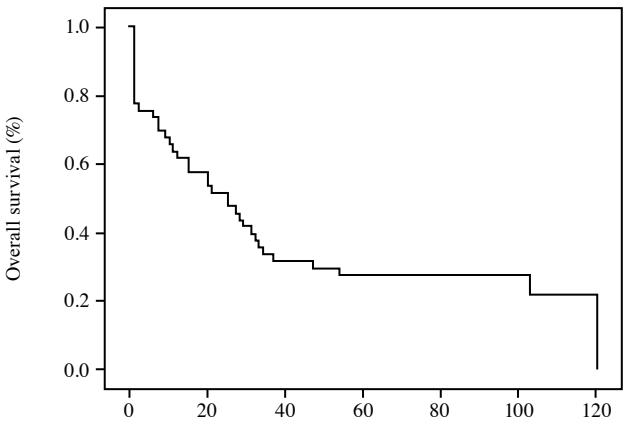


Figure 1. Overall survival analysis.

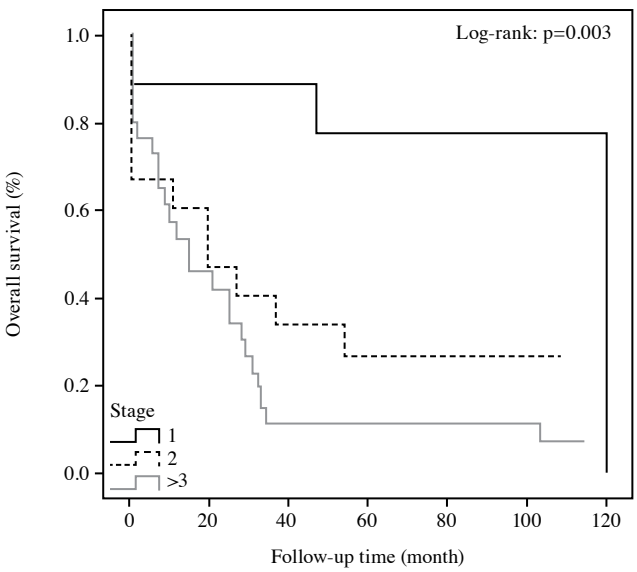


Figure 2. Survival analysis according to disease stage.

Complications were observed in 18 (36%) patients during the early postoperative period, of whom six had pneumonia, four had anastomotic leak, four had sepsis, two had arrhythmia, and two had bleeding. Chemotherapy and radiotherapy were administered to 52% of the patients following surgery.

The overall survival rates of the patients are shown in Figure 1. The one-year, three-year, and five-year survival rates of the patients were found to be

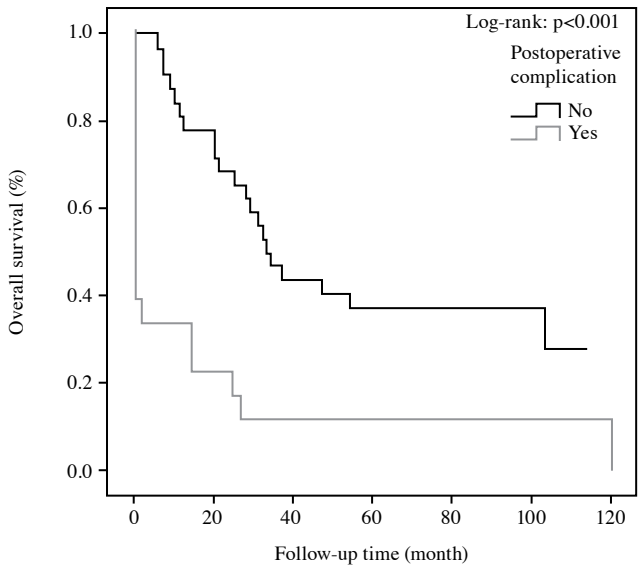


Figure 3. Survival analysis according to postoperative complications.

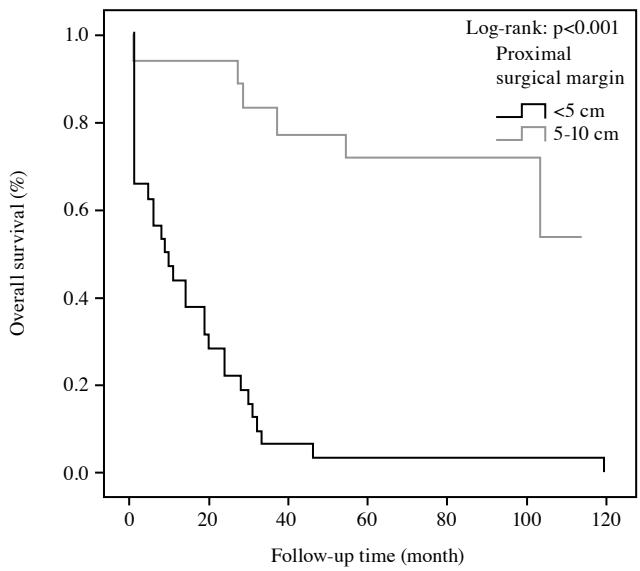


Figure 4. Survival analysis according to proximal surgical margins.

62%, 34%, and 28%, respectively. The median overall survival time was calculated as 25 (range, 12.14 to 37.86) months.

Survival rates according to the disease stage are given in Figure 2. Accordingly, one-year and three-year survival rates of Stage 1 patients were 88.9%, whereas five-year survival rate was 77.8%. Additionally, one-year, three-year, and five-year survival rates of Stage 2 patients were calculated as 60%, 40%, and 26.7%, respectively. Both one-year and three-year survival rates of the patients who were in Stage >3 disease were 53.8%, whereas five-year survival rate was found to be 11.5%. The survival rates of Stage 1 patients were found to be statistically higher than the other disease stages (p=0.003; log-rank test).

Survival rates according to the postoperative complications are given in Figure 3. Accordingly, one-year, three-year, and five-year survival rates of the patients without any complications were 78.1%, 46.9%, and 37.5%, respectively. Where as the one-year survival

Table 2. Multivariate Cox regression analysis of prognostic factors affecting overall survival

Variables	HR (%95 CI) p	*p*
Tumor size (cm)		
<3 (reference)		
3-5	1	-
3-5	2,584 (0,794-8,408)	0.115
>5	1,113 (0,317-3,916)	0.867
Macroscopic type		
Exophytic (reference)	1	-
Ulcerative	2.06 (0,187-22,743)	0.555
Histological type		
SCC (reference)	1	-
Adenocarcinoma	0,547 (0,175-1,713)	0.300
Stage		
1 (reference)	1	-
2	53,372 (3,788-752,09)	0.003
>3	16.26 (1,003-267,017)	0.048
Perineural invasion		
(No reference)	2,155 (0,691-6,724)	0.186
Differentiation degree		
Good (reference)	1	-
Moderate	0,417 (0,048-3,615)	0.427
Poor	0,291 (0,031-2,758)	0.282
N category		
0 (reference)	1	-
1	1,012 (0,281-3.65)	0.986
2	1,405 (0,316-6,258)	0.655
3	3,223 (0,446-23.31)	0.246
Postoperative complications		
(No reference)	4,888 (1.72-13,894)	0.003
Metastatic lymph nodes/resected lymph nodes		
<0.2 (reference)	1	-
>0.2	2,726 (0,832-8,937)	0.098
Proximal surgical margin (cm)		
<5	14,231 (3,299-61,383)	<0.001
5-10 (reference)	1	-

HR: Hazard ratio; CI: Confidence interval; SCC: Squamous cell carcinoma.

rate of patients with postoperative complications were found to be 33.3%; three- and five-year survival rate of patients with postoperative complications were found to be 11.1%. The survival rates of the patients with complications were statistically lower than the patients without any complications (p<0.001; log-rank test).

Survival rate analysis according to the proximal surgical margins revealed that one-year, three-year, five-year survival rates of the patients with proximal surgical margins less than 5 cm were 43.8%, 6.3%, and 3.1%, respectively. Additionally, one-year, three-year, and five-year survival rates of the patients with proximal surgical margins between 5 and 10 cm were found to be 94.4%, 83.3%, and 72.2%, respectively. The survival rates of the patients with proximal surgical margins between 5 and 10 cm was statistically higher than the survival rates of other patients (p<0.001; log-rank test) (Figure 4).

The results of the multivariate Cox regression analysis which was performed to identify the prognostic factors affecting overall survival are shown in Table 2. Accordingly, the tumor size, macroscopic/histological type of the tumor, PNI, degree of differentiation, N category, and the number of metastatic lymph nodes/resected lymph nodes did not have any statistically significant effect on overall survival independently (p>0.05). However, Stage 2 patients and patients who had Stage >3 disease had worse overall survival rates, compared to Stage 1 patients (HR: 16.26; 95% CI: 1.003-267.017; p=0.048). Postoperative complications negatively affected overall survival (HR: 4.888; 95% CI: 1.72-13.894; p=0.003). A proximal surgical margin of less than 5 cm had also a negative effect on overall survival (HR: 14.231; 95% CI: 3.299-61.383; p<0.001).

DISCUSSION

Esophageal cancer is caused by an extremely aggressive tumor and has become a general health problem worldwide. The mean age of the onset of esophageal cancer is 67 years and it is predominantly seen in males (male/female ratio, 3:1).[4] In comparison, the mean age of the patients included in this study was 57.8±11.8 years, indicating a relatively younger population. The ratio of male patients-to-female patients was 1.9:1. Consistently, Koppert et al.[7] reported an increase in postoperative mortality in patients aged >70 years in their retrospective study including 923 ESCC and 1,881 EAC patients; however, age factor alone was not a prognostic indicator in the long-term overall survival. Similarly, in this study, no significant difference was found between the survival rates in terms of age groups (p=0.469 for <70 years and p>0.05 for >70 years, respectively).

There is no consensus on the natural course or treatment results of neither EAC nor ESCC. Therefore, the literature data regarding the relationship between histopathological tumor type and prognosis are contradictory. In a study including 577 patients, of whom 314 were ESCC patients and 263 were EAC patients, Mirnezami et al.[1] observed that EAC reduced overall survival times more than ESCC. The findings reported by Cummings et al.[3] also support the results of Mirnezami et al.'s[1] study. In contrast, Stein et al.[2] reported that the survival rates associated with early EAC were superior to the survival rates associated with ESCC, and attributed this result to the fact that patients exposed to ESCC pathology had usually more severe comorbid conditions, a poorer diet and functional status, and a lower socioeconomic status. In this study, the five-year survival rates of ESCC and EAC patients were found to be 34.3% and 13.3%, respectively, indicating a statistically significantly higher survival rates of ESCC patients (p=0.022).

In this study, 84% of the patients had ulcerative and 16% of the patients had exophytic tumors. Comparison of the survival rates associated with both groups revealed that the survival rates of patients with exophytic macroscopic type tumor were statistically significantly higher than the other type (p=0.001). Similarly, Xiue et al.,[8] in their study including 199 patients, reported that the ulcerative-infiltrative macroscopic type tumor had a high risk of lymph node metastasis and that it was a negative prognostic factor for disease-free survival.

In many studies, tumor length has the potential to predict prognosis. Hollis et al.[9] retrospectively examined 389 patients via endoscopy, endoscopic ultrasonography, positron emission tomography-computed tomography and pathology, and found that a tumor size of >3 cm was a significant prognostic factor for survival. A tumor length over 3 cm yielded the same results in Zeybek et al.'s[10] study including 116 patients, supporting the aforementioned finding reported by Hollis et al.[9] In addition, in a retrospective study involving 1,453 patients who underwent curative resection, Wu and Chen[11] reported that the tumor size increased the predictive accuracy of the TNM classification in respect of overall survival. On the contrary, in this study, survival rates of the patients with a tumor size of <3 cm were found to be statistically significantly higher than the survival rates of other patients (p=0.002).

In the current study, the survival rates in the group of patients with a good degree of differentiation were statistically significantly higher than the groups of patients with a moderate and poor degree of differentiation (p=0.047). Situ et al.[12] investigated the postoperative survival of 317 patients with T2N0M0 type ESCC based on the degree of differentiation and found that the differentiation degree of the tumor was an independent prognostic factor for overall survival. Li et al.[13] also reported that the degree of differentiation was a predictive factor for lymph node metastasis, and that survival was negatively affected, as the lymph node involvement rate was high in poorly differentiated tumors.

Migration according to PNI has been shown to be a new type of metastasis in recent years. In a meta-analysis including 13 cohort studies, Gao et al.[14] reported that 1,475 of 2,770 patients who underwent esophagectomy had PNI, and that PNI positivity (+) predicted a low overall survival, regardless of the histological type of the tumor. On the other hand, in this study, the five-year survival rates of the patients with PNI were found to be statistically significantly lower than those who did not have PNI (p=0.001).

The most important prognostic factor during the post-esophagectomy period is the TNM pathological stage.[15] Kunisaki et al.[15] evaluated 257 patients, who underwent R0 esophagectomy, in terms of survival, and found that the TNM stage was an independent prognostic factor until the third year of the postoperative period. Similarly, Mirnezami et al.[16] and Haisley et al.,[17] in studies including 383 patients and 98 patients, respectively, found that the disease stage was an independent prognostic factor for both disease-free and overall survival and that an increase in disease stage, as defined based on the TNM classification, was associated with reduced survival. However, in this study, the survival rates of Stage 1 patients were found to be significantly higher than the survival rates of patients of other stages (p=0.003).

Pathological tumor size stage (pT) and pathological nodal stage (pN), which are among the components of the staging system, are important prognostic factors for survival. A correlation was reported between pN and pT, tumor size, and the degree of differentiation in the studies available in the literature. Lymph node metastasis significantly affects survival and the survival rates decrease as the metastasis rate increases. In a study including 336 patients, Bus et al.[18] reported that the pT and N category were independent prognostic factors for survival. Sun et al.[19] reported similar results in their study in 117 patients. In another study, in which survival of 446 patients following curative esophagectomy was investigated, N category was an independent prognostic factor for survival, and that the survival rates were significantly higher in pT1 and pT2, compared to other pT groups (p=0.002).[20] Unlike these results, in this study, survival rates significantly decreased, as the T category increased (p=0.043). The same correlation was also identified for the N category and, accordingly, the survival rates of the patients in the N0 category were found to be statistically significantly higher than those in other categories, namely, N1, N2, and N3 (p<0.001).

Furthermore, the number of metastatic lymph nodes is an important prognostic factor. Metastatic LNR is the ratio of the number of positive lymph nodes to the total number of dissected lymph nodes. In general, the base potential prognostic value of LNR is 0.2. In a study including 387 patients who underwent curative esophagectomy, Zhang et al.[21] found that the overall survival improved (p<0.001) in the patients with LNR <0.2, and that the prognosis was poor in patients with LNR >0.4. In another study involving 1,301 patients, a significant decrease was observed in overall survival in the group with LNR >0.2.[22] Unlike these findings, in this study, the survival rate of the patients with LNR <0.2 was found to be statistically significantly higher (p<0.001).

One of the key prognostic factors affecting the local recurrence and long-term survival following esophagectomy is the resection of borderline. Taking into account that the distal esophagus may be completely resected in esophagectomy, the remaining proximal esophageal border becomes even more important. There are different results as to the length of the safe proximal margins in the literature, ranging from 3 to 10 cm.[23] In one of these studies, which was conducted in 352 patients, Barbour et al.[24] reported that a clear proximal border of approximately 5 cm was an independent prognostic factor in survival. On the other hand, in another study in 516 patients with ESCC, Kang et al.[25] found the mean proximal resection margin to be 3.4±2.5 cm, and they found the possibility of recurrence to be significantly higher in patients with N (+) with a border length of >5 cm. However, in the current study, the survival rates of the patients with a proximal surgical margin length between 5 and 10 cm were statistically significantly higher than the others (p<0.001).

Esophagectomy is an invasive procedure with serious postoperative complications that can lead to pneumonia, anastomotic leak, and even multiorgan

failure. Many studies have been carried out to investigate the effect of postoperative complications on long-term survival. In one of these studies, Kateoka et al.[26] investigated 152 patients who underwent transthoracic esophagectomy in terms of postoperative complications and identified pneumonia in 22 (14%), anastomotic leakage in 21 (14%), and infection in 54 patients (36%). They also found that the survival time of patients with pneumonia was significantly shorter than those without pneumonia. In another study, Boaka et al.[27] investigated 402 patients and performed survival analysis in 284 patients who could be followed for a period of five years. As a result, they found that pneumonia was a negative prognostic factor for overall survival (p=0.035). In a large-scale study, in which the files of 2,439 patients between 2000 and 2010 which were obtained from 30 hospital databases were investigated, anastomotic leakage was developed in 208 patients (8.5%), and the anastomotic leakage was associated with advanced-stage tumors and other complications, resulting in a significant reduction in the overall survival (p=0.002) and disease-free survival (p=0.005).[28] However, in this study, the most frequent postoperative complications were respiratory complications, and the survival rates of the patients with complications were statistically significantly lower (p<0.001).

There are some limitations to this study. The fact that the healthcare center where the study was conducted is not in the endemic region for esophageal cancer led to the small sample size, which may have affected the statistical analysis results of overall survival.

In conclusion, our study showed that the tumor size, degree of differentiation, T and N categories, and the metastatic lymph node rate were important prognostic factors affecting long-term survival of esophageal cancer patients following esophagectomy. However, these factors did not have a statistically significant effect on the overall survival independently. Accordingly, the main factors affecting the prognosis were the presence of a tumor of Stage ≥2, any postoperative complications, and a proximal surgical margin of less than 5 cm. Based on these findings, all these prognostic factors seem to affect long-term survival of this patient population. Nevertheless, further large-scale, prospective studies are needed to draw a firm conclusion.

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