Factors affecting survival in esophageal squamous cell carcinoma: Single-center experience

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ABSTRACT

OBJECTIVE: Squamous cell esophageal cancer (ESCC) is a highly fatal malignancy. This study aims to investigate the factors affecting survival in patients with metastatic and non-metastatic ESCC.

METHODS: Between 2008 and 2016, 107 patients with ESCC who were followed up in an oncology clinic were included in the analysis. Patients were grouped based on the stage of disease as clinical-stage II to IV.

RESULTS: Of the 107 patients, 55 (55.1%) of them were male and 52 (48.6%) of them were female. The mean age was 60.8 years. Based on the clinical-stage, 28 (26.2%) patients had stage II disease, 33 (30.8%) had stage III disease, and 46 (43.0%) had stage IV disease. Twenty-nine (27.1%) patients with the non-metastatic disease underwent surgery following neoadjuvant chemoradiotherapy (CRT), while 29 (27.1%) patients received definitive CRT. Twenty-six (56.5%) patients with metastatic disease received chemotherapy (CT). While median overall survival (mOS) could not be reached in patients who underwent surgery following neoadjuvant CRT, mOS for patients receiving definitive CRT versus patients treated with surgery alone–was 22.0 months and 24.0 months, respectively (p=0.008). In the metastatic stage, mOS was 8.0 months for the patients treated with a first-line CT and 3.0 months for patients receiving best supportive care (p<0.001). In multivariate analysis, factors predicting survival in patients with the non-metastatic disease were ECOG PS 3-4 (Hazard ratio [HR], 6.13), undergoing surgery (HR, 0.22), clinical-stage III disease (HR, 3.19), and presence of recurrence (HR, 24.12). For patients with metastatic disease, ECOG PS 3-4 (HR, 3.31), grade-III histology (HR, 3.39), liver metastasis (HR, 2.53), and receiving CT (HR, 0.15) were the factors associated with survival in multivariate analysis.

CONCLUSION: In our study, surgery and early clinical-stage increased survival, whereas experiencing recurrence adversely affected survival in non-metastatic ESCC. In the metastatic stage, ECOG PS 3-4, grade-3 histology and liver metastasis adversely affected survival, while receiving CT significantly improved survival.

Keywords: Chemoradiotherapy; chemotherapy; esophageal cancer; squamous cell carcinoma; survival.

Esophageal cancer (EC) is a highly fatal malignancy. In the USA, approximately 17,750 people are diagnosed with EC each year, with 16,080 deaths from EC for the same year [1]. Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) account for more than 95% of EC cases [2]. Although

the incidence of ESCC in the USA has declined, the incidence of EAC has increased dramatically over the last few years. However, ESCC still remains dominant worldwide [3, 4].

Some risk factors associated with ESCC have been identified in the studies. It is estimated that around 90% of the ESCC cases in the USA are due to smoking, alcohol consumption, and a lower intake of fruits and vegetables. The importance of certain risk factors varies considerably in other parts of the world. In Iran and other Asian countries, the main risk factors for SCC are not well-understood but are thought to be poor nutritional status, low fruit and vegetable intake, and higher temperatures of beverage consumption [5–8].

At the time of diagnosis, 50–80% of the EC patients have locally-advanced or metastatic disease, regardless of histology [6]. While surgery alone may be curative in early stages of the disease, multimodality treatments, including definitive chemoradiotherapy (CRT) and neoadjuvant chemoradiation (NCRT), followed by surgery is recommended for most locally-advanced EC cases. The 5-year survival rate for locally-advanced cases rarely exceeds 30% [9, 10].

Previous studies have reported that stage, Glasgow Prognostic Score, neutrophil-to-lymphocyte ratio, serum squamous cell carcinoma antigen and cytokeratin-19 are the important prognostic markers for ESCC [11–15]. This study aims to investigate the factors affecting survival in ESCC patients.

MATERIALS AND METHODS

Patients

Medical record of ESCC patients who were followed up and treated at the oncology clinic between 2008 and 2016 were included in this retrospective study. Histological subtypes other than ESCC, patients <18 years of age, patients with multiple malignancies, patients with missing data were excluded from the analysis. A total of 107 eligible patients were included for the analysis in this study.

Data Collection

The following parameters for each patient were collected from the medical records: age, gender, comorbidities (hypertension, diabetes mellitus, chronic ischemic heart disease, and chronic obstructive pulmonary disease), smoking status, alcohol consumption, initial symptoms,

Eastern Cooperative Oncology Group performance status (ECOG-PS), tumor grade, presence of obstruction, treatments [NACRT, chemotherapy(CT), surgery], treatment regimens [carboplatin-paclitaxel (CP) or cisplatin-5- Fluorouracil (CF)], clinical tumor stage, the site of recurrence or metastasis, and primary tumor localization. The patients were staged according to findings of thoracoabdominal computed tomography and/or PET/CT. NACRT or definitive CRT was given with CF or CP. Radiotherapy was delivered at a total dose of 50.4–66.0 Gy given in 28–35 fractions of 1.8–2.0 Gy per fraction in definitive CRT and total dose of 41.4–50.4 Gy given in 23–28 fractions of 1.8 Gy per fraction in NACRT. Patients were divided into two groups according to ECOG-PS as follows: ECOG-PS 0–2 and ECOG-PS 3–4. Tumor grades were stratified into two groups as follows; grade 1–2 and grade 3. Overall survival (OS) was calculated as the time from the date of diagnosis to the date of death or last follow-up.

Statistical Analysis

Statistical Package for Social Sciences 22.0 for Windows software (Armonk NY, IBM Corp. 2013) was used for the statistical analysis. Descriptive statistics for categorical variables were given as number and percentage. Descriptive statistics for numerical variables were presented as mean, standard deviation, minimum and maximum. Chi-square analysis was used to compare the ratios in the groups. Monte Carlo simulation was applied when the conditions were not met. The determinant factors were examined by Cox Regression Analysis. The backward stepwise model was used for $p < 0.150$ values in univariate analysis. Survival analyzes were performed by Kaplan Meier Analysis. The statistical significance level was accepted as $p < 0.05$.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki and reviewed and approved by the Ethics Committee of the Okmeydani Training and Research Hospital, University of Health Sciences, with the decision number 48670771-514.10.

RESULTS

Of the 107 patients, 55 (55.1%) were male and 52 (48.6%) were female. The mean age was 60.8±12.8 (range, 27–95) years. Thirty-one (29.0%) patients had

TABLE 1. Patient data

	Patients (n=107) %	Stage II-III (n=61) %	Stage IV (n=46) %	p
Gender				
Female	51.4	39.3	67.4	**0.004**
Male	48.6	60.7	32.6	
Age (years) Mean±SD	60.8±12.8	57.5±12.8	64.5±12.0	**0.008**
Comorbidity				
HT	29.0	24.6	34.8	0.250
DM	8.4	8.2	8.7	0.927
CIHD	5.6	6.6	4.3	0.619
CPOD	3.7	3.3	4.3	0.774
Smoking	50.5	41.0	63.0	**0.024**
Alcohol consumption	3.7	0.0	8.7	**0.019**
Symptom				
Dysphagia	89.7	91.8	87.0	0.525
Abdominal pain	23.4	23.0	23.9	0.907
Weight loss	29.0	23.0	37.0	0.114
Presence of obstruction	49.5	36.1	67.4	**0.001**
ECOG PS				
0–2	93.5	96.7	89.1	0.336
3–4	6.5	3.3	10.9	
Grade				
I-II	82.2	88.5	73.9	0.051
III	17.8	11.5	26.1	
Clinical-stage				
II	26.2	45.9		
III	30.8	54.1		
IV	43.0		100.0	
Primary tumor localization				
Upper 1/3	12.1	9.8	15.2	0.120
Middle 1/3	57.0	65.6	45.7	
Lower 1/3	30.8	24.6	39.1	
Treatments				
Definitive CRT		27.1		
CRT followed by surgery		27.1		
Surgery alone		4.9		
Neoadjuvant CRT regimen				
CP	48.3	48.3		
CF	51.7	51.7		
Definitive CRT regimen				
CP	44.8	44.8		
CF	55.2	55.2		
Surgery	35.5	52.5	13.0	**<0.001**
Recurrence				
No		55.7		
Local		8.2		
Systemic		36.1		
The site of metastasis at diagnosis				
Distant LN	41.3		41.3	
Liver	26.1		26.1	
Lung	30.4		30.4	
Bone	10.9		10.9	
Peritoneum	6.5		6.5	
First-line treatment in metastatic setting				
CT	53.4	48.1	56.5	0.489
BSC	46.6	51.9	43.5	
First-line CT regimen				
CF	66.7	46.2	76.9	0.077
CP	33.3	53.8	23.1	
Final status				
Dead	60.7	41.0	87.0	**<0.001**
Alive	39.3	59.0	13.0	

BSC: Best supportive care; CF: Cisplatin-5-florourasil; CIHD: Chronic ischemic heart disease; COPD: Chronic obstructive lung disease; CP: Carboplatin-paclitaxel; CRT: Chemoradiation; CT: Chemotherapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; DM: Diabetes mellitus; HT: Hypertension; Max.: Maximum; Min.: Minimum; LN: Lymph node; SD: Standard deviation.

hypertension, nine (8.4%) patients had diabetes mellitus, six (5.6%) patients had chronic ischemic heart disease, and four (3.7%) patients had chronic obstructive pulmonary disease. The ECOG PS was 3–4 in seven (6.5%) patients (Table 1).

Twenty-eight (26.2%) patients had clinical-stage II disease, 33 (30.8%) patients had stage III disease, and 46 (43.0%) patients had stage IV disease. Primary tumor was localized in upper 1/3 esophagus in 13 (12.1%) patients, middle 1/3 esophagus in 61 (57.0%) patients, and lower 1/3 esophagus in 33 (30.8%) patients. Recurrence developed in 27 (44.3%) patients with clinical-stage II to III disease during the follow-up, with five (8.2%) patients and 22 (36.1%) of them being lo-
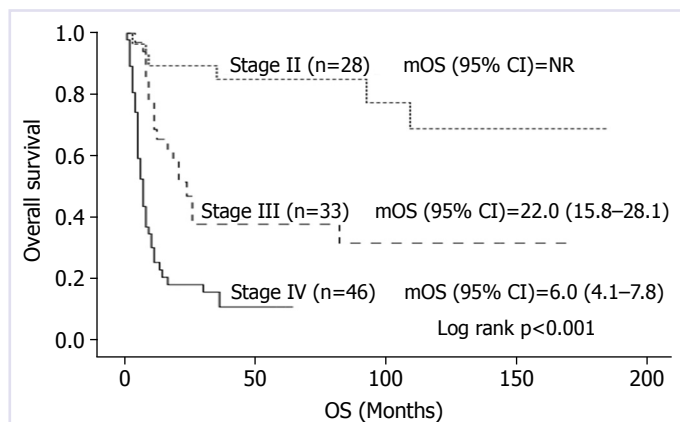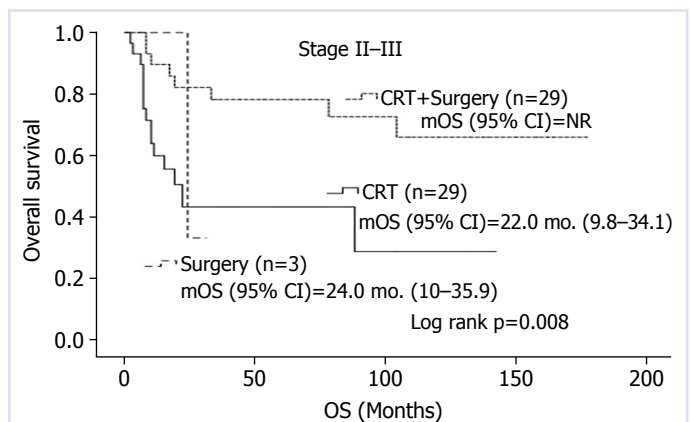
FIGURE 1. Overall survival according to the stage at diagnosis.

mOS: Median overall survival; NR: Not reached; OS: Overall survival.

FIGURE 2. Overall survivals according to the treatment modalities in non-metastatic patients.

mOS: Median overall survival; OS: Overall survival; CRT: Chemoradiation.

FIGURE 3. Overall survivals according to the treatment modalities in metastatic patients.

mOS: Median overall survival; OS: Overall survival.

cal recurrence and systemic metastasis, respectively. At the time of diagnosis, the site of metastasis was distant lymph nodes (LN) in 19 (41.3%) patients, liver in 12 (26%) patients, lung in 14 (30.4%) patients, bone in five (10.6%) patients, and peritoneum in three (6.5%) patients (Table 1).
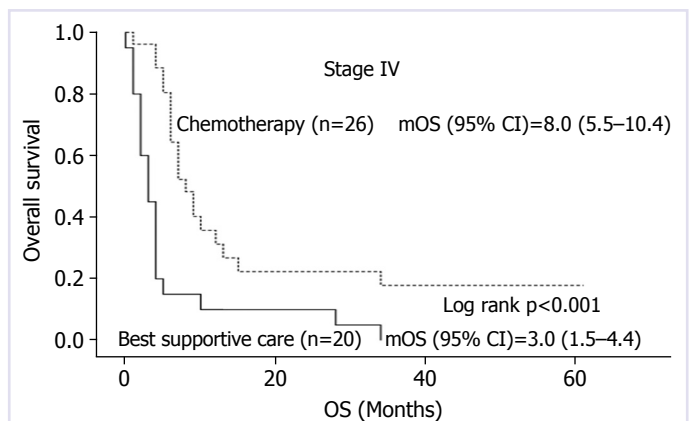
Of the 38 (35.5%) patients who underwent surgery, 32 (78.9%) had curative surgery. NACRT was given to 29 (27.1%) patients, 14 (48.3%) of whom received concurrent carboplatin (AUC2, iv. on day 1) and paclitaxel (50 mg/m², iv. on day 1) (CP) weekly for five weeks and 15 (51.7%) received concurrent cisplatin (75 mg/m², on days 1 and 29) and 5-Fluorouracil (iv continuous infusion over 24 hours daily on days 1–4 and 29–33) (CF) 35-day cycle. Definitive CRT was given to 29 (27.1%) patients, 13 (44.8%) of whom received carboplatin (AUC2, iv. on day 1) and paclitaxel (50 mg/m² iv on day 1) weekly for five weeks and 16 (55.2%) received cisplatin (75 mg/m² iv on days 1 and 29) and 5-Fluorouracil (1000 mg/m², iv continuous infusion over 24 hours daily on days 1–4 and 29–33) 35-day cycle. Of the 27 patients with the non-metastatic disease at diagnosis who developed recurrence during follow-up, 13 (48.1) received a first-line CT. Among 46 patients with metastatic disease at diagnosis, 26 (56.5%) received CT. During the median follow up time of 24 months, 65 (60.7%) patients died (Table 1).

Median overall survival (mOS) was not achieved in clinical-stage II patients, 22.0 (15.8–28.1) months in stage III patients, and 6.0 (4.1–7.8) months in stage IV patients (log rank p<0.001) (Fig. 1). In clinical-stage II-III patients, mOS could not be reached in patients who underwent surgery following neoadjuvant CRT, whereas

mOS was only 22.0 months in patients receiving definitive CRT and 24.0 months in those treated with surgery alone (log rank p=0.008) (Fig. 2). In metastatic stage, mOS was 8.0 months for those treated with first-line CT and 3.0 months for patients receiving best supportive care (log rank p<0.001) (Fig. 3).

In the univariate analysis; presenting with dysphagia (Hazard ratio [HR], 0.26), ECOG PS (HR, 4.50) undergoing surgery (HR, 0.31), presence of obstruction (HR, 3.62), receiving NACRT (HR, 0.28), stage (HR, 4.09), and experiencing recurrence (HR, 7.30) were the factors affecting survival in patients with stage II-III disease (p=0.016, p=0.049, p=0.006, p=0.003, p=0.003, p=0.004, p=0.003, p=0.001, respectively), while gender (HR, 0.43), smoking (HR, 2.50),–ECOG PS

TABLE 2. Univariate analysis for survival according to the stages

		Stage II-III			Stage IV		
		HR	95.0% CI		p	HR	95.0% CI		p
Gender	Female vs. male	0.584	0.264	1.290	0.184	0.430	0.206	0.898	**0.025**
Age	(year)	1.027	0.993	1.062	0.117	1.000	0.974	1.026	0.986
HT	Yes vs. no	1.533	0.658	3.572	0.322	1.205	0.627	2.318	0.575
DM	Yes vs. no	1.891	0.555	6.438	0.308	1.314	0.463	3.725	0.608
CIHD	Yes vs. no	2.089	0.622	7.014	0.233	1.056	0.253	4.412	0.940
COPD	Yes vs. no	1.333	0.179	9.921	0.779	1.246	0.297	5.235	0.764
Smoking	Yes vs. no	0.551	0.237	1.280	0.166	2.501	1.174	5.326	**0.018**
Alcohol consumption	Yes vs. no					0.535	0.278	1.706	0.510
Dysphagia	Yes vs. no	0.260	0.086	0.782	**0.016**	0.459	0.186	1.133	0.091
Abdominal pain	Yes vs. no	0.731	0.274	1.950	0.531	0.791	0.376	1.664	0.536
Weight loss	Yes vs. no	0.774	0.290	2.065	0.609	0.716	0.372	1.379	0.318
ECOG PS	3–4 vs. 0–2	4.505	1.007	20.164	**0.049**	3.603	1.297	10.009	**0.014**
Grade	III vs. I-II	0.216	0.029	1.620	0.136	1.918	0.949	3.879	0.070
Surgery	Yes vs. no	0.317	0.139	0.724	**0.006**	1.457	0.606	3.501	0.400
Obstruction	Yes vs. no	3.627	1.543	8.525	**0.003**	1.294	0.666	2.511	0.447
Neoadjuvant CRT	Yes vs. no	0.281	0.118	0.668	**0.004**				
Stage	III vs. II	4.096	1.615	10.387	**0.003**				
Recurrence	Yes vs. no	7.301	3.027	17.609	**0.001**				
Distant LN metastasis	Yes vs. no					1.704	1.006	2.885	0.047
Liver metastasis	Yes vs. no					3.117	1.585	6.131	**0.001**
Lung metastasis	Yes vs. no					0.365	0.202	0.658	**0.001**
Bone metastasis	Yes vs. no					0.802	0.251	2.559	0.709
Peritoneum metastasis	Yes vs. no					1.181	0.288	4.833	0.817
CT vs. BSC						0.327	0.172	0.620	**<0.001**

CI: Confidence interval; HR: Hazard ratio; BSC: Best supportive care; CIHD: Chronic ischemic heart disease; COPD: Chronic obstructive lung disease; CRT: Chemoradiation; CT: Chemotherapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; DM: Diabetes mellitus; HT: Hypertension; LN: Lymph node.

(HR, 3.60), liver metastasis (HR, 3.11), lung metastasis (HR, 0.36), and CT (HR, 0.36) were found to be the factors related to survival in patients with stage IV disease (p=0.025, p=0.018, p=0.014, p=0.001, p=0.001, p<0.001, respectively) (Table 2).

In multivariate analysis, ECOG PS (HR, 6.13), undergoing surgery (HR, 0.22), stage (HR, 3.19), and experiencing recurrence (HR, 24.12) were the factors associated with survival in patients with stage II-III disease (p=0.028, p=0.002, p=0.031, and p<0.001, respectively), while ECOG PS (HR, 3.31), tumor grade (HR, 3.39), liver metastasis (HR, 2.53), and receiving CT (HR, 0.15) were the independent predictors of survival in stage IV patients (p=0.004, p=0.002, p=0.023, and p<0.001, respectively) (Table 3).

DISCUSSION

In this study, we investigated the factors affecting survival in ESCC patients. In non-metastatic disease, undergoing surgery and early stage of the disease increased survival, whereas experiencing recurrence adversely affected survival. In patients with metastatic disease, the presence of ECOG PS 3–4, grade-III histology, and liver metastasis adversely affected survival, whereas CT administration significantly improved survival.

Although the main risk factors for ESCC are not well–understood, it is supposed that malnutrition, low fruit and vegetable consumption, and higher temperatures of food and beverage consumption are the possible risk factors [5]. In areas where ESCC is endemic, disease has no

Table 3. Multivariate analysis for survival according to stages

		Stage II-III					Stage IV		
		HR	95.0% CI	p			HR	95.0% CI	p
ECOG PS	3–4 vs. 0–2	6.138	1.212–31.075	**0.028**	ECOG PS	3–4 vs. 0–2	3.313	1.141–9.693	**0.004**
Surgery	Yes vs. no	0.229	0.092–0.570	**0.002**	Grade	III vs. I-II	3.397	1.551–7.439	**0.002**
Stage	III vs. II	3.195	1.111–9.183	**0.031**	Liver metastasis	Yes vs. no	2.537	1.134–5.672	**0.023**
Recurrence	Yes vs. no	24.128	6.455–90.180	**<0.001**	CT vs. BSC		0.156	0.069–0.348	**<0.001**

CI: Confidence interval; CT: Chemotherapy; BSC: Best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: Hazard ratio.

gender specificity. However, ESCC is more common in men in low incidence areas [16]. In our study, more than half of the patients were active smokers; however, smoking status in metastatic stage did not affect survival in multivariate analysis although it was associated with survival in univariate analysis. In our study, only 3.7% patients had a history of alcohol consumption. Interestingly, most of the patients with early stage were male, while the majority of the patients in the metastatic stage were female. The reason for the higher number of female patients with metastatic disease may be due to the delay in diagnosis because of late applications to health institutions.

In ESCC, tumoral obstruction of the esophagus causes progressive dysphagia, often accompanied by weight loss. Dysphagia usually occurs when the esophageal lumen diameter is less than 13 mm and this finding indicates advanced disease [17]. Half of the patients included in the study had obstruction at the time of diagnosis, approximately 90% of the patients had dysphagia, and 29% of the patients had weight loss. The rate of presenting with obstruction at metastatic stage was significantly higher. Three-fourths of patients in the study had locally-advanced or metastatic disease.

RTOG 85–01 study by Al Sarraf et al. [18] included 123 patients with ESCC or EAC and compared RT to definitive CRT in locally-advanced stage. Sixty-two patients received RT alone and 61 patients received definitive CRT with CF. The mOS in the definitive CRT arm was 14.1 months compared to 9.3 months in the RT alone arm. Later, 69 patients were treated with combined modality approach and the results were reported to be similar to the previous findings, with mOS being 17.2 months. In a study by Stahl et al. [19], 172 patients with locally-advanced EC were randomized to three cycles of induction CT followed by NACRT and surgery arm or

definitive CRT arm. There was no significant difference in mOS between the two groups after a 6-year of follow-up time. The 2-year locoregional control rate was better in patients undergoing surgery. In the metaanalyzes evaluating NACRT studies in EC, NACRT has been shown to provide better results compared to surgery alone [20–22]. In a meta-analysis by Jin et al. [20], which evaluated 14 randomized trials comparing NACRT to surgery alone, local control rates and survival rates were reported to be better with NACRT than surgery alone. Similarly, in meta-analysis conducted by Urschel et al. [21], which included nine randomized trials comparing NACRT to surgery alone, both 3-year survival and local control rate were found to be better in the NACRT arm.

In our study, 29 patients were treated with definitive CRT and had mOS of 22 months. In our study, there were no patients who received RT alone, whereas 29 patients underwent surgery following NACRT and mOS could not be reached. Only three patients were treated with surgery alone and had mOS of 24 months. In our study, no adjuvant treatment was administered. In multivariate analysis, undergoing surgery significantly improved survival. Of 29 patients treated with definitive CRT, 14 (49.3%) had recurrence, with 3 (10.3) of them experiencing local recurrence. Of 29 patients who underwent surgery following NACRT, 10 (34.5%) had recurrence, with only one (3.4%) of them experiencing local recurrence. All patients (n=3) who treated with surgery alone developed recurrence, with one (33.3%) of them having local recurrence.

Javle et al. [23] included 172 EC patients in their analysis, 74 of whom were ESCC. In the study, stage and surgery were found to be independent factors affecting survival. Similarly, Kumagai et al. [24] found that stage was the independent factor associated with survival in

ESCC patients treated with surgery. In our study, clinical-stage and ECOG PS in non-metastatic stage were the factors related to survival. In addition, experiencing recurrence increased the mortality by 24-fold. In non-metastatic disease, undergoing surgery following NACRT decreased mortality by 80%.

It has been shown CT administration in metastatic EC patients prolongs survival and reduces symptoms [25, 26]. Likewise, it was shown in our study that receiving CT significantly prolonged survival in patients with metastatic disease. In addition, grade 3 histology, liver metastasis, and ECOG PS adversely affected survival in metastatic stage.

The strengths of our study were that this study included only ESCC patients and analyzed metastatic and non-metastatic patients separately. Moreover, median follow-up time was relatively longer. However, its retrospective nature, single-center design, and small sample size were the limitations of the present study.

In conclusion, undergoing surgery, ECOG-PS, stage, and experiencing recurrence were the significant factors associated with survival in patients with the non-metastatic disease, while grade, ECOG PS, liver metastasis, and receiving CT were the independent predictors of survival in patients with metastatic disease.

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