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Clinicopathological features and outcomes of 251 patients with esophageal cancer in the Eastern Anatolian Region of Turkey where upper gastrointestinal system tumors are endemic: Single-center data

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ABSTRACT

***Background*:** We aimed to report demographic features, tumor characteristics, and survival outcomes of the patients with esophageal cancer (EC) in the Eastern Anatolian Region of Turkey, where upper gastrointestinal tumors are endemic. ***Materials and Methods*:** Our retrospective investigation was performed on patients with EC treated in Erzurum Regional Training and Research Hospital Clinics of Medical and Radiation Oncology between 2005 and 2017. The patients with stage IIA-IV disease and completed at least one treatment modality (surgery/ definitive chemoradiotherapy (CRT)/palliative chemotherapy(CT) or radiotherapy(RT)) had enrolled in the study. The demographic and clinicopathological characteristics, TNM stage, oncological treatment modalities applied, and survival outcomes were statistically analyzed. ***Results*:** Our study consisted of 251(women, 57.4%) patients with EC with a female/ male ratio of 1.34/1. The median age of the patients was determined as 62 years. The primary tumor was frequently localized in the middle(46.6%) and lower(46.2%) part of the esophagus, and the majority had squamous cell carcinoma histopathological subtype(86.1%). The median follow-up period and overall survival (OS) time were 21.2 and 19.0 months, respectively. A five-year OS rate was detected as 19.3%. As a result of multivariate analysis; grade, stage and concurrent CRT were determined as independent prognostic factors (p=0.004, p=0.019, and p=0.014, respectively). The median OS of stage II-III and IV patients were 25.79 versus 10.02 months (p<0.001). Among stage II-III patients, the best median OS was in the surgery+ adjuvan RT/CRT group(37.02 months). In stage IV patients, the median OS of female patients was found to be statistically significantly higher than that of males(15.77 versus 9.29 months p=0.007). ***Conclusion*:** EC is a significant health problem in the Eastern Anatolian Region of Turkey. Differences were detected according to age and gender, tumor characteristics, histological subtype, and disease stage rates in patients with EC living in this region, but the survival rate was similar with the literture. Surgery+ adjuvant RT/CRT provided better OS in the non-metastatic patients than other treatment modalities.

INTRODUCTION

Esophageal cancer (EC) comprises 5% of all cancer types. The mean annual incidence rate is 5/100.00 [(1)]. Because of its aggressive course and poor prognosis, it is generally the most frequent cause of cancer-related deaths globally [(2)]. Its median 5-year survival rate (19.9%) has not changed for a long time [(3)]. Its incidence increases with age and is seen more frequently in men [(4-6)].

According to SEER 18 (Surveillance, Epidemiology and End Results) data, a considerable number of ECs metastasize to regional lymph nodes and distant organs [(3)]. Since distant metastases have been detected in more than half of the patients or the tumors are unresectable at diagnosis, treatment of the cases is challenging [(7-8)].

Despite a slight decrease in the frequency of esophageal squamous cell carcinoma (SCC), an increase in the incidence of adenocarcinoma has been detected [(6)]. In some regions of the world, EC is endemic with higher incidence rates. In these endemic EC regions, its SCC subtype is more frequently encountered [(9-12)].

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Surgery alone or curative definitive chemoradiotherapy(CRT) has similar results in the treatment of esophageal cancer. 5-year survival rates are limited to 20% in both. As a result of the CALGB 9781 study, adjuvant radiotherapy (RT) with concomitant cisplatin and 5-fluorouracil (5-FU) chemotherapy (CT) were compared to surgery alone, and a 5-year survival advantage was demonstrated with trimodal therapy [13]. In subsequent studies, the 5-year survival rate was increased to 47% in patients who underwent preoperative CRT and subsequent surgery in resectable esophageal cancer [14].

The Eastern Anatolian Region of Turkey is an endemic region for upper gastrointestinal system tumors, and in this region, EC has a higher incidence [15]. Our study aimed to report demographic features, tumor characteristics and survival outcomes of EC patients living in this region.

MATERIALS AND METHODS

Patients

Our retrospective study was performed on histopathologically confirmed EC patients treated in Medical and Radiation Oncology Clinics of Erzurum Regional Training and Research Hospital between January 2005 and June 2017. Data were retrieved from hospital files and electronic data banks, and some of the information was obtained from the patient and his/her intimates. Patients with available follow-up data were included in the study.

The patients' age and gender, location of the primary tumor, histological subtype, grade, TNM stage, oncological treatment modalities applied, and survival rates were recorded. For staging, AJCC (2010 Guidelines of American Joint Committee on Cancer, 7th edition) criteria and histological diagnosis criteria of World Health Organization (WHO) were used, and 251 patients with EC were included in the study. For clinical staging thoracic and upper abdominal computed tomographies, in some patients mediastinoscopy and intraoperative observations and from June 2007, 18F-fluorodeoxyglucose positron emission tomography (PET-CT), still in selected patients whole-body bone scan, magnetic resonance imaging were used.

Treatment modalities

After the diagnostic work-up, all the patients were evaluated in the institutional tumor-board composed of a medical oncologist, radiation oncologist, and surgical oncologist. Surgery for early-stage disease, preoperative CRT for locally advanced disease, definitive CRT for upper-located disease, and palliative treatment for the elderly patients or those with poor performance status were recommended. The patients who did not have primary surgery were encouraged to the application of a feeding tube.

Partial or total esophagectomy with regional lymph node dissection was performed in patients who underwent surgery. Proximal subtotal gastrectomy is added for tumors located at the lower end or gastroesophageal junction. Adjuvant RT was recommended and applied to patients with R1 or R2 resection.

The patients treated in a curative intent were irradiated by a Cobalt-60 teletherapy device (Theratron, Elite 80) before 2011 and then, between 2011-2017, by a Helical Tomotherapy (Accuray Inc., Madison, USA). A total dose of 45-54 Gy in 1.8-2Gy once daily fraction dose was planned for definitive or adjuvant RT. For cervical located tumors, a definitive RT dose was delivered up to 66 Gy. The dose prescriptions for palliative intent were 30Gy in 10 fractions or 35Gy in 15 fractions. Palliative treatments were planned via 3-dimensional conformal radiotherapy and applied with a linear accelerator (Elekta Synergy between 2012-2017. Before 2012, the Cobalt-60 teletherapy device (Theratron, Elite 80) was also used for palliative RT. 225mg/m^2/day continuous infusional 5-fluorouracil (5-FU) or 85-100mg/m^2 cisplatin bolus intravenous infusion on the first day and 1000 mg/m^2/day 5-FU as a continuous intravenous infusion for 96 hours were administered concomitantly with RT.

Follow-up

All patients were followed up with physical examination, complete blood count, and biochemical tests every three months after primary treatment. PET/CT was performed for response evaluation in the first three months in cases who underwent curative definitive CRT. In addition, thoracic-abdominal CT was performed in case of clinical necessity. Salvage CT, surgery, or RT were recommended for patients with progression.

Statistical analysis and ethical considerations

The data processing and statistical analyzes were performed by Statistical Package for Social Sciences 20.0 for Windows (SPSS Inc., Chicago, IL). The clinicopathological and treatment characteristics were demonstrated via descriptive statistics. Survival curves were estimated using the Kaplan-Meier method. Univariate and multivariate analyzes were performed with cox regression analysis to investigate prognostic factors that may have an impact on overall survival (OS). This study was conducted in accordance with the World's Medical Association's Declaration of Helsinki. All the patients had informed consent to include their clinical data and treatment outcomes in retrospective studies keeping their identity concealed.

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RESULTS

Clinicopathological and treatment characteristics

Characteristic features of 251 study patients with EC and their survival rates are given in table 1. Patient population consisted of 144 (57.4%) female and 107 (42.6%) male. patients with a female/male ratio of 1.34/1. The median age of the patients at the time of diagnosis was 62 (range, 27 to 93) years.

Table 1. Characteristics and survival results of the 251 esophageal cancer patients enrolled into this study.

Characteristics	*Patients*	
	Number	*Percent [%]*
Age [year]		
Median	62 [Range:27-93]	-
<65	135	53.8
≥65	116	46.2
Gender		
-Male	107	42.6
-Female	144	57.4
Location		
-Upper	18	7.2
-Middle	117	46.6
-Lower	116	46.2
Histology		
-Adenocarcinoma	26	10.4
-Squamous cell carcinoma	216	86.1
-Other	9	3.6
Grade		
-I	50	19.9
-II	138	55.0
-III	63	25.1
Primery tumor [T]-clinical		
T_2	23	9.2
T_3	186	74.1
T_4	42	16.7
Regional lymph nodes [N]		
N_0	78	31.1
N_1	58	23.1
N_2	44	17.5
N_3	71	28.3
Stage		
II_A	24	9.6
II_B	57	22.7
III_A	37	14.7
III_B	22	8.8
III_C	37	14.7
IV	74	29.5
Surgery *Treatment*		
Yes	44	17.5
No	207	82.5
Oncologic Treatment modality		
Only operation	3	1.2
Definitive CRT (no operation)	80	31.9
Definitive RT	66	26.3
Paliation (CT or RT)	61	24.3
Operation + post op. Adj. RT/CRT	41	16.3
Exitus	165	65.7
Alive	86	34.3
Median follow-up time [month]	21.2 [1-98]	
Survival rate		
Median OS [95% CI] [month]	19.0 [15.8-22.1]	
1 year Survival rate [%]	65.8	
2 year Survival rate [%]	42.6	
3 year Survival rate [%]	29.7	
5 year Survival rate [%]	19.3	

RT: radiotherapy, CRT: chemoradiotherapy, CT: chemotherapy, OS: overall survival, CI: confidence interval

Primary tumor was localized in the upper (n=18; 7.2%), middle (n=117, 46.6%) and lower (n=116; 46.2%) segments of esophagus. Histopathologically, the most frequently observed subtype was SCC, which was detected in 216 (86.1%) patients. Grade I (n=50, 19.9%), II (n=138, 55%) and III (n=63, 25.1%) tumors were also detected in respective number of patients. Most of the tumors detected at the time of diagnosis were at stages T3 and N0 (74.1 and 31.1%, respectively). Still, Stage IV tumors were extremely frequent (n=74, 29.5%) (table 1).

Surgical treatment could be used only for 44 (17.5%) patients. Among oncological treatment modalities, most frequently palliative treatments (CT or RT) were administered (n=64, 24.3%). Among other oncological treatment modalities, implementation of surgery (n=3, 1.2%), surgery *plus* postoperative adjuvant RT/CRT (n=41, 16.3%), definitive CRT without surgery (n=80; 31.9%) and definitive RT (n=66, 26.3%) was also determined.

Survival outcomes and prognostic factors

The median follow-up period was 21.2 (range, 1 to 98) months. Totally 165 (65.7%) patients exited. The median OS was 19.0 months (figure 1). Survival rates were 65.8, 42.6, 29.7, and 19.3% at 1., 2., 3. and 5. years, respectively.

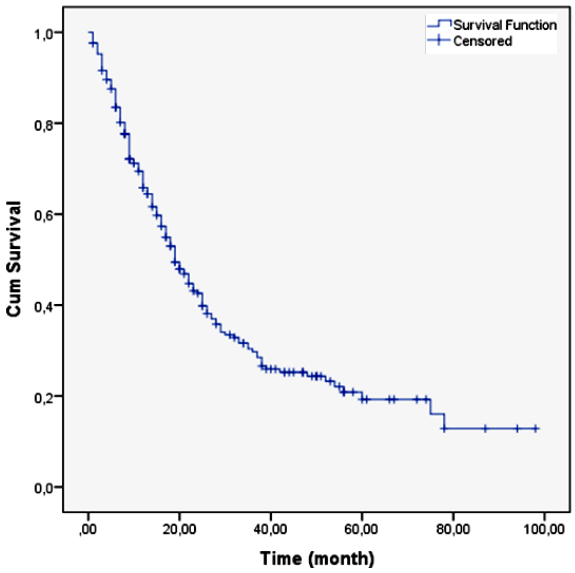

Figure 1. Kaplan-Meier graphic of overall survival of 251 patients with esophageal cancer.

Age, grade, N stage, stage, surgery, treatment modality, RT approach, and concurrent CRT were found to be statistically significant as a result of univariate analyzes performed to investigate the factors that may affect OS in all patients. As a result of multivariate analysis, grade, stage, and concurrent CRT were determined as independent prognostic factors (p=0.004, p=0.019, and p=0.014, respectively). Cox regression analysis results are shown in table 2. Survival curves are presented in figure 2.

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The median OS for stages IIA, IIB, IIIA, IIIB, IIIC and IV were 38.07, 28.09, 23.19, 29.17, 25.75, and 10.02 months, respectively (p<0.001). When the median OS of stage II-III and IV patients were compared, there was a statistically significant difference (25.79 versus 10.02 months, p<0.001). Therefore, cox regression analysis evaluating prognostic factors was also performed separately for stage II-III and IV patients.

As a result of multivariate analysis for stage II-III patients, only tumor grade was an independent prognostic factor (p=0.004 and HR=1.559 (95% CI=1.15-2.10)). The best median OS was in the trimodal treatment group in stage II-III patients. The median OS for surgery+adjuvant RT/CRT group was 37.02 months, definitive CRT group was 29.6 months, definitive RT group was 19.05, and palliative CT or RT group was 8.73 months (p<0.001) (figure 3A).

In stage IV patients, the median OS was higher in the patients treated with curative intent, but there was no statistically significant difference between treatment modalities. The median OS for the definitive CRT group was 17.5 months, the definitive RT group was 13.6, and the palliative CT/RT group was 9.85 months (p=0.108) (figure 3b). the only independent prognostic factor for stage ıv patients was gender. the median os for males was 9.29 months whereas, for females, it was 15.77 months (p= 0.007) (figure 3c).

Table 2. The results of univariate and multivariate Cox Regression analysis for overall survival of 251 patients.

	Univariate analysis		Multivariate analysis	
Variable	p value	HR (95% CI)	p value	HR (95% CI)
Age	**<0.001**	**1.023 (1,01-1.03)**	0.085	1.013 (0.99-1.02)
Gender	0.368	0.869 (0.63-1.18)	-	-
Histopathology	0.455	1.166 (0.77-1.74)	-	-
Tumor grade	**0.037**	**1.266 (10.01-1.58)**	**0.004**	**1.43 (1.11-1.83)**
T stage	0.107	1.278 (0.94-1.72)	-	-
N stage	**<0.001**	**1.412 (1.23-1.61)**	0.523	1.068 (0.87-1.30)
Location of tumor	0.638	1.061 (0.82-1.35)	-	-
Stage	**<0.001**	**1.303 (1.18-1.43)**	**0.019**	**1.20 (1.03-1.40)**
Surgery	**<0.001**	**0.405 (0.25-0.65)**	0.538	0.817 (0.42-1.55)
Treatment modality	0.293	1.068 (0.94-1.20)	**-**	**-**
RT(definitive/adjuvant/palliative)	**<0.001**	**0.532 (0.41-0.68)**	0.566	0.910 (0.65-1.25)
Concurrent CRT	**<0.001**	**0.447 (0.32-0.62)**	**0.014**	**0.623 (0.42-0.90)**

Notes. HR: hazard ratio; CI: confidence interval;; T: tumor; N: nodal; RT: radiotherapy; CRT: chemoradiotherapy. Statistically significant results are written in bold.

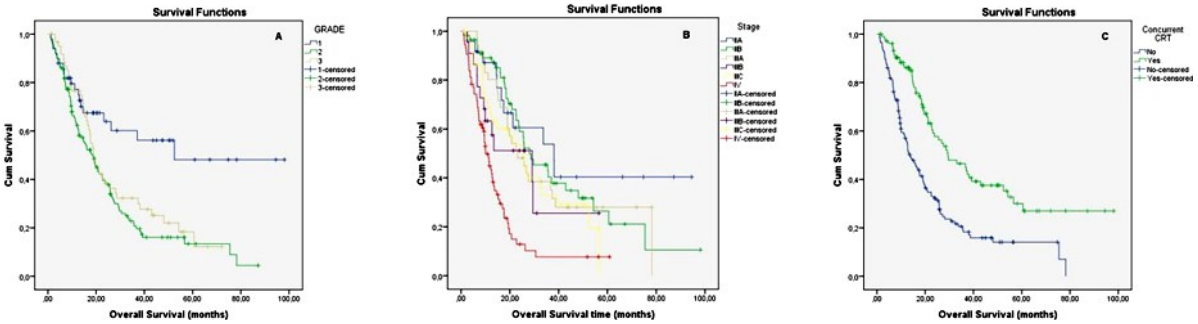

Figure 2. The Kaplan-Meier survival curves for overall survival (OS) of all patients. **A.** The median OS of the patients with grade 1 tumor is statistically significant higher than grade 2 and 3(p=0.001). The median OS for grade 1, 2 and 3 are 52.4, 18.5 and 18.9 months respectively). **B.** The median OS for stages IIA, IIB, IIIA, IIIB, IIIC, and IV were 38.07, 28.09, 23.19, 29.17, 25.75, and 10.02 months, respectively (p<0.001). **C.** The median OS of the patients treated by concurrent chemoradiotherapy is statistically significant higher than the patients treated without concurrent chemotherapy (29.43 versus 13.66 months, p<0.001).

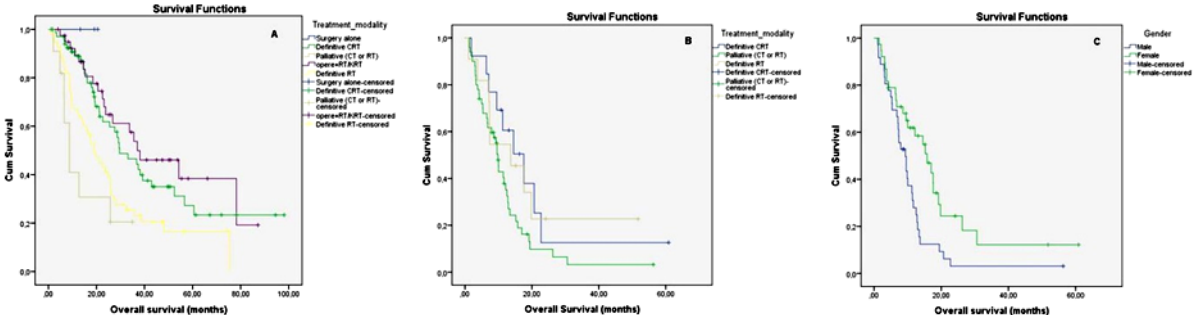

Figure 3. The Kaplan-Meier survival curves for overall urvival (OS) of Stage II-III and Stage IV patients. **A.** The survival curve for stage II-III patients. The median OS for surgery+adjuvant RT /CRT, definitive CRT, definitive RT, and palliative CT or RT group was 37.02, 29.6, 19.05, 8.73 months respectively(p<0.001). **B.** The survival curve for stage IV patients. The median OS for definitive CRT, definitive RT, and for palliative CT/RT groups were 17.5, 13.6, and 9.85 months respectively (p=0.108). **C.** The survival curve of stage IV patients. The median OS was of males and females were 9.29 and 15.77 months (p=0.007).

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DISCUSSION

In 2008, 482.000 newly diagnosed cases with EC were estimated in the whole world and, 406.800 patients died of esophageal cancer [9].

EC appears to be a rare tumor with an aggressive course from a worldwide perspective. The global incidence of EC differs greatly. In endemic regions, EC can be seen nearly 60 times more frequently when compared with non-endemic regions [16]. It has a higher incidence, especially in endemic EC regions, including Northern Iran, Kazakistan, Uzbekistan, Turkmenistan, Afghanistan, Northern and Central China, and Southern and Central Africa [9-12]. One of these endemic regions is Eastern Anatolian Region [15,17]. In these regions, where EC is an endemic disease, though not definitively accurate, as etiologic factors: lower consumption of vegetables and fruits, and habit of fluid intake under a hot climate [18-21]. Besides, in regions where EC is endemic, tumor and patient characteristics and survival rates demonstrate differences [10, 12, 21-23].

The global incidence of EC increases with age, and it is seen 22.3 times more frequently in people aged ≥65 years, and the median age at diagnosis is 68 years [3, 5]. Besides, it is observed 3.8-fold more often in women than men [4]. In our study, the incidence rate of the disease peaked during the seventh decade. The patients aged 65 or lower were more numerous, and EC was more frequently seen in women. These outcomes are similar to those obtained in a study performed in an endemic region in Iran and Turkmenistan [1].

According to SEER 18 data, at the time of diagnosis, ECs were localized either in the esophagus (18%) or metastasized into regional lymph nodes (33%) or remote organs (39%) [3]. In our study, most of the patients were in a locally advanced stage of the disease, while 29.5% of them metastasized into distant organs. When considering global rates, our EC incidence rates were comparatively lower.

In the 2010 guidelines of AJJC, histopathological subtype, grade of the tumor, and location of the primary tumor were included in the staging criteria [24]. In the histopathological classification of EC, SCC, and adenocarcinoma are primary subtypes [25]. SCC subtype is generally prevalent in Eastern Europe and Asia developing countries, while its adenocarcinoma subtype is seen more frequently in developed countries in North America and Western Europe [26-28]. In regions where endemic EC is observed, SCC is the most frequent (90%) histological subtype [10, 11]. SCC is localized in the middle (50-60%), lower (30%), and upper (10-20%) segments of the esophagus, while adenocarcinomas are mostly found in the lower esophageal segments [29]. However, in our study, 86.1% of the cases were of the SCC subtype, while 74.9% of the patients had grade I-II tumors. Tumor grade was the only independent prognostic factor in the present study. Primary tumors mainly were localized in 2/3 middle-lower esophageal segments. These results resemble those of a retrospective study performed in the vicinity of our region (Northwestern Iran), where EC is endemic [15-22].

Only 18% of EC patients with clinically resectable localized disease consult to the hospital [3]. However, surgical resection does not achieve complete remission in most cases. Even after surgical resection, the median 5-year survival rate is 25% [8, 30]. Currently performed randomized clinical studies have demonstrated significant survival benefits of preoperative CRT and perioperative CT in patients with resectable esophageal and esophagogastric cancers [7, 8]. In EC, definitive, preoperative, or palliative RT can be delivered and RT doses administered differ between protocols [31, 32]. Five-year survival rates in patients under external RT range between 0 and 10 percent [33-35]. Therefore, RT as a monotherapy has been recommended as a palliative treatment for patients not medically amenable to CT. Combined treatment modalities are indicated in esophageal and esophagogastric junction cancers with poor survival rates amenable only to surgery [36]. In our study, only 17.5% of the patients were surgically treated, while definitive CRT was detected to be the most frequently applied treatment modality (31.9%).

In EC, 5-year-survival rates were 47.1% in localized and 25.2% in regional disease, while 4.9% in distant metastases [3]. In our series, the median OS for stage II-III patients was 25.79 months, while it was 10.02 months for stage IV patients. When we considered the patients in all stages of the disease, a 0.6% difference was seen between the 5-year survival data of our patients and those of the SEER 18 registry (respectively, 19.3 *vs.* 19.9%) [3].

In conclusion, in this study which we conducted in the Eastern Anatolian Region of Turkey where as an essential health problem EC is seen endemically. Differences were detected according to age, gender of the patients, characteristics, and histological subtypes of the tumors and disease stage, but survival rates were similar. Surgery+ adjuvant RT/ CRT provided better OS in the non-metastatic patients than other treatment modalities. Tumor grade, Females had better OS than males in stage IV disease.

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***Conflict of interest*:** The authors have no conflict of interest to declare.

***Ethical consideration*:** This study was conducted in accordance with the ethical standards of

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theinstitutional and national research committee and with the 1975 Helsinki Decleration and its later amendments.

***Author contributions*:** Conception and design: Arslan D, Koca T, Kaymak ZA, Cevener M, Basaran H. Data collection: Arslan D, Koca T, Basaran H. Data analysis and interpretation: Arslan D, Kaymak ZA, Basaran H. Article drafting and revision: Arslan D, Koca T, Kaymak ZA, Cevener M, Basaran H.

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