

Evaluation of prognostic factors and Survival Results in Esophagus Cancer-single Center Experience from Eastern Black Sea Region of Turkey

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Abstract

Aims and background: Esophageal cancer consists of 5% of all cancers. In Eastern Blacksea region of Turkey, the rate was found to be 1.7% for the country. The primary aim of the study was to evaluate efficacy of the localization and histologic type of tumor, stage of cancer and treatment modality, patient's sex, age and smoking status, Karnofsky performance score, family history on survival period.

Methods and study design: 64 patients with esophagus cancer were enrolled into the study. The factors (sex, age, Karnofsky performance score, localization, histology, stage of the disease, treatment modality) on survival were evaluated.

Results: After the end of treatment, the overall survival was 18 months; median survival period was 12 months. The survival rates at 1, 3 and 5 years were 52.5%, 10.9% and 6.6% respectively.

Conclusions: For patients with esophagus cancer, Karnofsky performance score and stage, general survival rate were found to be the prognostic factors related to survival period ($p < 0.05$) in univariate analysis. At the same time the study showed that there were no effects of gender, age, smoking status, family history, treatment modality applied, chemotherapy protocol and number of cures, the localization of tumor and histologic type on the survival. The best survival in patients with esophageal cancer which cannot be operated is provided by 50.4 gray radiotherapy with concurrent chemotherapy.

Keywords: Esophagus cancer; Treatment; Survival.

Introduction

Esophageal cancer is seen at a rate of 5% among all cancers, being the sixth most common cause of cancer mortality. Its average annual incidence is 5/100.000 [1]. In Turkey, this rate increases to 16% in Eastern Anatolia Region and Eastern Black sea Region where the mean rate was 1.7% for the country [2]. Excessive consumption of hot drinks and food, nitrite and nitrosamine containing foods, genetic factors are some of the accused [3].

Treatment for esophageal cancer is characterized as curative (surgery alone, radiation therapy alone, preoperative radiation therapy, preoperative chemo radiotherapy, surgery + radiation therapy, and surgery + chemo radiotherapy) or palliative. Based on these data, standard dose of radiotherapy for esophageal tumors is usually 50-50.4 Gy at 1.8-2 Gy per fraction. Multiagent chemotherapy with cisplatin and 5-fluorouracil is used most frequently, although combinations of other agents (cisplatin and etoposide, 5-fluorouracil (5-FU) and calcium folinate) are being increasingly used [4]. Palliative treatment regimens range from 30 Gy over 2 weeks to 50 Gy over 5 weeks.

Histological type, stage, age, R-status, tumor grade, extracapsular lymph node extension and the treatment were found to have impacts on survival [5 - 7]. The average median survival was found to be smaller than 18 months [8]. Survival rates range from 25% to >35% at 5 years.

In this study, patients with esophageal presenting to our clinic who underwent radiation therapy were evaluated retrospectively and effects of known prognostic factors and treatment methods upon outcomes were investigated.

Patients and Methods

The study was conducted on 64 patients who were diagnosed with esophageal cancer, treated and followed up between January 1999 to November 2015 at Karadeniz Technical University Hospital. The information about patients was accessed with the retrospective analysis of patient files, and was updated by communication with patients or their relatives in November 2015.

Among 64 patients that were included in the study, 48 (75%) men and 16 (25%) were women. The average age was 59 (range 30-95 years). 60 years and below and, age 61 and over is allocated as the 29 (45%) and 35 (55%) respectively.

According to Karnofsky Performance Score (KPS); 9 (14%) patients were 60, 19 (30%) patients were 70, 18 (28%) patients were 80 and 18 (28%) patients were 90 and over.

According to patients tumor localization, 6 (9%) patients had the lesion in the upper esophagus, 9 (14%) patients in the mid-esophagus and 49 (77%) in lower esophagus.

Fifty-seven (89%) patients had squamous cell carcinoma (SCC), 6 (9%) patients had adenocarcinoma (ADC) and 1 (2%) patients had malignant epithelial tumors. 64 of patients (100%) had not family history of esophageal cancer. Smoking rate was detected in 44% (28 patients). In 17 patients (26%) was applied primary surgery. 47 (74%) patients inoperable was applied biopsy.

According to clinical staging, 23 (36%) patients were stage II, 35 (55%) patients were stage III and 6 (9%) patients were stage IV. One (2%) patient had not agreed to treatment. 22 (34%) patients had only radiotherapy, 23 (36%) patients had chemo radiotherapy, 5 (7%) patients had post-operative radiotherapy, 12 (19%) patients had post-operative chemo radiotherapy and 1 (2%) patients had chemotherapy. Radiotherapy dose given to 15 (23%) patients was 30 Gray, to 7 (11%) patients 45 Gray, to 17 (26%) patients 50.4 Gray, to 4 (6%) patients 54 Gray, to 10 (15.5%) patients 60 Gray and to 10 (15.5%) patients extra dose. 2 (3%) patients had not agreed to radiotherapy.

Twenty eight (44%) patients not received any chemotherapy. 7 (11%) patients received 1 cure, 25 (39%) patients received 2 cures, and 4 (6%) patients received 3 or more chemotherapy. As chemotherapy protocol, 29 (45%) patients had received cisplatin + 5-FU (1st and 5th week of radiotherapy), 4 (6%) patients had received weekly cisplatin, 2 (3%) patients had received 5-FU + calcium folinate (1st and 5th week of radiotherapy) and 1 (2%) patient had received cisplatin + etoposide

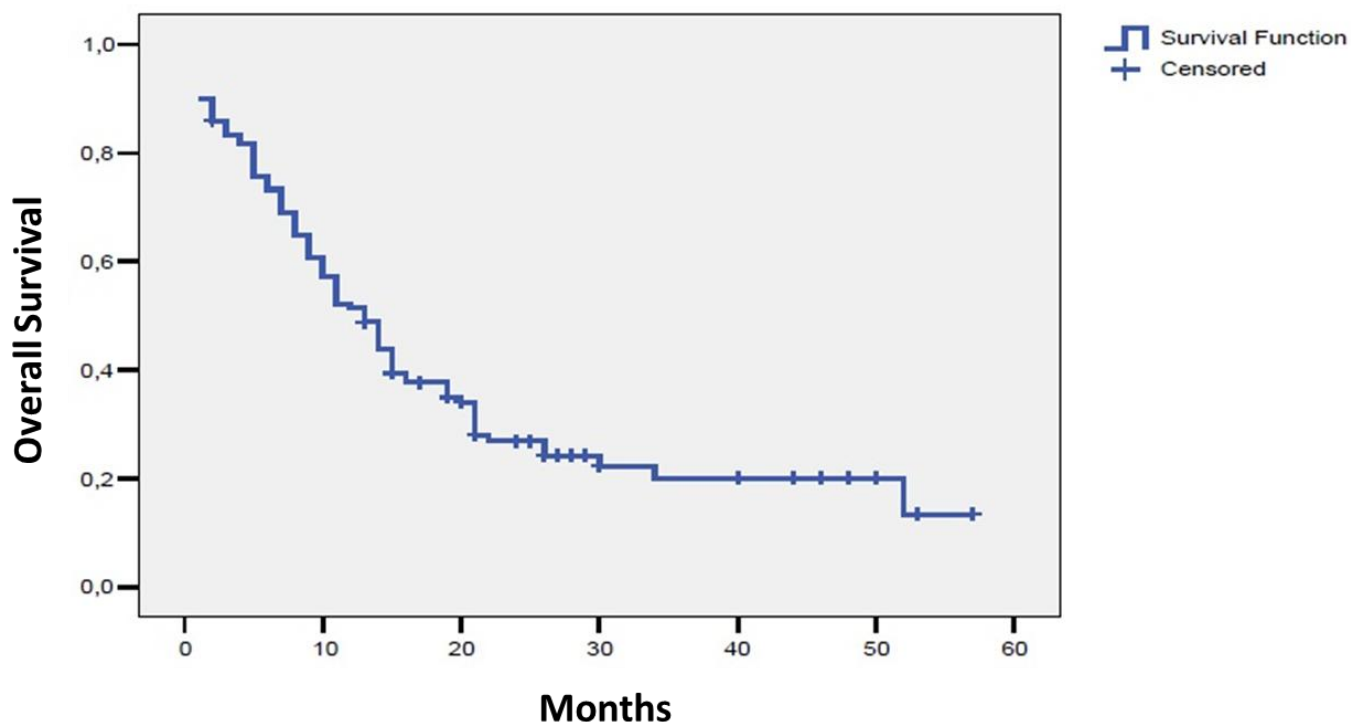
Radiotherapy field design: Gross tumor volume (GTV): tumor + involved lymph nodes. Clinical target volume: GTV + subclinical disease + safety margin (4cm proximal/distal and 1cm radial). Plan target volume (PTV): CTV + 1-2cm. Tumor above the carina; treat supraclavicular lymph nodes and mediastinal lymph nodes. Tumor at or below carina; treat celiac and mediastinal lymph nodes.

Analysis of the data was performed using SPSS software (version 13.0 for Windows). For survival analysis Kaplan-Meier test, for potential prognostic significance of variables to assess the effects on survival Log-Rank test were used.

Results

As concern acute side effects of treatment, 28 (44%) patients had gastrointestinal problems (mucositis, nausea, vomiting, diarrhea or constipation, weight loss) and 16 (25%) patients had hematologic problems (neutropenia, thrombocytopenia, pancytopenia, hyponatremia, hypokalemia, hypocalcaemia) were seen. As concern chronic complication of treatment, 4 (7%) patients had fibrosis and 3 (5%) patients had fistula.

Five patients (8%) are still alive and, 59 (92%) patients are dead. Sixty four patients, whose information updated, were evaluated in the survival analysis. Median survival time of all patients 12 and the average overall survival time were 18 months. 1, 3 and 5 years survival rates were 52.5%, 10.9% and 6.6% respectively (Figure 1. Overall survival).



Female patient's median survival time was 14 months and mean overall survival time was 25 months. For women 1, 3 and 5-year survival rates were 58.3%, 16.7% and 8.3% respectively. Male patient's median overall survival time was 10 months and the average overall survival time was 15 months. For male 1, 3 and 5-year overall survival rates were 47.5%, 8.9% and 3.0% respectively. Between the two sexes in terms of overall survival time was no statistically significant difference was seen ($p=0.219$).

Median survival time of the patients at the age of 60 or below was 10 months and average common survival time was 18 months. 1, 3 and 5 years survival rates were 42.9%, 14.3% and 4.8% respectively. 61 years old or above patients median survival time was 12 months and average common survival time was 16 months; 1, 3 and 5 years survival rates were 48.7%, 8.1% and 4.1% respectively. Between the two groups in terms of overall survival time was no statistically significant difference was seen ($p=0.651$).

For the patients, whose KPS were 60, median survival time was 2 months and average common survival time was 2 months. There was no patient that lived 1 year. For the patients whose KPS were 70, median survival time was 7 months and average common survival time was 5 months. There was no patient that lived 1 year. For the patients whose KPS were 80, median survival time was 14 months and average common survival time was 12 months. 1 year survival rate were 53.8%, there was no patient that lived 3 years. The patient's who's KPS were 90, median survival time was 29 months and average common survival time was 40. 1, 3 and 5 years survival rates were 92.9%, 35.7% and 14.3% respectively. There was a relation between patients KPS and survival in duration of diagnosis. Survival of the patients whose KPS were 90 and above was statistical significantly better than the survival of the patients whose KPS were 80 and below ($p = 0.0001$).

When we consider tumor's localization in esophagus, in proximal (upper) esophagus involvement median survival time was 12 months and average common survival time was 13 months. 1 year survival rate were 60.0%, and there was no patient that lived 3 years. In middle esophagus involvement median survival time was 6 months and average common survival time was 5 months. There was no patient that lived 1 year. In distal (lower) esophagus involvement median survival time was 12 months and average common survival time was 19 months. 1, 3 and 5 years survival rates were 47.7%, 13.2% and 5.3% respectively. There was no statistical significant difference between median survival time and average survival time when compared the tumor localization at esophagus (p=0.107).

When the patients are divided for histological groups; patients with SCC had median survival time of 12 months and average common survival time was 18 months. 1, 3 and

5 years survival rates were 45.2%, 11.9% and 4.8% respectively. The patients with ADC had median survival time of 10 months and average common survival time was 12 months. 1 year survival rate was 25% and there was no patient that lived 3 years. There were no statistical significant difference between two groups (p = 0.661).

When the patients are analyzed for stages, stage II median survival time was 27 months and average common survival time was 34 months. 1, 3 and 5 years survival rates were 88.2%, 29.4% and 11.8% respectively. Stage III median survival time was 7 months and average common survival time was 9 months. 1 year survival rate was 32.0% and there was no patient that lived 3 years. Stage IV median survival time was 4 months and average common survival time was 5 months. There was no patient that lived 1 year. There were a significant relation between patient stages and survival while diagnosis (p = 0.0001) (Table 1. Survival Analysis (patient characteristics)).

Table 1: Survival Analysis (patient characteristics)

	n	Median survival period (month)	Mean survival period (month)	p	Survival rate 1 year (%)	Survival rate 3 years (%)	Survival rate 5 years (%)
General	64	12 ± 2	18		52.5	10.9	6.6
Gender Women	16	14 ± 3	25		58.3	16.7	8.3
Men	48	10 ± 2	15	0.219	47.5	8.9	3.0
Age ≤60	29	10 ± 2	18		42.9	14.3	4.8
≥61	35	12 ± 2	16	0.651	48.7	8.1	4.1
KPS 60	9	2 ±0,5	2		0	0	0
70	19	7 ± 3	5		0	0	0
80	13	14 ± 1	12		53.8	0	0
90 and ↑	14	29 ± 4	40	0.0001	92.9	35.7	14.3
Smoking							
No	36	14 ±4	21		50.5	12.6	0
Yes	28	8 ±2	14	0.243	40.9	9.1	0

Localization							
upper	6	12 ± 2	13		60.0	0	0
middle	9	6 ± 2	5		0	0	0
lower	49	12 ± 3	19	0.107	47.7	13.2	5.3
Histology							
SCC	57	12±3	18		45.2	11.9	4.8
ADC	6	10±3	12		25.0	0	0
Others	1	12±2	18	0.661	0	0	0
Stage							
II	23	27 ± 2	34		88.2	29.4	11.8
III	35	7 ± 0.4	9		32.0	0	0
IV	6	4 ± 1	5	0.0001	0	0	0

ADC, adenocarcinoma; CT, chemotherapy; CRT, chemoradiotherapy; KPS, Karnofskyperformancescore; RT, radiotherapy; S, surgery; SCC, squamouscellcarcinoma.

In patient (stage II, SCC) who didn't accept any treatment, mean survival time was 9 months. For the patients who received only radiotherapy, median survival time was 8 months and average survival time was 16 months. 1 and 3 years survival rates were 43.8%, 12.5% and no patient that lived 5 years. For the patients who received CRT, median survival time was 14 months and average common survival time was 20 months. 1, 3 and 5 years survival rates were 52.9%, 11.8% and 11.8% respectively. For the patients who received surgery + radiotherapy, median survival time was 7 months and average common survival time was 25 months. 1 year survival rate was 33.3% and there was no patient that lived 3 years. For the patients who received surgery + chemo radiotherapy, median survival time was 10 months and average common survival time was 14 months. 1 and 3 years survival rates were 33.3% and 11.1% respectively, there was no patient that lived 5 years. Between the groups in terms of overall survival time was no statistically significant difference was seen (p = 0.917).

When we analyze chemotherapy protocol, the patients who received cisplatin + 5-fluorouracil had median survival time 14 months and average common survival time was 20 months. 1, 3 and 5 years survival rates were 53.1%, 9.7% and 9.7% respectively. For the patients who received weekly cisplatin, median survival time was 7 months and average common survival time was 8 months. 1 year survival rate was 25.0% and there was no patient that lived 3 years. For the patients who received weekly FUFA (5-fluorouracil + calcium folinate), median survival time was 7 months and average common survival time was 8 months. There was no patient that lived 1 year. For the patients who

no application chemotherapy, median survival time was 12 months and average common survival time was 18 months. 1, 3 and 5 years survival rates were 47.4%, 15.8% and 5.3% respectively. Between the groups in terms of overall survival time was no statistically significant difference was seen (p = 0.405).

When we analyze radiotherapy doses, the patients who received 30 Gray radiotherapy had median survival time 3 months and average common survival time was 8 months. 1 year survival rate was 9.1% and there was no patient that lived 3 years. In patients who received 45Gray radiotherapy, median survival time was 7 months and average common survival time was 10 months. 1 year survival rate was 20.0% and there was no patient that lived 3 years. In patients who received 50.4 Gray radiotherapy, median survival time was 18 months and average common survival time was 30 months. 1, 3 and 5 years survival rates were 83.3%, 16.7% and 16.7% respectively. In patients who received 54 Gray, median survival time was 12 months and average common survival time was 16 months. 1 year survival rate was 33.3% and there was no patient that lived 3 years. In patients who received 60 Gray, median survival time was 7 months and average common survival time was 16 months. 1 and 3 years survival rates were 28.6% and 14.3% respectively, there was no patient that lived 5 years. In patients who received >60 Gray, median survival time was 14 months and average common survival time was 21 months. 1 and 3 years survival rates were 57.1% and 14.3% respectively, there was no patient that lived 5 years. Between the groups in terms of overall survival time was no statistically significant difference was seen (p=0.062) (Table 2. Survival Analysis (treatment characteristics)).

Table 2. Survival Analysis (treatment characteristics)

	n	Median survival period (month)	Mean survival period (month)	p	Survival rate 1 year (%)	Survival rate 3 years (%)	Survival rate 5 years (%)
Treatment							
noappl.	1	9 ± 0	9		0	0	0
RT	22	8±3	16		43.8	12.5	0
CTRTR	23	14±3	20		52.9	11.8	11.8
S + RT	5	7±1	25		33.3	0	0
S + CTRTR	12	10±4	14		33.3	11.1	0
CT	1	-	-	0.917			
CT							
noappl.	28	12±4	18		47.4	15.8	5.3
Cisp.-FU	29	14±4	20		53.1	9.7	9.7
Weekly Cisp.	4	7±5	8		25.0	0	0
FUFA	2	7	8		0	0	0
Cisp-Etoposid	1	6	7	0.405	0	0	0
RT							
noappl	1	9 ± 0	9		0	0	0
0-3000	15	3 ± 1	8		9.1	0	0
4500	7	7 ± 1	10		20.0	0	0
5040	17	18 ± 8	30		83.3	16.7	16.7
5400	4	12 ±4	16		33.3	0	0
6000	10	7 ±1	16		28.6	14.3	0
>6000	10	14 ±7	21	0.062	57.1	14.3	0

ADC, adenocarcinoma; CT, chemotherapy; CTRTR, chemoradiotherapy; KPS, Karnofskyperformancescore; RT, radiotherapy; S, surgery; SCC, squamouscellcarcinoma.

Discussion

Despite all advances, treatment of esophageal carcinoma is still unsatisfactory and most of the patients die due to local or distant tumor effects. Esophagus cancer is a high mortality and morbidity cancer type and it has the sixth

most common cancer mortality in worldwide [9] it is not very common in Turkey. After all in Eastern Anatolia region its incidence is higher and it is an important reason of cancer mortality [10]. This fact can be explained with geographic predisposition and environmental exposure [3].

Median survival is 9 - 12 months. 1, 3 and 5 years survival rates were 35-45%, 10-12% and 0-15% respectively [7, 11, 14]. In this study, median survival was 12 months compatible with literature data, 1, 3 and 5 years average survival rates were 52.5%, 10.9% and 6.6% respectively.

Esophagus cancer is seen more in men at worldwide. But, at the region that includes Turkmenistan and Iran, its incidence in women is higher [1]. A study performed in Van and its vicinity is notified that a rate of women/men is 1.5/1. In this study, women/men rate was found to be 1/3.

In Rouvales study [6] resulted that survival is lower in women. In a study performed in France is notified that sex is not a prognostic factor on survival [8]. Average common survival in women and men, 1, 3 and 5 years survival rates were found approximately the same and there were no statistical significant difference between them in this study ($p = 0.219$).

Esophagus cancer occurrence age is average of 67 and its peak is 7th decade [11]. Average age was found 59 in this study. There are many research results about the fact that age has no effect on survival or survival is lower with the age [6]. In this study, median survival of the patients at the age of 60 and below is 10 months, 1, 3 and 5 years survival rates were 42.9%, 14.3% and 4.8% respectively. Median survival of the patients at the age of 61 and above is 12 months, 1, 3 and 5 years survival rates were 48.7%, 8.1% and 4.1% respectively.

There was a significant relation between the patient's performance status and total survival in multivariate analyses and, when the performance state groped up the survival increased, was showed [12]. In this study similarly, for the patients whose KPS were 90 and above, median survival was 29 months, 1, 3 and 5 years survival rates were 92.9%, 35.7% and 14.3% and, there was a statistical significant difference ($p = 0.0001$).

Tumor localization is an important factor in prognosis. Especially, however 1/3 upper esophagus cancers occurs rarely, survival is better than 2/3 lower esophagus cancers [13]. In another paper, at 1/3 lower esophagus cancers survival is better [8]. Median survival was better at 1/3 upper and lower esophagus compatible with literature data in this study.

SCC and ADC histological types are seen 95% at esophagus [14]. In this study, we determined 98% of SCC

and ADC histological types of esophageal cancer. In many papers it was shown that survival was better for ADC [8]. In this study, median survival and 1, 3 and 5 years survival rates were better for SCC.

3 years survival rates at stage I 70-100%, at stage II 65-100%, at stage III 60-90% and stage IV 50-70%, 5 years survival rates at stage I 50-60%, at stage II 10-30%, at stage III 0- 10% and at stage IV 0-5% were detected [15]. In our study, 1, 3 and 5 years survival rates were at stage II %88.2, 29.4% and 11.8%, in stage III 32.0%, %0 and 0% , in stage IV 0%, %0 and 0%; median survival time was at stage II 27 months, in stage III 7 months and in stage IV 4 months.

Survival advantage was shown in the papers that compare only radiotherapy and simultaneously chemo radiotherapy [16]. In this study, median survival rate changed from 8 to 14 months, 1 year survival rate changed from 43.8% to 52.9%. Additionally, rescue surgery can be done after chemo radiotherapy recurrences.

There were many studies that search the contribution of chemo radiotherapy after surgery on survival. The results of these studies showed that average survival were 16-19 months and 3 years survival rate was 30-40% [17]. In this study, median survival and 1, 3 and 5 years survival rate were worse.

When the esophageal disease is metastatic, median survival is 2 months. It was raised to 10 months by palliative chemotherapy. In another study to be esophagus cancer by hematogenous way remote organ metastases median survival was found to be 7.3 months [18]. Median survival was raised to 15 months by radiotherapy appended to the palliative chemotherapy. In this study, median survival was found 4 months.

As a result of this retrospective analysis, the best survival in patients with esophageal cancer which cannot be operated is provided by 50.4 gray radiotherapy with concurrent chemotherapy. Clinically, in the light of this information we have adopted this protocol and have launched its routine application.

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