

Evaluation of Prognostic Factors in Patients with Esophageal Cancer

Özofagus Kanseri Hastalarda Prognostik Faktörlerin Değerlendirilmesi

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ABSTRACT Objective: Several factors were identified affecting the disease-free and overall survival of esophageal cancer patients. In the present study, we evaluated factors affecting the prognosis of patients with esophageal cancer. **Material and Methods:** In this study, medical records of 110 patients with esophageal cancer, who were admitted to the Ankara Numune Training and Research Hospital between December 2002 and December 2007, were retrospectively reviewed. **Results:** The disease-free survival and overall survival were significantly shorter in patients over 65 years of age. Longer disease-free and overall survivals were determined in cases with tumors located in the distal portion of esophagus. Patients who had tumors with lymphovascular invasion had shorter disease-free survival. The overall survival was longer in patients with better performance status, patients in early-stage disease, and patients who had undergone surgical treatment or had received postoperative adjuvant treatment. **Conclusion:** There are numerous factors, which may affect the prognosis of esophageal cancers. The most important factor is the stage of cancer at initial diagnosis. Our study demonstrates that, the stage of esophageal cancer is important on the survival times of the patients.

Key Words: Esophageal neoplasms; esophagus; therapeutics; prognosis

ÖZET Amaç: Özofagus kanserlerinin genel sağkalımı ve hastaliksız sağkalımı etkileyen bazı faktörler tanımlanmıştır. Yapmış olduğumuz çalışmada özofagus kanserli hasta grubumuz üzerinde prognoza etkili faktörler ortaya konmaya çalışılmıştır. **Gereç ve Yöntemler:** Bu çalışma Aralık 2002 ile Aralık 2007 tarihleri arasında Ankara Numune Eğitim ve Araştırma Hastanesi'ne başvuran 110 özofagus kanserli hastanın dosyalarının retrospektif olarak taranması sonucu yapılmıştır. **Bulgular:** 65 yaş üstünde hastalarda hem genel sağkalım hem de hastaliksız sağkalım anlamlı olarak kısalmaktaydı. Özofagusun distal bölgesine yerleşen tümör olgularında hem hastaliksız hem de genel sağkalım süreleri daha uzun tespit edildi. Lenfovasküler invazyonu olan tümörlü olgular daha kısa hastaliksız sağkalım süresine sahipti. Performans durumu daha iyi olanların, erken evrede olanların, cerrahi tedavi alanların ve cerrahi sonrası adjuvan tedavi alanların genel sağkalım süreleri daha uzundu. **Sonuç:** Özofagus kanserlerinin prognozunda etkili olabilecek birçok faktör vardır. Bunlar içinde en önemlisi hastanın geliş evresidir. Bizim çalışmamız özofagus kanserlerinde evrenin sağkalım süreleri için önemli olduğunu göstermektedir.

Anahtar Kelimeler: Özofagus tümörleri; özofagus; tedavi bilimi; prognoz

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Esophageal cancer accounts for 1.5% of all cancer types and ranks fourth among cancers of the gastrointestinal system. It is ranked among the ten most frequently observed cancers worldwide.¹ Esophageal cancer is of importance due to the difficulties in its treatment and associated high mortality and morbidity rates. Among gastrointestinal system cancers,

esophageal cancer has a mortality rate of 9.7%. The incidence and prevalence of esophageal cancer have been increasing in the western communities. Particularly, while the incidence of squamous cell carcinoma has remained constant, the incidence of adenocarcinoma has been increasing.²

In patients with esophageal cancer, dysphagia is the most frequent symptom at presentation, which significantly decreases the quality of life of these patients. Thus, the majority of patients with esophageal cancer have a low quality of life at the time of admission.

When the overall and disease-free survivals were evaluated in patients with esophageal cancer, generally poor outcomes are observed. This results from the presentation of patients at an advanced stage of the disease, high mortality associated with resection, and low curability rates.³⁻⁶

The aim of the current study was to evaluate the prognostic factors affecting the overall and disease-free survivals of patients with esophageal cancer admitted to our center.

MATERIAL AND METHODS

In the present study, medical records of 110 patients with esophageal cancer, who were admitted to the Ankara Numune Training and Research Hospital between December 2002 and December 2007, were retrospectively reviewed.

The patients' data were recorded on a study form which includes items regarding descriptive characteristics, date of diagnosis, clinical findings on admission, risk factors, pathological characteristics of the tumor, treatments, patients' responses to the treatments, and duration of follow-up.

We calculated the factors affecting on overall survival (OS) and disease free survival (DFS). OS was a time of diagnosis to exitus date or last follow up. DFS was a time at remission to progression.

American Joint Committee on Cancer (AJCC) tumour-lymph node-metastasis (TNM) Classification of Carcinoma of the Oesophagus and Esophago-gastric Junction (7th ed, 2010) was used. Patients were divided three stages on presentation. Early

stage, locally advanced stage and metastatic stage. According to AJCC classification if tumour invades lamina propria, muscularis mucosa or submucosa called that early stage disease (Tx, To, Tis, T1, T1a, T1b). If tumour invades muscularis propria and adjacent structures called that locally advanced stage (T2, T3, T4, T4a, T4b).

Patients were treated three modality: surgery, adjuvant chemoradiotherapy (CRT) and primary CRT. Distal esophagectomy and total esophagectomy were preferred for surgery. Preoperative and postoperative CRT were applied to some patients. Adjuvant treatment and primary CRT were included combination of chemotherapy (Cisplatin 75 mg/m² IV on day 1 and 5-fluorouracil 1,000 mg/m²/day by continuous IV infusion or 4 days) and radiotherapy (6,000 cGy) or only CT or only RT.

The analysis of the data was performed using the Statistical Package for Social Sciences (v13; SPSS, Chicago, IL). For descriptive analysis, percentages, median, and mean values were calculated. The survival was calculated using the Kaplan-Meier survival analysis and the log-rank analysis. All reported p values were bilateral and a p value of <0.05 was considered statistically significant.

RESULTS

On admission, there were 30 (27.3%) patients in the early stage, 56 (50.9%) patients in the locally advanced stage, and 24 (21.8%) patients in the metastatic stage. In the metastatic patients, the most frequent site of metastasis was liver in 9 (37.5%) patients, followed by lung in 4 (16.7%) patients. The tumor was located in the proximal portion of esophagus in 22 (20.6%) patients, in the mid-portion of esophagus in 11 (10.3%) patients, in the distal portion of esophagus in 71 (66.4%) patients, and both in the proximal and mid portions of esophagus in 3 (2.8%) patients.

Eighty-five (77.3%) patients had squamous cell carcinoma and 21 (19.1%) had adenocarcinoma. Table 1 and 2 show the characteristics of patients and tumors.

Surgery was performed on 49 (45%) patients. Of them, 28 (58.3%) patients underwent distal

TABLE 1: General characteristics of the patients.

Characteristics	n (%)
Median age, years	57.5 (24-88)
Gender	
Male	69 (62.7)
Female	41 (37.3)
Risk factors	
Smoking	44 (40)
Alcohol consumption and smoking	8 (7.3)
None	58 (52.7)
ECOG Performance status	
0	5 (4.6)
1	48 (44)
2	40 (36.7)
3	11 (10.1)
4	5 (4.6)
Clinical findings	
Pain	6 (5.7)
Weight loss	5 (4.7)
Dysphagia	72 (67.9)
Nausea/Vomiting	5 (4.7)
Stage on presentation	
Early stage	30 (27.3)
Locally advanced stage	56 (50.9)
Metastatic stage	24 (21.8)
Site of metastasis	
Liver	9 (37.5)
Lungs	4 (16.7)
Others	11 (45.8)
Location of the tumor	
Proximal portion	22 (20.6)
Mid portion	11 (10.3)
Distal portion	71 (66.4)
Proximal and mid portions	3 (2.8)

ECOG, Eastern Cooperative Oncology Group.

esophagectomy and 14 (29.2%) patients underwent total esophagectomy. Thirty-two patients received adjuvant therapy, of which 25 (78.1%) received chemoradiotherapy (CRT). Among 50 patients undergoing primary CRT as the initial treatment, a complete response to treatment was achieved in 2 (4.0%) patients, and no response to treatment was achieved in 32 (64%) patients. Following the treatment, it was observed that 52 (59%) patients had died and 28 (31.8%) patients were in remission. The disease relapsed in 1 (1.1%) patient, and progressed in 7 (8%) patients.

The median follow-up period was 243 days (minimum 1 day, maximum 1300 days). While the median length of survival was 420 days (range, 30-1300 days), the median length of disease-free survival was 360 days (range, 30-1278 days).

The effects of the general characteristics of the patients, tumor characteristics, and the treatments administered to the patients on the overall survival and disease-free survival were evaluated. The patients were divided into 3 age groups; the first group comprised patients aged 24-45 years, the second group comprised patients aged 45-65 years, and the third group comprised patients over 65 years of age. Assessment of the effect of age on overall survival revealed that the survival was significantly shorter in patients over 65 years of age. To evaluate the effects of performance status of patients on survival, the patients were evaluated in two groups as the first group comprising those with an ECOG performance status of 0 or 1 and the second group comprising those with an ECOG performance status of 2 or 3 or 4. Accordingly, the overall survival of the group comprising patients with an ECOG performance status of 0 or 1 were found to be better than that of patients with poorer performance status ($p=0.032$).

TABLE 2: Characteristics of the tumors.

Characteristics	
Tumor diameter; median (min-max)	5.0 (1-12)
Number of removed lymph nodes; median (min-max)	15.5 (0-83)
Tumor type, n (%)	
Squamous cell carcinoma	85 (77.3%)
Adenocarcinoma	21 (19.1%)
Others	4 (3.6%)
Differentiation, n (%)	
Good	20 (18.2%)
Moderate	28 (25.5%)
Poor	24 (2.8%)
Unknown	38 (53.5%)
Lymphovascular invasion, n (%)	
Present	11 (10.1%)
Absent	10 (9.2%)
Perineural invasion, n (%)	
Present	14 (12.8%)
Absent	6 (5.5%)

The survival of patients in the early stage were found to be longer than that of patients in the locally advanced stage and that of metastatic patients ($p=0.008$, $p=0.001$, respectively).

The patients with tumor in the distal esophagus were found to have a longer overall survival than patients with tumors in the mid portion and in the proximal portion ($p=0.0006$, $p=0.009$; respectively).

When the effects of type of treatments on overall survival were evaluated, significant differences were found between patients undergoing surgery and those receiving palliative supportive treatment ($p<0.001$). Moreover, of the patients undergoing surgery, a significant difference was found between those receiving adjuvant therapy and those not receiving adjuvant therapy ($p=0.01$) in terms of overall survival.

In summary, the overall survival was found to be longer in patients with better performance status (those with an ECOG performance status of 0 or 1), in those in the early stage of the disease, in those with tumours located in the distal portion of oesophagus, in those undergoing surgery, and in those receiving postoperative adjuvant therapy. The Kaplan-Meier curve showing the overall survival was presented in Figure 1.

Significant differences were also determined in terms of disease-free survival when the patients were grouped according to the location of the tumour and the presence or absence of lymphovascular invasion (LVI) and among age groups ($p=0.001$, $p=0.001$, $p=0.001$ respectively). The Kaplan-Meier curve demonstrating the disease-free survival was presented in Figure 2.

DISCUSSION

The incidence and prevalence of esophageal cancer has been increasing worldwide, and despite the contribution of CRT to the treatment, its prognosis remains poor compared with other malignancies. Various factors affecting the overall survival and the disease-free survival in patients with esophageal cancer have been reported. In the cur-

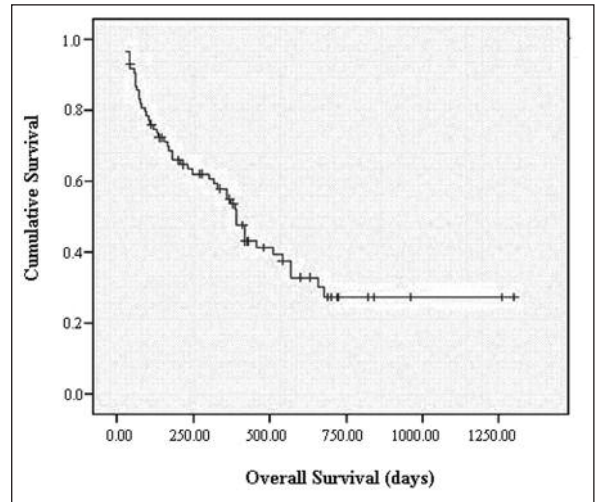


FIGURE 1: Overall survival according to Kaplan-Meier analysis curve.

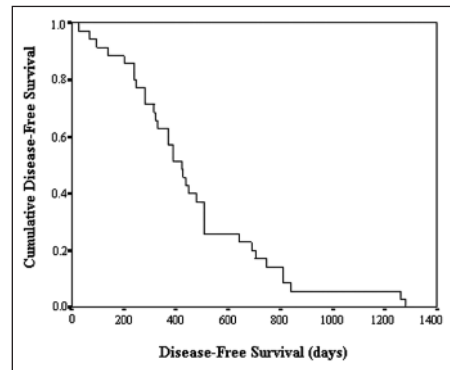


FIGURE 2: Disease-free survival according to Kaplan-Meier analysis curve.

rent study, we evaluated factors affecting the prognosis in patients with esophageal cancer.

Esophageal cancer ranks fourth among all gastrointestinal cancers.^{3,5,7} The majority of patients have lost the chance of curative operation at the time of diagnosis.

Esophageal cancer is generally regarded as a disease of the elderly and its frequency increases after the age of 60.⁸⁻¹² The reported incidence in males is 2-7 times higher than in females.^{1,12}

The major symptom of esophageal cancer is dysphagia. Thus, the most important step in the diagnosis is to consider the possibility of esophageal cancer in every patient with difficulty in swallowing.¹³⁻¹⁵ The rate of dysphagia was reported to be

93% in the study by Katlic et al., whereas it was reported to be 77% in the study by King et al.¹⁶

In the literature, while the stage of the disease have been reported as an important prognostic factor, tumor invasion and the number of metastatic lymph nodes have been emphasized to be principal factors affecting survival in patients with esophageal cancer.^{12,17,18}

In the literature preferred methods of treatment is very important point for survival. No significant difference has been reported between the patients undergoing surgery and the patients undergoing chemotherapy (CT) in terms of survival, the 5- and 10-year survival of patients receiving preoperative and/or postoperative CT have been reported to be shorter than that of patients not receiving preoperative and/or postoperative CT.¹² Ando et al. reported no difference in terms of 5-year survival between the patients undergoing radical surgical treatment and those receiving CT after surgery.¹⁹ However, they found that the 5-year survival was significantly longer in patients with metastatic lymph nodes who received CT following surgery than in those who underwent surgery alone.¹⁹ In the study by Kleinberg et al., the patients were treated with 44 Gy radiotherapy (RT) with cisplatin and 5-fluorouracil (5-FU) preoperatively, and the patients undergoing surgery alone were compared with those receiving CRT; the long-term survival was reported to be better in patients receiving preoperative CRT.²⁰ In another

study, in which CRT, RT, and CT were compared, CRT was demonstrated to be substantially effective in patients with locally advanced tumor as compared to the other two treatment methods.²¹ However, patients undergoing surgery or patients receiving CRT after surgery were not enrolled in that particular study.²¹

In another study, surgery followed by CRT has been emphasized to be the best treatment method for locally advanced esophageal cancer.²² In other studies suggesting the contrary, no advantage was determined in terms of survival in the 1- and 2-year follow-ups between patients undergoing surgery alone and those undergoing surgery and postoperative CRT.^{23,24} Similarly, there are studies emphasizing that there is no significant difference regarding survival between patients undergoing CRT alone and those undergoing surgery and postoperative CRT.^{25,26} For early stage esophageal cancers, however, it has been emphasized that RT is effective in tumors less than 5 cm in length, and that other treatment alternatives like CRT are preferred in the treatment of tumors greater than 5 cm in length, for which surgical treatment cannot be performed.²⁷

In our series surgical treatment was preferred in the early stage also primary CRT was preferred in advanced stage. The important point of our study was stage of cancer and methods of treatment were the most important prognostic factors on survival of oesophageal cancer patients.

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