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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Survival and Failure Outcomes of Neoadjuvant/Definitive Radiotherapy in Locally Advanced Esophageal and Gastro-Oesophageal Junction Cancer: A Single Institute Experience

Lokal İleri Evre Özofagus ve Gastroözofageal Bileşke Tümörlerinde Neoadjuvan / Definitif Radyoterapinin Sağkalım ve Başarısızlık Sonuçları: Tek Merkez Deneyimi

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ABSTRACT

Aim: The aim of this study was to present our clinical experience as survival and failure outcomes in patients with locally advanced esophageal and gastro-oesophageal junction (GEJ) cancer who received neoadjuvant /definitive radiotherapy (RT).

Material and Method: Twenty-eight patients with locally advanced stage (cT3-T4 any N and any T, N +) esophageal and GEJ cancer who received RT were retrospectively analyzed. Intensity-modulated radiotherapy (IMRT) was implemented to the patients in 25-33 fractions at a total dose of 45-59.4 Gy (median, 50 Gy).

Results: Twelve of 28 patients were alive during up to the four-year follow-up period. The overall recurrence rate was 28% (8/28). The median overall survival (OS) and recurrent-free survival (RFS) were 17 and 8 months, respectively. The one-year OS and RFS were 65% and 28%, respectively. Surgery was performed on only 9 of 28 patients. Pathological complete response (pCR) was observed in 5 (55%) of 9 operated patients. In 19 non-operated patients, local control was achieved with RT/CRT in 90%, only 2 (10%) patients were locally progressed.

Conclusion: Multidisciplinary treatment is crucial in patients with locally advanced esophageal cancer with poor survival rates. Neoadjuvant/definitive RT is an effective treatment option for local control.

Keywords: Esophageal cancer, neoadjuvant treatment, radiotherapy, chemoradiotherapy, survival

ÖZ

Amaç: Bu çalışmanın amacı, neoadjuvan / definitif radyoterapi (RT) alan lokal ileri evre özofagus ve gastroözofageal bileşke (GEJ) tümörlü hastalarda sağkalım ve başarısızlık sonuçlarını ve klinik deneyimimizi sunmaktır.

Yöntem ve Gereç: Lokal ileri evre (cT3-T4 herhangi bir N ve herhangi bir T, N +) özofagus ve GEJ tümörlü, RT alan 28 hasta geriye dönük olarak incelendi. Hastalara 25-33 fraksiyonda toplam 45-59,4 Gy (medyan, 50 Gy) dozda yoğunluk ayarlı radyoterapi uygulandı.

Bulgular: Maksimum dört yıllık takip süresi boyunca 28 hastadan 12'si hayattaydı. Genel nüks oranı % 28 (8/28) idi. Medyan genel sağkalım (OS) ve rekürrensiz sağkalım (RFS) sırasıyla 17 ve 8 aydı. Bir yıllık OS ve RFS sırasıyla% 65 ve% 28 idi. Yirmi sekiz hastanın sadece dokuzu opere oldu. Patolojik tam yanıt (pTY), opere olan 9 hastanın 5'inde (% 55) sağlandı. Opere olmayan hastaların (n=19) % 90'ında RT ile lokal kontrol sağlandı, sadece 2 (% 10) hasta lokal olarak progrese idi.

Sonuç: Kötü prognozlu, lokal ileri özofagus kanserli hastalarda multidisipliner tedavi yaklaşımı önemlidir. Neoadjuvan / definitif RT, lokal kontrol için güvenli ve etkili bir tedavi seçeneği olabilir.

Anahtar Kelimeler: Özofagus kanseri, Neoadjuvan tedavi, Radyoterapi, Kemoradyoterapi, Sağkalım

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INTRODUCTION

Esophageal cancer is one of the most aggressive gastrointestinal system (GIS) malignancies and its long-term prognosis is poor even with multimodal treatments. The 5-year survival rates are around 15-25%. Despite the poor prognosis, approximately 50% of the cases have local or local-advanced disease (1, 2).

In recent years, neoadjuvant chemoradiation (CRT) followed by surgical resection has been determined as the standard treatment for locally advanced esophageal and gastroesophageal junction (GEJ) cancer. Previous studies showed that survival outcomes were worse with surgery alone or radiotherapy alone (3, 4). With recent trials, CRT has been demonstrated to improve survival outcomes (2, 5). It has been reported that neoadjuvant chemotherapy does not improve overall survival (OS) compared to surgery alone (6). However, large randomized trials and meta-analyses illustrated that combined neoadjuvant therapy provided a survival benefit compared to surgery alone or neoadjuvant chemotherapy (2, 5, 7, 8). Phase 3-randomized Cross trial demonstrated neoadjuvant CRT followed by surgery, expressed as trimodal therapy, increased the chance of pathological complete response (pCR), R0 resection and so improved survival (2). Clinical complete response (cCR) and/or pCR, which occurs as a consequence of neoadjuvant treatments, are important prognostic marker in esophageal cancers, as in other GIS malignancies (9-11).

In this retrospective study, we aimed to present our clinical experience as survival and failure outcomes in patients with locally advanced esophageal and GEJ cancer who received neoadjuvant / definitive RT.

MATERIAL AND METHOD

Patient selection

Twenty-eight patients with locally advanced stage (cT3-T4 and any T, N +) esophageal and GEJ cancer who received RT between April 2015 and September 2020 in the Radiation Oncology clinic of Tokat Gaziosmanpaşa University were retrospectively analyzed. The study was conducted in accordance with the Helsinki declaration and this was approved by the ethics committee of our hospital (Decision no: 21-KAEK-089). Patient interview information, patient files and electronic system data were used for the study. Patients who completed their full courses and received definitive or neoadjuvant RT were included. Whereas, patients with unavailable information, metastatic disease, and received palliative RT were excluded from the study.

Treatment details

All patients before treatment were evaluated in a multidisciplinary treatment council. The patients were graded according to the AJCC TNM staging classification (8th edition). Computed tomography (CT), 18F-FDG PET/CT, and endoscopy were used for clinical staging. The gross target volume (GTV) was contoured according to the fusion of CT and PET/CT images, as well as endoscopic examination information. Clinical target volume (CTV) was created by expanding the GTV 3-4 cm from superior-inferior, and 0.5-1 cm margin from radial directions. CTVs are expanded 0.5 cm to accomplish planning target volume (PTV). With the Varian Clinac DHX Linac device, intensity-modulated radiotherapy (IMRT) was implemented to the patients in 25-33 fractions at a total dose of 45-59.4 Gy (median, 50 Gy). Definitive doses of RT (59.4 Gy) were delivered to three patients with cervical localization. Concurrent chemotherapy was applied to 86% of the patients. Weekly carboplatin-paclitaxel was administered to the majority of the patients (83% n: 20). CT and / or PET/CT were repeated 4-6 weeks after RT for re-evaluation. Patients were invited to follow-up visits for the first 1-month and then 3-months after the treatment and their tests were performed.

The primary endpoint of the study was to present data on overall (OS) and recurrent-free survival (RFS). In addition, factors affecting survival were examined. The endpoint for OS was the last control date (for survivors) and date of death (for dead ones). The endpoint for RFS was the date of progression.

Statistical analysis

Analyzes were performed using the SPSS software program (Version 20.0). Categorical variables were defined as absolute numbers. Continuous variables were reported as mean ± standard deviation or median values and ranges. Kaplan-Meier analysis was used for overall survival analysis. Univariate cox-regression analysis was performed to evaluate the effect of available parameters on overall survival. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Of the 28 patients included in the study, 9 (32%) were female and 19 (68%) were male. Their mean age was 63.7 ± 12.3 years. The median follow-up period was 14 months (range, 3-48 months). 7 patients received neoadjuvant chemotherapy. The most common localization of the tumor was distal (14 patients (50%)). The most common clinical stage was T3N0 (10 patients (36%)). The mean SUVmax of the tumor on PET CT before treatment was 15.8 ± 6.6. While 9 patients (32%) were operated after neoadjuvant CRT, 19 (68%) patients did not undergo surgical resection. The histopathology of the patients was SCC in 23 (82%), and adenocarcinoma in 5 (18%). No patient had distant metastases at the time of diagnosis. The demographic and clinical data of the patients are summarized in **Table 1**.

Table 1. Demographic and clinical data of the patients

Characteristics	n (%)
Sex	
Male	19 (68%)
Female	9 (32%)
Tumor location	
upper	3 (10.7%)
middle	7 (25%)
distal	14 (50%)
GEJ	4 (14.3%)
Clinical TN Stage	
T3N0	10 (36%)
T3N1	6 (21%)
T4N0	2 (7%)
T4N1	3 (11%)
T3N2	7 (25%)
Operation	
No	19 (68%)
Yes	9 (32%)
Histology	
Squamous cell carcinoma	23 (82%)
Adenocarcinoma	5 (18%)
Relapse Status	
No	20 (71%)
Yes	8 (29%)
Last Status	
Alive with healthy	9 (32%)
Alive with disease	3 (11%))
Ex	16 (57%)
Neoadjuvant Chemotherapy	
No	21 (75%)
Yes	7 (25%)

During the follow-up period, 16 (57%) patients died. The overall recurrence rate was 28% (8/28). Of the 28 patients, two had loco-regional relapse, five had distant metastasis, and one had local + distant relapse. The median OS was 17 months (95% Confidence interval (CI): 9-24) (**Figure 1**), while the median RFS was 8 months (95% CI: 5-10) (**Figure 2**). The one and two-year OS were 65% and 36%, respectively. The one-year RFS was 28.6%. In 19 non-operative patients following RT, while local control was achieved with RT in 17 (90%) patients (complete or partial response), local progression was observed in only 2 (10%) patients in the last control.

In univariate cox-regression analysis, there was no statistically significant relationship between OS and the factors such as concurrent chemotherapy (p: 0.132), whether or not surgery (p: 0.09), RT dose (0.46), clinical stage (p: 0.672), lymphovascular invasion (LVI) (p: 0.534), perineural invasion (PNI) (p: 0.065), weight loss (p: 0.137), neoadjuvant chemotherapy (p: 0.8), pre-therapy PET/CT SUV max (p: 0.869).

After treatment 6 patients (21%) were evaluated with only PET/CT, 11 (39.5%) with only CT, the remaining 11 (39.5%) with both CT and PET/CT. When they were restaged after treatment, clinical complete response (cCR) was observed in 8 (28.6%) patients, clinical partial response (cPR) in 19 (67.9%) patients and stable response in 1 (3.6%) patient.

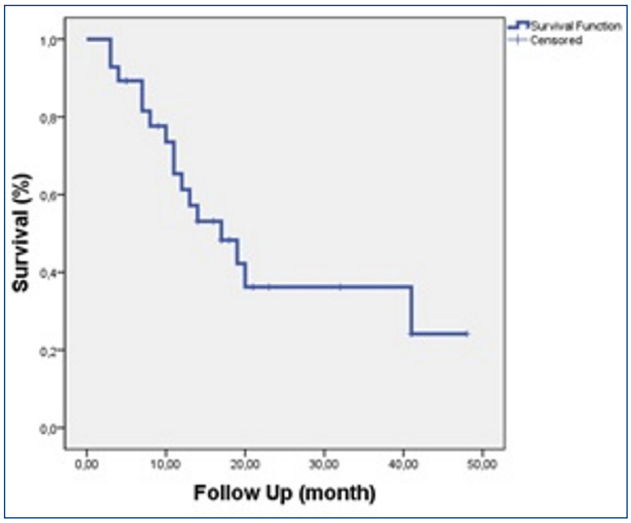

Figure 1. Kaplan-Meier curve for overall survival (OS)

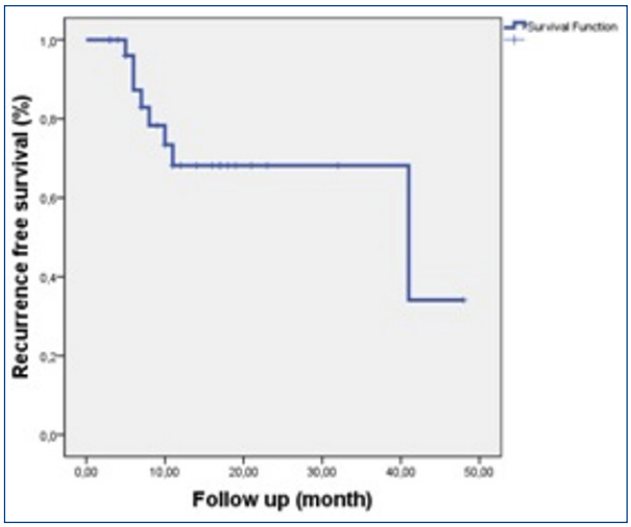

Figure 2. Kaplan-Meier curve for recurrence-free survival (RFS)

Surgery was performed on only 9 of 28 patients. Pathological CR (i.e. pT0N0) was achieved in 5 (55.5%) of 9 operated patients. Of the 5 patients with pCR, 2 had a complete metabolic response on post-RT PET/CT. On the other hand, the remaining 3 patients with pCR did not have post-RT PET/CT. All 4 patients with pPR had a partial response on post-RT PET/CT, as well as correlated with pathology. While only one patient was clinically N0 before neoadjuvant treatment, it was detected that the patient had occult nodal disease at the time of esophagectomy.

DISCUSSION

Esophageal cancer is one of GIS malignancies with a poor prognosis and in which the majority of patients are present at a locally advanced stage at the time of diagnosis. Recently, many phase 3 studies and meta-analyses have revealed that neoadjuvant CRT significantly improved survival in locally advanced esophageal cancer (2, 8, 12). In this study, we aimed to present the survival and local control outcomes of neoadjuvant treatments in patients with locally advanced esophageal cancer. Twelve of 28 patients were alive during up to the four-year follow-up period. The overall recurrence rate was 28% (8/28). The median OS and RFS were 17 and 8 months, respectively. The one-year OS and RFS were 65% and 28%, respectively. Surgery was performed on only 9 of 28 patients. Pathological CR was observed in 5 (55%) of 9 operated patients. In 19 non-operated patients, local control was achieved with RT in 90%, only 2 (10%) patients were locally progressed.

Response to neoadjuvant CRT has been found to be an independent predictor in terms of disease relapse in many studies (9, 14-16). In the literature, there are differences in pCR rates after trimodal treatment (17-20). Cristina et al. reported that the rate of pCR was 28% in patients with esophagus and GEJ tumors diagnosed with adenocarcinoma who underwent neoadjuvant CRT (17). In another retrospective study, consequences of neoadjuvant CRT were investigated in 46 patients with esophageal squamous cell carcinoma (SCC), and they found the pCR rate to be 44% (18). Some researchers reported this rate of around 20% (19, 20). Furthermore, SCC histology has been found to be associated with higher rates of pCR (2, 21). In the current study, although patients with both SCC and adenocarcinoma histology were included, we found the pCR rate to be 55%. Although it seems to be a higher rate compared to the literature, this rate may change downward as the number of patients increases. Unfortunately, due to reasons such as patient preference, comorbidities, socio-economic level, etc. most patients could not undergo surgery.

Some researchers have shown that patients with pCR have better OS as well as less locoregional failure (9, 14-16). No statistically significant relationship was found between pCR and survival in the current study, probably due to the small number of patients included in the study and also undergoing surgery. In the follow-up of five patients with pCR, one died due to post-op complications, one had isolated distant metastasis, and the remaining three patients live disease-free and healthy. As a matter of fact, patients who receive neoadjuvant therapy have a higher risk of postoperative mortality compared to those who receive surgery alone (22).

Masahiro et al. reported the results of CRT with IMRT in 36 patients with cervical esophageal cancer, 3-year-progression-free survival (PFS) and 3-year-OS were 40% and 46%, respectively (23). Cao et al found that 2-year locoregional control (LRC) and 2-year OS were 67.4% and 46% in 101 patients with esophageal cancer as an outcome of definitive CRT, respectively (24). In the phase 3 Cross study, the 1-, 2-, and 3-years OS rates in the preoperative CRT + surgery arm were 82%, 67%, and 58%, respectively (2). In the present study, because of trimodal therapy could not be applied to all patients, our survival rates were lower compared to the literature. Recently, in a study conducted with 769 esophageal cancer patients with N3 diseases, it was reported that surgery after neoadjuvant therapy improved survival (25). In the current study, only 32% of the patients had surgery, however, there was no N3 disease as in the aforementioned study.

In esophageal cancer, 18F-FDG PET/CT has an essential role in staging and re-evaluation after neoadjuvant therapy, as in other malignancies. PET/CT can predict poor response to neoadjuvant therapy and poor prognosis. Moreover, determining the best candidate for surgical resection is possible with PET/CT. Tustumi F et al. (26) examined the prognostic effect of pre-neoadjuvant PET/CT parameters on survival in 113 esophageal cancer patients. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) in the primary tumor; SUVmax in the suspicious lymph node was found to be significantly correlated with survival (26). In another similar study, 43 patients with esophageal cancer were evaluated with PET/CT before and after neoadjuvant therapy. Pathological CR was obtained in 56% of the patients and the predictive value of PET/CT for pCR was examined. The assessment of 18F-FDG PET/CT showed overall sensitivity of 57.9%, specificity of 62.5% (27). In our study, merely 17 of 28 patients had post-treatment PET/CT. Unfortunately, the analysis could not be performed for its effect on predicting the pathological response, as there were few patients whose pathological stage could be determined. However, in pre-treatment PET CT, primary tumor SUVmax was not found prognostic for survival (p: 0.869). We think that the reason for this result may be related to the low number of patients.

CONCLUSION

Multidisciplinary treatment is crucial in patients with locally advanced esophageal cancer with poor 5-year survival rates. Neoadjuvant/definitive radiotherapy may be a safe and an effective treatment option for local control.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Tokat Gaziosmanpaşa University with the decision no 21-KAEK-089 on 1 April 2021.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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