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Survival Outcomes of Cervical Esophageal Cancer Treated with Definitive Chemoradiotherapy using Intensity-modulated or 3D Conformal Radiation Therapy: A Single Institute Experience

Yoğunluk Ayarlı veya 3 Boyutlu Konformal Radyasyon Tedavisi Kullanılarak Definitif Kemoradyoterapi ile Tedavi Edilen Servikal Özofagus Kanserinin Sağkalım Sonuçları: Tek Merkez Deneyimi

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Abstract

Aim: The aim of this study is to report the survival and treatment results of patients with cervical esophageal cancer treated with definitive chemoradiotherapy, whose incidence is very low in the population and there is not enough information about treatment and toxicity results in the literature.

Material and Method: Between 2013 and 2022, 10 patients (six males and four females) with cervical esophageal cancer treated with definitive chemoradiotherapy were included. Among these patients, seven had stage II disease, one stage III, and 2 stage IVA. All patients received radiotherapy at a median dose of 50.4 Gy and concurrent weekly chemotherapy.

Results: The median follow-up period was 18 months. The two-year and 5-year overall survival rates were 42.2% and 21.1%, respectively. The two-year and 5-year disease-free survival rates were 45.7% and 22.9%, respectively. Disease progression was noted in 3 out of 10 patients (30%). Three patients were still alive during analyze. Percutaneous enteral gastrostomy was performed in 3 of 10 patients. These requirement occured in 1 due to local progression, and in the remaining 2 patients due to the side effect of RT.

Conclusions: Overall survival rates were low, as similar findings appear in the literature. It was remarkable that the need for a percutaneous enteral gastrostomy was not observed in the IMRT group. All patients with complete remission were in stage 2.

Keywords: Cervical esophageal cancer, squamous cell carcinoma, definitive chemoradiotherapy, survival, toxicity

Öz

Amaç: Bu çalışmanın amacı, popülasyonda insidansı çok düşük olan ve literatürde tedavi ve toksisite sonuçları hakkında yeterli bilgi bulunmayan, definitif kemoradyoterapi ile tedavi edilen servikal özofagus kanserli hastaların sağkalım ve tedavi sonuçlarını bildirmektir.

Gereç ve Yöntem: 2013-2022 yılları arasında definitif kemoradyoterapi ile tedavi edilen servikal özofagus kanserli 10 hasta (altı erkek ve dört kadın) dahil edildi. Bu hastaların yedisinde evre II hastalık, birinde evre III ve ikisinde evre IVA hastalık vardı. Tüm hastalar medyan 50.4 Gy dozda radyoterapi ve eş zamanlı haftalık kemoterapi aldı.

Bulgular: Ortanca takip süresi 18 aydı. İki yıllık ve 5 yıllık genel sağkalım oranları sırasıyla %42.2 ve %21.1 idi. İki yıllık ve 5 yıllık hastalıksız sağkalım oranları sırasıyla %45.7 ve %22.9 idi. 10 hastanın 3'ünde (%30) hastalık progresyonu kaydedildi. Analiz sırasında üç hasta hala hayattaydı. 10 hastanın 3'üne perkütan enteral gastrostomi uygulandı. Bu gereksinim 1 hastada lokal progresyon nedeniyle, geri kalan 2 hastada RT'nin yan etkisi nedeniyle ortaya çıktı.

Sonuçlar: Literatürdekine benzer şekilde genel sağkalım oranları düşüktü. IMRT grubunda perkütan enteral gastrostomi ihtiyacının görülmemesi dikkat çekiciydi. Tam remisyona tespit edilen tüm hastalar evre 2'deydi. Çok merkezli randomize çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Servikal özofagus kanseri, skuamöz hücreli karsinom, definitif kemoradyoterapi, sağkalım, toksisite

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INTRODUCTION

Only 4.6% of all esophageal malignancies are cervical esophageal carcinoma (CEC).[1] According to retrospective trials in the past, it has been demonstrated that radiotherapy (RT) with concurrent chemotherapy (CT) for CEC has a similar survival rate to curative surgery.[2,3] A reduced rate of acute morbidity and the opportunity for laryngeal preservation make definitive chemoradiotherapy (dCRT) preferable to surgery.[2–4] In earlier research, the locoregional failure (LRF) rate ranged from 12 to 50%, while the 5-year overall survival (OS) rate following chemoradiotherapy (CRT) for CEC was between 18 and 54%.[4–8] The aim of this study is to analyze the survival outcome in patients with cervical esophageal cancer treated with chemoradiotherapy.

MATERIAL AND METHOD

The Case Recording System was authorized to track down the individuals who had a cervical esophageal cancer diagnosis and who were treated as dCRT at our faculty between January 2013 and January 2022. Patients who underwent surgery as the primary treatment, those who only received chemotherapy or radiotherapy, those who had another cancer diagnosis either before or after receiving dCRT, and those who already had distant metastases at the time of initial diagnosis were all excluded from the study. A total of ten patients diagnosed with CEC who received dCRT were identified and included in the study for survival analyses.

Statistical Method

Using the Kaplan-Meier method, the survival curve was calculated. Outpatient follow-up visits were normally conducted once every three months up until two years after the therapy and once every six months thereafter up to five years utilizing a blood test, esophagogastroduodenoscopy with biopsy, if necessary, a CT scan, and an FDG-PET, if necessary.

No signs of disease were detected by radiological and/or endoscopic biopsy results in post-treatment follow-ups; a complete response; detection of regression in the T or N stage with the presence of disease finding; a partial response; similar persistence of disease finding; stable disease; and progression of the disease from the pre-treatment stage to a more advanced stage was considered progression. Toxicity was evaluated considering the RTOG toxicity criteria.

Ethics Statement

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of the Selçuk University Ethics Committee (Date: 21.06.2022, Decision No: 2022/132). All patients provided informed consent before their treatment started.

RESULTS

The clinical characteristics, treatment details, and results of this study are summarized in **Table 1**. The median age of the cohort was 67 (range, 37-69). There were six males and four females in the patient cohort. The histopathologic diagnosis of all patients in the study was squamous cell carcinoma. The pretreatment clinical stages were as following; stage II (7 patients), stage III (1 patient), and stage IVA (2 patients). The median follow-up period was 18 months (range, 5-111). The median irradiation dose of 50.4 Gy (45-50.4) was delivered. The estimated 2-year and 5-year overall survival (OS) rates were 42.2% and 21.1%, respectively. The estimated median value of OS was 25±8.6 months (95% CI 8-41.9) (**Figure 1**). The estimated 2-year and 5-year disease-free survival (DFS) rates were 45.7% and 22.9%, respectively. The estimated median value of DFS was 14±25.2 months (95% CI 0-63.3) (**Figure 2**).

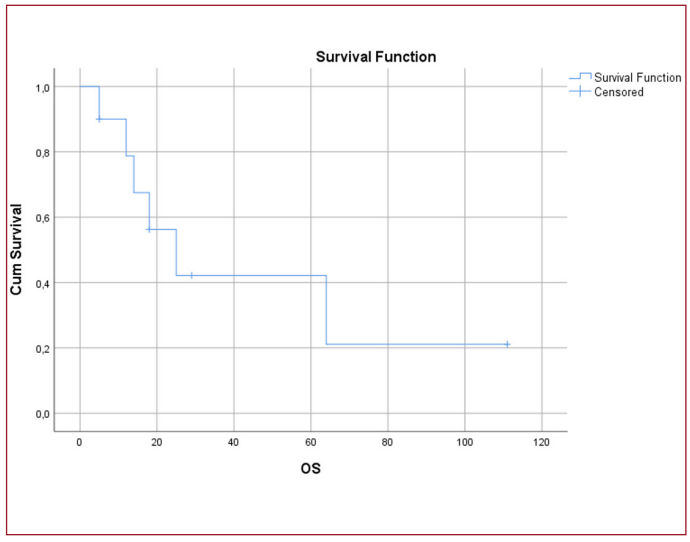

Figure 1. Overall survival (OS) curve

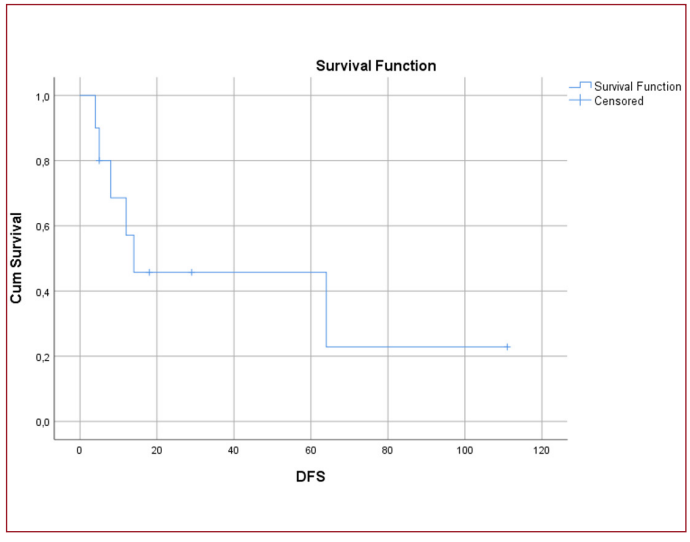

Figure 2. Disease-free survival (DFS) curve

Table 1. Patient demographics, disease features, treatment, side effects, and survival informations

Case No	Age	Gender	ECOG	Location	Tumor type	Clinical stage	Irradiation dose (Gy) and technic	Concurrent Chemo/No.	PEG	Response evaluation	Clinical course	OS (months)	DFS (months)
1	52	M	0	CeUt	SC	T2N0, stage II	45 Gy/ 25 fr 3D-CRT	Cisplatin (30- 40 mg/m²) / weekly/5	-	CR	CR continue	111	111
2	37	F	1	Ce	SC	T4N0, stage IVA	50.4 Gy/ 28 fr 3D-CRT	Cisplatin (30- 40 mg/m²) / weekly/5	+ (due to LR)	PR	Progression, salvage operation, recurrence, cancer death	14	8
3	44	F	1	CeUt	SC	T4N2, stage IVA	50.4 Gy/ 28 fr 3D-CRT	Paclitaxel (50 mg/m²) +Carboplatin AUC 2/ weekly/ 6	+ (due to RT toxicity)	PR	death of other disease (MI)	5	5
4	69	F	1	Ut	SC	T3N0, stage II	50.4 Gy/ 28 fr 3D-CRT	Paclitaxel (50 mg/m²) +Carboplatin AUC 2/ weekly/ 5	+ (due to RT toxicity)	CR	death of other disease (intestinal perforation)	64	64
5	47	F	0	Ut	SC	T2N2, stage III	50.4 Gy/ 28 fr 3D-CRT	Paclitaxel (50 mg/m²) +Carboplatin AUC 2/ weekly/ 6	-	CR	reccurred (bone), cancer death	25	4
6	61	M	0	Ut	SC	T3N0, stage II	50.4 Gy/ 28 fr IMRT	Paclitaxel (50 mg/m²) +Carboplatin AUC 2/ weekly/ 6	-	CR	CR continue	29	29
7	69	M	0	Ut	SC	T3N0, stage II	50.4 Gy/ 28 fr IMRT	Oxaliplatin (85 mg/m²) IV on Day 1, 15, and 29 for 3 doses, FU (180 mg/m²) IV on days 1, and 33	-	PR	peritoneal and omental metastatic implants. Loss of follow-up. Considered to be death.	18	14
8	67	M	0	Ut	SC	T3N0, stage II	50.4 Gy/ 28 fr IMRT	Oxaliplatin (85 mg/m²) IV on Day 1, 15, and 29 for 3 doses, FU (180 mg/m²) IV on days 1, and 33	-	Stable	death of other disease (MI)	12	12
9	67	M	1	Ut	SC	T3N0, stage II	50.4 Gy/ 28 fr IMRT	Paclitaxel (50 mg/m²) +Carboplatin AUC 2/ weekly/ 5	-	CR	CR continue	18	18
10	67	M	0	Ut	SC	T3N0, stage II	50.4 Gy/ 28 fr IMRT	Paclitaxel (50 mg/m²) +Carboplatin AUC 2/ weekly/ 5	-	PR	Loss of follow-up	5	5

PEG: percutaneous enteral gastrostomy, CR: complete response, PR: partial response, OS: overall survival, DFS: disease-free survival, ECOG: Eastern Cooperative Oncology Group performance scale, SC: squamous cell, Ce: cervical, Ut: upper thoracal, M: male, F: female, Gy: gray, fr: fraction, IMRT: intensity modulated radiotherapy, 3D-CRT: 3 dimensional conformal radiotherapy

DISCUSSION

Being an uncommon tumor with a poor oncological prognosis, CEC has mostly been treated with surgery as the primary option. Nevertheless, locally advanced CEC has been disallowed for definitive surgery. Additionally, patients frequently decline surgical approaches in order to maintain laryngeal function and prevent the procedure's significant risk of morbidity and mortality. For these particular patients, dCRT is regarded as a successful treatment with declared survival rates as similar with surgical excision. Owing to the low disease prevalence, comprehensive prospective studies are uncommon, and the majority of the available data is based on tiny retrospective series.[1-4]

Cervical esophageal cancer can be detected in a wide age range (18–87).[8] The age distribution of our study cohort was between 37 and 69 years. Men were the most commonly affected patient group in most studies as in ours (60%). In the study reported by Nakata et al., six of 10 patients were men.[9] Some studies have reported a much higher male gender predominance. In the study reported by Kim et al., which included 79 patients, almost all of the patients (n=75) were male.[10] Similarly, 6 of 10 patients were male in our study. Undoubtedly, it is not surprising that the male gender is dominant in this disease group, where smoking and alcohol consumption are the main risk factors.

A better dosage coverage and conformity to target volumes in their CEC have reportedly been made possible by advancements in RT techniques, which also permit less excessive doses to neighboring organs. However, because there are so few studies evaluating RT procedures in terms of survival and side effects, and because the sample sizes in the studies are so tiny and diverse, it is very challenging to draw a conclusive judgment about the clinical significance of this situation. The patient groups who got IMRT and 2D conventional RT were retrospectively assessed in the study reported by Cao et al., which included 101 patients with a diagnosis of CEC. In spite of the fact that there was no statistically significant difference in OS, regional failure-free survival, or local failure-free survival between the IMRT group and the 2D-RT group, the incidence of late toxicity decreased with IMRT (6.3 vs. 8.1%), which developed the beneficial ratio for CEC patients (4). In the study published in 2017 and reported by Ito et al., the clinical results of 80 patients were evaluated, Patients with a diagnosis of CEC who were treated with IMRT and 3D conformal RT were compared in terms of OS, failure patterns and toxicity. They achieved complete response in 24 of 32 patients (75%) in the IMRT group and in 33 of 48 patients (68.75%) in the 3D conformal RT group. These results did not create a statistically significant difference between the two groups in terms of complete responses. The median RT dose was 60 Gy (50–70.2). There was no significant difference in the incidence of late toxicities between the IMRT and 3D conformal RT groups. Esophageal stricture was one of the notable toxicities. Among patients those had esophageal stricture, in 9 patients with locally their tumor undercontrol in the esophagus (11%), comprising 5 (16%) in the IMRT group and 4 (8%) in the 3D conformal RT group. Four of those nine patients (44%) were diagnosed with T4 lesions. One

grade 4 pericardial effusion developed in the 3D conformal RT group. No grade 3 or higher pulmonary toxicity was observed.[11] Surgical treatment of CEC is associated with an early postoperative morbidity rate of up to 30–40%, such as anastomotic leakage, wound healing problems, fistula, and the need for reoperation, which negatively affects quality of life.[12,13] Unfortunately, both RT alone and CRT, which are alternatives to surgical treatment due to the high morbidity rates of surgery and have reported similar survival rates, are associated with relevant side effects that should not be ignored at all. Forsooth, severe acute and late toxicity have been reported in almost 20-30% of patients receiving RT or CRT.[6,14] In addition to the frequently seen side effects such as mucositis and cytopenia, more severe toxicities such as dysphagia or esophageal stenosis, which is the toxicity of RT or CRT treatments in both acute and chronic periods, may develop. This situation negatively affects the quality of life. In these cases, nutritional support can be provided parenterally or with a feeding tube. In our treatment outcome report, PEG was performed in 3 of 10 patients. While PEG requirement occured in 1 of these 3 patients due to local progression, this procedure was performed in the remaining 2 patients due to the side effects of RT. All 3 patients who underwent PEG were in the 3D CRT group. It was remarkable that none of the 5 patients treated with IMRT developed a need for PEG. Neither pulmonary nor hematological grade 3 or higher toxicity was observed. There are currently insufficient and heterogeneous reports on what the optimal radiotherapy dose should be, considering the balance related to oncological outcomes and toxicities. Although doses as high as 60–70 Gy are given to the tumor based on data with squamous cell cancer in the head and neck, it is not clear whether these contribute to local or overall survival. In a study evaluating 260 patients with any histological diagnosis and in any location of the esophagus, it was reported that the administration of 61.6 Gy to 50.4 Gy radiotherapy doses did not increase local control.[15] In our study, 9 patients received an irradiation dose of 50.4 Gy, while 1 patient received 45 Gy. A complete response was detected in 5 patients. Recurrence occurred in 2 of the 5 patients who developed a complete response. Three patients continue their lives with a complete response. It was quite remarkable that all of these patients were at stage II.

Despite major advances in drug production and technological improvements, the survival of patients with CEC is still not promising. In the meta-analysis published in 2022, in which 22 studies regarding definitive RT or CRT were applied to patients with CEC were analyzed, estimated pooled OS rates at 1, 3, and 5 years were 77.9% (73.9–82.2), 48.4% (43.2–54.3), and 35.3% (29.7–41.9), respectively. The median OS was 33.4 months (25.8–42.2).[8] In the present study, the estimated 2-year and 5-year OS rates were 42.2% and 21.1%, respectively, which were slightly lower than those mentioned in the meta-analysis.

According to statistics pertaining to the thoracic location, combining CT with RT has significantly improved outcomes in the treatment of esophageal cancer. However, because to a lack of data, an enhanced survival rate for the upper esophagus could not be proven. Several chemotherapy regimens have been suggested and modified by proven treatments for lower esophageal and hypopharyngeal squamous cell carcinoma. One of the current therapeutic options for CEC is high-dose cisplatin-based CT, frequently in conjunction with paclitaxel or 5-fluorouracil (5-FU). A limitation in the ability to draw any inferences is that the individual chemotherapeutic drugs utilized were heterogeneous, and no stratified data were presented. In our study, the patients those with who had concurrent RT and CT treatment selected for the trial. There were no standart CT scheme in analysed group.

The current study's mayor limitations were that it was designed at a single-centre, only covered a limited number of patients, and was retrospective in nature.

CONCLUSION

In the presented study, OS and DFS rates were low, consistent with the literature. It was remarkable that the need for PEG did not develop in those treated with IMRT. Side effects may be reduced with IMRT. All patients with complete remission were in stage 2. As a result of findings, there is a chance of cure with dCRT in early-stage patients without lymph node involvement.

Based on our trial results and the literature, there are important issues to be mentioned regarding CEC. Since the number of CEC patients is very small, information on this subject in the literature is so limited. Postoperative morbidity is very high. Currently, the primary recommended treatment is dCRT. Survival rates are very low. There are no strong recommendations regarding its treatments depending on randomized studies. There is a strong need for studies regarding chemotherapy schemes, the dose of radiotherapy, and the radiotherapy field.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Selçuk University Ethics Committee (Date: 21.06.2022, Decision No: 2022/132).

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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