Original Article

Definitive Chemoradiotherapy versus Neoadjuvant Chemoradiotherapy Followed by Surgery in Locally Advanced Esophageal Cancer: A Retrospective Evaluation of Clinical Data of Two Centers

Lokal İleri Özofagus Kanserinde Definitif Kemoradyoterapi ile Neoadjuvant Kemoradyoterapiyi Takiben Cerrahinin Karşılaştırılması: İki Merkezin Klinik Verilerinin Retrospektif Değerlendirilmesi

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ABSTRACT

Aim: The aim of this study is to investigate the results of neoadjuvant chemoradiotherapy /radiotherapy (neo-CRT/RT)+surgery and definitive chemoradiotherapy (def-CRT) approaches in locally advanced esophageal cancer

Methods: Between January 2012 and December 2021, in two centers, patients who received def-CRT or neo-CRT/RT with the diagnosis of locally advanced esophageal cancer, were retrospectively analyzed. Cases were evaluated for treatment response, overall survival (OS), disease-free survival (DFS), and local recurrence (LR).

Results: In total, fifty cases were included. The median follow-up was 10 months (range 2-26). In the def-CRT group; OS at one year, and two years were 67 % and 32 %, respectively; DFS at one year, and two years were 62 % and 32 % respectively. In the neo-CRT group; OS at one year was 81 % and DFS at one year was 73 %. In the follow-up time, LR was 12.1% in def-CRT and 11.8% in the neo-CRT group. For two treatment arms, there were no significant differences in OS (p=0.404), DFS (p=0.593) and LR (p=0.670). The neo-CRT group was evaluated according to the time of surgery, more mortality was found in patients who underwent surgery after 8 weeks, although statistical significance was not reached.

Conclusion: Considering the morbidity and mortality of surgery, def-CRT may be an alternative to neoadjuvant-surgical treatment in selected cases whose treatment response is considered a complete response. In these patients, waiting until recurrence and then salvage surgery can be considered.

Key words: Esophageal cancer, chemoradiotherapy, esophagectomy

ÖZET

Amaç: Lokal ileri özofagus kanserinde neoadjuvan kemoradyoterapi/radyoterapi (neo-KRT/RT)+cerrahi ve definitif kemoradyoterapi (def-KRT) yaklaşımlarının sonuçlarını araştırmaktır

Yöntemler: Ocak 2012 ile Aralık 2021 tarihleri arasında iki merkezde lokal ileri özofagus kanseri tanısı ile def-KRT veya neo-KRT/RT alan hastalar retrospektif olarak incelendi. Olgular tedavi yanıtı, genel sağkalım, hastalıksız sağkalım ve lokal nüks açısından değerlendirildi.

Bulgular: Toplamda elli vaka çalışmaya dahil edildi. Medyan takip süresi 10 (2-26) ay'dı. Def-KRT grubunda; Bir yıllık ve iki yıllık genel sağkalım sırasıyla %67 ve %32; bir yıllık ve iki yıllık hastalıksız sağkalım sırasıyla %62 ve %32 idi. Neo-KRT grubunda; bir yıllık genel sağkalım %81 ve bir yıllık hastalıksız %73 idi. Takip süresince lokal nüks oranı, def-KRT grubunda %12.1 ve neo-KRT grubunda %11.8 idi. İki tedavi kolu arasında, genel sağkalım (p=0,404), hastalıksız sağkalım (p=0,593) ve lokal

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nüks (p=0,670) açısından anlamlı fark yoktu. Neo-KRT grubu ameliyat zamanına göre değerlendirildiğinde, 8 haftadan sonra ameliyat edilen hastalarda istatistiksel anlamlılığa ulaşılamasa da daha fazla mortalite saptandı..
Sonuç: Cerrahinin morbidite ve mortalitesi göz önüne alındığında, tedaviye yanıtı tam yanıt olarak kabul edilen seçilmiş olgularda def-KRT, neoadjuvan+cerrahi tedaviye bir alternatif olabilir. Bu hastalarda nükse kadar bekleyip ardından salvaj cerrahi düşünülebilir.

Anahtar kelimeler: Özofagus kanseri, kemoradyoterapi, özofajektomi

Introduction

Esophageal cancer (EC) is one of the most common types of cancer worldwide. It was estimated over 600 thousand new cases and over 500 thousand deaths according to 2020 data [1]. The two major histopathological subtypes of esophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma (AC). The incidence of both subtypes differs by geographic region: SCC has a high prevalence in East Asia, East and Southern Africa, and Southern Europe; AC is more common in North America and other parts of Europe [2]. Although the 5-year overall survival is 20% [3], better outcomes can be seen in patients with early-stage disease [4]. Early-stage disease is usually treated with endoscopic resection [5]. Although esophagectomy remains the mainstay of surgical treatment, it has high morbidity and mortality rates [6]. EC is often diagnosed in advanced stages where surgery alone cannot cure it. Therefore, curative treatment options in advanced disease are neoadjuvant chemoradiotherapy (neo-CRT) followed by surgery or definitive chemoradiotherapy (def-CRT) [7].

Def-CRT is seen as an alternative to surgery with an increasing proportion of resectable diseases, especially in patients who are not suitable for surgery [8,9]. In neo-CRT, it is aimed to reduce both the tumor burden and the extent of the planned surgery, as well as the risk of distant metastasis (through the elimination of potential micrometastases) [8]. In advanced disease, multimodal therapy is needed to reduce relapse rates and achieve higher local control and survival rates [9]. A multidisciplinary approach is needed to determine the appropriate treatment option for each patient.

There are limited data comparing def-CRT to neo-CRT with esophagectomy in patients with esophageal carcinoma. This study aims to evaluate treatment response and survival according to def-CRT and neo-CRT+surgical approaches in patients with locally advanced esophageal cancer.

Materıal and Methods

We retrospectively analyzed the data of patients diagnosed with locally advanced esophageal cancer who underwent def-CRT or neo-CRT+ surgery in the Radiation Oncology Department of two centers. Between 2012 and 2021, in total, 50 patients were included in this study.

This study was conducted by considering ethical responsibilities according to the World Medical Association and the Declaration of Helsinki. The study was approved by XXX University Ethical Committee for non-invasive investigations (Date: 30.11.2021, Decision No: E-71522473-050.01.04-83316-513).

The patients were evaluated in terms of treatment options by the multidisciplinary tumor board. Clinical staging of all patients was performed with PET-CT. The AJCC-2017 staging system [10] was used for clinical staging. Patients with T2-4 and/or node positive, M0 esophageal cancer were included in the study. Eastern Cooperative Oncology

Group Performance Status Scale (ECOG PS) was used to assess the performance status of patients [11] and patients with ECOG PS 0, 1 or 2 were included. Demographic characteristics, clinical and pathological data of the patients, the purpose of treatment, doses, and areas of radiotherapy (RT), response to treatment, overall survival (OS), disease-free survival (DFS), and local recurrence (LR) were recorded.

For RT planning; CT scans of the patients were taken in a 2.5 mm section thickness, in the supine position, and using a wing board. The target volume was determined by fusing PET-CT images and planning CT images. The median dose of RT for the primary tumor and lymphatic region was 5040 cGy (4140-6000 cGy) in median 28 fractions (range 23-30). RT was performed for all patients using the Intensity-modulated radiation therapy (IMRT) or Volumetric modulated arc therapy (VMAT) technique.

Post-treatment response rates of patients were evaluated by radiological imaging and/or endoscopic examination. Response Evaluation Criteria in Solid Tumors (RECIST 1.0) are used for evaluation of response [12]. Accordingly, patients were evaluated as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

Statistical analysis

Patient characteristics were compared with a chi-square test. The median ages of the patients were compared with Mann-Whitney U test. The survival analysis was performed by the actuarial Kaplan-Meier method and differences between the curves were analyzed using the log-rank test. OS was defined as the time from diagnosis to death or the date of last control for patients who were alive. DFS was defined as the time from diagnosis to recurrence of tumor or death. Statistical analysis was carried out using the SPSS 21.0 software package. $p < 0.05$ was considered statistically significant.

Results

Clinical Data and Tumor Characteristics

In total, fifty cases were included. The median age of patients was 60 (37-75) years. There was no significant difference in the distribution of age (p=0.500), gender (p=0.060), and ECOG PS (p=0.230). Patient characteristics are shown in Table 1.

Thirty-three patients (66%) were treated with def-RT/CRT and 17 patients received neo-CRT (34%). Carboplatin-paclitaxel combination was applied to 38 (83%) patients and cisplatin- 5-fluorouracil combination was used for eight (17%) patients as concomitant chemotherapy. Concomitant chemotherapy could not be applied to four patients who were scheduled for definitive treatment, due to their comorbidities.

Treatment Response

In all study groups; 18 patients (36%) had complete responses (CR), 13 patients (26%) had partial responses, and 12 patients (24%) had stable responses. Progressive disease was present in seven patients (14%).

In the def-CRT group; the CR was observed in nine patients (27.3%) after treatment. There was partial response in 10 patients (30.3%), stable response in seven patients (21.2%), and progressive disease in seven patients (21.2%). In the neo-CRT group, the median time between surgery and CRT was seven (3-17) weeks. According to the surgical specimen, 9 of 17 patients had a pathological complete response (pCR) and three patients had a partial response. In three patients, the radiological and pathological stages were the same. The treatment doses of these three patients were 41.4 Gy. The RT dose of patients with a CR was median of 50 Gy (45-50,4); for patients with downstaging was median of 50 Gy (45-56).

Table 1: Patient and tumor characteristics

		All patients (n=50)	Def-CRT and Def-RT (n=33)	Neo-CRT +Surgery (n=17)	p-value
Follow-up (months)	Median (Range)	10 (2-26)	10 (2-26)	9 (3-20)	0.400
Age	Median	60 (37-75)	60 (40-75)	61 (37-73)	0.500
	60≤	25 (50)	17 (51.5)	8 (47.1)	
	60>	25 (50)	16 (48.5)	9 (52.9)	
Gender	Female	26 (52)	14 (42.4)	12 (70.6)	0.060
	Male	24 (48)	19 (57.6)	5 (29.4)	
ECOG PS	0	37 (74)	22 (66.6)	15 (88.2)	0.230
	1	11 (22)	9 (27.3)	2 (11.8)	
	2	2 (4)	2 (6.1)		
Stage	IIB	24 (48)	14 (42.4)	10 (58.8)	
	IIIA	1 (2)	14 (42.4)	1 (5.9)	0.150
	IIIB	20 (40)	-	6 (35.3)	
	IVA	5 (10)	5 (15.2)		
Tumor Location	Upper esophagus	5 (10)	5 (15.1)	0 (0)	
	Middle esophagus	20 (40)	15 (45.5)	5 (29.4)	0.070
	Lower esophagus	25 (50)	13 (39.4)	12 (70.6)	
Histopathology	SCC	43 (86)	30 (90.9)	13 (76.5)	0.170
	AC	7 (14)	3 (9.1)	4 (23.5)	
Chemotherapy	Yes	46 (92)	29 (87.9)	17 (100)	0.180
	No	4 (8)	4 (12.1)	0 (0)	
Treatment Response	CR	18 (36)	9 (27.3)	9 (52.9)	
	PR	13 (26)	10 (30.3)	3 (17.6)	0.080
	SD	12 (24)	7 (21.2)	5 (29.4)	
	PD	7 (14)	7 (21.2)		
LR	Yes	6 (12)	4 (12.1)	2 (11.8)	0.674
	No	44 (88)	29(87.9)	15 (88.2)	
Distant Metastasis	Yes	9 (18)	7 (21.2)	3 (17.6)	0.539
	No	41 (82)	26 (78.8)	14 (82.4)	

SCC: Squamous cell carcinoma, AC: Adenocarcinoma, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease. LR: Local Recurrence.

Overall Survival /Disease-Free Survival

At a median follow-up of 10 months (2-26 months), overall survival (OS) at 1 year, and 2 years 70 % and 38 % were, respectively (Figure 1) and disease-free survival (DFS) at 1 year, and 2 years were 66 % and 30 % respectively (Figure 2).

In the Def-CRT group; At a median follow-up of 10 months (2-26 months), OS at 1 year, and 2 years were 67 % and 32 % respectively and DFS at 1 year, and 2 years were 62 % and 32 % respectively. In the neo-CRT group; At a median follow-up of 10 months (2-20 months), OS at 1 year was 81 % and DFS at 1 year was 73 %. There was no significant difference between the treatment groups for OS (p=0.593) and DFS (p=0.404).

This study showed that treatment option (def-CRT or neo-CRT+ surgery) (p=0.404), patients' gender (p=0.320), age of diagnosis (p=0.130), tumor histology (p=0.970), tumor location (p=0.740) and stage of diagnosis (p=0.110) had no significant impact on survival rate.

24 patients (%48) died. Although there was no significant difference between the treatment groups (p=0.513), OS was higher in the neo-CRT group. In the neo-CRT+ surgery group, five patients died due to surgery-related complications (%29) and two patients (%12) died due to distant metastases, and 1 (%6) patient died from pneumonia. In the def-CRT group, five patients (%15) died due to distant metastases, four patients (%12) died due to

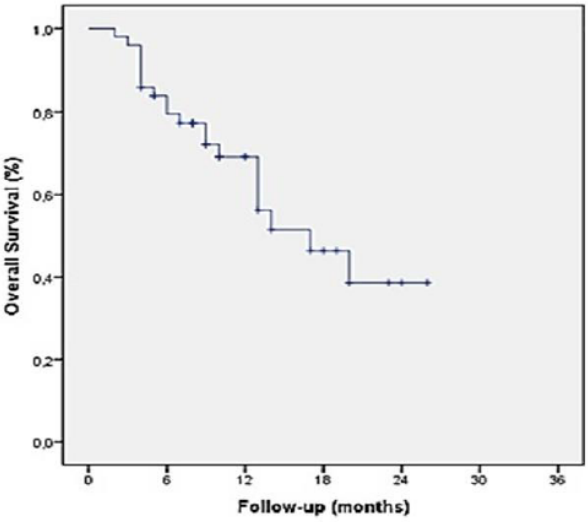

Figure 1. Overall survival at 1 year and 2 years

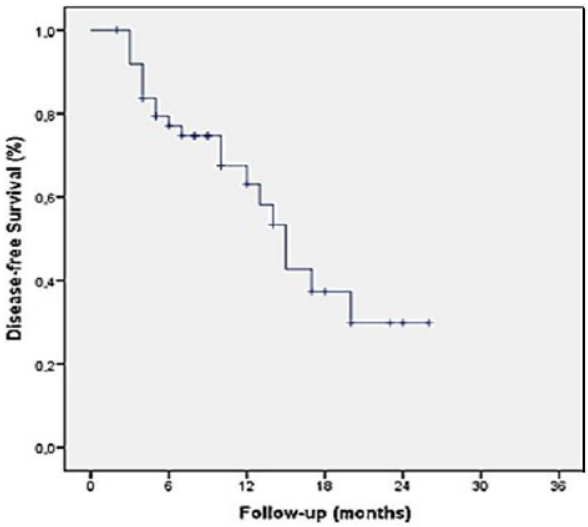

Figure 2. Disease-free survival at 1 year and 2 years

non-cancer reasons, and seven patients (%21) died due to primary disease after CRT.

Patterns of Failure

In the follow-up of the patients after the treatment, local recurrence (LR) was 12.1% in def-CRT and 11.8% in the neo-CRT group. There was no significant difference between the two treatment groups (p=0.670). In the follow-up of the patients, metastases developed in nine patients (18%) and there was no significant difference between the two treatment groups (p=0.539). Of the patients who developed distant metastases, four had lung metastases (44.5%), two had liver metastases (22.2%), two patients had lymph node metastases (22.2%), and one patient had brain metastases (11.1%).

Discussion

This retrospective study shows no significant difference in DFS and OS in patients with locally advanced EC when comparing def-CRT with neo-CRT followed by surgery. A preoperative chemoradiotherapy regimen that was based on carboplatin and paclitaxel was manageable and had a favorable safety profile. However, the neo-CRT group was evaluated according to the time of surgery, more mortality was found in patients who underwent surgery after 8 weeks, although statistical significance was not reached.

In a recently published systematic review and meta-analysis, patients with EC who received neo-CRT and esophagectomy had better survival than patients who received def-CRT [13]. However, in our study, in terms of OS, there was no significant difference between the two treatment groups. We also showed better at 1-year OS in the neo-CRT group (81% vs 67%), but not statistically significant, potentially due to follow-up time and/or sample size issues. In published two different studies of patients with locally advanced EC, for OS, there was no significant difference between patients who underwent def-CRT and surgery after neo-CRT [7,14]. The 2-year overall survival in patients who received neo-CRT followed by surgery and def-CRT were 69.1% and 40.0%, respectively [15]. Similarly, in our study, 2-year OS was 32 % in def-CRT. Since the longest follow-up period

was 20 months in the neoadjuvant group, 2-year survival could not be evaluated.

Dong Qian et al., more than 40% of patients with esophageal SCC had pCR after neo-CRT [14]. In other studies, The pCR of this approach ranges from 13 to 47% [15,16]. Similarly, in our cohort, 53% of the patients who received neoadjuvant therapy, had pCR. While increasing the pCR rate with neo-CRT was expected to have a positive effect on overall survival, no significant advantage in overall survival could be demonstrated despite the downstaging. Two separate studies have shown that surgical delay of >8 weeks doesn't lead to a favorable outcome in patients with esophageal cancer. These studies showed that an 8-week interval between neo-CRT and surgery is sufficient to produce a maximum RT response in patients with esophageal cancer, thus longer surgical delay may have adverse consequences for patients with a good response to neo-CRT [17,18]. In our study, CR was obtained in 29% of the patients in the surgical group. However, all patients who died from surgical complications had an interval of >8 weeks from CRT to surgery. Therefore, the positive effect of pathological complete response on overall survival may not have been observed in the neo-CRT group.

Carlo C. et al found that in patients with clinical CR after neo-CRT, waiting until relapse and then salvage surgery didn't adversely affect survival compared to patients treated with surgery [19]. We could not compare these two patient groups in our study. Because all patients in the neo-CRT group, underwent surgery regardless of clinical response to treatment. A case-control study showed that patients with CR had a better prognosis after CRT compared to surgery [20].

Kenji et al. compared def-CRT doses in patients with thoracic EC; CR rates in the 50.4 Gy and 60 Gy groups were 49.1% and 46.4%, respectively. Also, no significant difference was found between the two groups in terms of OS, and they revealed that 50.4 Gy was non-inferior compared to 60 Gy [21]. Similarly, in the INT 0123 study, doses of 50.4 and 64.8 Gy were compared in EC patients and it was shown that survival and local control results weren't better at higher doses [22]. In our study; in patients with CR and downstaging, the median dose was 50 Gy, and the lowest dose was 45 Gy. Treatment response was stable in both patients who received 41.4 Gy. Based on this, it can be interpreted that the treatment dose should be at least 45 Gy to get a treatment response, but to reach a meaningful result, it is necessary to compare the number of patients and the dosing schedule.

Marieke P. et al showed that the 1 and 3-year DFS were 67% and 43%, respectively, in a neo-CRT+surgery group, and 56% and 24%, respectively, in def-CRT group. DFS significantly shorter in the def-CRT group compared to resected patients [23]. Unlike this study, in our cohort 1 and 2-year DFS were 62% and 32%, respectively, in def-CRT group; and 1-year DFS was 73% in neo-CRT+surgery group. No significant difference was found between the two treatment arms. That reason may be due to the unequal distribution of patients in the groups and the relatively short follow-up period.

In our study, the cumulative LR incidence rate was found to be 12%. Considering the groups, it was 12.1% in def-CRT and 11.8% in neo-CRT group. Similarly, Lin J.W. et al found the 3-year cumulative incidence rate of LR was 13.3% of patients (15). In contrast to our study, Münch S. et al showed that in locally advanced EC patients treated with either def-CRT or neo-CRT+surgery group (38% vs. 10%), a higher rate of LR was seen in patients treated with def-CRT than in patients treated with neo-CRT+surgery [24]. Unlike that study, the reason why there was no difference in LR between the groups may be that all patients were N0 patients located in the thoracic and lower esophagus.

Some limitations of this study are that the study was designed retrospectively and the follow-up period was short. In addition, some imbalances in tumor parameters between patient groups (lymph node metastasis rate and tumor location) may affect the results and should be kept in mind. The small number of patients in our study didn't allow us to perform subgroup analysis. The results of clinical studies with larger patient groups will contribute to the creation of the most appropriate multidisciplinary strategy according to histological subtype, localization, stage, and post-CRT tumor response.

Conclusion

In this study, no significant difference was found between the two treatment groups in terms of OS, DFS, and LR. Def-CRT may be an alternative to neoadjuvant-surgical treatment, considering the morbidity and mortality of surgery in selected cases whose treatment response is considered CR. Salvage surgery may be considered after recurrence in these patients

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