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RESEARCH ARTICLE

Chemoradiotherapy Results Without Surgery in Patients with Locally Advanced Esophageal Squamous Cell Carcinoma

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Abstract

Introduction: It aimed to evaluate the overall survival (OS) results of chemoradiotherapy (CRT) without surgery in patients with locally advanced esophageal squamous cell carcinoma (ESCC).

Methods: Patients who received chemoradiotherapy with a diagnosis of ESCC at the Radiation Oncology Department of Ankara Bilkent City Hospitals were retrospectively analysed. The primary endpoint was OS.

Results: The results of 46 patients who underwent radiotherapy (RT) between 26.06.2012 and 21.03.2023 were analysed. Median follow-up was 14 (range 1-47) months. The localisation was upper thoracic in 8(17.4%), middle thoracic in 36(78.3%) and lower thoracic in 2(4.3%) patients. Surgery was considered at the time of admission to the radiotherapy clinic in 25 (54.3%) of our patient group, and neoadjuvant treatment was given, but no surgery was subsequently performed. Patients referred to the radiotherapy clinic for neoadjuvant chemoradiotherapy received a significantly lower total dose than those referred directly for definitive chemoradiotherapy (p0.006; Z-2.768). Patients were evaluated by endoscopic biopsy and computed tomography 6-8 weeks after the end of treatment, and clinical complete response (cCR) was observed in 15 (32.6%) patients. At last follow-up, 19 (41.3%) patients were dead and 27 (58.7%) were alive. Median OS was 25 months (range 1.5-47). 1-year OS was 66%; 2-year OS was 54.7%; 3-year OS was 40.4%. Significantly higher OS was observed in patients with cCR (HR 4.2; 95% CI 1.2-14.7).

Conclusion: Patients referred to the radiotherapy clinic for neoadjuvant therapy received a significantly lower total dose than patients referred for definitive chemoradiotherapy. Patients who received cCR after chemoradiotherapy had significantly higher OS.

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Introduction

Esophageal cancer (EC) is the 7th most common cancer worldwide. Esophageal cancer ranks 5th in terms of cancer-related deaths. 500,000 people die of esophageal cancer each year.[1] Esophageal cancer, which is more common in eastern countries, has a poor prognosis. Although a statistically significant but small improvement in the prognosis of esophageal cancer has been achieved, treatments do not achieve the expected high results and esophageal cancer is still considered to be one of the most aggressive malignancies.[1,2]

There are two main pathological subtypes of esophageal cancer: adenocarcinoma and squamous cell carcinoma (SCC). These two pathological subtypes differ in terms of localisation, spread and prognosis. Squamous cell carcinoma is more common in eastern countries, and smoking/alcohol consumption and dietary habits are important aetiological factors.[3,4]

Surgery is the main treatment for esophageal cancer, but the prognosis of surgery alone is poor. Neoadjuvant therapy has been shown to improve OS. According to the European Society for Medical Oncology (ESMO) guidelines[5] and the National Comprehensive Cancer Network (NCCN) guidelines,[6] the standard treatment for patients with locally advanced esophageal squamous cell carcinoma (ESCC) is surgery after neoadjuvant chemoradiotherapy. However, due to the effect of surgery on prolonged quality of life up to 20 years later,[7] omission of surgery is being considered for patients who have achieved a clinical complete response (cCR). Promising results for overall survival in patients who achieved cCR and did not undergo surgery have been reported in studies.[8,9]

The aim of this study was to evaluate OS outcomes in patients with locally advanced esophageal squamous cell carcinoma (ESCC) who received chemoradiotherapy without surgery.

Material and Methods

In the current study, patients who received chemoradiotherapy with a diagnosis of ESCC at the Radiation Oncology Department of Ankara City Hospital were retrospectively analysed. Patient interview information, patient records, dose-volume histograms and electronic system data were used for the data obtained. Patients' demographic status, admission complaints, clinical stages, radiotherapy (RT) and chemotherapy details, and treatment response status were recorded. Staging was performed according to the American Joint Committee on Cancer ver(version) 8.[25] The Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.[26]

Patient selection

Adult patients with pathological evidence of thoracic esophageal cancer, pathological subtype squamous cell carcinoma, undergoing curative chemoradiotherapy were included in the study. Patients without path)ological evidence, patients receiving palliative radiotherapy, patients with adenocarcinoma, cervical or gastroesophageal junction tumours and patients with Eastern Cooperative Oncology Group performance scale 4 (ECOG PS) esophageal cancer were excluded.

Primary and secondary endpoints

The objective was to analyse the oncological outcome of patients who received chemoradiotherapy without surgery. The primary endpoint of the study was overall survival (OS). OS was defined as the time from the end of radiotherapy to the patient's death or last follow-up. The secondary endpoint of the study was initial response status after chemoradiotherapy. All patients underwent endoscopy and biopsy 6-8 weeks after chemoradiotherapy. Patients whose tumour was found in the control endoscopic biopsy or who could not pass the probe due to stenosis were not considered to have a complete response. Patients underwent computed tomography (CT) scans within 6 to 8 weeks after completion of chemoradiotherapy and were compared with pre-treatment CT scans. Response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) criteria.[10] It was aimed to analyze the oncological outcomes of patients who underwent chemoradiotherapy without surgery. The primary endpoint of the study was overall survival. OS was defined as the period from the end of radiotherapy to the patient's death or the last control date. The secondary endpoint of the study was the first response status after chemoradiotherapy. All our patients underwent endoscopy and biopsy 6-8 weeks after chemoradiotherapy. Patients whose tumor was detected as a result of control endoscopic biopsy or who could not pass the probe due to stenosis were not considered to have a complete response. After chemoradiotherapy was completed, our patients were scanned with computed tomography (CT) within 6-8 weeks and a comparative evaluation was made with the pre-treatment computed tomography. Response

Evaluation Criteria in Solid Tumors (RECIST 1.0) criteria were used for response evaluation,[10]

Statistical analysis

Data were analysed using SPSS version 26. The conformity of the data to a normal distribution was evaluated with the Shapiro–Wilk test; as the data were not normally distributed, parametric tests were used. The Chi-squared test and Fisher's exact test were used to analyse categorical variables. The Mann–Whitney U test was used for independent two-group analyses. The Kruskal–Wallis test was used for the analysis of 3 or more independent groups and Tukey's post hoc test was performed in cases of significance. In the statistical analysis method section; Kaplan Meier is used for survival analysis and Cox regression analysis is used for ultravariate and multivariate analysis. The hazard ratios (HR) and 95% confidence intervals (CI) of results that were significant in our survival analyses were calculated. A HR > 1 denotes an increased relative risk compared to the reference category. The significance limit of this study was set to 0.05.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Ankara City Hospital No. 1 on 15.5.2023 with the number E1-23-3568.

Results

The results of 46 patients who were diagnosed with ESCC between 26.06.2012 and 21.03.2023 at the Radiation Oncology Department of Ankara Bilkent City Hospital were analysed (Table 1). The median follow-up was 14 (range 1-47) months. The median age of the patients undergoing chemoradiotherapy was 61 years (range 40-74). The clinical stage of the patients was stage 2 in 13(28.3%), stage 3 in 22(47.8%), stage 4 in 11(23.9%). There were 3 patients with brain, lung and cervical lymph node metastases. Intensity-modulated radiation therapy (IMRT) with 6 MV photons was applied to all patients. The median total radiotherapy dose was 50 (37.8-60) Gy. The median neoadjuvant prescription dose was 5000 cGy (4140-5600) and the median definitive prescription dose was 5040 cGy (3780-6000). Chemotherapy was given to all patients, and the most commonly used chemotherapeutic agents were carboplatin and paclitaxel in 37 patients (80.4%). Neoadjuvant chemoradiotherapy was planned in 25 patients (54.3%) and definitive chemoradiotherapy in 21 patients (45.7%). Patients referred to the radiotherapy clinic for neoadjuvant chemoradiotherapy received a significantly lower total dose than patients referred for definitive chemoradiotherapy (p0.006; Z-2.768) (Figure 3).

Table 1. Patients and Treatment Details

Age	Median(range)	61 (40-74)
Gender	Women	18(39.1%)
	Man	28(60.9%)
Localisation	Upper Thoracic	8 (17.4%)
	Middle Thoracic	36(78.3%)
	Lower Thoracic	2(4.3%)
Clinic T Stage	cT2	4(8.7%)
	cT3	33(71.7%)
	cT4	9(19.6%)
Clinic N Stage	cN0	16(34.8%)
	cN1	21(45.7%)
	cN2	6(13%)
	cN3	3(6.5%)
M Stage	M0	43(93.5%)
	M1	3(6.5%)
Stage	Stage2	13(28.3%)
	Stage3	22(47.8%)
	Stage4	11(23.9%)
RT Purpose (RT başlangıcında)	Definitive	21 (45.7%)
	Neoadjuvan	25(54.3%)
RT Total Dose	< 50 Gy	14 (30.4%)
	≥50 Gy	32 (69.6%)
Chemotherapy	Cisplatin	2 (4.3%)
	Cisplatin +5 FU	7 (15.2%)
	Carboplatin + Paclitaxel	37 (80.4%)
Clinic Response	cCR	15 (32.6%)
	cPR	18 (39.1%)
	Stabil	6 (13%)
	Progression	7 (15.2%)
Last Status	Ex	19 (41.3%)
	Alive	27 (58.7%)

RT: radiotherapy; cCR: clinic complete response; cPR: clinic partial response

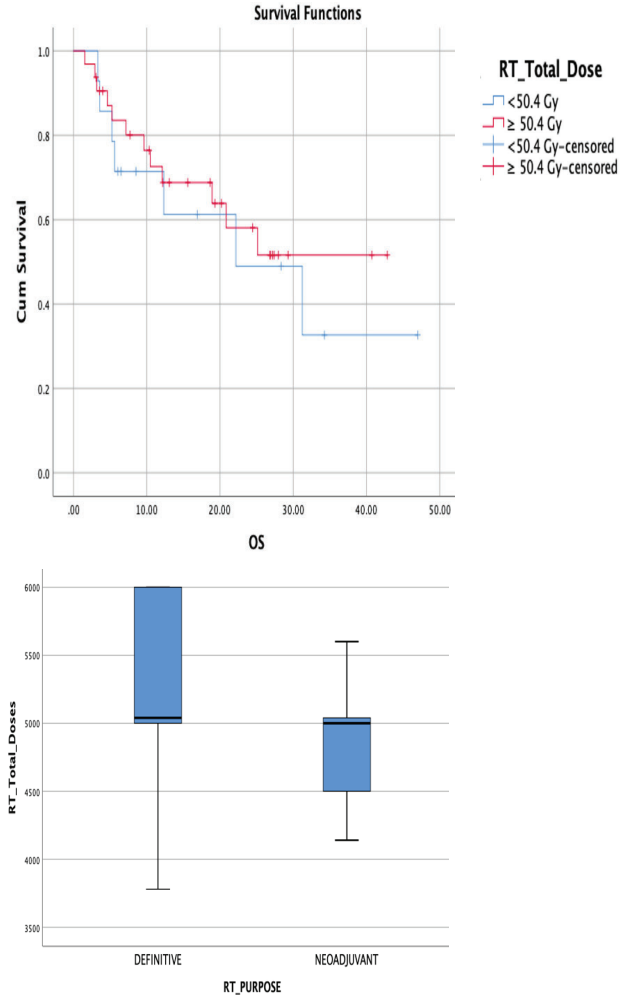

Figure 3. Similar overall survival rates were observed at doses greater than 50.4 Gy compared to lower doses.

Evaluation of clinical response after neoadjuvant therapy

After NA treatment, patients were evaluated by endoscopic biopsy and computed tomography. In patients receiving definitive radiotherapy, clinical complete response was observed in 8 (38.1%), clinical PR in 6 (28.6%), SD in 3 (14.3%) and progression in 4 (19%).

And in patients who received neoadjuvant radiotherapy, clinical complete response was seen in 7 (28%) of patients, clinical PR 12 (48%), SD in 3 (12%) and progression in 3 (12%) of patients.

Clinical response status was not significantly associated with age (p0.507), gender (p0.633), location (upper thoracic - middle thoracic - lower thoracic) (p0. 671), stage (p0.230), cT (p0.671), cN (p0.142), cM (p0.085), purpose of treatment (neoadjuvant or definitive) (p0.590) and total radiotherapy dose (< 50 Gy vs ≥50 Gy) (p0.634).

Overall Survival Result

During follow-up, 19 (41.3%) patients died; 27 (58.7%) patients were alive; median OS was 25 (range 1.5-47) months. 1-year OS is 66%; 2-year OS is 54.7%; 3-year OS is 40.4%. The following parameters were not significantly associated with overall survival (OS): age (p0.674); gender (p0.830); stage (p0.703); cT (p0.842); cN (p0.820), cM (p0.189); purpose of treatment (neoadjuvant or definitive) (p0.273); total radiotherapy dose (< 50 Gy vs ≥50 Gy) (p0.620). A significantly lower OS was observed in patients with lower thoracic localisation compared to upper and middle thoracic esophageal tumours (p0.012; HR 9.6; CI 95% 1.3-16.9)(Figure 1). However, only 2 patients had distal localisation and these patients were discharged at 3.1 and 3.5 months after NA treatment due to general discomfort and inability to eat. A significantly higher OS was observed in patients with cCR compared to others (p0.023; HR 4.2; 95%CI 1.2-14.7)(Figure 2). Patients with cCR did not achieve median survival (Figure 4).

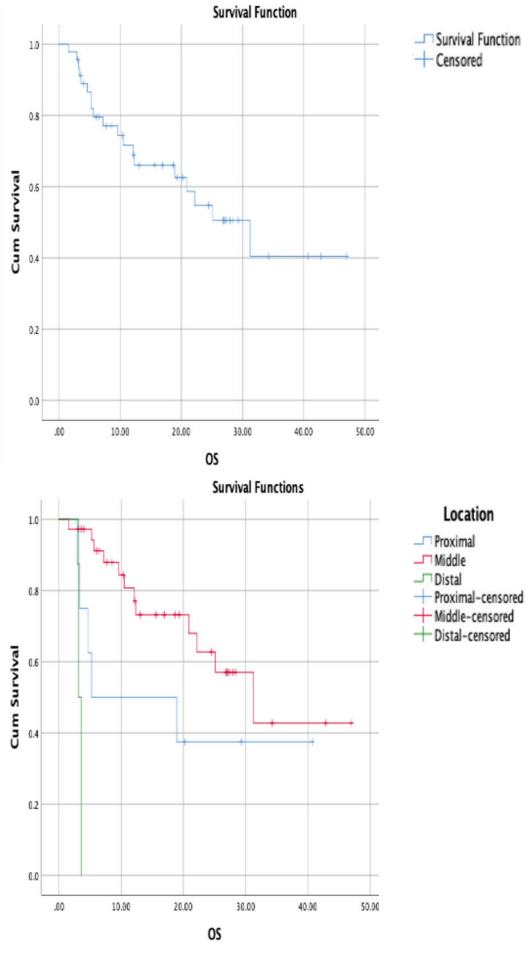

Figure 1. Kaplan Meier overall survival of the patients. According to the localization, no significant changes were observed in overall survival.

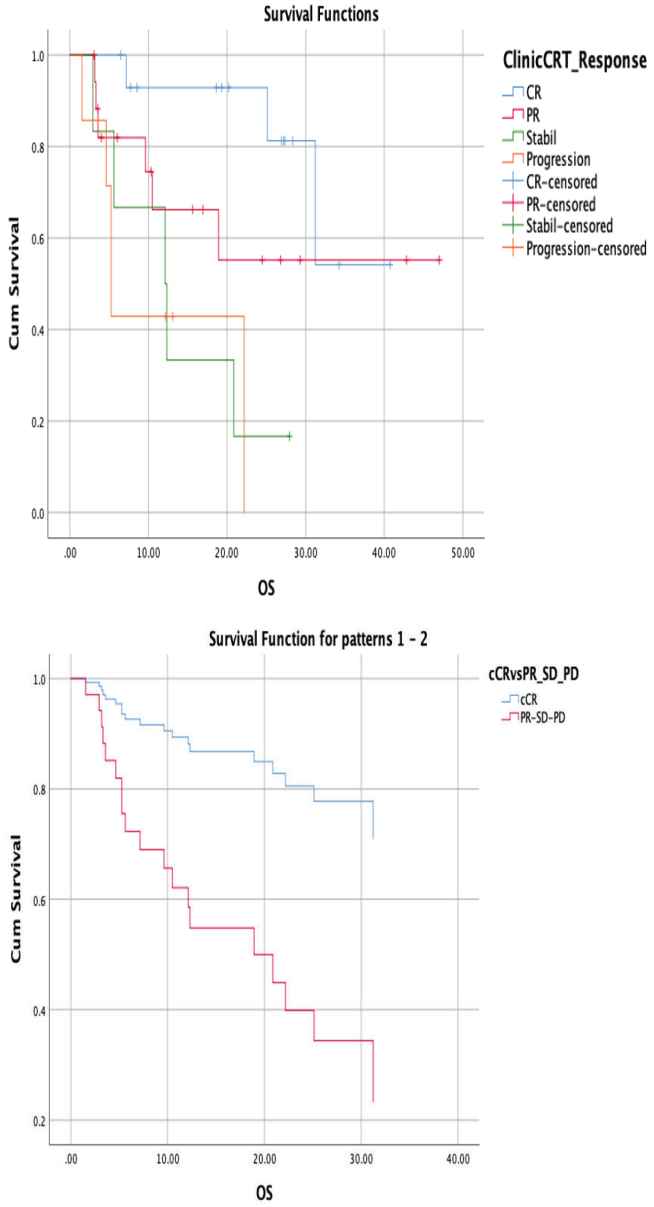

Figure 2. Significantly higher survival was achieved in the patient arm with clinical complete response.

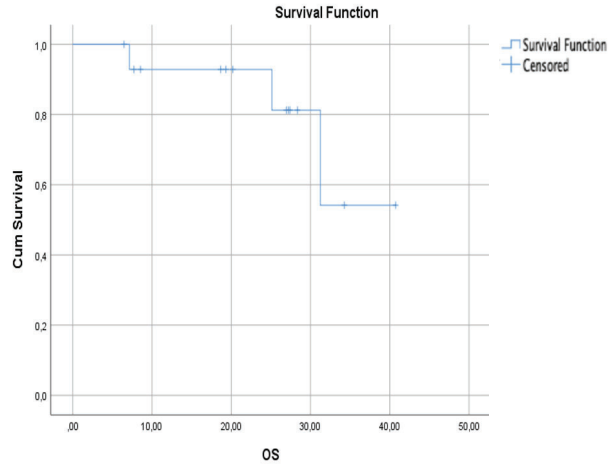

Figure 4. Cox regression analysis results of patients with cCR.

Discussion

In our study, we retrospectively analysed the results of 46 patients who received chemoradiotherapy without surgery for the diagnosis of ESCC, with a median follow-up of 14 months. Forty-six of the patients included in our study were referred to the radiotherapy clinic for neoadjuvant therapy, but did not subsequently undergo surgery. During the follow-up period, approximately 40% of the patients were excited and the median OS was 25 months. Of the parameters we evaluated, only CR had a significant impact on OS. In locally advanced ESCC, non-surgical follow-up is an alternative treatment for patients with cCR. According to Stahl et al, in a prospective randomised trial, patients were divided into two arms: those who received surgery after 40 Gy chemoradiotherapy and those who received chemoradiotherapy alone (60 Gy). The addition of surgery improved local tumour control but did not contribute to survival.[11] In the FFCD 9102 trial, patients were divided into 2 arms after 46 Gy of radiotherapy; those who underwent surgery and those who underwent definitive chemoradiotherapy (total 66 Gy).

Median survival was similar between the two arms (17.7 months in the surgery arm vs 19.3 months in the chemoradiotherapy arm). However, the 3-month mortality rate was significantly higher in the surgery arm (9.3% in the surgery arm versus 0.8% in the chemoradiotherapy arm (p0.002)).[12] In the prospective phase 2/3 SCOPE-1 trial using modern radiotherapy techniques, definitive chemoradiotherapy was used in ESCC patients and in this trial the 3-year OS was 47.2% and the median OS was 34.5 months.[13] Regarding this issue, Van Der Wilk et al in their review published in 2022 analysed 788 patients from 7 studies and found that 5-year survival was 58% and 2-year local regional control was 33% in patients without surgery after chemoradiotherapy.[14] According to Best et al. in a review published in 2016, which included 8 randomised trials, definitive chemoradiotherapy was compared with surgery after NA chemoradiotherapy; there was no significant difference between the two arms in terms of long-term mortality and recurrence.[15] However, according to Chow et al. in a meta-analysis comparing esophagectomy and definitive chemoradiotherapy arms after neoadjuvant chemoradiotherapy, which included 8 trials and 16,647 patients, higher survival rates were observed in the surgical arm, contrary to Best and colleagues.[16] Based on our current knowledge, nonsurgical treatment is an

appropriate alternative for locally advanced ESCC. Of the ongoing trials, SANO (NCT04886635), Esostrate (NCT02551458), PreSINO (NCT03937362); Needs trial (NCT04460352) will contribute to the standardisation of non-surgical regimens. In our trial, there was no surgical arm and no comparison could be made. And 46 ESCC patients who did not undergo surgery were followed for 14 months and our median OS was 25 months.

The contribution of surgical evaluation in patients with complete response after NA treatment is controversial. In the trials that set the standard of care, the treatment decision was not changed according to clinical response status, patients underwent surgery regardless of response status.[1,17] Patients with cCR have a better prognosis. A meta-analysis by Wang et al. of 648 patients with cCR (620 with squamous cell carcinoma and 28 with adenocarcinoma) showed that the addition of surgery contributed to 2-year disease-free survival. However, 5-year OS was similar between arms.[9] In a meta-analysis of 609 patients published by Park et al. in 2021, better OS was achieved in patients with cCR without surgery (HR = 0.80, 95% confidence interval [CI] 0.64-0.99, p = 0.04). The addition of surgery may increase morbidity and mortality and decrease quality of life. Therefore, chemoradiotherapy alone may be an appropriate approach for patients with cCR.[8]. In our study, cCR was achieved in 15 (32.6%) patients, and a significantly higher OS was observed in patients with CR compared to others (HR 4.2; 95% CI 1.2-14.7).

In our study, 54% of our patient group who were consulted for neoadjuvant therapy did not have surgery after NA chemoradiotherapy. Neoadjuvant and definitive radiotherapy doses are different (Figure 3). For this reason, each patient should be evaluated by the multidisciplinary tumour board to assess the patient's treatment in a multifaceted manner and select the most appropriate dose. 41.4 Gy is often preferred for neoadjuvant treatment and 50.4 Gy for definitive treatment. Dose escalation in radiotherapy for esophageal cancer has been attempted in the Intergroup 0123 and Artdeco trials. In the Intergroup 0123 study, 236 patients with esophageal cancer were divided into two arms: high dose (64.8 Gy) and standard dose (50.4 Gy). There was no significant difference between the two arms in median survival (13.0 vs 18.1 months), 2-year OS (31% vs 40%) and local regional disease continuity (56% vs 52%). In addition, 11 treatment-related deaths were observed in the high-dose arm compared to 2 treatment-related deaths in the 50.4 Gy arm.[18] The Artdeco trial was published in 2021 and used modern radiotherapy techniques. This study included patients diagnosed with esophageal cancer without surgery. The median follow-up was 50 months. 61.6 Gy was given with SIB (simultaneous integrated boost) in the high-dose arm and 50.4 Gy in the standard arm. There was no significant difference between the two arms for 3-year OS (70% vs 73%), 3-year local progression-free survival (52% vs 59%), grade 4 acute side effects (ASE) (12.5% vs 14.5%) and grade 5 ASE (3.3% vs 7.6%).[19]According to the results of these studies, higher doses did not provide better local control. Although there is a tendency to prescribe higher primary doses in boost/SIB, there is insufficient evidence to support the contribution of doses of 50.4 and above. In our study, a significantly lower total radiotherapy dose was administered to patients who presented to the clinic and underwent neoadjuvant planning. However, this dose difference did not show a significant effect on clinical response and OS.

The main limitation of our study is its retrospective nature and short follow-up. In our study, clinical response was assessed by computed tomography and endoscopy. PET-CT was not performed in all patients, so the metabolic response status was not included in the study. In addition, toxicity could not be assessed because not enough data were available in the records and system notes.

Conclusion

Definitive chemoradiotherapy is a viable option for patients diagnosed with locally advanced ESCC without surgery. In our own clinical experience, patients referred for neoadjuvant therapy receive lower doses. Patients should be assessed for operability and acceptance of surgery prior to radiotherapy. A complete response at week 6 after chemoradiotherapy is associated with improved survival.

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