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ORIGINAL ARTICLE

Chemoradiotherapy followed by surgery versus observation in esophageal squamous cell carcinoma

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Summary

Purpose: *We aimed to examine the effect of esophagectomy after chemoradiotherapy (CRT) or non-surgical follow-up after CRT in patients with locally advanced esophageal squamous cell carcinoma (ESCC).*

Methods: *A total of 653 patients under follow-up for locally advanced ESCC between 2010-2019 were reviewed for enrollment. Patients with no distant metastasis at the time of diagnosis who underwent esophagectomy or were taken under observation following CRT were included in the study. Overall, 127 eligible patients were included, 55 of whom were male (43.3%) and 72 female (56.7%).*

Results: *After CRT, 59 patients (53.5%) had undergone surgery and 68 (46.5%) were taken under observation. Median disease-free survival (mDFS) was not reached in the group that underwent surgery and was 13 months in the observation group ($p<0.001$). Median overall survival (mOS) was significantly longer in the operated group ($p=0.006$). There was no statistically significant difference in DFS and OS between patients who underwent surgery and those included in the observation group after achieving clinical and pathological complete response following CRT ($p=0.119$, $p=0.699$, respectively). The multivariate analysis identified surgery and increased CRT response as the factors that affect DFS ($p=0.042$, $p<0.001$, respectively).*

Conclusion: *In this study, surgery provided no additional benefit on survival in locally advanced ESCC patients with complete response while prolonged survival was observed in those without complete response.*

Key words: *esophageal cancer, chemoradiotherapy, squamous cell carcinoma, observation*

Introduction

Esophageal squamous cell carcinoma (ESCC) has a high recurrence rate and is one of the leading causes of cancer-related deaths globally [1-3]. The vast majority of esophageal cancers (ECs) are either squamous cell cancers or adenocarcinomas. While the incidence of ESCC has decreased in the United States, the incidence of esophageal adenocarcinoma (EAC) has shown a steadily increasing trend over the past few years [1-3].

Despite the recent advances in treatment, EC remains one of the deadliest malignancies. In patients with resectable EC, 5-year overall survival (OS) rate is 15-20% with surgery alone [4-6].

While guidelines recommend esophagectomy for ESCC patients in early stage (cT1b/T2, N0, size <2 cm, well differentiated), patients in clinical stage cT1b-T4a, N0/N+ are recommended to receive definitive chemoradiotherapy (CRT) or esophagec-

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tomy after neoadjuvant CRT [7]. However, the optimal treatment modality has not been clearly established.

Previous studies have shown the therapeutic efficacy of definitive CRT [8,9]. Given the significant operative risks of esophagectomy, a non-surgical treatment modality appears more reasonable [9]. In a prospective study by Park et al conducted in 86 Korean patients, 37 patients with clinical complete response (cCR) were randomized to surgery or observation. No difference was observed in terms of disease-free survival (DFS) duration [10].

In a randomized phase III study comparing surgery or observation following CRT after induction chemotherapy in locally advanced ESCC, the inclusion of surgery to the treatment plan was shown to provide further locoregional control. Since surgery-related mortality was added to the study results, there was no difference in survival between the treatments [11]. Similarly, in a study involving both EAC and ESCC patients, there was no additional survival benefit of surgery after CRT in ESCC patients [12].

The aim of our study was to compare neoadjuvant CRT followed by esophagectomy versus definitive CRT for locally advanced ESCC patients using real world data of Turkish patients.

Methods

Patients

The present study included patients who were followed up at the oncology clinic of Yuzuncu Yil University Medical School between 2010-2019. Patients with clinical stage II-III, ESCC histology, non-metastatic status aged 18 years and over, who received CRT after diagnosis were included in the study. Exclusion criteria included being under 18 years of age, histological subtypes other than ESCC, having undergone direct surgery, proximal localization, multiple malignancies, metastatic stage, and missing data. A total of 653 patient files were reviewed and 127 eligible patients were included in the study (Figure 1).

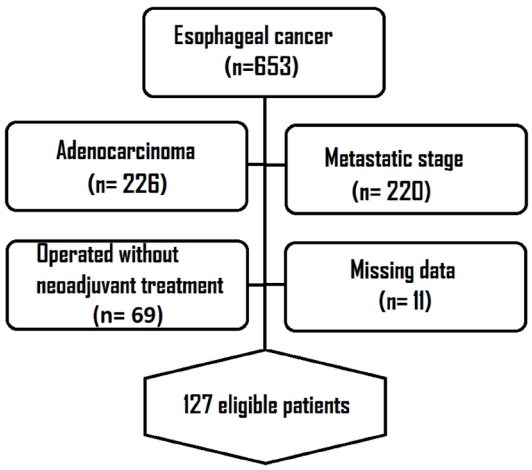

Figure 1. CONSORT diagram

Data collection

Patient information were retrieved from documented patient files including gender, age, comorbidities (hypertension, diabetes mellitus), smoking status, initial symptoms, Eastern Cooperative Oncology Group performance status (ECOG-PS), clinical stage, localization (middle vs. lower), length in endoscopy, tumor grade, carcinoembryonic antigen (CEA) and cancer antigen 19-9 levels at the time of diagnosis, neoadjuvant treatment regimen [weekly paclitaxel 50 mg/m^2+ carboplatin with area under the curve (AUC) of concentration*2 (CP) or two cycles of 75 mg/m^2 cisplatin day 1 of weeks 1 and 5+1000 mg/m^2 5-flourouracil per day, days 1 to 4, weeks 1 and 5 (CF)], neoadjuvant CRT response, pathological tumor stage (ypT), pathological lymph node stage (ypN), the number of lymph nodes removed, the number of involved lymph nodes, pathological stage (ypTNM), recurrence status and recurrence localization, first-line treatment and status at the last follow-up.

Clinical staging of the patients was based on computed tomography (CT) and/or 18F-fluorodeoxyglucose positron emission tomography (PET-CT). Post-treatment clinical staging was based on gastroscopy and CT performed 1 month after the end of treatments. In our center, surgery is recommended for all patients after CRT 6-8 weeks after the completion of treatment. Endoscopic ultrasound could not be performed before and after the treatment, as there was no endoscopic ultrasound facility in our center. At our center, we take the patients' history, and perform physical examination, blood analyses, chest and abdomen CT every three to four months for the first three years. We perform endoscopy every three to four months for the first three years for patients who do not want surgery. For operated patients, we perform endoscopy when there was a questionable margin at the time of surgery, or if the patient has signs of stricture.

Operated patients were stratified as complete response (pCR: fibrosis with no evidence of tumor cells), partial response (pPR: fibrosis and rare residual tumor cells), no-response (pNR= fibrosis and residual tumor). NACRT or definitive CRT was given with CF or CP. Radiotherapy was delivered at a total dose of 50.4 Gy given in 23-28 fractions of 1.8 Gy per fraction. DFS was defined as the time from treatment completion to relapse or progression. Overall survival (OS) was calculated as the time from the date of diagnosis to date of death or last follow-up.

Statistics

SPSS 22.0 software for Windows (Armonk NY, IBM Corp. 2013) was used for the statistical analyses. Descriptive statistics were expressed as number and percentage for categorical variables while mean, standard deviation, minimum, and maximum were presented for numerical variables. Chi square analysis was used to compare the ratios in the groups. Monte Carlo simu-

Table 1. Patient data

Characteristics	*All patients (n=127)* *n (%)*	*Observation group (n= 68)* *n (%)*	*Surgery group (n=59)* *n (%)*	*p*
Gender				0.202
Male	55 (43.3)	33 (48.5)	22 (37.3)	
Female	72 (56.7)	35 (51.5)	37 (62.7)	
Age (years), median (min-max)	57 (41-84)	58 (36-84)	58 (41-74)	0.320
Comorbidities				
Hypertension	8 (6.3)	3 (4.4)	5 (8.5)	0.471
Diabetes mellitus	5 (3.9)	3 (4.4)	2 (3.4)	0.768
Smoking status				0.261
No	86 (67.7)	49 (72.1)	37 (62.7)	
Yes	41 (32.3)	19 (27.9)	22 (37.3)	
Presentation				
Dysphagia	122 (96.1)	66 (97.1)	56 (94.9)	0.663
Abdominal pain	9 (7.1)	4 (5.9)	5 (8.5)	0.732
Weight loss	34 (26.8)	17 (25.0)	17 (28.8)	0.628
ECOG PS				0.007
0	79 (62.2)	35 (51.5)	44 (74.6)	
1	48 (37.8)	33 (48.5)	15 (25.4)	
Clinical stage				0.153
II	56 (44.1)	26 (38.2)	30 (50.8)	
III	71 (55.9)	42 (61.8)	29 (49.2)	
Tumor location				0.911
Middle	76 (59.8)	41 (60.3)	35 (59.3)	
Lower	51 (40.2)	27 (39.7)	24 (40.7)	
Tumor length (cm), mean ±SD	4.4 ±1.9	4.4±2.4	4.5±2.9	0.292
Grade				0.003
Well differentiated	6 (4.7)	3 (4.4)	3 (5.1)	
Moderate	107 (84.3)	52 (76.5)	55 (93.2)	
Poor/undifferentiated	14 (11.0)	13 (19.1)	1 (1.7)	
Carcinoembryonic antigen (ng/mL), mean ±SD	2.34±1.91	2.33±1.53	2.91±1.75	0.116
Carbohydrate antigen 19-9 (U/mL), mean ±SD	8.53±7.49	14.60±13.39	7.62±7.06	0.005
CRT regimen				0.386
CP	115 (90.6)	63 (92.6)	52 (88.1)	
CF	12 (9.4)	5 (7.4)	7 (11.9)	
CRT response				0.002
Complete response	63 (49.6)	29 (42.6)	34 (57.6)	
Partial response	33 (26.0)	14 (20.6)	19 (32.2)	
No response	31 (24.4)	25 (36.8)	6 (10.2)	
pT				
0	25 (50.0)		25 (50.0)	
1	1 (2.0)		1 (2.0)	
2	9 (18.0)		9 (18.0)	
3	14 (28.0)		14 (28.0)	
4	1 (2.0)		1 (2.0)	
pN				
0	41 (83.7)		41 (83.7)	
1	2 (4.1)		2 (4.1)	
2	6 (12.2)		6 (12.2)	

Continued on the next page

Characteristics	*All patients (n=127)* *n (%)*	*Observation group (n= 68)* *n (%)*	*Surgery group (n=59)* *n (%)*	*p*
Removed lymph nodes, median (min-max)	9 (3-32)		9 (3-32)	
Positive lymph nodes, median (min-max)	1 (0-3)		1 (0-3)	
Surgical margin positive	2	1.5	2 (3.3)	
ypTNM				
0	32 (55.2)		32 (55.2)	
1	5 (8.6)		5 (8.6)	
2	13 (22.4)		13 (22.4)	
3	8 (13.8)		8 (13.8)	
Recurrence				<0.001
Yes	59 (46.5)	43 (63.2)	16 (27.1)	
Recurrence location				0.953
Locoregional	10 (16.9)	7 (16.3)	3 (18.8)	
Lung	21 (35.6)	14 (32.6)	7 (43.8)	
Liver	18 (30.5	14 (32.6)	4 (25.0)	
Distant lymph node	8 (13.6)	6 (14.0)	2 (12.5)	
Bone	2 (3.4)	2 (4.7)	0 (0.0)	
First-line treatment				0.012
Yes	20 (33.9)	12 (27.9)	8 (50.0)	
Status at the last follow-up				0.004
Exitus	40 (31.5)	29 (42.6)	11 (18.6)	
Alive	87 (68.5)	39 (57.4)	48 (81.4)	

ECOG PS: Eastern Cooperative Oncology Group performance status; CF: Cisplatin+5-Flourouracil; CP: Carboplatin paclitaxel; CRT: Chemotherapy; pN: pathological node stage; pT: pathological tumor stage.

lation was applied when the conditions were not met. The determinant factors were examined by Cox regression analysis. The backward stepwise model was used for p <0.100 values in the univariate analysis. Survival analyses were performed by the Kaplan-Meier method. Statistical significance level was accepted as p <0.05.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and reviewed and approved by the Ethics Committee of Yüzüncü Yıl University with the decision number 2020/04-03.

Results

Overall, 127 eligible patients were included, 55 of whom were male (43.3%) and 72 female (56.7%). After CRT, 59 patients (53.5%) had undergone surgery and 68 (46.5%) were taken under observation. In this study, there was no difference between demographic and clinical data, except for ECOG PS, grade, CA 19-9, CRT response, recurrence, and status at the time of last follow-up (Table 1). One patient died due to surgical complications. The median follow-up time in the study was 18 months.

According to the Kaplan-Mayer analysis, median DFS was not reached in the surgical group while it was 13 months in the observation group (log-rank p<0.001). Similarly, mOS was significantly longer in the surgical group compared to the observation group (log-rank p=0.006) (Figure 2). Regarding subgroups, no significant difference was found in terms of DFS and OS in patients who underwent surgery and those who were followed up with non-surgical observation after achieving complete response following CRT (log-rank p=0.119 and log rank p=0.699, respectively) (Figure 3).

In the univariate analysis, smoking status, ECOG PS, undergoing surgery, CRT regimen and CRT response were found as the factors that affect significantly DFS (p=0.009, p=0.001, p=0.001, p=0.038, p<0.001, respectively) (Table 2). Multivariate analysis identified undergoing surgery and CRT response as the factors that affect significantly DFS (p=0.042 and p<0.001, respectively) (Table 3).

Discussion

The present study used real-life data to evaluate whether surgery is necessary after CRT in Turkish patients. The results showed that surgery performed after CRT significantly increased survival compared to observation. However, there was no additional benefit of surgery in patients who achieved CR after treatment.

Previous studies have demonstrated the superiority of definitive CRT only versus radiotherapy [9,13]. Surgery after CRT remains the most preferred therapeutic approach in eligible patients with resectable ESCC. On the other hand, the role of surgery in long-term outcomes needs to be clarified, especially in patients with response to CRT. In a study conducted by Wang et al with patients from Taiwan, esophagectomy was shown to be superior to definitive CRT in clinical stage I and II, while surgery did not provide an additional survival benefit in clinical stage III patients [14]. Chiu et al performed a study in 80 patients where they randomized the subjects to definitive CRT or surgery. In their study, patients who did not achieve cCR after definitive CRT underwent surgery. They found no difference between the study arms in terms of short-term survival. While more recurrences were observed in the mediastinum in patients in the surgical arm, there were more recurrences in the cervical and abdominal region in the definitive CRT arm [15]. In another study, 81 resectable patients were randomized to surgical and definitive CRT arms. The results of that study showed no differ-

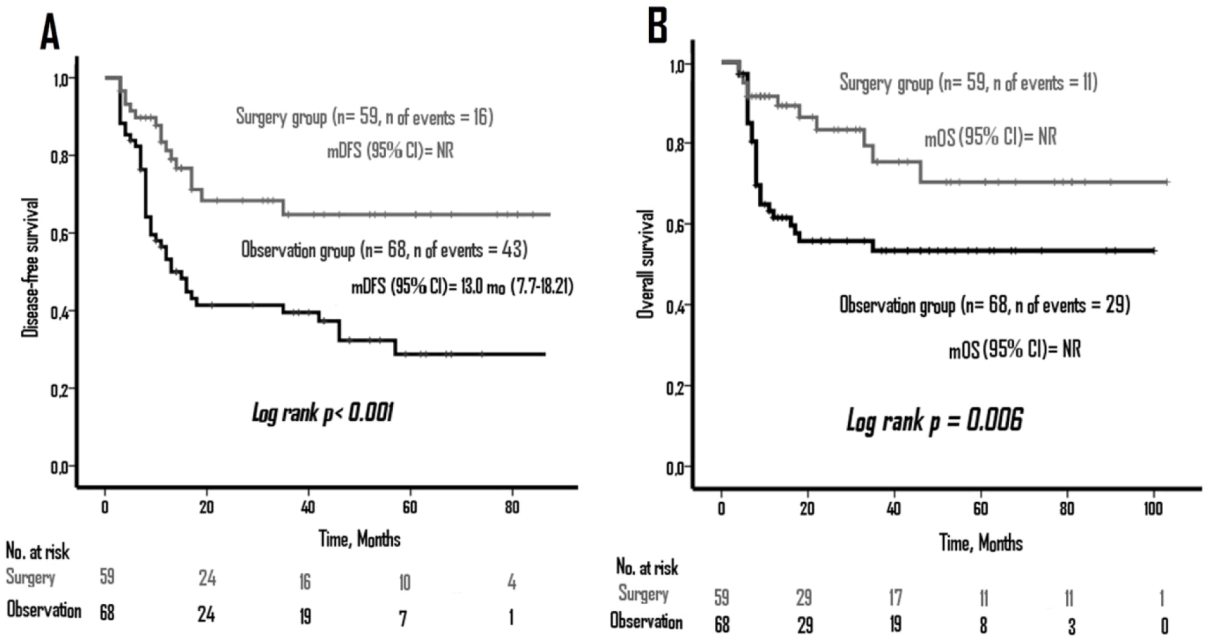

Figure 2. Disease-free survival (DFS) and overall survival (OS) according to treatment groups.

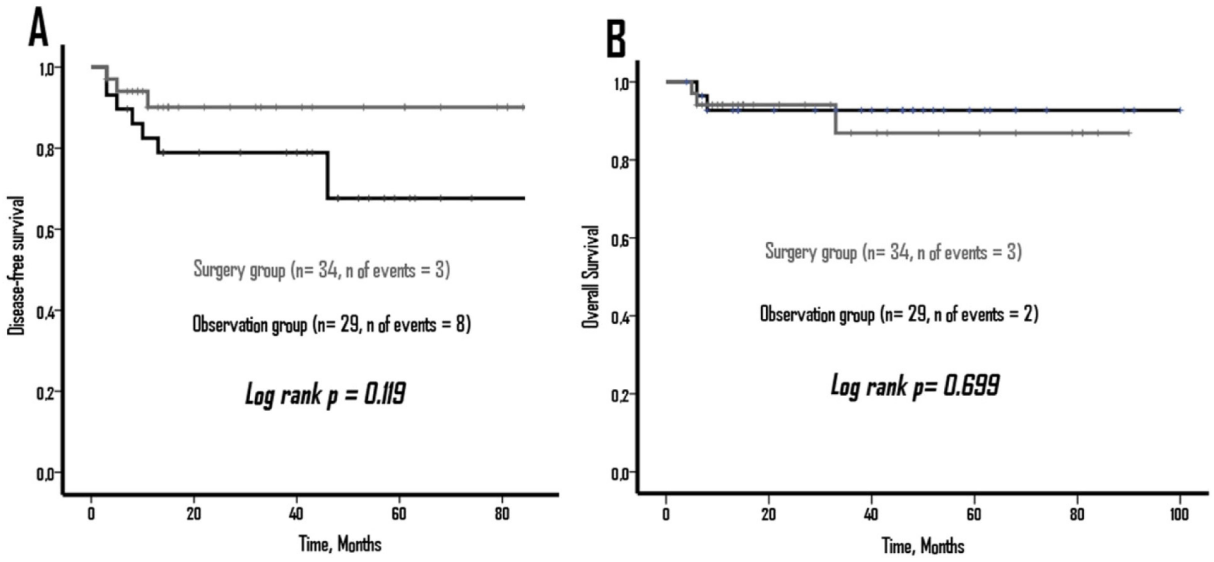

Figure 3. Disease-free survival (DFS) and overall survival (OS) according to treatment groups in patients with complete response.

Table 2. Univariate analysis for disease-free survival

Characteristics	*HR*	*95% CI*	*p*
Age, years	1.004	0.982- 1.026	0.707
Gender			0.385
Female vs. Male	1.261	0.747-2.129	
Hypertension			0.702
Yes vs. No	0.797	0.249-2.548	
Diabetes mellitus			0.783
Yes vs. No	0.820	0.200-3.361	
Smoking			0.009
Yes vs. No	2.411	1.248-4.658	
Dysphagia			0.356
Yes vs. No	0.578	0.180-1.851	
Abdominal pain			0.491
Yes vs. No	0.665	0.208-2.125	
Weight loss			0.666
Yes vs. No	0.879	0.489-1.580	
ECOG PS			0.001
1 vs. 0	2.821	1.682-4.732	
Clinical stage			0.097
3 vs. 2	1.571	0.922-2.679	
Tumor location			0.065
Lower vs. Middle	0.588	0.334-1.033	
Tumor length, cm	1.037	0.918-1.173	0.558
Grade			0.621
Well differentiated (ref.)	1.000		0.392
Moderate	1.854	0.450-7.637	
Poor/undifferentiated	2.163	0.459-10.191	0.329
Treatment			0.001
Surgery vs. Observation	0.374	0.210-0.664	
CRT regimen			0.038
CF vs. CP	0.223	0.054-0.919	
CRT response			0.000
Complete response (ref.)			0.002
Partial response	3.164	1.528-6.553	
No response	11.409	5.681-22.912	0.000
Carcinoembryonic antigen, ng/mL	1.003	0.999-1.007	0.103
Carbohydrate antigen 19-9, U/mL	0.998	0.993-1.004	0.490

For abbreviations see footnote of Table 1.

Table 3. Multivariate analysis for disease-free survival

Characteristics	*HR*	*95 % CI for HR)*	*p*
Treatment			
Surgery vs. Observation	0.528	0.285-0.978	0.042
CRT regimen			
CF vs. CP	0.242	0.058-1.008	0.051
CRT response			
Complete response (ref.)			<0.001
Partial response	3.530	1.681-7.397	0.001
No response	9.861	4.795-20.277	<0.001

For abbreviations see footnote of Table 1.

ence between the study arms in terms of long-term survival [16]. In these studies, neoadjuvant CRT was not administered in the surgical arm.

A recent Cochrane analysis suggested that CRT appeared non-inferior to surgery in terms of short- and long-term survival in ESCC patients eligible for surgery who respond to neoadjuvant CRT [17].

In the present study, we observed significantly increased DFS by performing surgery after CRT. The risk of recurrence after CRT was decreased by 48% with surgery. However, the subgroup analysis showed no additional benefit of esophagectomy in terms of DFS or OS in patients who achieved cCR. In our study, no significant difference was observed between the arms in terms of recurrence localization. On the other hand, unlike other studies, the patients in both arms in our study had received similar CRT treatments. In addition, we observed a significantly increased risk of recurrence with decreased CRT response.

Due to the harsh winter conditions in the region we live in, women use a closed-roof oven to bake bread. For these reasons, it may lead to serious smoke exposure. We attribute the high rate of female patients in our study to this reason. In addition, since smoking by women is not socially welcomed in our region, the rate of smoking among women is extremely low. This shows why the smoking rate among woman was low.

At our clinic, CRT followed by surgery is recommended for patients with locally advanced ESCC patients. However, some of these patients refuse undergoing surgery. For this reason, there is no difference between the study arms in terms of the RT doses. Moreover, our study is the first conducted with Turkish patients. Only locally advanced ESCC patients were included in the present study. Our study was a retrospective single-center and in addition, since there was no endoscopic ultrasound facility in our center, CRT response was assessed based on radiological imaging and gastroscopy in the observation group.

In conclusion, in light of this data, we believe that patients with cCR may be followed up under close observation without surgery, and esophagectomy should be definitely recommended after CRT in patients who fail to achieve CR and cannot be followed up under close observation. Our study results need to be supported by large-scale, multicenter studies.

Informed consent statement

Patient informed consent was not required since this retrospective study used anonymous data.

Author contributions

Concept: AS, SS, MNA; Design: AS, UHI, MCK; Supervision: AS, MNA; Resources: AS, SS, MMA; Materials: AS, UMI, MCK; Data Collection and/or processing: SS, MNA; Analysis and/or interpretation: AS, SS, MCK; Literature Search: AS, MCK; Manuscript writing: AS, UHI; Critical review: SS, UHI; Other: AS, SS, MNA.

Conflict of interests

The authors declare no conflict of interests.

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