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Research Article

Surgery: The Fundamental Part of Treatment in Elderly Esophageal Squamous Cell Carcinoma Patients

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Abstract

Objectives: Non-metastatic esophageal squamous cell carcinoma (ESCC) patients are treated with neoadjuvant chemoradiotherapy (CRT) followed by surgery. Older patients may have treatment-related toxicity at higher rates. We presented our experience regarding CRT followed by surgery on survival in older ESCC patients.

Methods: Older ESCC patients diagnosed between 2009-2021 were included. Overall survival (OS) estimates were calculated by Kaplan-Meier analyses and compared by Log-rank tests. Effects of ECOG performance status and age groups on survival were also presented.

Results: A total of 66 older ESCC patients were included. The median duration of follow-up was 62.3 months. The median OS of patients who were treated with surgery was significantly higher than those who were treated with CRT alone (48+, CI 95%: - vs. 14.1 months, CI 95%: 9.3-18.8, respectively, p=0.005). The median OS of patients who underwent surgery was significantly higher after adjusting by ECOG performance status and age groups than those who were treated with CRT alone (adjusted p=0.008 for ECOG and adjusted p=0.011 for age groups at diagnosis).

Conclusion: Surgery after CRT improves survival in older ESCC patients compared to CRT alone. Therefore, surgery should not be avoided in older patients solely due to patient age.

Keywords: Esophageal squamous cell cancer, older patient, surgery

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Esophageal cancer (EC) is one of the most frequent cancers worldwide with 604,100 new cases in 2020 and 22.1% of those patients were diagnosed at 75 years old or older.[1] Global Burden of Disease Study revealed that 30% of patients with EC were over 70 years of age.[2]

Non-metastatic EC is treated with chemoradiotherapy (CRT) followed by surgery in many countries due to the survival benefit which was shown in CROSS Trial.[3] Definitive CRT is another option for patients who are not surgical candidates. Stahl et al. showed that 2-year overall survival (OS) was 49% in esophageal squamous cell carcinoma (ESCC) patients treated with definitive CRT.[4] Older patients, who tend to have multiple comorbidities and poor performance status, may have higher treatment-related toxicity and impaired tolerance to treatment, regardless of treatment approach.[5-7] Due to the underrepresentation of older patients in clinical trials, evidence-based treatment approaches are limited in this vulnerable population.[8] Therefore, determining the optimal treatment strategy is challenging for clinicians. In this study, we presented the effect of surgery on survival in our older ESCC patients treated with CRT.

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Methods

Patient Data

This study included older ESCC patients who were diagnosed between 2009-2021 in our center. Patients ≥65 years old and those who were treated with CRT were included in the study. Patients who had EC with different histologies other than squamous cell carcinoma and those who were treated with surgery alone were excluded from the study. Patients with missing data were also excluded. Demographic characteristics, pathologic features, tumor locations, comorbid diseases, treatment data regarding surgery, chemotherapy, radiotherapy, and survival data of patients were retrieved from patient files. We compared patient groups treated with CRT followed by surgery and CRT alone in terms of survival. Approval for the study was obtained from the independent ethics committee. Written informed consent was obtained from all participants for this study.

Statistical Analysis

Categorical variables were compared with the Chi-square or Fisher's exact test, as appropriate. Survival estimates were calculated by Kaplan–Meier analysis and median survival times were compared by log-rank test. Progression-free survival (PFS) was defined as the time from the last treatment date to progression and OS was defined as the time from date of diagnosis to death. $p<0.05$ was considered to show statistical significance. Separate log-rank tests were performed to identify the independent effect of surgery on survival, after adjusting by Eastern Cooperative Oncology Group (ECOG) performance status and age groups at diagnosis.

The possible factors detected in univariate analyses were further entered into multivariate Cox regression analysis with enter selection to determine independent risk factors for patients. Variables with $p=0.20$ in univariate analysis or with clinical significance regardless of p-value were included in multivariate analyses. SPSS Software Version 26 (IBM, Chicago, Illinois, USA) was used for the analysis.

Results

After the exclusion of patients who were diagnosed with EC with different histologies other than squamous cell carcinoma and those with incomplete follow-up data (n=48), a total of 66 older patients were included in the study. The median age of diagnosis was 73 years. Twenty-eight patients (42.4%) were diagnosed with ESCC at 75 years old or older. Male (n=34) and female (n=32) patients were constituted 51.5 and 48.5% of the entire population, respectively. The vast majority of patients were in low (n=43, 65.2%) and medium (n=22, 33.3%) Charlson Comorbidity Index weighted classes. Fifty-nine (89.4%) patients had clinical T3 disease. Twenty-nine (43.9%) and 28 (42.2%) patients had clinical N3 and N0 disease, respectively. Metastatic disease was detected in 24 (36.4%) patients. The middle thoracic esophagus was the most frequent location of the primary tumor with a ratio of 37.9% (n=25). Twenty-seven patients (40.9%) received chemotherapy. Fifty-four patients (81.8%) were treated with CRT alone while 12 (18.2%) patients were treated with both CRT and surgery. The most frequent chemotherapy regimen which was delivered concurrently with radiotherapy was weekly paclitaxel carboplatin (n=49, 74.2%). During follow-up, 49 (74.2%) patients were dead. Other clinicopathologic features of the entire population are summarized in Table 1.

The ratio of patients who were younger and those who had better ECOG performance status was significantly higher in the surgery group ($p=0.05$ and $p=0.009$, respectively). Other clinicopathologic features were distributed similarly between patients treated with or without surgery (Table 2). None of the patients treated with CRT alone underwent salvage esophagectomy in case of recurrence.

The median duration of follow-up was 62.3 months (min: 1.6-max: 76.5). The median PFS and OS of the entire population were 5.8 and 17.4 months, respectively (Fig. 1). The 5-year OS of the entire population was 21%. The median PFS was not significantly different in patient groups treated with or without surgery (7.7 months, CI 95%: -, vs. 5.8 months, CI 95%: 0.19–11.3, respectively, $p=0.78$). The median OS of patients who were treated with CRT followed by surgery was significantly higher than those who were treated with CRT alone (48+, CI 95%: - vs. 14.1 months, CI 95%: 9.3–18.8, respectively, $p=0.005$). The 2-year and 5-year OS of patients who were treated with or without surgery was 67%, 67%, and 34%, 17%, respectively. The OS superiority of patients treated with both surgery and CRT to those who were treated with CRT alone has been still observed after adjusting by ECOG performance status and age groups at diagnosis (adjusted $p=0.008$ for ECOG and adjusted $p=0.011$ for age groups at diagnosis). According to multivariate Cox regression analysis, age of diagnosis and Charlson Comorbidity Index were independent prognostic variables to predict survival (Table 3).

Table 1. Clinicopathologic features of the entire population

	n	%		n	%
Age (years) (median) (min–max.)	73 (65-87)	-	Metastasis sites		
Age groups at diagnosis			Only LAP	22	33.3
65–74 years	38	57.6	Only distant organ	1	1.5
75≤	28	42.4	Both LAP and distant organ	1	1.5
Gender			Tumor Location		
Male	34	51.5	Upper thoracic esophagus	4	6.1
Female	32	48.5	Middle thoracic esophagus	25	37.9
ECOG performance status			Lower thoracic esophagus	31	47
0	7	10.6	Esophagogastric junction	5	7.6
1	31	47	Unknown	1	1.5
2	28	42.4	CT at diagnosis		
Charlson comorbidity index (median) (min.-max.)	0 (0–3)	-	Present	27	40.9
Charlson comorbidity index weighted comorbidity classes			Absent	39	59.1
			CT regimens at diagnosis		
Low	43	65.2	Paclitaxel carboplatin	8	12.1
Medium	22	33.3	CF	7	10.6
High	1	1.5	DCF	7	10.6
Lymphovascular invasion			Other¥	44	66.7
Present	1	1.5	Local treatment modalities		
Absent	0	0	Only chemoradiation	54	81.8
Unknown	65	98.5	Only surgery	0	0
Perineural invasion Unknown	66	100	Chemoradiation plus surgery	12	18.2
Tumor grade			Resection type R0	12	18.2
Grade 2	2	3	Chemotherapy regimen concurrent with radiotherapy		
Grade 3	1	1.5			
Unknown	63	95.5	Paclitaxel carboplatin	49	74.2
Staging modality			Capecitabine	4	6.1
Only PET	64	97	5-fluorouracil	4	6.1
Others*	1	1.5	Unknown	9	13.6
Unknown	1	1.5	Progression		
Clinical T stage			Present	20	30.3
T2	3	4.5	Absent	46	69.7
T3	59	89.4	Progression pattern		
T4	3	4.5	Locoregional	1	5
Unknown	1	1.6	Distant	4	20
Clinical n stage			Both locoregional and distant	15	75
N0	28	42.4	Progression time		
N1	7	10.6	≤12 months	15	22.7
N2	1	1.5	>12 months	5	7.6
N3	29	43.9	Survival status		
Unknown	1	1.6	Alive	17	25.8
Clinical disease stage			Dead	49	74.2
Locally advanced	42	63.6			
Metastatic	24	36.4			

PET: Positron emission tomography; LAP: Lymphadenopathy; CT: Chemotherapy; CF: Cisplatin and 5-Fluorouracil; DCF: Docetaxel; Cisplatin, and 5-Fluorouracil. *Other staging modalities include thorax-mediasten magnetic resonance imaging and endoscopic ultrasound. ¥: Other Regimens Include 5-Fluorouracil, Calcium Leucovorin and Oxaliplatin (FOLFOX), Capecitabin and Oxaliplatin (CAPOX), Epirubicin, Cisplatin, and 5-Fluorouracil (ECF), Paclitaxel, Cisplatin and 5-Fluorouracil (Paclitaxel CF) and Capecitabin.

Table 2. Clinicopathologic features of older esophageal squamous cell carcinoma patients who are treated with or without surgery

	Without surgery n (%)	With surgery n (%)	p
Age (years)(median)(min-max)	74 (65–87)	69 (65–77)	-
Age groups at diagnosis			
65–74 years	28 (51.9)	10 (83.3)	0.05
75≤	26 (48.1)	2 (16.7)	
Gender			
Male	27 (50)	7 (58.3)	0.6
Female	27 (50)	5 (41.7)	
ECOG performance status			
0	3 (5.6)	4 (33.3)	0.009
1	25 (46.3)	6 (50)	
2	26 (48.1)	2 (16.7)	
Charlson comorbidity index (median)(min.-max.)	0 (0–3)	0 (0–1)	-
Charlson comorbidity index weighted comorbidity classes			
Low	32 (59.3)	11 (91.7)	0.1
Medium	21 (38.9)	1 (8.3)	
High	1 (1.9)	0 (0)	
Clinical T stage			
T2	1 (1.9)	2 (16.7)	0.07
T3	49 (92.5)	10 (83.3)	
T4	3 (5.7)	0 (0)	
Clinical n Stage			
N0	23 (43.4)	5 (41.7)	0.21
N1	6 (11.3)	1 (8.3)	
N2	0 (0)	1 (8.3)	
N3	24 (45.3)	5 (41.7)	
Clinical disease stage			
Locally advanced	34 (62.3)	8 (66.7)	0.81
Metastatic	20 (37.7)	4 (33.3)	
Metastasis sites			
Only LAP	18 (90)	4 (100)	0.8
Only distant organ	1 (5)	0 (0)	
Both LAP and distant organ	1 (5)	0 (0)	
Tumor location			
Upper thoracic esophagus	4 (7.5)	0 (0)	0.46
Middle thoracic esophagus	20 (37.7)	5 (41.7)	
Lower thoracic esophagus	26 (49.1)	5 (41.7)	
Esophagogastric junction	3 (5.7)	2 (16.7)	
CT at diagnosis			
Present	24 (44.4)	3 (25)	0.33
Absent	30 (55.6)	9 (75)	
CT regimens at diagnosis			
Paclitaxel carboplatin	7 (13)	1 (8.3)	0.93
CF	6 (11.1)	1 (8.3)	
DCF	6 (11.1)	1 (8.3)	
Other†	35 (64.8)	9 (75)	
Chemotherapy regimen concurrent with radiotherapy			
Paclitaxel carboplatin	38 (82.6)	11 (100)	0.33
Capecitabine	4 (8.7)	0 (0)	
5-fluorouracil	4 (8.7)	0 (0)	

Table 2. CONT.

	Without surgery n (%)	With surgery n (%)	p
Progression			
Present	19 (35.2)	1 (8.3)	0.09
Absent	35 (64.8)	11 (91.7)	
Progression pattern			
Locoregional	1 (5.3)	0 (0)	0.84
Distant	4 (21.1)	0 (0)	
Both locoregional and distant	14 (73.7)	1 (100)	
Progression time			
≤12 months	14 (73.7)	1 (100)	1
>12 months	5 (26.3)	0 (0)	
Survival status			
Alive	9 (16.7)	8 (66.7)	0.001
Dead	45 (83.3)	4 (33.3)	

LAP: Lymphadenopathy, CT: Chemotherapy, CF: Cisplatin and 5-Fluorouracil, DCF: Docetaxel, Cisplatin, and 5-Fluorouracil; FLOT: 5-Fluorouracil, Oxaliplatin, and Docetaxel; †: Other Regimens Include 5-Fluorouracil, Calcium Leucovorin and Oxaliplatin (FOLFOX), Capecitabin and Oxaliplatin (CAPOX), ECF: Epirubicin, Cisplatin, and 5-Fluorouracil, Paclitaxel CF: Paclitaxel, Cisplatin and 5-Fluorouracil, Capecitabin; CRT: Chemoradiotherapy.

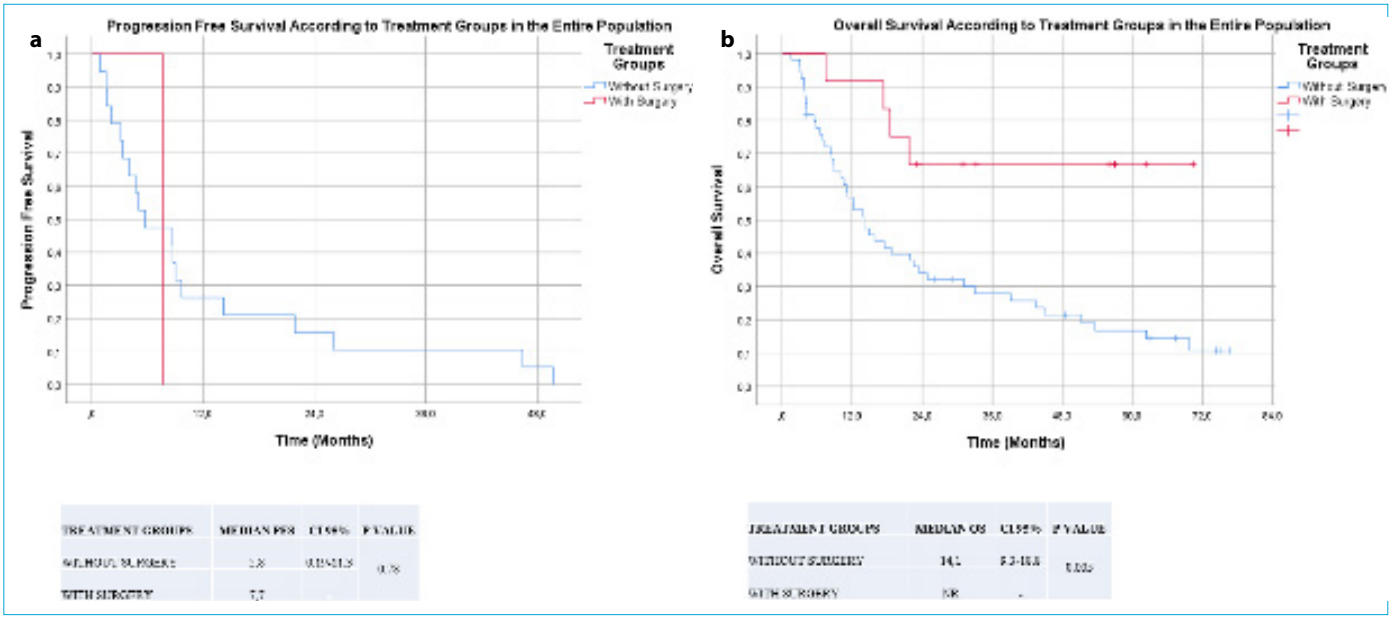

Figure 1. Progression Free Survival (a) and Overall Survival in the Entire Population According to Treatment Groups.

PFS: Progression Free Survival; CI: Confidence Interval; NR: Not Reached; OS: Overall Survival.

Discussion

In this study, we have showed that CRT followed by surgery improved survival compared to CRT alone in older ESCC patients. This effect was independent of ECOG performance status and age of the patients.

The mostly adopted treatment option for EC is neoadjuvant CRT followed by surgery.[3] However, several trials showed that definitive CRT without surgery had provided similar outcomes, particularly in ESCC.[9-13] In two meta-analyses, it was shown that adding surgery to CRT had not provided survival improvement.[4,14] A Cochrane review by Best et al. showed no significant difference between surgical and non-surgical approaches in terms of long-term recurrence.[15] In the same trial, long-term mortality was similar among definitive and neoadjuvant CRT. However, a more comprehensive and recent meta-analysis showed that trimodality treatment including CRT followed by surgery had provided a 45% decrease in death risk (HR 0.55; 95% CI: 0.49–0.62) with similar toxicity.[16]

Table 3. Univariate and multivariate cox regression analyses for overall survival

	Univariate				Multivariate			
	HR	95.0% CI for HR		p	HR	95.0% CI for HR		p
Age of diagnosis	1.08	1.03	1.14	0.004	1.07	1.01	1.14	0.02
Charlson comorbidity index	1.62	1.15	2.27	0.006	1.57	1.09	2.24	0.01
surgery Absent (ref.)								
Present	0.26	0.09	0.72	0.009	0.44	0.15	1.34	0.15
Clinical disease stage locally advanced (ref.)								
Metastatic	1.24	0.69	2.21	0.47				
Tumor location upper thoracic esophagus (ref.)								
Middle thoracic esophagus	1.58	0.37	6.79	0.54				
Lower thoracic esophagus	1.57	0.37	6.71	0.54				
Esophagogastric junction	2.45	0.45	13.45	0.30				
ECOG performance status 0 (ref.)								
1	1.12	0.33	3.79	0.85				
2	2.41	0.72	8.07	0.15				
Disease progression absent (ref.)								
Present	0.83	0.24	2.89	0.77				
CT at diagnosis absent (ref.)								
Present	0.99	0.56	1.75	0.98				

CRT: Chemoradiotherapy; CT: Chemotherapy.

Older patients tend to have poorer performance status and higher frequency of comorbidities. This situation renders them frail and makes them difficult to recover after surgery[17] and these patients significantly have a higher risk of post-operative mortality.[6,18,19] Thus, older patients were underrepresented in many clinical trials and treatment preferences may differ with increasing age. Molena et al. found that nearly a half of EC patients aged over 65 years in the surveillance, epidemiology, and end results program (SEER)-Medicare cohort was treated with CRT rather than surgery.[20] This trend was also seen in our study and the ratio of patients aged over 75 years in surgery group was significantly lower than those in non-surgery group. After adjusting by age groups, we proved the significant benefit of trimodality treatment over surgery alone on OS. The literature does not recommend avoiding surgery solely on age and suggests taking into consideration comorbidity, histology, patient preferences, and hospital conditions.[21-24] Our patients were distributed equally between surgery and non-surgery groups in terms of Charlson Comorbidity Index weighted classes. Patients with poorer ECOG performance status were included predominantly in the CRT group in this trial. Nevertheless, a separate log-rank test adjusted by ECOG performance status showed that a significant OS benefit had still been present. These findings also strengthened our hypothesis.

Lv et al. showed that surgery had provided significant survival benefit when added to CRT in older EC patients although this was apparent in esophageal adenocarcinoma (EAC) patients according to subgroup analyses.[25] In this trial, the ratio of ESCC patients was lower than EAC in trimodality treatment group. Yang et al. showed a 3-year OS of 44.3% in older EC patients treated with CRT followed by surgery and according to pair-wise analyses, this approach provided significantly higher survival benefit than other treatment options.[26] The 2-year OS were 67% and 34% in our patients treated with and without surgery, respectively. The median OS, which is presumably more than 48 months based on Figure 1b, was not reached in the trimodality group. Five-year OS of locally advanced ESCC patients older than 65-year-old is 23.9% according to the Surveillance, Epidemiology, and End Results Program (SEER) database[27] and 5-year OS of our patients was 21%, similar to the literature. In our study, we revealed a significant 5-year OS improvement with CRT followed by surgery compared to CRT alone in older ESCC patients (67% vs. 17%).

The survival benefit of surgery was not proved in two trials which had included only ESCC patients.[4,14] In these trials, it was stated that surgery provided better locoregional control and a lower need for palliative procedures. Thus, a non-surgical approach in patients who responded to CRT emerged as a new option in ESCC rather than in EAC. Conversely, we showed the survival benefit of immediate surgery over CRT alone in this study. Esophageal surgical inter-

ventions may be more challenging for older ESCC patients who relapsed after CRT compared to their younger counterparts due to multiple factors such as malnutrition, poorer ECOG performance status, higher prevalence of toxicity caused by prior radiotherapy, and higher surgical morbidity. Immediate surgery enables clinicians to eliminate most of these unfavorable factors at the initiation of treatment.

The prominent limitation of our study was the small sample size and therefore, several statistical differences could not be presented clearly as PFS difference. Other limitations were lack of information on surgical complications, hospital mortality rates in the early post-operative period, and quality of life data.

Conclusion

We showed that CRT followed by surgery improves OS compared to CRT alone in older non-metastatic ESCC patients. Surgery should not be avoided promptly even if the patient had a poorer performance status or is older. Instead, a comprehensive assessment and a multidisciplinary approach may be better for accurate clinical decision-making.

Disclosures

Ethics Committee Approval: This study was approved by Erzurum Regional Training and Research Hospital Ethics Committee (Date: June 6, 2022, and Number: 2022/07-62).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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