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Definitive chemoradiotherapy versus upfront surgery in locoregional esophageal squamous cell cancer

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Abstract

Aim: Previous studies have indicated that definitive chemoradiotherapy and upfront surgery have comparable survival rates, and definitive chemoradiotherapy is a more applicable treatment option in resectable locally advanced esophageal squamous cell cancer (ESCC). We compared definitive chemoradiotherapy to upfront surgery for survival in locally advanced ESCC patients who denied the standard treatment approach, receiving definitive chemoradiotherapy or upfront surgery.

Materials and Methods: One hundred eighty eight locoregional ESCC patients with thoracic and distal involvement who had upfront surgery were compared with those who received chemoradiotherapy but declined surgery, although their tumor was resectable at presentation. Patients who underwent upfront surgery with negative surgical margins were included. The upfront surgery group received no adjuvant treatment (chemotherapy or radiotherapy). The definitive chemoradiotherapy group received standard therapy with 50.4 Gray/28 fractions/6 weeks concomitantly with weekly Paclitaxel 50 mg/m2 and Carboplatin AUC 2 combination regimen.

Results: A total of 102 patients (54.3%) underwent surgery up front, whereas 86 patients (45.7%) had definitive chemoradiotherapy. The median follow-up of the study was 31 months. Definitive chemoradiotherapy had a median disease-free survival (DFS) of 39 months compared to 16 months for upfront surgery (p:0.005). Median overall survival (OS) was 29 months in upfront surgery and 47 months in definitive chemoradiotherapy (p=0.01). Although the multivariate Cox regression analysis found no difference in DFS between upfront surgery and definitive chemoradiotherapy groups, OS was greater with the latter (HR, 0.69; 95% CI, 0.47 to 1.00; p=0.05).

Conclusion: In this non-randomized retrospective analysis, definitive chemoradiotherapy improved overall survival compared to upfront surgery in locally advanced ESCC patients.

Introduction

Being the sixth leading cause of cancer-related death, esophageal squamous cell carcinoma (ESCC) is one of the most aggressive cancers of the gastrointestinal system, with a 5-year survival rate of 15-25 [1]. Due to environmental etiologic factors, ESCC is more prevalent in East, South European, and East Asian countries [2]. Most patients present with locally advanced disease at the time of diagnosis and are treated according to a multidisciplinary approach that includes different combinations of surgery, radiotherapy and systemic treatments [3]. The unsatisfactory long-term results in patients with ESCC undergoing surgical resection without neoadjuvant chemoradiotherapy have prompted the search for new therapeutic strategies. In addition, the fact that the disease is generally diagnosed in an advanced stage has created the idea of initiating therapy with systemic treatment options. The current standard of care for resectable locally advanced ESCC is neoadjuvant chemoradiotherapy followed by surgery [4]. However, some non-randomized studies have shown that survival rates were actually similar between patients who proceeded with surgery following neoadjuvant chemoradiotherapy and those who did not [5]. In addition, postoper-

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ative procedural and systemic complications of esophageal surgery can cause significant mortality and morbidity or decrease patients' quality of life even after several years [6]. Consequently, this background evokes whether surgery could be ignored, especially in the squamous subtype of esophageal cancer, which is accepted as a distinct entity from adenocarcinomas regarding pathogenesis, epidemiology, tumor biology, and prognosis in the light of emerging evidence [7]. Currently, whether and how the histological subtypes of esophageal cancer should determine the therapeutic approach remains unclear. Added to this uncertainty, with little data on the efficacy of non-operative management for ESCC, surgery following neoadjuvant CRT is recommended for almost all patients. However, in real-world practice, physicians have to deal with a substantial number of patients who deny receiving some part of the standard treatment, surgery or chemoradiotherapy.

Definitive chemoradiotherapy is the treatment of choice for cervical esophageal cancer; it may also be the treatment of choice for selected patients who have unresectable disease, as well as those who are medically unfit for surgical resection, who cannot tolerate surgery-related morbidity, or who refuse surgery [8]. A meta-analysis by Ming-Wei Ma et al. compared the effectiveness of definitive chemoradiotherapy versus surgery as initial treatment options in patients with potentially resectable esophageal cancer at diagnosis. They showed that definitive chemoradiotherapy and surgery alone have comparable survival rates, and definitive chemoradiotherapy is a more applicable treatment option, especially in eastern populations with a high prevalence of ESCC [9]. Based on these data, we wanted to compare survival outcomes in patients with locally advanced ESCC who had either definitive chemoradiotherapy or upfront surgery.

Materials and Methods

The sample size was determined using the G*Power 3.1.9.2 program. Based on an effect size of 0.45, a Type I error rate of 0.05, and a test power of 95%, it was deemed appropriate to work with 180 patient tissue samples. To ensure robustness, it was deemed appropriate to design the study with a sample size of 188 cases.

The data of 188 patients with a diagnosis of locally advanced ESCC who were admitted to Van Yüzüncü Yıl University, Faculty of Medicine, Medical Oncology outpatient clinic between January 2010 and October 2021, were extracted from the medical records and analyzed retrospectively.

Those who had upfront surgical treatment without neoadjuvant chemoradiotherapy had their results compared to patients who did not agree to surgery but received definitive chemoradiotherapy. A total of 188 patients with locally advanced esophageal squamous cell carcinoma were reviewed retrospectively. ESCC patients with thoracic and distal involvement were included in the study. The patients in the upfront surgery group had resectable tumors at presentation. These patients received no adjuvant treatment (chemotherapy or radiotherapy) postoperatively.

Patients in the definitive chemoradiotherapy group were administered standard therapy with 50.4 Gray/28 fractions/6 weeks concomitantly with standard weekly Paclitaxel 50 mg/m^2 and Carboplatin AUC 2 combination regimen. In the second month after the completion of definitive chemoradiotherapy, patients were evaluated by endoscopy and radiological imaging. Patients with no macroscopic residual tumor were considered to achieve a complete response and were followed up.

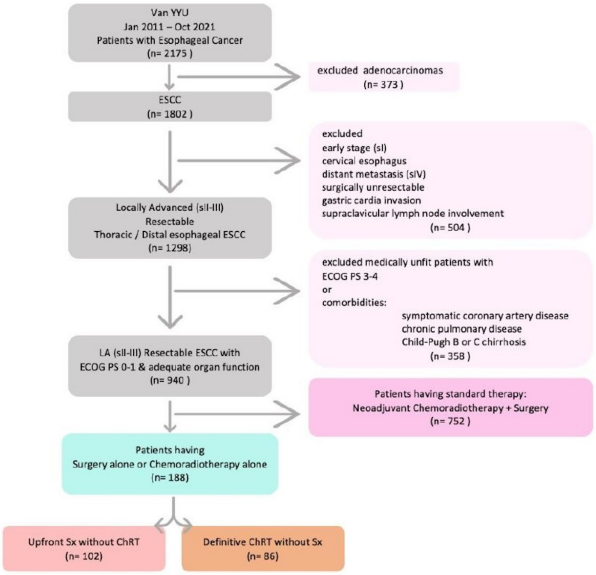

Figure 1. The flow chart for the inclusion and exclusion criteria of esophegal carcinoma patients.

Eligibility and exclusion criteria

Patients aged 18 years or above with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1 who had surgically resectable, locally advanced (stage 2/3), thoracic/ distal, histopathologically confirmed ESCC were included in our study. All patients also had adequate hematologic, renal, hepatic, and pulmonary functions. A history of secondary cancer or prior treatment with radiotherapy or chemotherapy was excluded. The upfront surgery group included the patients whose tumors were resected with negative surgical margins (R0) by total/subtotal esophagectomy and lymph node dissection. ECOG performance status score of 3-4, co-morbidities such as symptomatic coronary artery disease, chronic pulmonary disease, and Child-Pugh B or C cirrhosis were ineligible. Cervical esophageal cancers, early-stage (stage 1) disease, tumors with adenocarcinoma histology, gastric cardia invasion, metastasis to supraclavicular lymph nodes, or distant viscera were excluded. The patients who had residual disease on control endoscopy after definitive CRT were not included in the study.The flow chart for the inclusion and exclusion of esophageal carcinoma patients in this study is shown in Figure 1.

Staging

Clinical staging was performed according to the 8th TNM staging system by endoscopy, computerized tomography, or FDG-PET-CT. Because of the temporal unavailability, endoscopic ultrasound (EUS) could not routinely be

used in the staging process. Age, gender, tumor localization, and ECOG performance score at diagnosis were recorded. Patients with potentially resectable, locally advanced ESCC located at the thoracic or distal esophagus were included.

Treatment

In the decision-making process, the patient was evaluated by surgical and medical oncology teams, and then the treatment approach was determined by considering the patient's choice.

The gastric tube approach was used for reconstruction after esophagectomy for the patients in the upfront surgery group who did not receive any adjuvant chemotherapy or radiotherapy postoperatively.

For the patients in the definitive chemoradiotherapy arm, the standard dose of 50.4 Gray /28 fractions/6 weeks radiotherapy was administered with concomitant weekly Paclitaxel (50 mg/m^2) and Carboplatin (AUC2).

Response evaluation and follow-up

Patients in the definitive CRT group were evaluated by physical examination, upper gastrointestinal endoscopy, and radiological evaluations such as contrast-enhanced CT / FDG-PET-CT, initially at the second month after completion of CRT, and then at 3-month intervals during the first 2 years. The patients in the upfront surgery group were followed by physical examination and radiological imaging every 3 months after surgery. The Response Evaluation Criteria in Solid Tumors (RECIST 1.0) system was used to assess clinical response and was classified as complete response, partial response, and stable and progressive disease.

Definition of survival outcomes

Disease-free and overall survival rates of the patients undergoing upfront surgery and receiving definitive chemoradiotherapy were compared.

Overall survival (OS) was defined as the time from the start of the therapy to the latest follow-up or death date. The interval between the start of the treatment and the recurrence of the disease was defined as disease-free survival (DFS).

Statistical analysis

Statistical analysis was performed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Numerical variables with a normal distribution are presented as mean ± standard deviation, while those without a normal distribution are presented as median (min–max).The relationship between treatment type and clinical and pathological data was evaluated using the Chi-square and Fisher's exact tests. Kaplan-Meier curves and log-rank tests were used to determine disease-free and overall survival. Univariate and multivariate analyses were performed to determine the factors affecting the survival rates, and comparisons were made with Cox regression analysis. In the statistical analyses, a p-value of <0.05 was considered statistically significant.

Results

The median age of 188 patients in our study was 60 (range 29-85) years. Sixty-six percent of the patients (n=114)

Table 1. Association between treatment type and clinical features.

Patient characteristics	All patients (n=188) n (%)	Surgery (n=102) n (%)	CRT (n=86) n (%)	p
Gender				
Male	74 (39.4)	39 (52.7)	35 (47.3)	0.734
Female	114 (60.6)	63 (55.3)	51 (44.7)	
Age group				
<65	125 (66.5)	64 (51.2)	61 (48.8)	0.238
≥65	63 (33.5)	38 (60.3)	25 (39.7)	
Tumor localization				
Thoracic	105 (55.9)	59 (56.2)	46 (43.8)	0.540
Distal	83 (44.1)	43 (51.8)	40 (48.2)	
Smoking				
No	89 (47.4)	46 (51.7)	43 (48.3)	0.341
Yes	99 (52.6)	59 (59.6)	40 (40.4)	
Smoked food				
No	137 (72.9)	76 (55.5)	61 (44.5)	0.089
Yes	51 (27.1)	29 (56.9)	22 (43.1)	
ECOG				
0	62 (33.0)	51 (82.3)	11 (17.7)	**0.007**
1	126 (67.0)	51 (41.5)	75 (59.5)	
Grade				
1	64 (34.0)	36 (56.3)	28 (43.7)	
2	84 (44.7)	43 (51.2)	41 (48.8)	0.590
3	40 (21.3)	23 (57.5)	17 (42.5)	
Stage				
2	71 (37.8)	32 (45.1)	39 (54.9)	0.435
3	117 (62.2)	70 (59.8)	47 (40.2)	

CRT, Chemoradiotherapy; ECOG, The Eastern Cooperative Oncology Group.

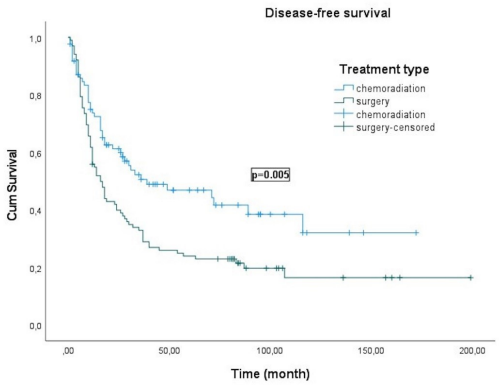

Figure 2. Disease free survival according to type of treatment.

Table 2. Univariate and multivariate analyses on disease-free survival of the patients.

	Disease-free survival Univariate Analysis				Disease-free survival Multivarite Analysis		
	HR	95%CI	p		HR	95%CI	p
Age (year)	0.77	0.54-1.11	0.16	Age (year)	1.10	0.72-1.60	0.72
Gender	0.96	0.67-1.37	0.82	Gender	0.89	0.61-1.29	0.52
Grade	0.19	0.12-0.29	**<0.001**	Grade	0.20	0.13-0.39	**<0.001**
Smoking	0.78	0.36-1.69	0.67	Smoking	0.49	0.36-0.79	0.57
Smoked food	1.38	0.78-1.14	0.78	Smoked food	1.01	0.66-1.12	0.46
Localization	0.92	0.65-1.30	0.62	Localization	0.93	0.64-1.35	0.70
ECOG	0.56	0.37-0.83	**0.004**	ECOG	0.50	0.33-0.75	**0.001**
Stage	1.28	0.89-1.85	0.18	Stage	0.79	0.54-1.29	0.25
Treatment	0.59	0.41-0.85	**0.004**	Treatment	0.78	0.53-1.13	**0.005**

HR, Hazard Ratio; CI, Confidence Interval; ECOG, The Eastern Cooperative Oncology Group.

Table 3. Univariate and multivariate analyses on the Overall Survival of the Patients.

	Overall Survival Univariate Analysis				Overall Survival Multivarite Analysis		
	HR	95%CI	p		HR	95%CI	p
Age (year)	0.71	0.49-1.02	0.69	Age (year)	0.96	0.65-1.22	0.35
Gender	1.13	0.79-1.61	0.51	Gender	0.83	0.56-1.43	0.34
Grade	2.46	1.90-3.19	<0.001	Grade	0.28	0.18-043	**<0.001**
Smoking	0.91	0.46-1.79	0.78	Smoking	0.45	0.26-0.79	0.47
Smoked food	1.28	0.66-1.94	0.66	Smoked food	0.98	0.54-1.02	0.56
Localization	1.18	0.83-1.69	0.58	Localization	0.83	0.57-1.22	0.35
ECOG	1.83	1.23-2.74	0.003	ECOG	0.52	0.34-0.82	**0.004**
Stage	1.28	0.89-1.85	0.18	Stage	0.81	0.54-1.20	0.29
Treatment	1.60	1.11-2.31	0.005	Treatment	0.69	0.48-1.00	**0.01**

HR, Hazard Ratio; CI, Confidence Interval; ECOG, The Eastern Cooperative Oncology Group.

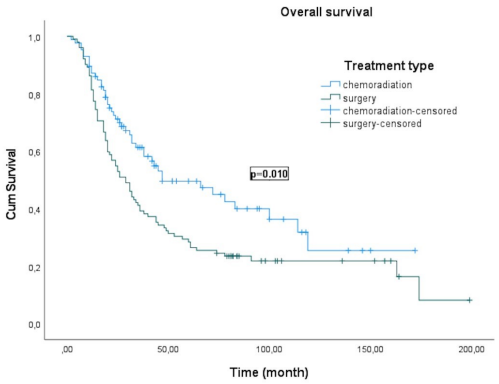

Figure 3. Overall survival according to type of treatment.

were female. Out of the patients, 99 (52.6%) smoked, and 51 (27.1%) consumed smoked food. Tumors were located at the thoracic esophagus in 105 patients (55.9%) and the distal esophagus in 83 patients (44.1%). Furthermore, 71 patients (37.8%) and 117 (62.2%) had stage 2 and 3 diseases, respectively. Upfront surgery was performed in 102 patients (54.3%), and 86 patients (45.7%) underwent definitive chemoradiotherapy. The patients' characteristics were generally balanced between the two treatment groups, with the notable exception of ECOG performance scores. A significant majority, 82.3% of patients with an ECOG performance score of 0, underwent upfront surgery, compared to 17.7% who received definitive chemoradiotherapy (p=0.007, Chi-square test). This disparity in ECOG scores between the groups indicates a potential bias in treatment selection, suggesting that the healthier patients, or those with fewer co-morbidities, were more likely to be selected for surgery. Table 1 presents the association between clinical features, patient characteristics, and treatment type.

During the median follow-up of 31 months, disease recurrence occurred in 79.4% of the patients who underwent upfront surgery alone, compared to 53.5% of the patients who were administered definitive chemoradiotherapy without surgery.

The DFS for all patients was 24 months, while the OS was 35 months. DFS was 16 months for the patients who underwent upfront surgery (95% CI: 11.1-20.8) and 39 months for the patients who received definitive chemoradiotherapy (95% CI:15-81.0). The p-value (log rank p=0.005, Kaplan-Meier test) was significant (Figure 2). Death occurred in 81 patients (79.4%) who underwent upfront surgery, while death occurred in 45 patients (52.3%) who received definitive chemoradiotherapy. OS was 29 months in those undergoing upfront surgery (95% CI: 21,3-36,6) and 47 months (95% CI: 16.5-77.4) in those receiving definitive chemoradiotherapy. The p-value (log rank p=0.01, Kaplan-Meier test) was significant (Figure 3).

Univariate and multivariate analyses were performed for the prognostic factors that may impact DFS and OS.

Univariate analysis for DFS revealed that ECOG-PS and grade were also prognostic in addition to the type of treatments (upfront surgery alone and definitive chemoradiotherapy without surgery). Multivariate analysis showed that the treatment type is not an independent factor for DFS (HR: 0.77, CI% 0.53-1.12, p= 0.18, Table 2). Univariate analysis for OS also revealed that ECOG-PS and grade were prognostic factors together with the type of treatment, similar to DFS.

Multivariate analysis for OS revealed that treatment type was an independent prognostic factor with a marginal level of significance (HR:0.69, CI% 0.47-1.00, p=0.05, Table 3).

Discussion

Many studies on the treatment of esophageal cancer have included both squamous cell and adenocarcinoma subtypes. However, the consensus is that these two subtypes should be considered two different cancers [10]. Therefore, excluding the early stage with isolated mucosal involvement, the primary treatment of ESCC is neoadjuvant chemoradiotherapy followed by surgery.

Van Hagen et al. reported that 26% of patients achieved a pathological complete response following neoadjuvant chemoradiotherapy, while the complete response rate was 49% in the squamous cell carcinoma subtype [11]. This study suggests that squamous cell carcinoma is more sensitive to chemoradiotherapy than adenocarcinoma. Although local control and survival outcomes are improved following neoadjuvant chemoradiotherapy, postoperative morbidity and mortality are still high in patients undergoing surgery, despite all the developments in the esophageal cancer surgery technique [12, 13]. Respiratory failure, sepsis, anastomosis leakage, esophageal stricture, fistula, reflux, obstruction, bleeding, chylothorax, pneumothorax, pancreatitis, spleen rupture, early satiety, dysphagia, and consequent malnutrition-induced cachexia are among both short-term and long-term complications of esophageal cancer surgery. The surgeon's personal experience is the most important determining factor in developing these complications. The rate of esophageal surgery-related mortality has been reported to be 5%, and the rate of general mortality is 10%, even in high-volume centers [14].

The patients usually decline surgery because of these surgery-related adverse events [15]. In patients who refuse surgery despite its potential resectability, definitive chemoradiotherapy is administered as a treatment option [16]. In a meta-analysis by Ming-Wei Ma et al., definitive chemoradiotherapy and upfront surgery were shown to have comparable efficacy as initial treatment in ESCC patients, especially in eastern populations with a tendency for increased prevalence [9] . In another study by Stahl et al. comparing definitive chemoradiotherapy with upfront surgery in patients with locally advanced ESCC, there were no significant differences between 3-year survival rates [17].

Similarly, our study found no difference in disease-free survival rates between definitive chemoradiotherapy and upfront surgery groups in the multivariate analysis, suggesting that these two treatments have comparable efficacy. However, multivariate analysis for overall survival showed that definitive chemoradiotherapy has more prolonged survival with a marginal statistical significance.

The selection bias is evident in the treatment assignment, as depicted by the significant disparity in ECOG performance scores between the two groups, which reflects a prevailing treatment trend in clinical practice. Clinicians and medically fit patients tend to prefer upfront surgery, presumably perceiving it as a more definitive intervention. This bias potentially reflects the general assumption that healthier patients are more likely to withstand the rigors of surgery and recover effectively post-operation. However, our results challenge this assumption by demonstrating improved overall survival in patients receiving definitive chemoradiotherapy, despite poorer performance scores.

Additionally, it is crucial to consider this observed selection bias when interpreting the results and drawing conclusions from this study, especially given its non-randomized and retrospective design. This discrepancy in baseline characteristics, if not appropriately considered, can lead to skewed interpretations and applications of the study's findings.

Shorter overall survival in patients in the upfront surgery arm suggests that the lack of definitive chemoradiotherapy, which provides both systemic and local disease control, is the most critical step in treating this considerably aggressive tumor. We think that the administration of surgery alone, which is a local treatment, especially in the treatment-naive period, has led to a deficiency in the systemic control of the disease and a decrease in the overall survival rate. In addition, another reason for shorter overall survival can be related to the long-term complications of the surgery.

Stahl et al. found in their study that there was no additional survival benefit of adding surgery to the neoadjuvant chemoradiotherapy treatment. Our study results support the fact that systemic chemoradiotherapy is essential for survival.

In contradiction to our study, another retrospective study in the literature comparing upfront surgery with definitive chemoradiotherapy reports that patients having upfront surgery had better overall survival. Probable reasons for this discordance are that patients in the chemoradiotherapy group had more co-morbid diseases than those in the upfront surgery arm of their study cohort, and stage 4 patients were included in their study [18].

While our study supports the efficacy of definitive chemoradiotherapy as a treatment option for locally advanced ESCC, it is essential to acknowledge its limitations. First and foremost, our study has retrospective observation data and lacks a standard treatment control group. Therefore, comparing the survival outcomes of the standard treatment approach recommended by the guidelines, i.e., neoadjuvant chemoradiotherapy followed by surgery, for patients with resectable ESCC is beyond the scope of our study.

In alignment with the inherent limitations of retrospective studies, the absence of observational data regarding treatment-related adverse reactions and complications in our study represents a significant constraint. This limitation is somewhat inevitable in retrospective analyses due

to the lack of controlled and standardized data collection methods, which are typical of prospective studies. Consequently, our study lacked access to reliable and comprehensive information concerning adverse reactions and complications related to the treatment administered.

However, the absence of observation regarding treatment-related complications may impact the overall findings and conclusions of our study. Specifically, treatment-related adverse reactions and complications can substantially affect patient quality of life and treatment outcomes, potentially influencing the overall survival and disease-free survival rates observed. It is crucial for readers and subsequent researchers to consider these constraints when interpreting our results and applying them to future studies and clinical practices.

New immunotherapy treatments have shown high effectiveness, particularly in esophageal squamous cell carcinoma, and it is anticipated that these treatments will shift the focus from treating the metastatic stage of the disease to addressing it at earlier stages. This approach aims to manage this highly aggressive disease without requiring esophageal surgery, using only definitive radiotherapy and immunotherapy, thereby enhancing the patient's quality of life. However, the most significant challenge in this promising immunotherapy approach is the current lack of a well-defined biomarker for accurately predicting patient responses to these treatments [19].

Moreover, acknowledging these limitations underlines the need for more comprehensive prospective studies or randomized controlled trials, which can provide more in-depth insights into treatment-related adverse reactions and complications, offering a more holistic understanding of treatment outcomes and their implications on patient well-being and recovery trajectories.

This acknowledgement not only serves to validate the authenticity and reliability of our study but also underscores the necessity for enhanced and meticulous data collection methodologies in future research endeavors, to comprehensively evaluate and understand the multifaceted impacts of treatment modalities on patients diagnosed with ESCC.

Conclusion

In conclusion, we found definitive chemoradiotherapy comparable with upfront surgery regarding DFS and superior in terms of OS in patients with resectable ESCC with thoracic and distal localization. The organ protection provided by definitive chemoradiotherapy will significantly improve the patients' quality of life. Further research, ideally randomized clinical trials including patients with homogeneous characteristics, and addressing the limitations identified in our retrospective analysis are needed to establish the optimum treatment approach.

Conflict of interest

The authors declare that they have no conflict of interests.

Informed consent

Not applicable.

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Ethical approval

The necessary ethics committee approval for the study was received by the Van Yüzüncü Yıl University Faculty of Medicine Clinical Research Ethics Committee with report number 15 on 21/01/2022.

Authors' contribution

All the authors contributed substantially to the study's conception and design. Material preparation and data collection were performed by N.Ö.K, A.G.M and U.Ç. Statistical analysis was performed by N.Ö.K, A.G.M ,M.N.A and Ç.K. The first draft of the manuscript was written by N.Ö.K., A.G.M and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381(9864):400-12.
2. Huang FL, Yu SJ. Esophageal cancer: Risk factors, genetic association, and treatment. Asian J Surg. 2018;41(3):210-5.
3. Watanabe M, Otake R, Kozuki R, et al. Recent progress in multidisciplinary treatment for patients with esophageal cancer. Surg Today. 2020;50(1):12-20.
4. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers (V.5.2022) 2022 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf.
5. Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol. 2007;25(10):1160-8.
6. Elliott JA, Docherty NG, Eckhardt HG, et al. Weight Loss, Satiety, and the Postprandial Gut Hormone Response After Esophagectomy: A Prospective Study. Ann Surg. 2017;266(1):82-90.
7. Keshava HB, Molena D. Squamous cell carcinoma and adenocarcinoma of the esophagus: same organ, different disease. Annals of Esophagus. 2020;4.
8. Ng SP, Leong T. Indications for definitive chemoradiotherapy for oesophageal cancer. Annals of Esophagus. 2021;4.
9. Ma MW, Gao XS, Gu XB, et al. The role of definitive chemoradiotherapy versus surgery as initial treatments for potentially resectable esophageal carcinoma. World J Surg Oncol. 2018;16(1):172.
10. Siewert JR, Ott K. Are squamous and adenocarcinomas of the esophagus the same disease? Semin Radiat Oncol. 2007;17(1):38-44.
11. Van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
12. Steyerberg EW, Neville BA, Koppert LB, et al. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. J Clin Oncol. 2006;24(26):4277-84.
13. Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003;349(22):2117-27.
14. Ellis F. Transthoracic Resection for Carcinoma of the Thoracic Esophagus and Cardia. In: Wanebo HJ, editor. Surgery for Gastrointestinal Cancer, A Multidisciplinary Approach. Philadelphia-New York: Lippincott-Raven; 1997. p. 217-28.
15. Rahouma M, Harrison S, Kamel M, et al. Consequences of Refusing Surgery for Esophageal Cancer: A National Cancer Database Analysis. Ann Thorac Surg. 2018;106(5):1476-83.
16. D'Journo XB, Thomas PA. Current management of esophageal cancer. J Thorac Dis. 2014;6 Suppl 2(Suppl 2):S253-64.

17. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol. 2005;23(10):2310-7.
18. Matsuda S, Tsubosa Y, Niihara M, et al. Comparison of transthoracic esophagectomy with definitive chemoradiotherapy as initial treatment for patients with esophageal squamous cell carcinoma who could tolerate transthoracic esophagectomy. Ann Surg Oncol. 2015;22(6):1866-73.
19. Shoji, Y., Koyanagi, K., Kanamori, K., Tajima, K., Ogimi, M., Ninomiya, Y., ... & Mori, M. (2024). Immunotherapy for esophageal cancer: Where are we now and where can we go. World Journal of Gastroenterology, 30(19), 2496.