

The Effect of Neoadjuvant Chemoradiotherapy on Pathological Stage in Locally Advanced Esophageal Cancer

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ABSTRACT

Esophageal cancer has an increasingly high incidence and mortality rate in Türkiye and the World. Although new treatment protocols are being developed day by day, there is no standard treatment protocol which is definitely accepted. This retrospective study aimed to determine the pathological complete response rates by examining the pathological material changes in patients diagnosed with locally advanced esophageal cancer and treated with trimodal therapy.

The age, imaging modalities, preoperative and postoperative disease stages, surgical procedure, mortality, morbidity and effects of pathological specific treatment were investigated in 27 patients with locally advanced esophageal cancer who underwent neoadjuvant chemoradiotherapy than surgery in our hospital between 2012-2016. In this study, patients received trimodal treatment upon a joint decision of members of the surgical oncology council.

There was no significant correlation between surgical procedure and mortality and morbidity. Sensitivity and specificity ratios were similar in detecting pathological response relationship with CT and PET clinical regression. 63% pathological complete response was seen in distal esophageal tumors ($p=0,012$) The rate of complete response with Trimodal therapy was higher in distal esophagus cancers than in other localizations. Squamous cell carcinoma has a higher pathological complete response rate.

Although the treatment modalities are very variable and open to development, mortality in esophageal cancers is still very high. Although pathological complete response was found to be high especially in squamous cell carcinoma patients after trimodal treatment, surgery still maintains its importance in the curative treatment of locally advanced esophageal cancer.

Keywords: Trimodal Therapy, Esophageal Cancer, Pathological Response

Introduction

Esophageal cancer is the eighth most common type of cancer worldwide, with a 5-year survival rate of less than 25% (1, 2). There are significant differences in the incidence of esophageal cancer in different regions of the world. Some regions of East Asia, the Middle East, South Africa, and South America have reported the highest rates of esophageal cancer, potentially due to dietary habits, environmental exposures, and possible genetic predispositions (3, 4). On the other hand, the incidence of esophageal cancer in Türkiye is high in the Eastern Anatolia Region, as associated with risk factors (5, 6).

Mostly, esophageal cancer manifests symptoms at a late stage and has a poor prognosis and high

mortality rate (7). However, the application of trimodal therapies has recently prolonged the life expectancy compared to patients who underwent surgery alone (8). Current treatment guidelines recommend the use of neoadjuvant chemoradiotherapy in esophageal cancer to eradicate the tumor and reduce postoperative recurrence (9).

A pathological complete response rate of at least 20-40% is expected in patients with esophageal cancer using trimodal therapy. Based on these high pathological complete response rates, a treatment policy is to recommend surgery after neoadjuvant treatment. This treatment strategy avoids unnecessary and aggressive surgical protocols with severe consequences. Otherwise, failure to detect residual disease in the early period

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in patients with incomplete pathological response results in delayed treatment (10-12).

This study aimed to determine the complete response rates and variables by retrospectively examining the pathological material changes of patients who applied to our hospital, were diagnosed with locally advanced (T2N1MO, T3-T4 N0-1-2-3, M0) esophageal cancer and underwent trimodal treatment upon the decision of the surgical oncology council.

Materials and Methods

This study was approved by the Ethics Committee of Yüzüncü Yıl University on November 30, 2016, under decision number 1.

Patients who were admitted to the General Surgery and Internal Medicine Oncology clinic of our hospital and diagnosed with locally advanced esophageal cancer following an endoscopic biopsy with a stage above T2NOMO, were evaluated by the Surgical Oncology Council, and for whom trimodal treatment was deemed appropriate were included in the study. Patients who had distant metastasis after neoadjuvant chemoradiotherapy and/or were unable to undergo surgery due to their insufficient performance, refused surgery, or died before or during surgery were excluded from the study. Cardioesophageal junction tumors were also excluded.

Two separate groups were treated with neoadjuvant therapy using carboplatin-paclitaxel-RT and 5-FU-cisplatin-RT protocols.

The performance of the patients was evaluated according to the ECOG scale and the AJCC TNM was evaluated before and after neoadjuvant treatment according to the AJCC staging system with CT and PET. Surgery was performed approximately 4-6 weeks after the end of neoadjuvant treatment, and the pathologic samples of the patients were examined twice within 10 days and evaluated with the pathological treatment effect staging scale of WHO. Mortality in the first 30 days and comorbidities until discharge were analyzed using the computer database.

No clinical and radiological findings of disease was considered as a complete response, shrinkage of more than 50% of the tumor was considered as a partial response, shrinkage of 50% or less of the tumor was considered as a stable disease, and further course of the disease despite treatment was considered as progression. Upon examination of the pathological sample, no residual tumor was

classified as grade 0, indicating a complete response. Furthermore, the first 30 days after surgery were assessed as hospital mortality.

Statistical Analysis: Descriptive statistics for continuous variables in the present study were expressed as mean, standard deviation, minimum and maximum values; categorical variables were expressed as number and percentage. The correlations between categorical variables were analyzed by Chi-square or Z-ratio test. The sensitivity and specificity between the imaging method and pathological complete response were calculated. The statistical significance level was taken as 5% and SPSS (ver.21) statistical software was used for calculations.

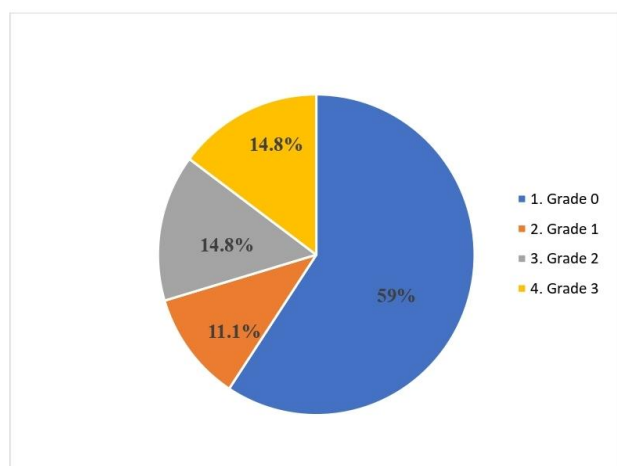
Result

In the present study, the data of 27 patients who completed neoadjuvant treatment and underwent surgery were evaluated. Eight of the patients were male, 19 were female, the age range was 23-74 years and the mean age was 53.9 years. Analysis of the histologic types revealed 26 cases of squamous cell carcinoma and 1 case of adenocarcinoma. Table 1 shows the demographic characteristics of the patients.

When tumor localization was examined, 19 patients (70%) had distal localization, and 8 patients (29%) had midthoracic localization. Five patients with distal esophagus and three patients with mid-thoracic localization died. No significant correlation was found between tumor localization and mortality. However, a pathological complete response was found to be statistically significant in distal esophageal tumors ($p=0.012$). The complete response rate (63%) with trimodal treatment was higher in distally located esophageal cancers compared to the other localizations (Table 2).

After trimodal treatment, pathological materials were graded using the AJCC WHO scale, and the pathological complete response rate was 59%, while the rate of patients with no response was 14.8%. The present study indicated a pathological complete response in 15 of 26 patients diagnosed with squamous cell carcinoma and in one patient diagnosed with adenocarcinoma. Our mortality, morbidity, and pathological complete response rates in the squamous cell carcinoma group were found to be 30.7%, 50%, and 57.7%, respectively (Graph 1).

While 16 patients were examined with CT before and after neoadjuvant treatment, 11 patients were examined with PET. Clinical regression and a



Graph 1. Pathological complete response staging rates with trimodal treatment

complete response adaptation to pathological material after surgery were analyzed with imaging methods in patients who underwent neoadjuvant chemoradiotherapy; CT had sensitivity of 88.8% and specificity of 85.7%, while PET had sensitivity of 60% and specificity of 50% (Table 3).

The transhiatal esophagectomy surgical procedure was the most frequently used trimodal treatment, while the transthoracic esophagectomy protocol was detected with the highest mortality rate at 50%. Table 4 shows the correlation between surgical procedure and patient outcomes.

While 16 patients in the present study were treated with carboplatin+paclitaxel+RT, 11 patients were treated with 5-FU+cisplatin+RT. While a pathological complete response of 62% was achieved with carboplatin+paclitaxel+RT and a pathological complete response of 54% was achieved with 5-FU+cisplatin+RT, the correlation between the oncological agent and the pathological complete response was found to be statistically insignificant ($p=0.680$).

Discussion

There are many treatment options for early-stage esophageal cancer and T2N0 clinical-stage esophageal cancer. The treatment protocol needs to be well-researched and carefully considered. At our clinic, the standard treatment method for early-stage esophageal cancer patients (T1NOMO) is surgery.

On the other hand, surgery after neoadjuvant chemoradiotherapy is the standard treatment regimen for T2 and locally advanced esophageal cancers. Neoadjuvant chemoradiotherapy leads to

sensitization, and meanwhile, micro-metastatic disease is brought under control (13). The related studies have shown that combined chemoradiotherapy and surgery used in esophageal cancer is more beneficial than surgery alone. Tepper et al., used the chemotherapy branch of chemoradiotherapy with 5-FU and cisplatin and found a 5-year survival rate of 39% in trimodality and 16% in surgery alone (14). In a study conducted by Van Hagen et al., using neoadjuvant chemoradiotherapy with carboplatin and paclitaxel, they reported a survival of 49 months with trimodality but 26 months in the surgery alone (15). These two studies showed that trimodal treatment improved both overall recovery and survival in people with locally advanced esophageal cancer.

Endoscopic ultrasound (EUS) is recognized as the most accurate imaging method in the evaluation of patients before and after neoadjuvant chemoradiotherapy in trimodal treatment and in the evaluation of regional diseases in esophageal cancer (6, 16). On the other hand, CT is more useful in the retraction of T4 disease and the detection of distant metastases (13). Furthermore, many studies have demonstrated that PET has better sensitivity, specificity, and accuracy in the detection of lymph node metastases compared to CT (6).

A retrospective study including 36 patients with esophageal cancer reported that accuracy of PET was 76% (17), while another retrospective study found PET had higher sensitivity (15% and 52%, respectively) and accuracy (77% and 84%), and similar specificity (97% and 94%) compared to CT (18). Another prospective study on 75 patients with esophageal cancer reported similar sensitivities of PET, CT, and EUS for nodal staging (82%, 84%, and 85%, respectively) (19). On the other hand, in the present study, we used CT and/or PET for staging and evaluation of TNM response after treatment. As a result of the evaluation, we decided to proceed with surgery according to regression and partial regression. Sensitivity and specificity of CT and PET in the present study were found to be compatible with previous studies.

A total of 14 patients underwent transhiatal esophagectomy, 6 underwent transthoracic esophagectomy, and 7 underwent the McKeown procedure in the present study. The mortality rate was found to be 14% for transhiatal esophagectomy, 50% for transthoracic esophagectomy, and 42% for McKeown. The lower mortality rate in transhiatal esophagectomy

Table 1: Demographic Characteristics of the Patients

Characteristics		All patients	
		n:27	%
Gender	Male	8	29.6
	Female	19	70.3
Age [Median (December)]		[53.9 (23-74)]	
Tumor localization	Cervical	-	-
	Upper thorax	-	-
	Middle thorax	8	29.6
	Lower thorax	19	70.3
		-	-
Histology	Squamous cell carcinoma	26	96.3
	Adenocarcinoma	1	3.7
Stage	1B	1	3.7
	2A	4	14.8
	2B	2	7.4
	3A	7	25.9
	3B	1	3.7
	3C	12	44.4
Operation	Transhiatal esophagectomy	15	55.5
	Transthoracic esophagectomy	5	18.5
	McKeown	7	25.9

Table 2: Mortality and Pathological Complete Response Rates After Trimodal Therapy According To Tumor Localization

Tumor Localization	Number of Patients (n:27)	Mortality	Pathological complete response
Middle Thoracic	8 (29.6%)	3 (42%)	4 (50%)
Distal Thoracic	19 (70.3%)	5 (18.5%)	12 (63%)
	p=0.001	p=0.619	p=0.012

Table 3: Sensitivity and Specificity of Imaging Methods Used Before and After Neoadjuvant Treatment (Correlation With Pathological Complete Response)

Imaging Method	Patient n (%)	Rates of Detecting Complete Regression and Partial Regression or Stable Disease in TNM After Neoadjuvant	Pathological Complete Response
CT	16 (59%)	Full Regression 9	8 (88.8%) *
		Partial or None 7	6 (85%) **
PET	11 (40.7%)	Full Regression 9	6 (66.6%) *
		Partial or None 2	1 (50%) **

*sensitivity, **specificity

may be correlated with the inability of the thorax to be dilated. Postoperative patient satisfaction was better, analgesic requirements were less, and patient mobilization and discharge were earlier compared to the other two methods. No vocal cord paralysis was observed in any of our patients with cervical anastomosis, and no chyle leak was

observed in any of our patients. Simple wound site infection was observed in two of the patients, while wound evisceration was observed in one patient. A chest tube was required in four patients due to pleural effusion or leakage, and three patients suffered from anastomotic leak. During transhiatal esophagectomy, low-flow cervical

Table 4: Descriptive Statistics For Surgical Technique and Patient Outcomes

Surgical Procedure	Patients (n / %)	Mortality (n / %)	Morbidity (n / %)
Transhiatal esophagectomy	14 (51)	2 (14.2%)	7 (50%)
Transthoracic esophagectomy	6 (22.2%)	3 (50%)	3 (50%)
McKeown	7 (25.9%)	3 (42%)	5 (71%)

anastomotic leakage was observed in one patient, the clinical condition improved with medical treatment and the patient was discharged. One patient underwent transthoracic esophagectomy and experienced high flow intrathoracic anastomotic leak; however, this patient passed away. Similarly, one patient in the McKeown group had high-flow anastomotic leak, which led to the patient's death.

The present study revealed that surgical techniques did not lead to inadequacy of lymph node dissection when pathologic materials were analyzed. Neoadjuvant treatment did not prevent the choice of a tumor localization-dependent surgical procedure based on the available data. It is likely that minimally invasive esophagectomy will become the standard surgical modality for this patient group in the forthcoming years.

Pathological complete response is defined as the absence of tumor cells in the pathology after trimodal treatment (20). Based on the literature, the rate of pathological complete response is higher in squamous cell carcinoma compared to adenocarcinoma (21). During the CROSS study, patients with resectable esophageal cancer were treated with neoadjuvant chemoradiotherapy (paclitaxel + carboplatin) for 5 weeks. Subgroup analysis revealed a higher response to neoadjuvant treatment in the squamous cell cancer group. Pathological complete response was reported as 49% in squamous cell carcinoma and 23% in adenocarcinoma (15).

In the present study, the current WHO scale was used for the evaluation of the pathologic material stage. Pathological complete response rates were found to be correlated with tumor regression by imaging in our patients. Pathological complete response rates were obtained in 15 in 26 squamous cell carcinoma patients and 1 in one ADC patient. The remaining three patients with grade 1 pathological complete response, four patients with grade 2 pathological complete response, and four patients with grade 3 pathological complete response were identified. Generally, the radio-clinical tumor regression criteria and our pathological response grades were found to be correlated. Although the literature

reported that the correlation between the tumor regression stage and complete pathological response is 35%, the correlation in the present study was found to be 75%.

Recently, studies have been conducted to predict pathological response without surgery in patients who are treated with neoadjuvant chemoradiotherapy. Some parameters such as age, tumor length, endoscopic biopsy after chemoradiotherapy, regression rate in TNM after chemoradiotherapy, and history of smoking-alcohol-head and neck cancer have been used to establish a scoring system. Although an acceptable nomogram has not yet been established, the option of non-surgical oncologic treatment for squamous cell esophageal cancer may be discussed in the forthcoming years. However, based on current conditions and available data, the surgical branch in esophageal cancer treatment is an integral part of trimodal treatment.

In conclusion, esophageal cancer is a complex disease that should be treated in a multidisciplinary manner. Esophageal cancers should be treated in centers with a multidisciplinary approach since the efficacy of treatments and the morbidity and mortality rates related to treatments depend on factors such as the technique and experience of surgeons, the histology of the tumor, neoadjuvant chemotherapy agents administered, radiotherapy techniques and doses, and supportive therapies.

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