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Original Article / Özgün Makale

Comparison of outcomes between neoadjuvant treatment followed by surgery and surgical treatment alone in patients with locally advanced esophageal cancer: Our single-center experience

Lokal ileri özofagus kanserli hastalarda neoadjuvan tedavi sonrası cerrahi ile tek başına cerrahi tedavi sonuçlarının karşılaştırılması: Tek merkez deneyimimiz

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ABSTRACT

Background: This study aims to investigate the effect of neoadjuvant therapy on overall survival and recurrence-free survival in locally advanced esophageal cancer patients.

Methods: Between January 2010 and December 2019, a total of 143 patients (84 males, 59 females; mean age: 58.8±11.5 years; range, 26 to 87 years) operated for esophageal cancer were retrospectively analyzed. A comparison was made between the groups of 42 patients who underwent direct surgery and 42 patients who underwent surgery after neoadjuvant therapy. The patients were selected by matching one to one with propensity score with a sensitivty of 0.054.

Results: Pathological complete response was observed in 21 (50%) of 42 patients who received neoadjuvant therapy. No progression was detected in any of the patients. While the five-year overall survival rate was 58.3% in patients with a pathologic complete response, this rate was 52.8% in patients without a complete response (p=0.709). The five-year overall survival rate was 8% (median 22.3 months) in patients who did not receive neoadjuvant therapy and it was 52.9% (median 62.5 months) in those who received neoadjuvant therapy (p<0.001). The five-year recurrence-free survival rate for patients who did not receive neoadjuvant therapy was 26.2% (median 14.5 months), whereas this rate was 41.3% (median 35 months) for patients who received neoadjuvant therapy (p=0.025).

Conclusion: In patients with locally advanced esophageal cancer, the overall survival and disease-free survival rates are significantly better with surgical treatment after neoadjuvant chemotherapy/neoadjuvant chemoradiotherapy compared to surgery alone.

Keywords: Esophageal cancer, neoadjuvant treatment, thoracic surgery.

ÖZ

Amaç: Bu çalışmada, lokal ileri özofagus kanserli hastalarda neoadjuvan tedavinin genel sağkalım ve nükssüz sağkalım üzerindeki etkisi araştırıldı.

Çalışma planı: Ocak 2010 - Aralık 2019 tarihleri arasında özofagus kanseri nedeniyle ameliyat edilen toplam 143 hasta (84 erkek, 59 kadın; ort. yaş: 58.8±11.5 yıl; dağılım, 26-87 yıl) retrospektif olarak incelendi. Direkt cerrahi uygulanan 42 hasta ile neoadjuvan tedavi sonrası cerrahi uygulanan 42 hastadan oluşan gruplar arasında karşılaştırma yapıldı. Hastalar 0.054 hassasiyet ile eğilim skoru kullanılarak ve birebir eşleştirilerek şeçildi.

Bulgular: Neoadjuvan tedavi alan 42 hastanın 21'inde (%50) patolojik tam yanıt gözlendi. Hiçbir hastada progresyon saptanmadı. Patolojik tam yanıt alınan hastalarda beş yıllık genel sağkalım %58.3 iken, tam yanıt alınamayan hastalarda bu oran %52.8 idi (p=0.709). Neoadjuvan tedavi almayan hastalarda beş yıllık genel sağkalım oranı %8 (medyan 22.3 ay) ve neoadjuvan tedavi alanlarda %52.9 (medyan 62.5 ay) idi (p<0.001). Neoadjuvan tedavi almayan hastalarda beş yıllık nükssüz sağkalım oranı %26.2 (medyan 14.5 ay) iken, neoadjuvan tedavi alan hastalarda bu oran %41.3 (medyan 35 ay) idi (p=0.025).

Sonuç: Lokal ileri özofagus kanserli hastalarda neoadjuvan kemoterapi/neoadjuvan kemoradyoterapi sonrası cerrahi tedavi ile genel sağkalım ve hastalıksız sağkalım süreleri, yalnızca cerrahiye kıyasla anlamlı düzeyde daha iyidir.

Anahtar sözcükler: Özofagus kanseri, neoadjuvan tedavi, göğüs cerrahisi.

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Esophageal cancer is the eighth most common type of cancer diagnosed worldwide.[1] Although five-year survival rates have increased with the innovations in surgical techniques and oncological treatment methods over the years, almost half of the patients still die due to locoregional or distant recurrences.[2]

In recent studies, locoregional and distant recurrences are shown to be decreased, if surgical treatment is made after neoadjuvant chemotherapy (NCT) or neoadjuvant chemoradiotherapy (NCRT). In addition, a significant survival advantage can be achieved in these patients.[3] However, there is no study in Türkiye which showing the effect of neoadjuvant therapy on survival.

In the present study, we aimed to investigate the effect of neoadjuvant therapy on relapse-free survival and overall survival using the propensity score matching method.

PATIENTS AND METHODS

Study design and study population

This single-center, retrospective study was conducted at Ankara University Faculty of Medicine, Department of Thoracic Surgery between January 2010 and December 2019. A total of 164 patients operated for esophageal cancer in our clinic were included. Five patients diagnosed with a hypopharyngeal carcinoma and four patients with rare esophageal tumors, three patients who were lost to follow-up, and nine patients who had early postoperative mortality were excluded (n=21). The remaining 143 patients (84 males, 59 females; mean age: 58.8±11.5 years; range, 26 to 87 years) were included in the study.

Preoperative planning

In the preoperative period, cranial, neck, thoracic-upper abdominal computed tomography (CT) and positron emission tomography (PET)/CT were performed in all patients to evaluate tumor size, localization, lymph node, and distant metastasis. In addition, endoscopic ultrasound (EUS) was performed to assess the distance of the tumor to the upper dental arch, length and depth of the tumor, and the presence of metastases in the accompanying lymph nodes.

The patients were staged according to the 8th Tumor, Node, Metastasis (TNM) staging system, and treatment was planned (neoadjuvant therapy or direct surgery) according to the decision of the Multidisciplinary Tumor Council. In our clinic, until 2010, direct surgery was performed in patients with locally advanced esophageal cancer who had Stage T2-T3 tumors, suspected metastasis in neighboring lymph nodes, but had resectable tumors. Since 2010, NCT or NCRT has been planned for these patients with an increasing frequency.

All patients were re-evaluated with the thoracic-upper abdominal CT, PET/CT, and EUS to demonstrate tumor response and re-staging after neoadjuvant therapy. In patients with stable disease or regression after evaluation, surgical treatment was performed within four to six weeks after completion of neoadjuvant therapy.

Surgical method

The Ivor-Lewis operation with standard D2 dissection was performed for middle and lower esophageal tumors, while the McKeown procedure was preferred for upper esophageal tumors. Minimally invasive thoracoscopic and laparoscopic esophagectomy was done in cases where the patient and tumor were suitable.

Postoperative evaluation and follow-up

Pathological complete response assessment in patients receiving neoadjuvant therapy was performed according to the tumor regression grade (TRG) published by Becker in 2003.[4] The TRG-1a is a complete tumor regression without residual tumor tissue, TRG-1b as ≤10% residual tumor cells in tumor area (subtotal tumor regression), TRG-2 as the presence of 10 to 50% residual tumor cell (partial regression) and TRG-3 as ≥50% residual tumor cell existence.

If the patient had a high tumor burden in the preoperative period, adjuvant chemotherapy was given in the postoperative period. Adjuvant chemoradiotherapy (CRT)/radiotherapy (RT) was given to patients with lymph node metastases.

The patients were followed in the first month and at three-month intervals thereafter postoperatively. Two-view chest radiographs were taken at all controls, and complete blood count and routine biochemical analyses were made in all patients. Patients without recurrence suspicion and asymptomatic patients were evaluated with thoracic CT at six months postoperatively. At six-month intervals, thoracic and abdominal CT and/or PET/CT were performed. In case of development of dysphagia or suspicion of recurrence during follow-up, the anastomosis line was evaluated by endoscopy. Biopsy was taken in the presence of recurrence suspicion.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The difference between the two groups for continuous variables was evaluated using the Student t-test. The differences between the groups in terms of categorical variables were compared by using the chi-square test or Fisher exact test, where appropriate. The survival estimations were performed using the method of the Kaplan-Meier algorithm, and the comparison between groups was evaluated with a log-rank test. To minimize confounding factors introduced by the retrospective and non-randomized design, it was performed 1:1 propensity score matching (PSM) by age, sex, histological type, and clinical stage. The propensity score without replacement was calculated with a binary logistic regression for each patient in the NCT/NCRT

Table 1. Demographic characteristics of the patients (n=143)

Characteristics	n	%	Mean±SD	Min-Max
Age (year)			58.8±11.5	26-87
Sex				
Male	84	58.7		
Female	59	41.3		
cT				
T1	11	7.7		
T2	40	28		
T3	79	55.2		
T4a	13	9.1		
cN				
N0	25	17.5		
N1	72	50.3		
N2	43	30.1		
N3	3	2.1		
cS				
Stage 1	8	5.6		
Stage 2 (SCC)	34	23.8		
Stage 2A (AC)	3	2.1		
Stage 2B (AC)	1	0.6		
Stage 3	70	49		
Stage 4A	27	18.9		
Treatment				
Surgery	101	70.6		
Neoadjuvant CT/CRT + surgery	42	29.4		
Operation type				
Ivor-Lewis	87	60.8		
Left thoracophrenotomy	23	16.1		
McKeown	33	23.1		
Anastomosis localization				
Intrathoracic	110	76.9		
Cervical	33	23.1		
Postoperative hospitalization (day)			16.6±9.8	8-71
Histological type				
SCC	94	65.7		
AC	49	34.3		

SD: Standard deviation; cT: Clinical T; cN: Clinical N; cS: Clinical stage; CT: Chemotherapy; CRT: Chemoradiotherapy; SCC: Squamous cell carcinoma; AC: Adenocarcinoma.

Table 2. Distribution of neoadjuvant CT and CRT by cell type

	Adenocarcinoma	Squamous cell carcinoma	Total	
	n	n	n	%
Neoadjuvant CT	7	11	18	43
Neoadjuvant CRT	3	21	24	57

CT: Chemotherapy; CRT: Chemoradiotherapy.

Table 3. Response levels to neoadjuvant therapy by TRG

	n	%
TRG-1a	21	50
TRG-1b	6	14.3
TRG-2	4	9.5
TRG-3	11	26.2

TRG: Tumor regression grade.

followed by the surgery group and surgery alone group. For the matching process, the tolerance for the score in matching cases and controls was set at 0.05. A control was eligible to match a case, if the absolute value of the difference in the propensity scores was less than or equal to 0.05. The balance of the covariates was evaluated by standard mean difference (SMD) between two groups before and after the match. A p value of <0.05 was considered statistically significant.

RESULTS

Of 143 patients included in the study, 101 (70.6%) underwent direct surgery, while 42 (29.4%) underwent surgery after neoadjuvant therapy. The clinical and pathological features of the patients are summarized in Table 1. Eighteen (43%) of the patients who received neoadjuvant therapy underwent NCT and 24 (57%) underwent NCRT (Table 2).

We evaluated the tumor response rates of 42 patients who received neoadjuvant therapy according to the TRG classification. Twenty-one patients (50%) had a complete pathological response. No progression or distant metastasis was detected in any of the patients (Table 3).

When the tumor localization of the patients was classified according to the localization criteria in the 8th TNM staging performed by the American Joint Committee on Cancer (AJCC), seven (4.9%) had upper esophageal tumors, 35 (24.5%) had middle esophageal tumors, and 101 (70.6%) had lower esophageal tumors.

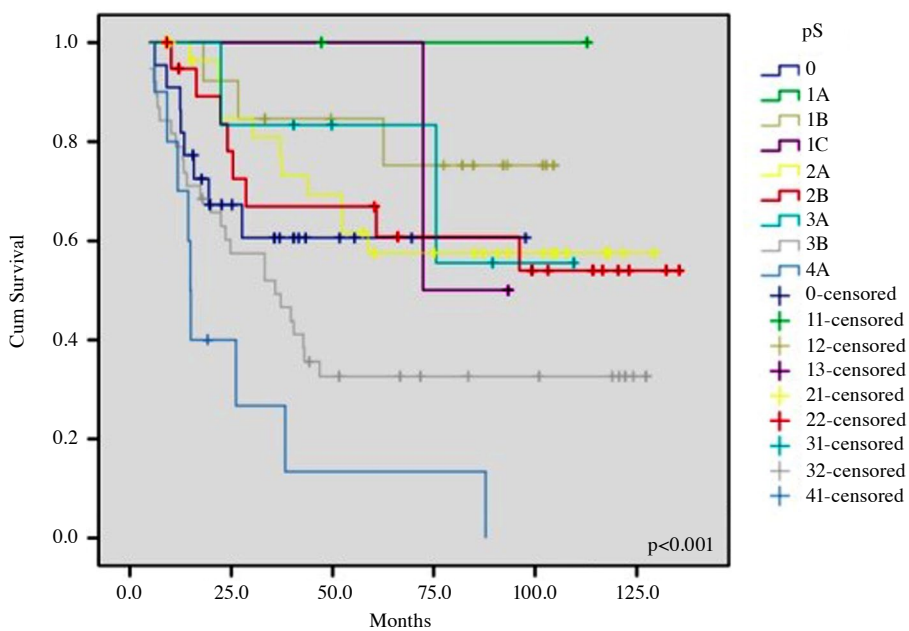

Figure 1. Analysis of overall survival by pathological stages.
pS: Pathological stage.

Table 4. Patient characteristics in pre-matching and post-matching patient groups

	Surgery										Surgery after neoadjuvant CT/CRT (n=42)					Pre-matching *vs.* surgery after neoadjuvant CT/CRT	Post-matching *vs.* surgery after neoadjuvant CT/CRT
	Pre-matching (n=101)					Post-matching (n=42)											
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*	*p*
Age (year)			59.1±12.2	60.0	26.0-87.0			59.2±13.1	59.0	26.0-87.0			58.1±9.4	60.0	26.0-87.0	0.613	0.642
Sex																0.902	0.362
Male	59	58.4				29	69				25	59.5					
Female	42	41.6				13	31				17	40.5					
cS																0.562	0.691
Stage 1	6	5.9				2	4.8				2	4.8					
Stage 2 (SCC)	24	23.8				12	28.6				10	23.8					
Stage 2A (AC)	3	3				1	2.4				-	-					
Stage 2B (AC)	1	1				-	-				-	-					
Stage 3	49	48.5				18	42.8				21	50					
Stage 4A	18	17.8				9	21.4				9	21.4					
Histological type																0.089	0.620
SCC	62	61.4				30	71.4				32	76.2					
AC	39	38.6				12	28.6				10	23.8					
Tumor localization																0.759	0.924
Upper	5	5				2	4.8				2	4.8					
Middle	23	22.7				10	23.8				12	28.5					
Lower	73	72.3				30	71.4				28	66.7					
pS																<0.001	<0.001
Stage 0	1	1				-	-				21	50					
Stage 1A	2	2				1	2.4				1	2.4					
Stage 1B	9	8.9				3	7.1				4	9.5					
Stage 1C (AC)	2	2				-	-				-	-					
Stage 2A	24	23.7					16.7				5	11.9					
Stage 2B	17	16.8				1	11.9				3	7.1					
Stage 3A	5	5				20	2.4				1	2.4					
Stage 3B	32	31.7				5	47.6				6	14.3					
Stage 4A	9	8.9					11.9				1	2.4					
Histological grade																<0.001	<0.001
Grade X	14	13.9				5	11.9				25	59.5					
Grade 1	17	16.8				12	28.6				2	4.8					
Grade 2	51	50.5				15	35.7				8	19					
Grade 3	19	18.8				10	23.8				7	16.7					
Anastomosis localization																0.241	0.192
Intrathoracic	75	74.3				30	71.4				35	83.3					
Cervical	26	25.7				12	28.6				7	26.7					
Number of lymph nodes removed			15.04±9.1	13.0	2.0-47.0			15.21±10	13.0	2.0-47.0			10±7.3	8.0	1.0-35.0	<0.001	0.006

CT: Chemotherapy; CRT: Chemoradiotherapy; SD: Standard deviation; cS: Clinical stage; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; pS: Pathological stage.

The mean tumor length was 52.1 (range, 10 to 130) mm. The mean tumor maximum standardized uptake value (SUV_{max}) value was 14.3 (range, 2.4 to 30). The mean number of lymph nodes removed during the operation was 13.5 (range, 1 to 47). The mean number of lymph nodes removed from patients who did not receive neoadjuvant therapy was 15±10, and the mean number of lymph nodes removed from patients who received neoadjuvant therapy was 10±7, indicating a statistically significant difference (p=0.002).

During clinical follow-up, recurrence was observed in 54 (37.8%) of 143 patients. Twenty-one patients had local recurrence, 25 had a distant recurrence, and eight had a local and distant recurrence. While the five-year overall survival rate was 34.3% in patients with relapse, this rate was 65.2% in patients without recurrence (p<0.001).

The five-year overall survival rate of the patients was 53.1%. Considering the sex difference, this rate was 64.4% in female patients and 45.3% in male patients (p=0.012). According to the histopathological diagnosis, the five-year overall survival rate in patients with squamous cell carcinoma was 55.7% and 48.4% in patients with adenocarcinoma (p=0.231).

Survival analysis was performed according to pathological stages, and the difference in survival between stages was found to be statistically significant (p<0.001) (Figure 1). While the five-year overall survival rate was 58.3% in patients with a complete pathological response (50%) with neoadjuvant therapy, this rate was 52.8% in patients without a complete response, indicating no statistically significant difference (p=0.709). In addition, although the difference in recurrence-free survival was not statistically significant between the same patient groups, the difference was more evident (70% and 25.2%, respectively, p=0.084).

To eliminate the effects of variables such as age, sex, clinical stage, and cell type that may influence survival between the two groups, statistical PSM was performed. Accordingly, two groups containing 42 patients who received neoadjuvant therapy and 42 patients who did not receive neoadjuvant therapy were formed with a match sensitivity tolerance of 0.054. Demographic and clinical characteristics of the patients after matching are summarized in Table 4.

In the post-matching survival analysis, the five-year overall survival rate was 8% (median 22.3 months) in patients who did not receive neoadjuvant therapy, while this rate was 52.9% (median 62.5 months) in those who received neoadjuvant therapy, and the difference was statistically significant (p<0.001) (Figure 2).

The five-year recurrence-free survival rate for patients who did not receive neoadjuvant therapy was 26.2% (median 14.5 months), compared to 41.3% (median 35 months) for patients who received neoadjuvant therapy. The difference in recurrence-free survival between the two groups was also statistically significant (p=0.025) (Figure 3).

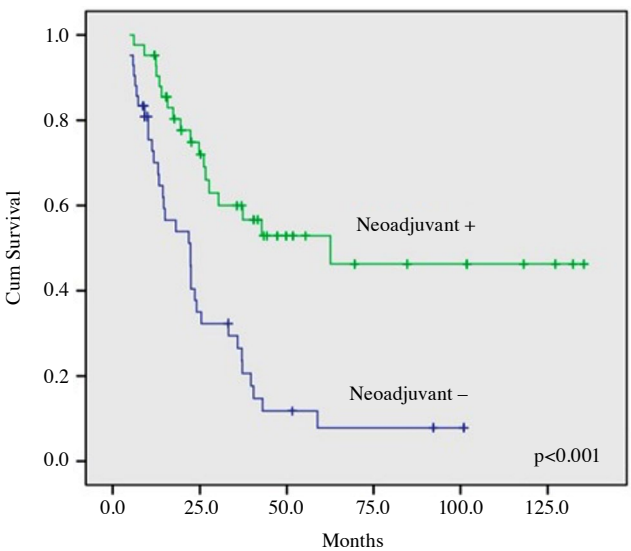

Figure 2. Analysis of overall survival by post-matching according to neoadjuvant therapy status.

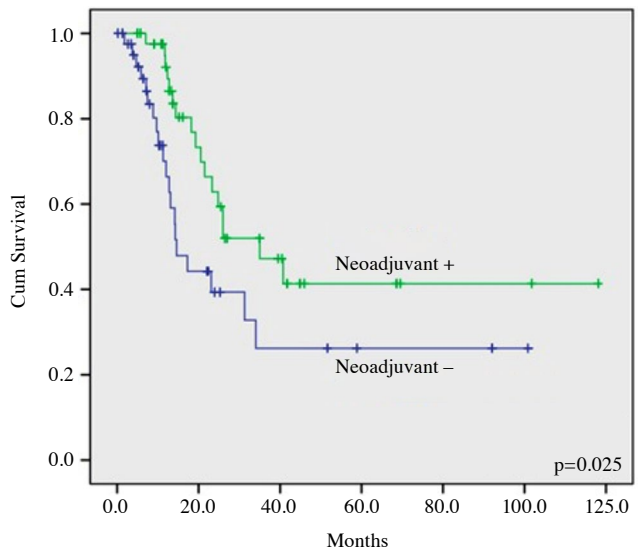

Figure 3. Analysis of recurrence-free survival by post-matching according to neoadjuvant therapy status.

DISCUSSION

It has been reported that NCRT is superior to NCT or surgery alone in terms of overall survival, recurrence-free survival, and complete pathological response in locally advanced esophageal cancer.[5] The main study about this is the multi-center randomized-controlled Phase III Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) study. In this study, 366 patients with T1-3, N0-1, M0 operable esophageal and esophagogastric junction cancers (75% adenocarcinoma, 23% squamous cell carcinoma) were randomized into surgery after NCRT (n=178) and surgery only (n=188). While the median survival was 49 months in the neoadjuvant treatment arm, it was 24 months in the surgery arm (hazard ratio [HR]: 0.657; 95% confidence interval [CI]: 0.495-0.871; p=0.003). Expected five-year overall survival rates were similar to median survivals (47% *vs*. 34%, respectively). While the R0 resection rate was 92% in the neoadjuvant treatment arm, it was 69% in the surgery arm (p<0.001).[6] In the recurrence data published after at least two years of follow-up, 35% recurrence was observed in the neoadjuvant arm, while 58% recurrence was observed in the surgical arm.[7] In the study in which long-term survival data were published, NCRT was found to be superior to surgery alone in terms of survival for both adenocarcinoma and squamous cell carcinoma patients.[8]

In the current study, after one-to-one matching, both five-year overall survival (median 62.5 months *vs*. 22.3 months, p<0.001, respectively) and five-year recurrence-free survival (median 35 months *vs*. 14.5 months, respectively, p=0.025) in the group receiving neoadjuvant therapy were significantly higher. The RO resection rate was similarly higher in the patient group receiving neoadjuvant therapy (100% *vs*. 95.8%, respectively). While the pathological complete response rate was 29% in the CROSS study, it was 50% in our study. We believe that this may be due to the developing RT techniques and the chosen chemotherapy regimens. In our study, patients were usually given cisplatin and fluorouracil, while carboplatin and paclitaxel were the choices in the CROSS study. In addition, unlike the CROSS study, 76.2% of the patients who received neoadjuvant therapy in our study consisted of squamous cell carcinoma patients. This situation, which is compatible with the geography we live in, may also explain the high pathological complete response rates obtained. The histopathological type was not detected as a prognostic factor in both studies.[6]

In the literature, there are also publications reporting that patients receiving only CRT in squamous cell esophageal cancers had similar overall survival rates compared to those who underwent surgery after NCRT.[9,10] These studies have shown that there is no need for surgery, particularly in patients with complete response after CRT. One of the important problems is to detect the complete pathological response. The power of classical imaging and endoscopic methods to evaluate complete pathological response is limited. The pathological response can be evaluated most safely after surgery. In our study, 71.4% of squamous cell carcinoma patients who received NCRT had a complete pathological response. Therefore, we recommend surgical treatment in squamous cell esophageal cancers with a good response to CRT, both to evaluate the pathological complete pathological response and to prevent early local recurrences.

Another point of discussion for esophageal cancers is choosing a treatment method in clinical T2NO patients.[11] According to the NCCN Clinical Practice Guidelines in Oncology guidelines, NCT is recommended for T2N0 patients, if they are at high risk. High-risk patients include a tumor size of ≥3 cm, presence of lymphovascular invasion, and poorly differentiated tumor.[5] In other cases, direct surgery is recommended. In our study, there were eight (8%) clinical T2N0 patients in the direct surgery group and two (5%) patients in the neoadjuvant therapy group. Recurrence was observed in one patient in each group during follow-up. Although these data are not sufficient to perform survival analysis, our opinion is to give neoadjuvant therapy, if there is a high risk in T2N0 patients.

Although PSM was performed, the results are limited to the power of retrospective, non-randomized study. Due to the coverage of the timeline of the study, neoadjuvant and adjuvant therapy protocols were changed, and also some of the patients had their neoadjuvant therapies in other clinics; therefore, it is impossible to give a standard therapy protocol for this study. This is the main limitation of the study. As there is no published neoadjuvant therapy study in esophageal cancer in Turkey, this is the first one.

In conclusion, surgery after neoadjuvant chemotherapy/neoadjuvant chemoradiotherapy is associated with significant overall and disease-free survival rates in locally advanced esophageal cancer. Further multi-center, randomized studies are needed on neoadjuvant therapy in patients without lymph node metastasis.

Ethics Committee Approval: The study protocol was approved by the Ankara University Faculty of Medicine Ethics Committee (date: 13.02.2020, no: İ1-60-20). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: C.Y.; Design: G.K.; Control/supervision: C.Y., S.E., Data collection and/or processing: B.M.Y., Y.K.; Analysis and/or interpretation: A.H.E., S.S.T.; Literature review: S.S.T., G.K.; Writing the article: S.S.T., C.Y.; Critical review: B.M.Y., A.K.C.; References and fundings: Y.K., G.K.; Materials: S.S.T., G.K.

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