Original Article

Neoadjuvant therapy combined with surgery is superior to chemoradiotherapy in esophageal squamous cell cancer patients with resectable supraclavicular lymph node metastasis: a propensity score-matched analysis

Yongkui Yu[1], Lei Xu[2], Xiankai Chen[2], Haomiao Li[1], Qi Liu[1], Ruixiang Zhang[2], Hounai Xie[2], Yongfeng Chen[3], Ling Yuan[4], Bo Tan[4], Yin Li[2], Wenqun Xing[1]

[1]Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; [2]Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [3]Department of Information Center, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; [4]Department of Radiotherapy, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China

Contributions: (I) Conception and design: Y Li, W Xing; (II) Administrative support: Y Li, L Xu, Y Yu, L Yuan; (III) Provision of study materials or patients: Y Yu, L Xu, L Yuan, B Tan, X Chen, H Li, H Xie; (IV) Collection and assembly of data: Y Yu, L Xu, R Zhang, X Chen; (V) Data analysis and interpretation: Y Chen, Y Yu, L Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Wenqun Xing, MD. Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China. Email: littleboy8788@163.com.

Background: Multiple clinical trials were conducted to evaluate the efficacy of neoadjuvant therapy in esophageal cancer but exhibited mixed results, indicating that the efficacy of neoadjuvant therapy remains controversial in the treatment of esophageal cancer. Our study was conducted to investigate the value of neoadjuvant therapy in patients with esophageal cancer with supraclavicular lymph node metastases.

Methods: We retrospectively enrolled 231 patients who had resectable esophageal squamous cell carcinoma (ESCC) with supraclavicular lymph node metastases from June 2008 to November 2018. All patients were divided into three groups: the neoadjuvant therapy combined with surgery (Neo + S) group, the radical chemoradiotherapy (CRT) group, and the single radiotherapy (RT) group. Propensity score matching (PSM) was conducted to exclude the impact of potential interferences. Kaplan-Meier analysis, the log-rank test, and competitive risk model analysis were used to assess the efficacy of different therapeutic methods.

Results: Patients in the Neo + S group had a better 3-year survival rate (72.0% *vs.* 35.8%; P=0.005), progression-free survival (PFS) (24 *vs.* 14 months; P<0.0001), and lower 3-year tumor-specific mortality risk (25.1% *vs.* 53.7%; P=0.005) than those in the CRT group. Furthermore, patients in the CRT group had a better 3-year survival (30.1% *vs.* 18.6%; P=0.012) and lower 3-year tumor-specific mortality risk (57.9% *vs.* 76.8%; P=0.011) than those in the RT group. Additionally, the supraclavicular lymph node metastasis rate was higher than the mediastinal lymph node metastasis rate in patients with upper esophageal cancer compared to middle and lower esophageal cancer

Conclusions: Neoadjuvant chemotherapy combined with surgery showed better efficacy than radical CRT in patients who had resectable ESCC with supraclavicular lymph nodes metastasis. Supraclavicular lymph nodes are more likely to be regional lymph nodes for upper and middle esophageal cancer.

Keywords: Esophageal cancer; propensity score matching (PSM); neoadjuvant therapy; chemoradiotherapy (CRT)

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Introduction

Esophageal cancer is the 6th leading cause of death from cancer and the 8th most common cancer worldwide world (1). China has the highest morbidity rate of esophageal cancer globally. There are about 470,000 new cases and 440,000 deaths from esophageal cancer every year (2). Histologically, esophageal cancer is classified into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Notably, the morbidity rate of esophageal cancer is relatively low in Europe and America, most of which are of the EAC subtype, whereas in China, ESCC accounts for about 90% of esophageal cancers (2). Therefore, ESCC is a unique type of cancer in China. Current management for esophageal cancer is composed of surgery, chemotherapy, and radiotherapy (RT). However, although great advancements have been achieved in therapies for esophageal cancer, the 5-year survival rates of patients with distant metastasis or lymph node metastasis are less than 5% and 25%, respectively (3). Therefore, there is a clear and urgent need for novel therapeutic methods for esophageal cancer. Neoadjuvant therapy was proposed to have potent efficacy in various types of cancer by enhancing the complete surgical resection of the cancer (4-6). Multiple clinical trials were conducted to evaluate the efficacy of neoadjuvant therapy in esophageal cancer but exhibited mixed results, indicating that the efficacy of neoadjuvant therapy remains controversial in the treatment of esophageal cancer, studies from Schuhmacher *et al.* and Greally *et al.* show negligible benefit from neoadjuvant therapy, while studies of Cunningham *et al.* and Shapiro *et al.* show positive results (7-10).

The complicated lymphatic network around the esophagus makes it easy for thoracic esophageal cancer to metastasize via lymphatics (11). Supraclavicular lymph node metastasis of thoracic esophageal cancer is defined as regional lymph node metastasis according to the Union for International Cancer Control (UICC) (12) and the American Joint Committee on Cancer (AJCC) Staging Guideline (7th edition) (13). However, the 5-year survival rate of patients with distant lymph node metastases, including supraclavicular and abdominal lymph node metastasis, is 10% higher than those with visceral metastases (14). Therefore, some scholars proposed that tumors with distant lymph node metastasis should be defined as N2 stage rather than M1a stage. The Japan Esophagus Society (JES) has released different staging criteria of esophageal cancer, in which cervical, upper, and middle esophageal cancers with supraclavicular lymph node metastasis belong to N2 stage, whereas lower esophageal cancer with supraclavicular lymph node metastasis belongs to N3 stage (15). According to JES guidelines, supraclavicular lymph nodes are defined as regional lymph nodes for cervical and upper esophageal cancer, which need to be resected during radical surgery (16). Furthermore, retrospective studies found that patients who had esophageal cancer with supraclavicular lymph node or regional lymph node metastasis had similar prognoses. Therefore, some scholars have proposed that supraclavicular lymph node metastasis should be regarded as regional lymph node metastasis in esophageal cancer and should not be considered as a contraindication for surgery (17-20).

The operation methods mainly include three-field and two-field lymph node dissections. Three-field lymph node dissection includes cervical, thoracic, and abdominal lymph node dissections, whereas two-field lymph node dissection only includes thoracic and abdominal lymph node dissections (21-23). Previous studies revealed that patients who received three-field lymph node dissection had better prognoses than those who received two-field lymph node dissection (17,24). Liu *et al.* found that three-field lymph node dissection had better efficacy than two-field lymph node dissection in upper esophageal cancer, whereas this superiority was not found for middle and lower esophageal cancer (25). However, Baba *et al.* suggested that although patients who received three-field lymph node dissection had better prognoses, their daily living activities such as eating and speaking were more severely affected than those who received two-field dissection (26). Therefore, it remains controversial whether patients with supraclavicular lymph node metastasis should receive three- or two-field lymph node dissections. In former studies, neoadjuvant therapy could achieve tumor downstaging prior to surgery, but with no overall survival benefit (27-29), and chemoradiotherapy (CRT) is only applied for patients who cannot tolerate surgery or are technically inoperable (30). Therefore, the efficacy of neoadjuvant therapy combined with surgery (Neo + S) compared with chemotherapy and RT remains unclear. Our study retrospectively analyzed the characteristics and prognoses of patients who had esophageal cancer with supraclavicular lymph node metastasis, aiming to explore the efficacy of Neo + S and determine the significance of supraclavicular lymph node metastasis in esophageal cancer. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-577/rc).

Methods

Study design

This is a single center and retrospective study. Patients who had resectable ESCC with supraclavicular lymph node metastases from June 2008 to November 2018 were enrolled according to the following inclusion criteria: (I) patients were more than 18 years old; (II) patients with esophageal cancer that was pathologically confirmed; (III) pathological and/or clinical evidence of supraclavicular lymph node metastasis; (IV) patients who had complete medical records, including information on age, sex, tumor location, tumor node metastasis classification (TNM) staging, and treatment; (V) patients who had complete follow-up data and cause of death. A total of 231 patients were enrolled in this study and they were divided into three groups: a Neo + S group [41], a radical CRT group [133], and a single RT group [23]. After PSM, the number of Neo + S group *vs.* radical CRT group were 38:64 and radical CRT group *vs.* RT group were 41:22.

All patients received examinations on the chest (by contrast CT), upper abdomen (by contrast CT and color Doppler ultrasound), heart, and supraclavicular lymph nodes. They also received gastroscopy or ultrasound gastroscopy and upper gastrointestinal angiography before treatment. Furthermore, some patients received additional PET-CT examinations according to their symptoms. Lymph nodes with a minimum diameter of ≥10 mm on CT were regarded as metastatic lymph nodes (31). TNM classifications of the tumor were defined according to AJCC and UICC staging guidelines for esophageal cancer and esophagogastric junction cancer.

The therapeutic regimen for each patient was discussed before treatment. Some clinicians hold the view that patients with supraclavicular lymph node metastasis cannot undergo surgical treatment and that these patients should receive RT and chemotherapy. However, other clinicians advocate surgical treatment. Therefore, there is no standard criterion to determine whether the patient should receive surgery or CRT. In our study, patients with bilateral cervical lymph node metastasis received three-field lymph node dissection, whereas patients with unilateral cervical lymph node metastasis received unilateral lymph node dissection. The neoadjuvant regimen consisted of cisplatin (80–100 mg/m^2), docetaxel (75 mg/m^2), or nedaplatin (80–100 mg/m^2) combined with paclitaxel (135–175 mg/m^2). CRT or RT was applied to esophageal lesions, mediastinal lymph nodes, and metastatic supraclavicular cervical lymph nodes. The dose of RT was 2.0 Gy/30 f or 1.8 Gy/33 f. The chemotherapy regimen was composed of cisplatin (20–30 mg/m^2), docetaxel (75 mg/m^2), or nedaplatin (80–100 mg/m^2) combined with paclitaxel (135–175 mg/m^2); cisplatin (20–30 mg/m^2) combined with 5-fluorouracil (500 mg/m^2); or tegafur combined with nedaplatin (80–100 mg/m^2).

Follow-up

All patients were followed up after the first treatment by a third party (LinDoc Company). The follow-up data were collected by phone calls. The follow-up was carried out once every 3 months in the first 1–2 years, once every 6 months in the next 3–4 years, and once a year thereafter. The date of death, the date of recovery and the recovery site were record. Overall survival was defined as the duration from the date of initial treatment to the date of death or the last follow-up. Tumor recurrence or metastasis were recorded alone with follow up or by their review results. The related clinical data of patients were checked to record the location and time of progression.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University (No. 2014ys38) and individual consent for this retrospective analysis was waived.

Statistical analysis

R version 3.6.0 (https://cran.R-project.org) was used for statistical analysis. The chi-square test was used to evaluate the differences between different groups ($P<0.05$). Propensity score matching (PSM) was conducted to exclude the influence of potential interferences. Age, sex, location, and TNM stage were matched by caliper matching. No replacement or duplication was allowed during the matching process. The caliper value was 0.01 and the matching ratio was 1:2. The chi-square test was applied to estimate the difference between two groups after PSM. Kaplan-Meier analysis and the log-rank test were used to evaluate survival differences. Competitive risk model analysis was performed to assess the mortality risks of patients in each group. Two-

sided P value <0.05 was regarded as statistically significant.

Results

Baseline characteristics of the enrolled patients

A total of 231 patients were enrolled in our study, with 153 males and 78 females (Table S1). The mean age was 63.36 [37–86] years old. Among these patients, 64, 138, and 29 patients had upper, middle, and lower esophageal cancers, respectively. Five patients who had received previous surgery were shown to have supraclavicular lymph node metastasis by PET-CT examination. Twenty-eight patients (27 received surgery and 1 received CRT) underwent supraclavicular lymph node biopsy to confirm the metastasis. Of the 231 patients, 85, 72, and 74 had left, right, and bilateral supraclavicular lymph node metastases, respectively. Furthermore, 57 patients received surgery, of which 16 patients did not undergo neoadjuvant therapy and 41 patients received neoadjuvant therapy. Among the 41 patients who received neoadjuvant therapy, 1 received therapy before the surgery and 40 received therapy after the surgery. Additionally, 12, 14, and 15 patients underwent left, right, and bilateral cervical lymph node dissections, respectively. Twenty-one patients received adjuvant therapy whereas 20 patients did not. The baseline characteristics of the enrolled patients are listed in Table S1.

Survival analysis and tumor-specific mortality risk in the three groups before PSM

Survival analysis was performed to evaluate the efficacy of Neo + S, CRT, and RT in the enrolled patients. Results revealed that the 3-year survival rates of the Neo + S, CRT, and RT groups were 71.3%, 32.3%, and 17.4%, respectively (P<0.0001) (*Figure 1A*). The progression-free survival (PFS) of patients in the Neo + S group was significantly better than that in the CRT and RT groups (24, 13, and 9 months, respectively; P<0.0001) (*Figure 1B*). Moreover, competitive risk model analysis showed that the tumor-specific mortality risks of patients in the Neo + S, CRT, and RT groups were 23.7%, 59.6%, and 78.3%, respectively (P<0.001) (*Figure 1C*).

Survival analysis and tumor-specific mortality risk in three groups after PSM

Given that the clinical features of patients were significantly different between the CRT and RT groups as well as the Neo + S and CRT groups (P<0.05), PSM was conducted to avoid the influence of potential interferences. Results showed that after PSM, there was no significant difference in the clinical characteristics of patients between the CRT and RT groups (P>0.05) (*Table 1*, Figure S1) as well as the Neo + S and CRT groups (P>0.05) (*Table 2*, Figure S2).

After PSM, the 3-year survival rates in the Neo + S and CRT groups were 72.0% and 35.8%, respectively. The survival time in the Neo + S group was significantly longer than that in the CRT group (P=0.005) (*Figure 2A*). The PFS of patients in the Neo + S group was significantly better than that in the CRT group (24 and 14 months, respectively; P<0.0001) (*Figure 2B*). The 3-year tumor-specific mortality risks in the Neo + S and CRT groups were 25.1% and 53.7%, respectively (P=0.005) (*Figure 2C*). Besides, the 3-year survival rates of patients in the CRT and RT groups were 30.1% and 18.6%, the median survival of 17 and 11 months, respectively (P=0.012) (*Figure 2D*). The PFS of patients in the CRT group was significantly better than that in the RT group (14 and 7 months, respectively; P=0.013) (*Figure 2E*). The 3-year tumor-specific mortality risks in the CRT and RT groups were 57.9% and 76.8%, respectively (P=0.011) (*Figure 2F*).

Characteristics of tumor progression and lymph node metastasis

Tumor progression and metastasis in different location of esophageal cancer Data on the location and time of tumor progression were obtained from 93 patients, among which 67 patients were censored. Among the 93 patients with tumor recurrence, 13 patients received surgery and 80 patients did not, while 19, 54, and 10 patients had upper, middle, and lower esophageal cancers, respectively. Among the 13 patients who had received surgery, 4 were in the surgery only group and 9 were in the Neo + S group (*Figure 3*, Table S2). Supraclavicular lymph node metastasis rates were higher in upper (41.38%) and middle (42.59%) esophageal cancer. For lower esophageal cancer, the abdominal lymph node metastasis rate (70.00%) was higher than the supraclavicular lymph node metastasis rate (20.00%). There were no significant differences in mediastinal lymph node metastasis rates between upper (31.03%), middle (46.30%), and lower (40.00%) esophageal cancer. The abdominal lymph node metastasis rates in upper (13.79%) and middle (35.19%) esophageal cancer were lower than those in lower (70.00%) esophageal cancer. In

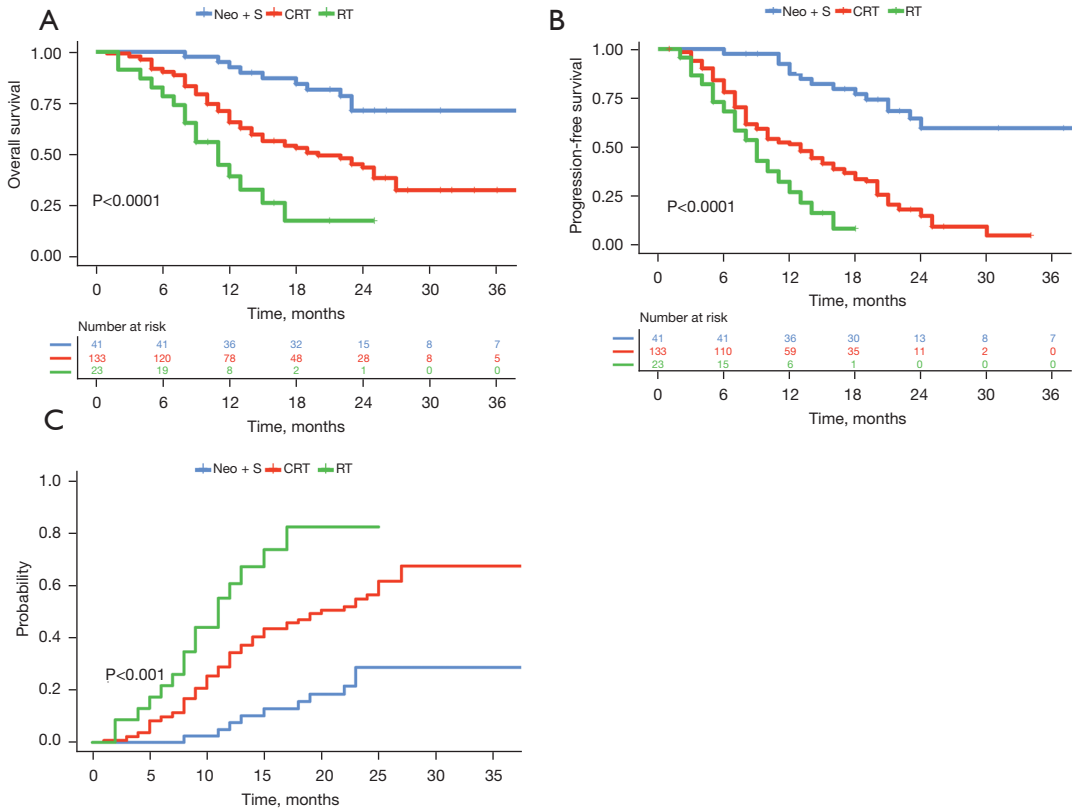

Figure 1 Prognostic analysis of patients in the Neo + S, CRT, and RT groups before PSM. (A) The 3-year survival rates of the Neo + S, CRT, and RT groups were 71.3%, 32.3%, and 17.4%, respectively (P<0.0001). The median survival rates of the CRT and RT groups were 20 and 11 months, respectively. (B) PFS in the Neo + S group was significantly better than that in the CRT and RT groups with times of 24, 13, and 9 months, respectively (P<0.0001). (C) The tumor-specific mortality risks of patients in the Neo + S, CRT, and RT groups were 23.7%, 59.6%, and 78.3%, respectively (P<0.001). Neo + S, neoadjuvant therapy combined with surgery; CRT, chemoradiotherapy; RT, radiotherapy; PSM, propensity score matching; PFS, progression-free survival.

patients with upper esophageal cancer, the supraclavicular lymph node metastasis rate was higher than the mediastinal lymph node metastasis rate (41.38% *vs.* 31.03%). In those with middle esophageal cancer, the mediastinal lymph node metastasis rate was higher than the supraclavicular lymph node metastasis rate but the difference was not statistically significant (46.30% *vs.* 42.59%). In those with lower esophageal cancer, the mediastinal lymph node metastasis rate was higher than the supraclavicular lymph node metastasis rate (40.00% *vs.* 20.00%).

Discussion

Our study revealed that in esophageal cancer patients with supraclavicular lymph node metastasis, those who received Neo + S had a better 3-year survival (72% *vs.* 35.8%) and PFS (24 *vs.* 14 months) than those who received radical CRT, suggesting the promising efficacy of the combination of neoadjuvant therapy and surgery in esophageal cancer patients with supraclavicular lymph node metastasis. Furthermore, upper and middle esophageal cancers were more likely to have supraclavicular lymph node metastases, indicating that supraclavicular lymph nodes might belong to regional lymph nodes in upper and middle esophageal cancer.

Our findings showed that the 3-year survival rate of patients in the Neo + S group was better than that in the CRT and RT groups (71.3%, 32.3%, and 17.4%, respectively), indicating the promising efficacy of neoadjuvant therapy and surgery. Tong *et al.* revealed that the median survival of patients treated with CRT plus surgery was significantly longer than those who did not

Table 1 Clinical characteristics of patients before and after PSM

Variables	Before PSM			After PSM		
	CRT (n=133), n (%)	RT (n=23), n (%)	P value	CRT (n=41), n (%)	RT (n=22), n (%)	P value
Age			0.003			0.898
<65	68 (51.1)	4 (17.4)		8 (19.5)	4 (80.5)	
≥65	65 (48.9)	19 (82.6)		33 (18.2)	18 (81.8)	
Sex			0.172			0.760
Male	89 (66.9)	12 (52.2)		24 (58.5)	12 (54.5)	
Female	44 (33.1)	11 (47.8)		17 (41.5)	10 (45.5)	
BMI			0.968			0.782
<22.34	63 (47.4)	11 (47.8)		22 (53.7)	11 (50.0)	
≥22.34	70 (52.6)	12 (52.2)		19 (46.3)	11 (50.0)	
Supraclavicular lymph node metastasis			0.412			0.607
Left	48 (36.1)	8 (34.8)		14 (34.1)	8 (36.4)	
Right	41 (30.8)	10 (43.5)		15 (36.6)	10 (45.5)	
Bilateral	44 (33.1)	5 (21.7)		12 (29.3)	4 (18.2)	
Location			0.837			0.759
Upper	44 (33.1)	7 (30.4)		10 (24.4)	6 (27.3)	
Middle	73 (54.9)	14 (60.7)		29 (70.7)	14 (63.6)	
Lower	16 (12.0)	2 (8.7)		2 (4.9)	2 (9.1)	
TNM stage			0.657			0.937
IIB–IIIA	29 (21.8)	7 (30.4)		12 (29.3)	7 (31.8)	
IIIB	86 (64.7)	13 (56.5)		26 (63.4)	13 (59.1)	
IVA	18 (13.5)	3 (13.0)		3 (7.3)	2 (9.1)	
Cause of death			–			–
Cancer-specific death	60 (45.1)	15 (65.2)		17 (41.5)	14 (63.6)	
Other-cause death	8 (6.0)	1 (4.3)		4 (9.8)	1 (4.5)	
Alive	65 (48.9)	7 (30.4)		20 (48.8)	7 (31.8)	

PSM, propensity score matching; CRT, chemoradiotherapy; RT, radiotherapy; BMI, body mass index; TNM, tumor node metastasis classification.

receive surgery (34.8 *vs.* 9.9 months; P<0.001), which was consistent with our finding (32). However, 91% (20/23) of patients in their study received CRT but not neoadjuvant therapy. Besides, 84.8% (39/46) patients in their CRT group were inoperable or had distant metastasis, whereas patients enrolled in our study with supraclavicular lymph node metastasis were operable. Additionally, some scholars reported that patients with supraclavicular lymph node metastasis had a 3-year survival of less than 40% and a 5-year survival of 24–29% (17,21,33,34). However, most patients enrolled in their studies did not receive neoadjuvant therapy, whereas 40 patients enrolled in the Neo + S group in this study had received neoadjuvant therapy. Therefore, our study may be more representative in evaluating the efficacy of neoadjuvant therapy in patients with supraclavicular lymph node metastasis. Moreover, most patients with esophageal cancer were elderly people, which might affect the evaluation of prognosis. Therefore, we

Table 2 Characteristics of patients before and after PSM

Variables	Before PSM			After PSM		
	Neo + S (n=41), n (%)	CRT (n=133), n (%)	P value	Neo + S (n=38), n (%)	CRT (n=64), n (%)	P value
Age			0.027			0.898
<65	29 (70.7)	68 (51.1)		26 (68.4)	43 (67.2)	
≥65	12 (29.3)	65 (48.9)		12 (31.6)	21 (32.8)	
Sex			0.679			0.841
Male	26 (63.4)	89 (66.9)		26 (68.4)	45 (70.3)	
Female	15 (36.6)	44 (33.1)		12 (31.6)	19 (29.7)	
BMI			0.225			0.594
<22.34	15 (36.6)	63 (47.4)		14 (36.8)	27 (42.2)	
≥22.34	26 (63.4)	70 (52.6)		24 (63.2)	37 (57.8)	
Supraclavicular lymph node metastasis			0.724			0.539
Left	12 (29.3)	48 (36.1)		12 (31.6)	26 (40.6)	
Right	14 (34.1)	41 (30.8)		13 (34.2)	22 (34.4)	
Bilateral	15 (36.6)	44 (33.1)		13 (34.2)	16 (25.0)	
Location			0.252			0.923
Upper	8 (19.5)	44 (33.1)		8 (21.1)	15 (23.4)	
Middle	27 (65.9)	73 (54.9)		25 (65.8)	42 (65.6)	
Lower	6 (14.6)	16 (12.0)		5 (13.2)	7 (10.9)	
TNM stage			0.134			0.754
IIB–IIIA	10 (24.4)	29 (21.8)		9 (23.7)	12 (18.8)	
IIIB	30 (73.2)	86 (64.7)		28 (73.7)	49 (76.6)	
IVA	1 (2.4)	18 (13.5)		1 (2.6)	3 (4.7)	
Cause of death			–			–
Cancer-specific death	8 (19.5)	60 (45.1)		8 (21.1)	26 (40.6)	
Other-cause death	2 (4.9)	8 (6.0)		1 (2.6)	5 (7.8)	
Alive	31 (75.6)	65 (48.9)		29 (76.3)	33 (51.6)	

PSM, propensity score matching; Neo + S, neoadjuvant therapy combined with surgery; CRT, chemoradiotherapy; BMI, body mass index; TNM, tumor node metastasis classification.

performed competitive risk model analysis to exclude the interference of death resulting from other causes. Results showed that the 3-year tumor-specific mortality risk was lowest in the Neo + S group and highest in the RT group. After PSM, significant differences still existed in 3-year survival rates (72.0% *vs.* 35.8%) and competitive morbidity risks (25.1% *vs.* 53.7%) between the Neo + S and CRT groups. These findings demonstrate the efficacy of Neo + S for patients with supraclavicular lymph node metastasis.

In this study, some patients only received unilateral lymph node dissection and exhibited good prognoses, indicating that supraclavicular lymph nodes are regional lymph nodes of esophageal cancer and surgery remains an effective therapy for patients with supraclavicular lymph node metastasis. Shibata *et al.* found that lymphatic vessels were distributed longitudinally along the cervical esophagus, whereas they were distributed like a network in the thoracic esophagus (35). These findings suggest

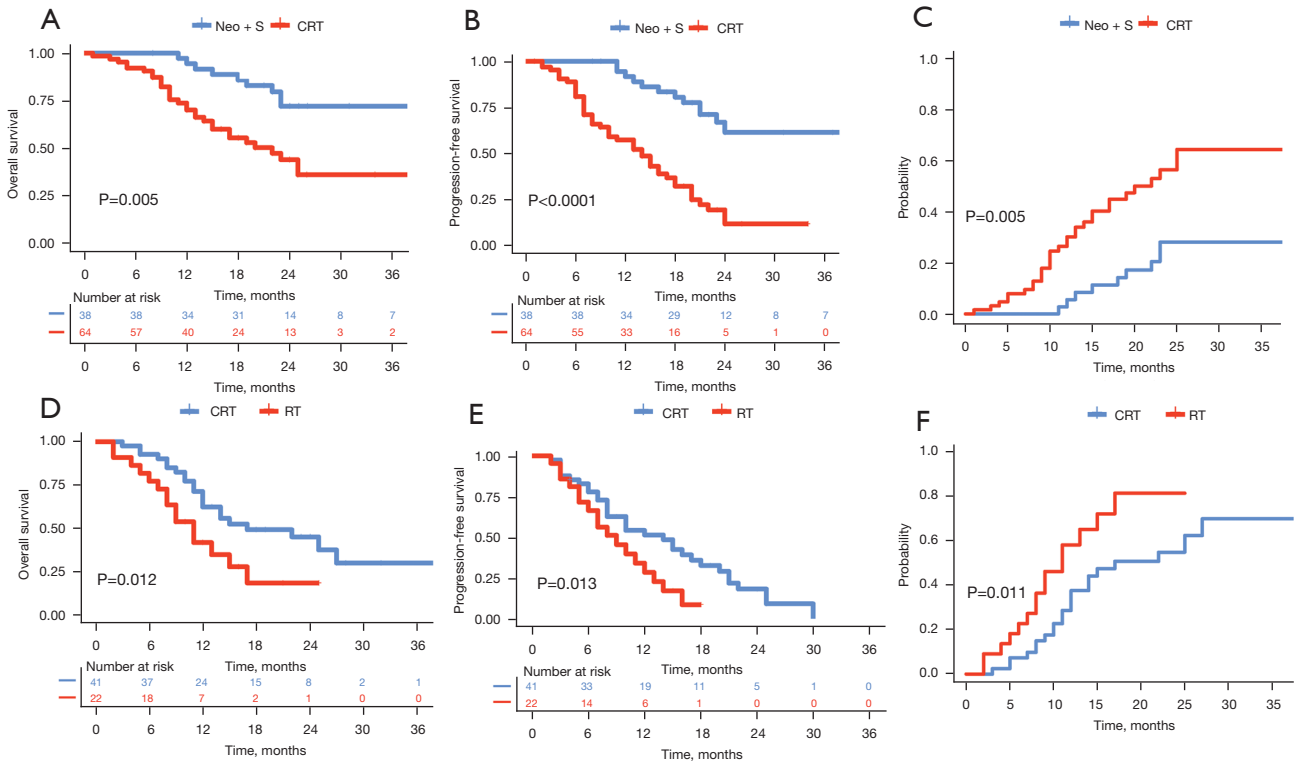

Figure 2 Prognostic analysis of patients in the Neo + S, CRT, and RT groups after PSM. (A) The 3-year survival rate of patients in the Neo + S group was significantly higher than that in the CRT group with values of 72.0% and 35.8%, respectively (P=0.005). (B) PFS in the Neo + S group was significantly better than that in the CRT group with durations of 24 and 14 months, respectively (P<0.0001). (C) The 3-year tumor-specific mortality risks of patients in the Neo + S and CRT groups were 25.1% and 53.7%, respectively (P=0.005). (D) The 3-year survival rates of patients in the CRT and RT groups were 30.1% and 18.6%, respectively (P=0.012). (E) PFS of patients in the CRT group was significantly better than that in the RT group (14 and 7 months, respectively; P=0.013). The 3-year tumor-specific mortality risks in the CRT and RT groups were 57.9% and 76.8%, respectively (P=0.011). Neo + S, neoadjuvant therapy combined with surgery; CRT, chemoradiotherapy; RT, radiotherapy; PSM, propensity score matching; PFS, progression-free survival.

that when thoracic esophageal cancer metastasizes to the cervical part, the tumor cells might continue metastasizing along a single direction, which provides evidence for the application of unilateral lymph node dissection. However, further prospective studies are needed to determine whether bilateral lymph node metastasis should be performed for patients with unilateral lymph node metastasis.

Our study revealed that CRT had better efficacy than RT. For patients in the RT group, their physical condition was too weak to tolerate CRT, which affected their prognosis. However, the body mass index (BMI) of patients in the CRT and RT groups had no significant difference, indicating that the nutritional status of patients in the two groups was equivalent. After PSM, results showed that the median survival of patients in the CRT group was better than that in the RT group (20 *vs.* 11 months), indicating that CRT had better efficacy. Hence, for patients who cannot accept or are unwilling to receive surgery, it is better to receive CRT if they are able to tolerable it.

As for tumor progression, the supraclavicular lymph node metastasis rate was higher than the mediastinal lymph node metastasis rate in patients with upper esophageal cancer (41.38% *vs.* 31.03%), but had no significant difference in patients with middle esophageal cancer (46.30% *vs.* 42.59%). The supraclavicular lymph node metastasis rate was lower than the mediastinal lymph node metastasis rate in patients with lower esophageal cancer (20.00% *vs.* 40.00%). Besides, upper, middle, and lower esophageal cancers were more likely to metastasize to supraclavicular, mediastinal, and abdominal lymph nodes, respectively, as shown in *Figure 3*. These results indicated that supraclavicular lymph nodes might belong to regional

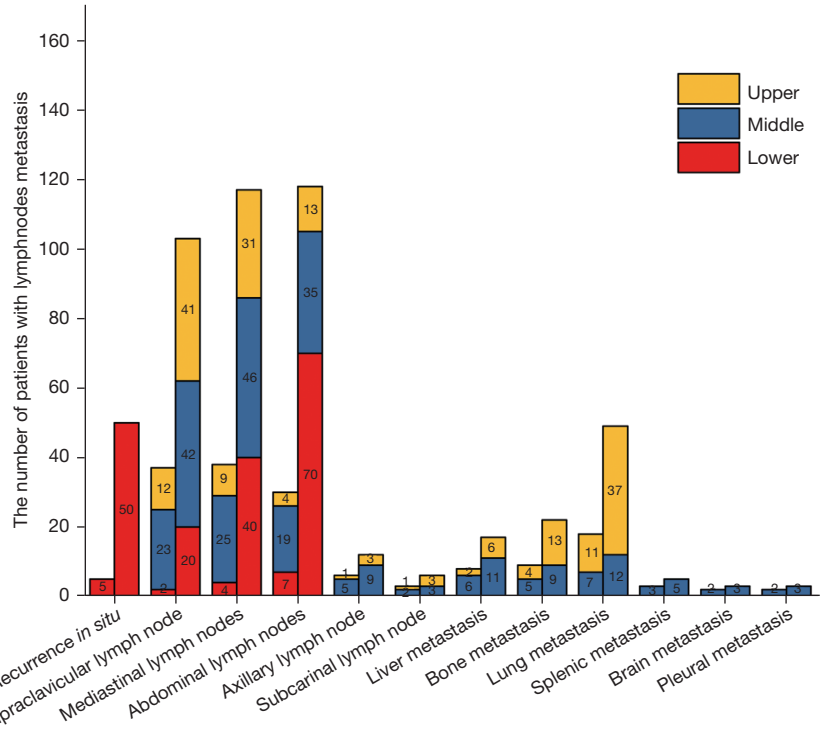

Figure 3 Association between tumor location and progression location. The first column represents the number of tumor metastasis or recurrence. The second column indicates the percentage. Data with a value of zero are not shown on the figure. Upper, upper esophageal cancer; middle, middle esophageal cancer; lower, lower esophageal cancer.

lymph nodes in upper and middle esophageal cancers.

Additionally, the UICC and AJCC staging guidelines only include data of patients who have received surgery, whereas data of induction therapy and adjuvant therapy were excluded. Therefore, the staging guidelines are limited in predicting the prognosis of patients who have esophageal cancer with supraclavicular lymph node metastasis. Our study revealed that Neo + S had better efficacy than radical CRT for patients with supraclavicular lymph node metastasis. Besides, upper and middle esophageal cancers were more likely to metastasize to supraclavicular and mediastinal lymph nodes. These findings indicated that supraclavicular lymph nodes belong to regional lymph nodes in upper and middle esophageal cancers, which was consistent with a previous study (17). Moreover, multiple studies suggested that patients with supraclavicular lymph node metastasis had a better prognosis than those with visceral metastasis (21,24,33,36), which also demonstrates that supraclavicular lymph nodes belong to regional lymph nodes of the esophagus. Therefore, surgical resection should be recommended for patients who have resectable esophageal cancer with supraclavicular lymph node metastasis.

There are a few limitations in our study. Firstly, selection bias was inevitable since operable patients have a better physical condition compared with those in the CRT and RT groups. Secondly, the sample size of our study is limited, so we did not have enough samples to compare the efficacy of unilateral and bilateral lymph node dissections, and it remains controversial whether these patients should receive three-field lymph node dissection. Additionally, since supraclavicular lymph node metastases were partially diagnosed by biopsy and pathological examinations, some benign lymph node enlargements may have been mistaken for cancer metastasis, which will affect the prognosis. Given that this is a retrospective study, additional prospective and randomized clinical trials are needed to confirm whether surgery has better efficacy than radical CRT.

Conclusions

Neo + S has better efficacy than radical CRT for patients

who have resectable esophageal cancer with supraclavicular lymph node metastasis. Supraclavicular lymph nodes are more likely to be regional lymph nodes in upper and middle esophageal cancers. Further prospective and randomized clinical trials are needed to verify our findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-577/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-577/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University (No. 2014ys38) and individual consent for this retrospective analysis was waived.

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