Original Article

The impact of adjuvant therapy on survival for node-negative esophageal squamous cell carcinoma: a propensity score-matched analysis

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Background: At present, the primary treatment of esophageal cancer is surgery-based comprehensive treatment, including adjuvant therapy such as chemotherapy and/or radiotherapy. However, the role of adjuvant therapy for esophageal squamous cell carcinoma (ESCC) with pathologically node-negative (pN0) disease is controversial. This study aimed to evaluate the impact of postoperative adjuvant therapy on survival in patients with pN0 ESCC.

Methods: Patients with ESCC who underwent R0 esophagectomy in the Department of Thoracic Surgery of Sichuan Cancer Hospital from January 2008 to December 2013 were enrolled. Patients were divided into two groups: a surgery alone (Group S) group or a surgery + adjuvant therapy (Group S + A) group. The primary outcomes were overall survival (OS) and disease-free survival (DFS), and every consecutive case was followed up until death or the last follow-up.

Results: A total of 387 patients with ESCC patients who had pN0 were enrolled in the study. After propensity score matching (PSM), each group consisted of 150 patients. In the overall cohort, the 5-year OS (75.6% *vs.* 69.7%; P=0.004) and 5-year DFS (64.9% *vs.* 48.2%; P=0.003) rates were higher in Group S + A than in Group S. In the matched samples, the same outcomes were observed (5-year OS: 75.6% *vs.* 69.7%, P=0.026; 5-year DFS: 67.6% *vs.* 69.6%, P=0.036). Multivariate regression analysis indicated that postoperative chemotherapy was associated with longer OS [hazard ratio (HR): 0.622, 95% confidence interval (CI): 0.416–0.928; P=0.02] and DFS (HR: 0.571, 95% CI: 0.390–0.836; P=0.004); in contrast, T3 stage tumors (HR: 1.953, 95% CI: 1.238–3.082; P=0.004) and <15 lymph node dissections (HR: 1.81; 95% CI: 1.238–2.648; P = 0.002) were found to be independent risk factors for pN0 ESCC.

Conclusions: Adjuvant therapy, especially chemotherapy, prolonged OS and DFS for patients with ESCC who had pN0 disease. Fewer lymph node dissections and T3 stage tumors were independent risk factors for OS and DFS.

Keywords: Adjuvant therapy; esophageal squamous cell carcinoma (ESCC); lymph node-negative

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Introduction

The prognosis of esophageal cancer is poor, with the 5-year overall survival (OS) being lower than 40% (1,2). The most common pathological type of esophageal cancer in China is esophageal squamous cell carcinoma (ESCC) (3), and the dominant treatment for esophageal cancer is comprehensive treatment based on surgery. The National Comprehensive Cancer Network (NCCN) guidelines suggest that pathologically node-negative (pN0) patients with R0 resection require only follow-up and not adjuvant therapy. However, in clinical practice, postoperative adjuvant therapies are selectively applied to patients with pN0 ESCC. Indeed, for some time now, postoperative adjuvant therapy has been performed on the basis of doctors; judgment, and thus adjuvant therapy strategies for ESCC are diverse. Some studies have discussed the relationship between postoperative adjuvant therapy and the survival status of patients with pN0 ESCC, but the conclusions remain controversial (4-9); overall the number of studies focusing on this issue is insufficient, and so the value of postoperative adjuvant treatment for pN0 ESCC remains unclear. Previous related studies have mostly concentrated on the relationship between the prognosis of patients with lymph node-positive esophageal cancer and adjuvant therapy. This study focuses on lymph node-negative ESCC. Different treatment methods are included in the analysis. The case data is closer to the current time, the follow-up survival data is complete, and the application of propensity-score matching eliminates bias as much as possible. Consequently, exploring therapies to improve the prognosis of patients with pN0 ESCC might be considerably beneficially, and thus this study was performed to evaluate the value of postoperative adjuvant therapies for patients with pN0 ESCC. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-2539).

Methods

Study population

The initial data consisted of 387 patients in total, and patients who underwent radical esophagectomy in Sichuan Cancer Hospital from January 2008 to December 2013 were involved. Inclusion criteria were as follows: (I) patients with pN0 ESCC according to the postoperative pathology reports; (II) no neoadjuvant therapy or molecular targeted therapy before esophagectomy; and (III) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The exclusion criteria were as follows: (I) pathologically positive margin; (II) death related to the surgery in 3 months; (III) diagnosis of any other malignancy simultaneously; and (IV) refusal of follow-up. Data collection and the last follow-up were completed in December 2013, and the data were collected from telephone follow-ups, the hospital information center, and local household registration management departments. All patients were divided among two groups: a surgery alone (Group S) group or a surgery + adjuvant therapy (Group S + A) group, the flow chart is shown in *Figure 1*. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Sichuan Cancer Hospital, and all patients were informed of the study and consented to participate.

Surgery

All patients underwent radical esophagectomy and two (mediastinal and perigastric) or three (cervical, mediastinal, and perigastric) fields of regional lymphadenectomy. Surgical methods included right thoracotomy with or without thoracoscopy but with transhiatal esophagectomy. The anastomotic site was related to tumor location. In general, cervical anastomosis was performed in patients with upper esophageal tumors. A supra-aortic arch esophagogastric anastomosis was performed for patients with middle or lower esophageal lesions. Reconstruction of the alimentary tract was performed using the stomach or jejunum after esophageal resection for carcinoma.

Adjuvant therapy

The general postoperative adjuvant treatment procedure at our institution is pathological T1a-3N1-3 and T4a-4bNx,

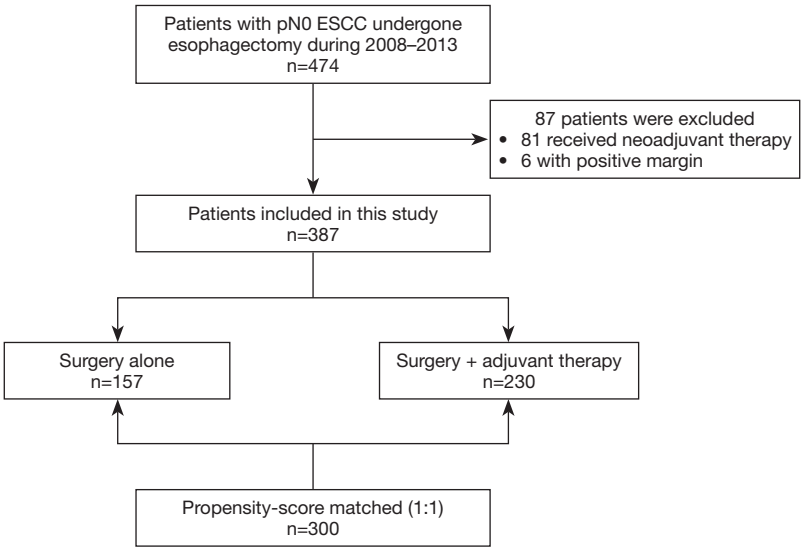

Figure 1 Flow chart of the study. pN0, pathologically node-negative; ESCC, esophageal squamous cell carcinoma.

R1 resection, and nerve or vascular invasion. However, when we provide postoperative adjuvant treatment for pN0 patients, the surgeon not only takes into account the patient's pathological results and intraoperative conditions but also the patient's wishes. The following adjuvant chemotherapy regimens were applied: paclitaxel (a dose of 135–175 mg/m^2) combined with cisplatin (a dose of 80–100 mg/m^2) or carboplatin (a dose of 300 mg/m^2) for 2–4 courses; each course of chemotherapy lasted 28 days (4 weeks). A subsequent or concurrent radiotherapy course of a total dose of 50–60 Gy in 25–30 fractions 5 days a week was given 2–4 weeks after or during chemotherapy administration. According to the results of the computed tomography (CT) scan, the radiation field was delineated using conformal intensity-modulated radiation therapy, including mediastinal, bilateral supraclavicular, and epigastric radiation.

Outcomes

The primary outcomes were 5-year OS and disease-free survival (DFS) after the operation. OS was assessed as the interval between the date of surgery and the date of death from any cause, loss to follow-up, or last follow-up. DFS was assessed as the interval between the date of surgery and the date of first recurrence, death from any cause, loss to follow-up, or last follow-up. Recurrence was defined as local regional recurrence, lymph node metastasis, or distant metastasis.

Statistical analyses

Survival data were analyzed by the Kaplan-Meier method, while the log-rank method was applied to compare survival curves between groups. Univariate and multivariate analyses of OS and DFS were conducted by Cox regression models with stepwise selection. Fisher's exact test or chi-square test for categorical variables and Student's *t*-test or Wilcoxon-Mann-Whitney test for continuous variables were applied as appropriate. To balance covariates (10), 1:1 propensity score matching (PSM) was performed, with age, gender, tumor location, differentiation, and lymph node dissection being the covariates considered, and the matching tolerance set to 0.1. A two-tailed P value <0.05 was defined as statistically significant. Statistical analysis was performed using the SPSS 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' demographics

From 2008 to 2013 in a total of 387 patients at Sichuan Cancer Hospital with postoperative pathology of pN0 ESCC were included in the overall cohort (*Table 1*). Of the total cohort, 157 patients were in Group S, and 230 patients were in Group S + A. In Group S + A, 196 patients received postoperative chemotherapy and 34 patients received chemoradiotherapy. The covariates of age, sex, and tumor location were unbalanced in the two groups. After PSM, 87 patients were excluded, and the matched cohort included

Table 1 Patients' characteristics before and after PSM

Characteristics	Before PSM						After PSM					
	Total, N=387	Surgery alone		Surgery + adjuvant therapy		P	Total, N=300	Surgery alone		Surgery + adjuvant therapy		P
		N=157	%	N=230	%			N=150	%	N=150	%	
Average age		62.69±8.680		58.56±7.237		<0.001		62.43±8.678		59.09±7.447		<0.001
Age						0.001						0.064
≤60	189	61	38.9	128	55.7		139	61	40.7	78	52.0	
>60	198	96	61.1	102	44.3		161	89	59.3	72	48.0	
Sex						0.029						0.785
Male	307	116	73.9	191	83.0		230	114	76.0	116	77.3	
Female	80	41	26.1	39	17.0		70	36	24.0	34	22.7	
T stage						0.111						0.816
T2	84	40	25.5	44	19.1		76	40	26.7	36	24.0	
T3	287	108	68.8	179	77.8		211	103	68.7	108	72.0	
T4	16	9	5.7	7	3.1		13	7	4.6	6	4.0	
Tumor location						0.002						0.08
Upper	95	57	36.3	48	20.9		88	50	33.3	38	29.3	
Middle	195	74	47.1	121	52.6		145	74	49.3	71	47.3	
Lower	87	26	16.6	61	26.5		67	26	17.4	41	27.4	
Differentiation						0.592						0.923
Well	100	42	26.8	58	25.2		74	37	24.7	37	24.7	
Moderate	165	62	39.4	103	44.8		119	61	40.7	58	38.7	
Poor or unknown	122	53	33.8	69	30.0		107	52	34.6	55	36.7	
Vascular invasion						0.307						0.791
Negative	364	150	95.5	214	93.0		285	143	95.3	142	94.7	
Positive	23	7	4.5	16	7.0		15	7	4.7	8	5.3	
Nerve invasion						0.772						0.202
Negative	352	142	90.4	210	91.3		276	135	90.0	141	94.0	
Positive	35	15	9.6	20	8.7		24	15	10.0	9	6.0	
Average LN dissection		16.58		18.34		0.113		16.55		16.29		0.884
Median LN dissection [range]		14 [0–62]		17 [0–69]				14 [0–62]		14 [0–68]		
Adjuvant therapy												
Chemotherapy				196	85.2					128	85.3	
Chemoradiotherapy				34	14.8					22	14.7	
LN dissections						0.074						0.563
<15	176	80	51.0	96	41.7		157	76	50.7	81	54.0	
≥15	211	77	49.0	134	58.3		143	74	49.3	69	46.0	

PSM, propensity score matching; LN, lymph node.

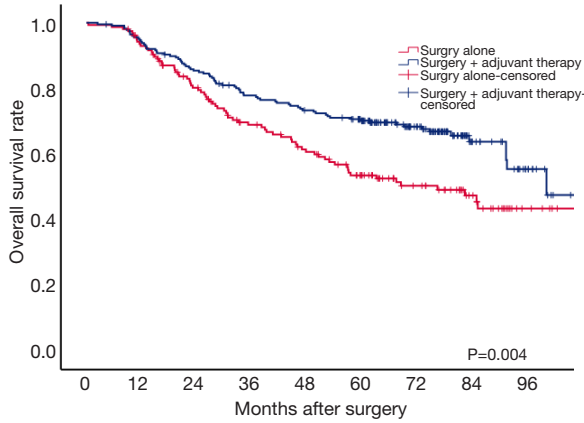

Figure 2 OS between surgery alone and surgery + adjuvant therapy groups before PSM. OS, overall survival; PSM, propensity score matching.

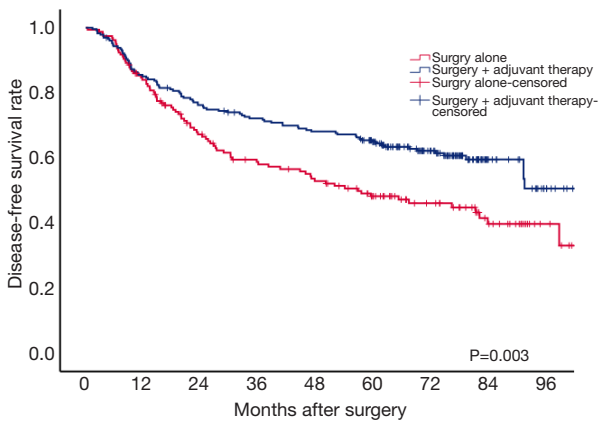

Figure 3 DFS between surgery alone and surgery + adjuvant therapy groups before PSM. DFS, disease-free survival; PSM, propensity score matching.

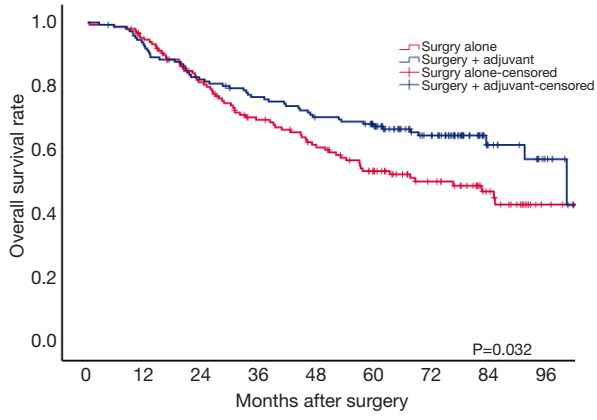

Figure 4 OS between surgery alone and surgery + adjuvant therapy groups after PSM. OS, overall survival; PSM, propensity score matching.

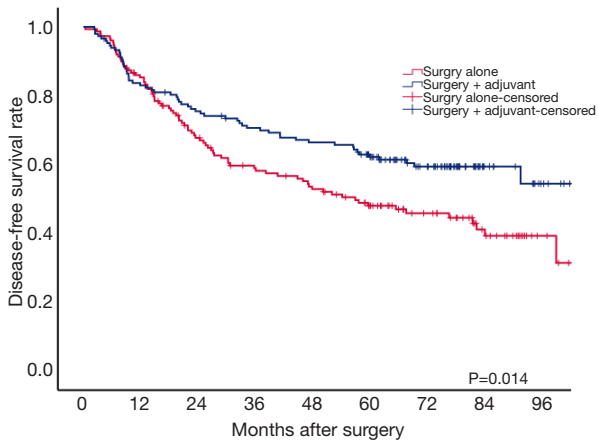

Figure 5 DFS between surgery alone and surgery + adjuvant therapy groups after PSM. DFS, disease-free survival; PSM, propensity score matching.

150 patients in Group S and 150 patients in Group S + A (*Table 1*).

OS and DFS

Across the whole study population, the median follow-up was 75.60 [95% confidence interval (CI): 73.17–78.03] months. The median follow-up was 76.27 (95% CI: 65.44–87.09) months in Group S and 75.6 (95% CI: 73.89–77.31) months in Group S + A. In the overall cohort, 74 patients died in Group S, and 79 in Group S + A; the 3- and 5-year OS rates were 69% and 53.6% in Group S, respectively, which were significantly lower than the OS rates in Group S + A (3-year: 77.9%; 5-year: 70.2%; log-rank χ^2=8.222; P=0.004; *Figure 2*). The 3- and 5-year DFS rates in Group S were 58% and 48.2%, respectively, which were lower than the DFS rates in Group S + A (3-year: 72.2%; 5-year: 64.9%; log-rank χ^2=8.684; P=0.003; *Figure 3*).

In the matched cohort, the 3- and 5-year OS rates were 69.6% and 53.6% in Group S, respectively, which were significantly lower than the OS rates in Group S + A (3-year: 76.7%; 5-year: 67.6%; log-rank χ^2=4.614; P=0.032; *Figure 4*). In Group S, the 3- and 5-year DFS rates were 58.2% and 48%, respectively, which were significantly lower than the DFS rates in Group S + A (3-year: 70.6%; 5-year: 62.6%; log-rank χ^2=6.083; P=0.014; *Figure 5*). In

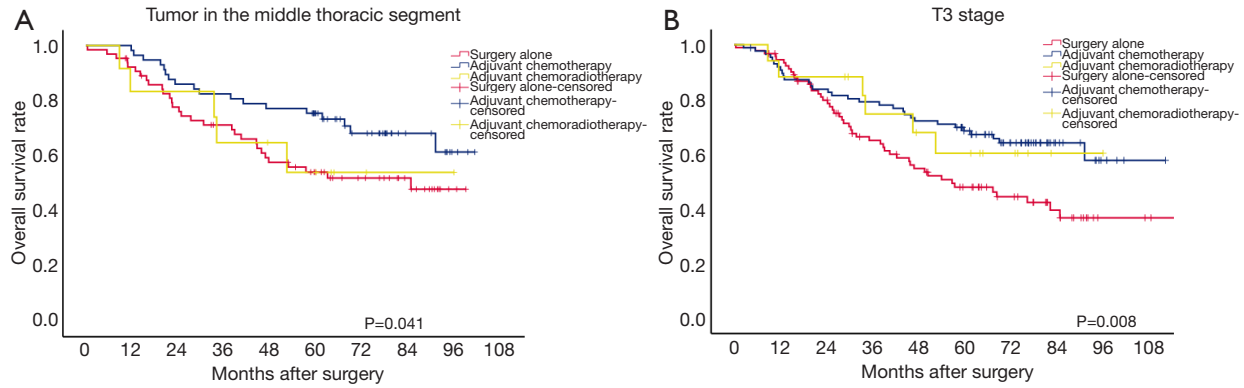

Figure 6 Surgery + adjuvant chemotherapy improved OS in patients with tumor in the middle thoracic segment (P=0.041, A) and T3 stage (P=0.008, B). OS, overall survival.

hierarchical analysis, postoperative chemotherapy prolonged OS in patients with tumors in the middle thoracic segment (P=0.041) and T3 stage tumors (P=0.008) compared with surgery alone (*Figure 6*), but differences were not found between postoperative chemoradiotherapy and surgery alone or postoperative chemotherapy. Compared with surgery alone, postoperative chemotherapy improved DFS in patients with moderate differentiation (P=0.023), tumors in the middle thoracic segment (P=0.028), T3 stage tumors (P=0.004), and <15 lymph node dissections (P=0.038; *Figure 7*), and no significant differences were observed between postoperative and other therapies (surgery alone and postoperative chemotherapy).

Multivariate analysis of DFS

Multivariate analysis was performed in a matched cohort. Time, sex, age, T stage, tumor location, vascular invasion, nerve invasion, histologic differentiation, type of treatment, and lymph node dissection were included in the Cox regression analysis to evaluate the prognostic factors for DFS through calculation of hazard ratios (HRs) and their 95% CIs (*Table 2*). The results showed that postoperative adjuvant chemotherapy was an independent protective factor (HR: 0.571; 95% CI: 0.390–0.836; P=0.004; *Figure 8*), and T3 stage tumors (HR: 1.953; 95% CI: 1.238–3.082; P=0.004) and <15 lymph node dissections (HR: 1.81; 95% CI: 1.238–2.648; P=0.002) were independent risk factors for prognosis.

Discussion

We assessed the value of postoperative adjuvant therapy in patients with pN0 ESCC. The results suggested that postoperative adjuvant therapy prolonged OS and DFS in patients with pN0 ESCC, which is converse to results reported for esophageal adenocarcinoma (11). Univariate analysis of the two groups in the PSM cohort revealed that T3 stage, moderate and poor differentiation, and <15 lymph node dissections were risk factors for prognosis. Moreover, Cox multivariate regression analysis indicated that postoperative adjuvant chemotherapy was an independent protective factor, and T3 tumors and <15 lymph node dissections were independent risk factors for prognosis. We chose DFS as the primary outcome in this study because, after recurrence, patients could be treated with any therapy considered useful. In the comparison of postoperative adjuvant therapy and surgery alone, Yang *et al.* reported that postoperative modified conformal radiotherapy was associated with improvements in both OS and DFS in patients with pT3N0M0 ESCC (12). Another study indicated that radiotherapy and postoperative chemoradiation did not significantly improve DFS and OS (P=0.692; P=0.368) (13), but the study focused on patients with ESCC with positive lymph node(s). Chen *et al.* examined 426 patients and found that postoperative adjuvant chemotherapy did not improve OS, regardless of lymph node metastasis (14), but the authors pointed out the problem of inconsistent chemotherapy regimens. We also found that postoperative adjuvant treatment affected the patient's nutritional status, which in turn affected immune function. A meta-analysis of surgery + adjuvant chemotherapy and surgery alone for patients with resectable thoracic ESCC revealed that postoperative chemotherapy did not

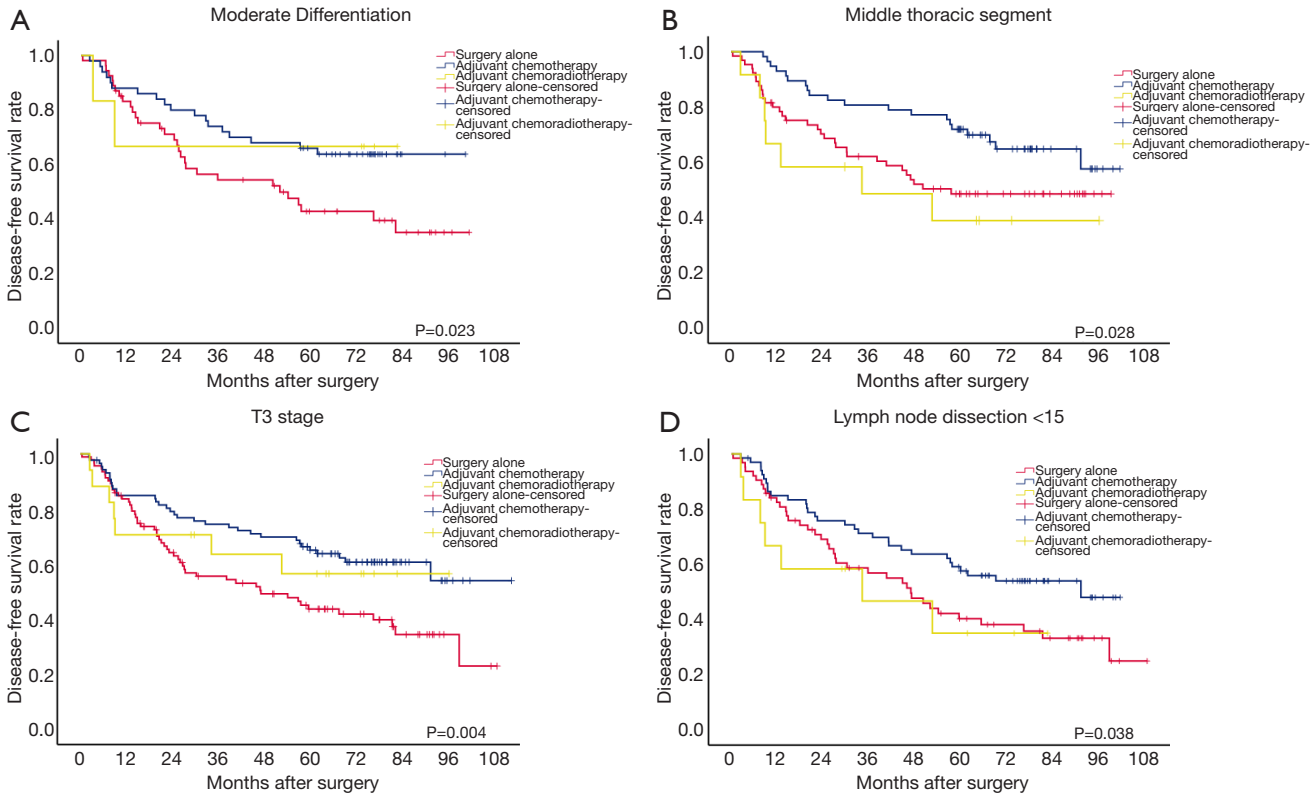

Figure 7 Surgery + adjuvant chemotherapy improved DFS in patients with moderate differentiation (P=0.023, A), tumor in the middle thoracic segment (P=0.028, B), T3 stage tumor (P=0.004, C), and <15 lymph node dissections (P=0.038, D). DFS, disease-free survival.

improve the patient's OS but did extend 1-year DFS (15). A Japanese multicenter randomized controlled trial (JCOG9204) found that postoperative adjuvant therapy alone prolonged 5-year DFS compared with the surgery alone (55% *vs.* 45%; P=0.037) in patients with pN0 ESCC (5). A more remarkable difference was found in patients with pN1 ESCC (P=0.041). The regimen of JCOG9204 was cisplatin and fluorouracil, but the treatment applied to patients was complicated due to individual discrepancies after recurrence. Some study results have supported the JCOG9204 conclusion and indicated that patients with stage III–IV disease can obtain a long-term survival benefit from postoperative chemotherapy (8,9), but this may be a dependent on invasion depth. In a study focusing on patients with stage III disease, Yang *et al.* found that adjuvant therapy improved the OS and DFS of patients with ESCC (16). Further analysis indicated that lesions of the middle thorax and well-differentiated tumors had a longer OS (P<0.05). Additionally, Zhang *et al.* observed that concurrent chemoradiotherapy improved the OS of patients with resectable stage III–IV ESCC (17), but did not examine N0 patients. In Zhang *et al.*'s analysis of patients with pT3N0M0 thoracic ESCC with surgery alone versus those with postoperative adjuvant therapy (chemotherapy/radiotherapy/radiochemotherapy), the results suggested that postoperative adjuvant therapy improves the DFS of these patients; furthermore, postoperative radiotherapy was found to improve DFS in the mid-segment, moderately differentiated, and <15 lymph node dissections subgroups, while multivariate analysis demonstrated that adjuvant radiochemotherapy and female sex can improve survival (7).

There were several limitations to our study that should be noted. First, our study had a retrospective design. Although the PSM procedure can avoid potential biases, unlike in randomized controlled trials, these biases still may not be completely eliminated. Second, this was a single-institution study, and the rate of administration of chemoradiation (n=22) in our cohort was much lower than that of surgery alone (n=150) and postoperative chemotherapy (n=122). Nonetheless, our findings may provide some guidance for

Table 2 Univariate and multivariate Cox analysis of patients after PSM

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age						
<60	1			1		
≥60	0.931	0.667–1.299	0.675	0.925	0.643–1.330	0.673
Sex						
Male	1			1		
Female	0.855	0.570–1.282	0.448	0.925	0.583–1.467	0.74
Tumor location			0.413			
Upper	1					
Middle	1.213	0.807–1.822	0.353			
Lower	1.37	0.857–2.189	0.189			
T stage			0.055			0.015
T2	1			1		
T3	1.675	1.098–2.555	0.017	1.953	1.238–3.082	0.004
T4	1.328	0.511–3.451	0.561	1.444	0.470–4.441	0.521
Differentiation			0.029			0.414
Well	1			1		
Moderate	1.761	1.094–2.832	0.02	1.272	0.805–2.012	0.303
Poor or unknown	1.867	1.157–3.014	0.011	1.466	0.880–2.443	0.142
Vascular invasion						
Negative	1					
Positive	1.578	0.646–3.855	0.317			
Nerve invasion						
Negative	1					
Positive	1.153	0.586–2.267	0.68			
Treatment			0.15			0.015
Surgery alone	1			1		
Surgery + chemotherapy	0.694	0.480–1.004	0.052	0.571	0.390–0.836	0.004
Surgery + chemoradiotherapy	0.913	0.438–1.902	0.808	0.67	0.310–1.450	0.309
LN dissections						
≥15	1			1		
<15	1.935	1.363–2.748	< 0.001	1.81	1.238–2.648	0.002

PSM, propensity score matching; LN, lymph node; HR, hazard ratio; CI, confidence interval.

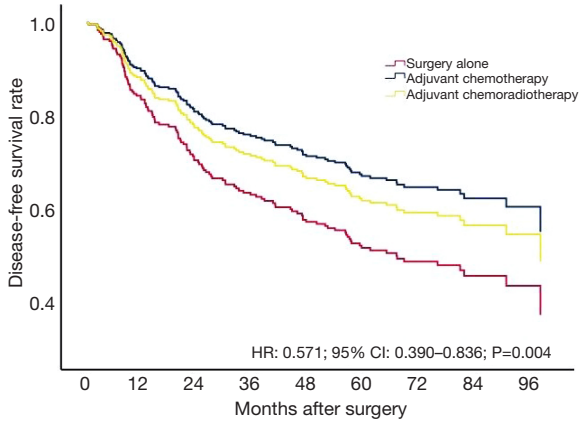

Figure 8 Multivariate analysis of postoperative treatment in the matched cohort across Cox regression. HR, hazard ratio; CI, confidence interval.

clinical work, but more cases and studies are needed to draw more convincing conclusions.

Conclusions

Postoperative chemotherapy significantly improved the OS and PFS of patients with thoracic pN0 ESCC. A future multicenter, randomized controlled clinical trial is warranted to confirm our findings.

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Footnote

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Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-2539

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-2539). 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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Sichuan Cancer Hospital. Informed consent was taken from all the patients.

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