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Role of chemotherapy after curative esophagectomy in squamous cell carcinoma of the thoracic esophagus: A propensity score-matched analysis

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Abstract

Background: The efficacy of postoperative treatment of squamous cell carcinoma of the esophagus has not yet been determined. In this retrospective study, we investigated whether postoperative adjuvant chemotherapy (POCT) confers a survival benefit on patients who undergo curative esophagectomy.

Methods: A total of 782 patients were enrolled in our study. The patients were divided into surgery alone (S) and surgery plus postoperative chemotherapy (S + POCT) groups. Propensity score matching (PSM) was used to eliminate the differences in baseline characteristics. The primary endpoint was overall survival (OS), which was calculated by the Kaplan–Meier method and compared with the log-rank test. A Cox proportional hazards model was used to identify factors influencing the prognosis.

Results: Of 782 patients, 343 (43.9%) underwent S alone, and 439 (56.1%) underwent S + POCT before PSM. The five-year OS rates were 42.3% and 47.8% in the S and S + POCT groups (p = 0.080), respectively. After PSM (296 patients per group), the five-year OS rates were 48.7% and 56.2% in the S and S + POCT groups (p = 0.025), respectively. For different cycles of POCT, patients with more than three cycles had a better survival than those with less than three cycles. The significant predictive factors for OS were pN stage (HR = 1.861, 95% CI: 1.310–2.645, p = 0.001), number of dissected nodes (HR = 0.621, 95% CI: 0.494–0.781, p < 0.001) and POCT received (HR = 0.699, 95% CI: 0.559–0.875, p = 0.002), which were identified by multivariate Cox regression analyses in the matched samples.

Conclusions: POCT appears to improve the OS rate of patients with ESCC after resection, and at least four chemotherapy cycles are necessary. These conclusions warrant further confirmation in large-scale multicenter randomized controlled trials.

KEYWORDS
esophageal squamous cell carcinoma, postoperative adjuvant chemotherapy, metastasis-positive lymph nodes, chemotherapy cycles

INTRODUCTION

Esophageal cancer has a high degree of malignancy and a poor prognosis. The latest epidemiology studies indicate that the incidence and mortality rates of esophageal cancer rank seventh and sixth in the world, respectively.[1] The incidence of esophageal cancer is higher in China due to diet and other factors, and it is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in China, and the vast majority of cases are squamous cell carcinomas.[2] Surgery is still the primary treatment for resectable esophageal cancer, but the overall five-year survival rate is only

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15%–25%, and postoperative recurrence and metastasis in postoperative are the primary causes of poor survival.[3] Therefore, a multimodality therapy for esophageal cancer is needed.

Several large randomized controlled trials have suggested that preoperative chemoradiotherapy can significantly improve the overall survival (OS) of patients.[4–6] As a result, the latest National Comprehensive Cancer Network (NCCN) guidelines have listed it as a standard treatment for locally advanced resectable esophageal squamous cell carcinoma (ESCC). However, neoadjuvant therapy may contribute to subsequent postoperative complications. Kumagai et al.[7] performed a meta-analysis including 23 relevant studies, and found that neoadjuvant chemoradiotherapy increased the risk of postoperative mortality and treatment-related mortality in ESCC. Therefore, postoperative adjuvant therapy should also be considered.

More than 90% of patients with esophageal cancer in China have squamous cell carcinomas.[8] Although no adjuvant treatment is recommended for ESCC after R0 resection according to the NCCN guidelines, many patients still receive postoperative adjuvant chemotherapy (POCT) in China. The use of this treatment is based solely on the experience of the physicians and even the wishes of the patients. Few studies have focused on postoperative adjuvant chemotherapy versus surgery alone, and the results are controversial.[9–11] Hence, we conducted a retrospective study to investigate the effect of POCT on the OS of patients and to further analyze which subgroups of patients were most suitable for POCT.

METHODS

Patients

We selected 782 patients with esophageal cancer who visited the Tianjin Medical University Cancer Institute and Hospital from 2005 to 2015. All patients underwent standard radical esophagectomy. The inclusion criteria included the following: (i) did not accept any neoadjuvant therapy, (ii) pathologically confirmed as squamous cell carcinoma, and (iii) pathologically indicated as R0 resection. Exclusion criteria included the following: (i) pathologically confirmed as adenocarcinoma, small cell carcinoma, or other types of cancer, (ii) accepted postoperative radiotherapy or concurrent chemoradiotherapy, (iii) severe perioperative complications resulting in death, (iv) patients with T4b or M1, or (v) incomplete clinicopathological data or follow-up data. The flowchart of patient enrollment is shown in Figure 1. Approval was obtained from the institutional review board. Informed consent was waived because of the retrospective nature of this study.

Surgery

We selected the appropriate surgical types according to the preoperative evaluation of each patient, and the
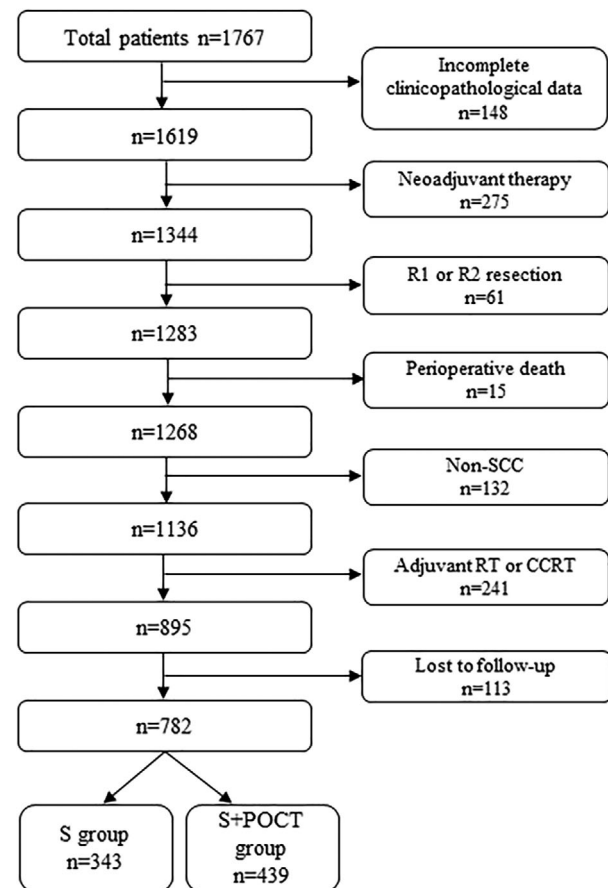

FIGURE 1 Flowchart of patient selection. CCRT, concurrent chemoradiation; POCT, postoperative adjuvant chemotherapy; RT, radiotherapy; S, surgery; SCC, squamous cell carcinoma

surgery was always performed by experienced surgeons in our high-volume center. The majority of patients underwent right thoracotomy ($n = 734$), including the Ivor-Lewis procedure with two incisions, McKeown with three incisions, and left thoracotomy in a small number of patients ($n = 48$). All patients underwent reconstruction of the digestive tract with tubular gastroplasty, and a thoracic drainage tube was routinely placed. The tumor specimens and lymph nodes were dissected for pathological examination, and the eighth edition of the AJCC TNM classification for esophageal cancer was used for defining the pathological stages.[12] The specific operation methods used for surgery were as previously described in the literature.[13–15]

Chemotherapy

All patients ($n = 439$) who received POCT underwent a comprehensive examination prior to chemotherapy to ensure its tolerability, including routine blood tests, coagulation function, liver function, renal function, and electrolytes. Chemotherapy regimens were varied as the role of POCT was controversial during that period. The most frequent

TABLE 1 Clinicopathological characteristics of the patients before and after propensity score matching (PSM)

	Before PSM				After PSM			
	S ($n = 343$)	S + POCT ($n = 439$)	p-value	SD	S ($n = 296$)	S + POCT ($n = 296$)	p-value	SD
Sex			0.846				0.916	
Male	281 (81.9)	362 (82.5)		0.014	241 (81.4)	240 (81.1)		0.007
Female	62 (18.1)	77 (17.5)		0.007	55 (18.6)	56 (18.9)		0.003
Age (years)			<0.001				0.796	
≤65	194 (56.6)	317 (65.3)		0.139	191 (64.5)	194 (65.5)		0.017
>65	149 (43.4)	122 (34.7)		0.111	105 (35.5)	102 (34.5)		0.012
Length of tumor (cm)			0.519				0.723	
<4.5	231 (67.3)	286 (65.1)		0.038	205 (69.3)	201 (67.9)		0.025
≥4.5	112 (32.7)	153 (34.9)		0.027	91 (30.7)	95 (32.1)		0.017
Tumor location			0.971				0.444	
Upper	24 (7.0)	31 (7.1)		0.001	24 (8.1)	32 (10.8)		0.028
Middle	227 (66.2)	287 (65.4)		0.014	196 (66.2)	184 (62.2)		0.067
Lower	92 (26.8)	121 (27.5)		0.009	76 (25.7)	80 (27.0)		0.015
Differentiation			0.968				0.864	
Well	15 (4.4)	19 (4.3)		0.001	12 (4.1)	11 (3.7)		0.004
Moderate	261 (76.1)	331 (75.4)		0.014	228 (77.0)	224 (75.7)		0.027
Poor	67 (19.5)	89 (20.3)		0.009	56 (18.9)	61 (20.6)		0.019
Pathological T stage			0.301				0.793	
T1/T2	111 (32.4)	127 (28.9)		0.042	99 (33.4)	96 (32.4)		0.012
T3/T4a	232 (67.6)	312 (71.1)		0.063	197 (66.6)	200 (67.6)		0.017
Pathological N stage			<0.001				0.867	
N0	214 (62.4)	215 (49.0)		0.201	176 (59.5)	174 (58.8)		0.011
N1–3	129 (37.6)	224 (51.0)		0.180	120 (40.5)	122 (41.2)		0.009
No. of dissected nodes			0.406				0.675	
≤15	136 (39.7)	87 (42.6)		0.037	122 (41.2)	117 (39.5)		0.022
>15	207 (60.3)	252 (57.4)		0.045	174 (58.8)	179 (60.5)		0.027
Eighth TNM stage			<0.001				0.805	
I/II	173 (50.4)	153 (34.9)		0.205	141 (47.6)	144 (48.6)		0.014
III/IV	170 (49.6)	286 (65.1)		0.237	155 (52.4)	152 (51.4)		0.014

Abbreviations: SD, standard deviation; TNM, tumor-node-metastasis.

adjuvant chemotherapy included fluoropyrimidine- plus platinum-based regimen, docetaxel- plus platinum-based regimen, paclitaxel- plus platinum-based regimen, or some irregular regimens.

Follow-up and statistical analysis

All patients were followed up by telephone or by the outpatient service. The median follow-up time was 47.2 months (range 3–136 months). The first follow-up was usually within three months after surgery. Subsequently, it was every three months for the first two years, every half year during the third to fifth year, and then annually thereafter. Routine examination included a physical examination, abdominal ultrasonography, chest and abdominal CT.

The endpoints of our study were three- and five-year OS. OS was defined as the time from the date of surgery to death or the date of the last follow-up. The survival time between the two groups was analyzed using the Kaplan–Meier method, and significance was determined using the log-rank test. Pearson's χ^2 test was used to compare categorical variables. Propensity score matching was performed to eliminate the differences in baseline characteristics between the S group and the S + POCT group. The propensity score was estimated by building a logistic regression model to predict the probability of receiving POCT. We included the following covariates: age, pathological T stage, pathological N stage, number of dissection nodes and TNM stage. Nearest neighbor matching (1:1) was used, with a caliper width equal to 0.2 of the standard deviation. We used standardized differences to assess the degree of balance in the baseline
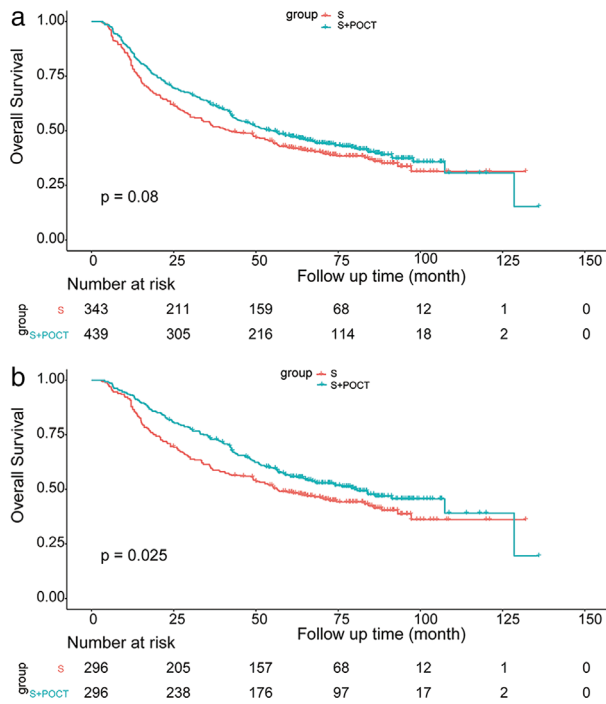
FIGURE 2 Survival curves of overall survival among (a) the entire cohort and (b) among the matched cohort

covariates between the matched groups. A standardized difference of ≤10% denotes a high degree of balance.[16] Cox regression analysis was used in the univariate and multivariate analyses to investigate independent prognostic factors for ESCC. Statistical significance was considered at $p < 0.05$. All statistical analyses were performed with SPSS software, version 25.0.

RESULTS

Patient characteristics

A total of 782 patients were enrolled. The S group consisted of 343(43.9%) patients and there were 439 (56.1%) patients in the S + POCT group. Because of the nature of this retrospective study, the distribution of patient characteristics was not comparable. No significant differences in sex, tumor length, tumor location, degree of tumor differentiation, pathological T stage, or number of lymph nodes dissected were found between the two groups. However, due to the potential bias in the physician's treatment selection, patients in the S + POCT group were younger than those in the S group ($p < 0.001$). In addition, more patients had lymph node involvement in the S + POCT group ($p < 0.001$) than in the S group. Thus, the patients were at the more advanced stages in TNM classifications ($p < 0.001$). Therefore, we used propensity score matching to ensure well-balanced characteristics between the two groups. The clinicopathological characteristics of the patients before and after PSM are summarized in Table 1.

Survivals

In the entire cohort, the three-year OS rates were 53.3% and 61.3% in the S and S + POCT groups, respectively. The five-year OS rates were 42.3% and 47.8% in the S and S + POCT groups, respectively. No statistical significance (log-rank $\chi^2 = 3.069$ $p = 0.080$) was observed between the two groups, although the survival curves did not overlap (Figure 2(a)).

In the matched groups, the respective OS rates at three- and five-years were 60.4% and 48.7% in the S group, as compared with 73.3% and 56.2% in the S + POCT group. The difference between the two groups (log-rank $\chi^2 = 5.014$ $p = 0.025$) was statistically significant (Figure 2(b)).

Univariate and multivariate analyses of the matched groups

We incorporated the variables with p-values less than 0.05 in the univariate analysis into the multivariate Cox proportional hazard models. These variables included pT stage, pN stage, number of dissection nodes, TNM stage, and POCT received. The multivariate Cox regression analyses indicated that POCT received was independently associated with a better OS (HR = 0.699, 95% CI: 0.559–0.875, $p = 0.002$). In addition, pN stage (N0 vs. N1-3, HR = 1.861, 95% CI: 1.310–2.645, $p = 0.001$) and the number of dissection nodes (≤15 vs. >15, HR = 0.621, 95% CI: 0.494–0.781, $p < 0.001$) were also independent factors for OS (Table 2).

Subgroup analyses in the matched groups

We performed subgroup analysis in the matched groups and drew a forest plot (Figure 3). In younger patients (≤65 years), the S + POCT group had better OS rates than the S group ($p < 0.001$). In terms of lymph node involvement, the OS rates were similar between the S and S + POCT groups in patients with N0 disease. However, in patients with N+(N1-N3), the OS rates significantly improved in the S + POCT group ($p < 0.001$). For patients with lymph node dissection greater than 15, no significant difference in OS rates was found between the S and S + POCT groups ($p = 0.310$). For patients with ≤15 lymph nodes dissected, the S + POCT group had significantly better OS rates than the S group ($p = 0.007$). In terms of pathological T stage, patients with advanced T stage (T3/T4a) were more likely to benefit from POCT ($p = 0.004$). In addition, patients with more advanced TNM stage (III/IV) were also likely to benefit from POCT ($p < 0.001$) (Figure 4).

Survival in matched groups according to different chemotherapy cycles

Among 296 patients receiving postoperative chemotherapy in the matched samples, the median number of

TABLE 2 Univariate and multivariate Cox analysis of overall survival in the matched groups (n = 592)

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*-value value	HR (95% CI)	*p*-value value
Sex				
Female	1			
Male	1.322 (0.977–1.789)	0.071		
Age (year)				
≤65	1			
>65	1.185 (0.942–1.490)	0.147		
Length of tumor (cm)				
<4.5	1			
≥4.5	1.155 (0.912–1.463)	0.232		
Tumor location				
Upper	1			
Middle	1.102 (0.739–1.645)	0.634		
Lower	0.813 (0.521–1.268)	0.361		
Differentiation				
Well	1			
Moderate	1.576 (0.810–3.066)	0.180		
Poor	1.382 (0.685–2.790)	0.366		
Pathological T stage				
T1/T2	1		1	
T3/T4a	1.528 (1.190–1.961)	0.001	1.287 (0.977–1.696)	0.073
Pathological N stage				
N0	1		1	
N1–3	2.136 (1.709–2.670)	<0.001	1.861 (1.310–2.645)	0.001
No. of dissection nodes				
≤15	1		1	
>15	0.761 (0.609–0.952)	0.017	0.621 (0.494–0.781)	<0.001
Eighth TNM stage				
I/II	1		1	
III/IV	1.262 (1.168–1.355)	<0.001	1.324 (0.902–1.944)	0.152
POCT received				
No	1		1	
Yes	0.777 (0.622–0.970)	0.026	0.699 (0.559–0.875)	0.002

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; POCT, postoperative chemotherapy.

chemotherapy cycles was five (range 1–12). X-tile software was used to calculate the optimal grouping cutoff points for the number of cycles (Supplement Figure S1). The cutoff point of the cycle was "3", divided into "≤ 3 group" and "> 3 group."[17] The baseline of the patients who received POCT is shown in Table 3, and the baseline was comparable between the two groups. Survival was then analyzed using the Kaplan–Meier method according to different cycle groups. As a result, patients with more than three chemotherapy cycles had significantly better survival (*p* = 0.017) than those with fewer than three chemotherapy cycles (Figure 5).

DISCUSSION

We designed a retrospective study to investigate whether POCT improves OS in ESCC patients, and the results revealed a significant benefit compared with surgery alone. Many previous studies also found that POCT can improve OS, but they were all limited to patients with lymph node positivity or some particular pathological T stage.[18,19] This study should be the first time to show a survival benefit of POCT, regardless of lymph node status or pathological T stage.

The type of multimodality therapy that should be adopted for ESCC has always been a subject of debate.
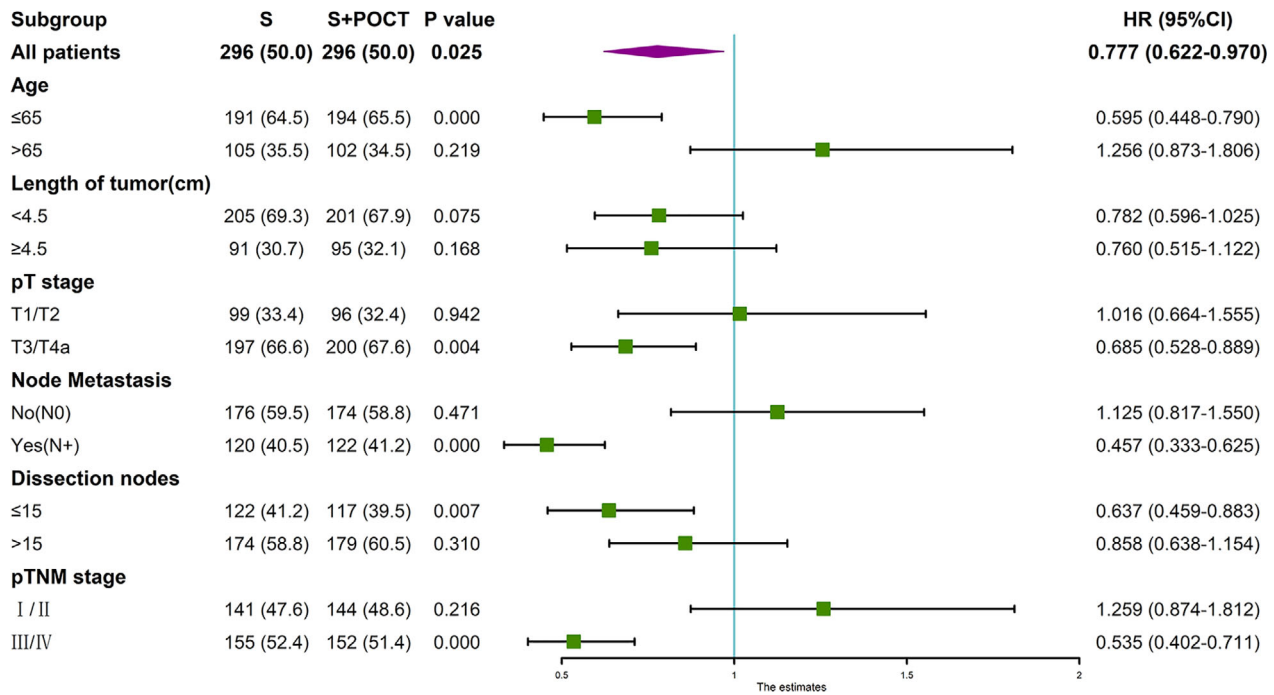
Subgroup	S	S+POCT	P value		HR (95%CI)
All patients	296 (50.0)	296 (50.0)	0.025		0.777 (0.622-0.970)
Age					
≤65	191 (64.5)	194 (65.5)	0.000		0.595 (0.448-0.790)
>65	105 (35.5)	102 (34.5)	0.219		1.256 (0.873-1.806)
Length of tumor(cm)					
<4.5	205 (69.3)	201 (67.9)	0.075		0.782 (0.596-1.025)
≥4.5	91 (30.7)	95 (32.1)	0.168		0.760 (0.515-1.122)
pT stage					
T1/T2	99 (33.4)	96 (32.4)	0.942		1.016 (0.664-1.555)
T3/T4a	197 (66.6)	200 (67.6)	0.004		0.685 (0.528-0.889)
Node Metastasis					
No(N0)	176 (59.5)	174 (58.8)	0.471		1.125 (0.817-1.550)
Yes(N+)	120 (40.5)	122 (41.2)	0.000		0.457 (0.333-0.625)
Dissection nodes					
≤15	122 (41.2)	117 (39.5)	0.007		0.637 (0.459-0.883)
>15	174 (58.8)	179 (60.5)	0.310		0.858 (0.638-1.154)
pTNM stage					
I / II	141 (47.6)	144 (48.6)	0.216		1.259 (0.874-1.812)
III/IV	155 (52.4)	152 (51.4)	0.000		0.535 (0.402-0.711)

FIGURE 3 Forest plot of subgroup analysis

Neoadjuvant therapy has achieved remarkable results and has been widely used in clinical practice.[4,6] However, the tumor volume has been reported to be significantly reduced in many patients who received neoadjuvant therapy, and some even achieved a clinical complete response (CCR). As a result, most patients are no longer willing to undergo surgery. However, the tumor may already have micrometastases that are not visible on imaging.[20] This phenomenon may lead to the recurrence of the tumor, causing the patient to miss their best opportunity for surgery and could affect their survival.[21] In addition, preoperative adjuvant therapy may also increase the occurrence of postoperative complications. Hideo et al. found that neoadjuvant chemotherapy could cause changes in body composition, such as skeletal muscle, body cell mass, and fat-free mass. These changes were related to the incidence of postoperative complications.[22] In addition, postoperative adjuvant therapy also has advantages over preoperative therapy because it is based on accurate pathological staging. Therefore, finding a beneficial postoperative treatment for these patients is essential.

Chemotherapy has long been the classic adjuvant therapy for ESCC. As early as 1992, Sharma et al. performed a preliminary exploration of POCT for squamous cell carcinoma of the esophagus. They concluded that postoperative chemotherapy improves disease-free survival (DFS) and OS. However, the study had a small sample size and no control group; thus, the results were not convincing.[23] To our knowledge, three randomized controlled trials have compared postoperative chemotherapy with surgery alone.[11,24,25] However, none of them demonstrated an increase in OS among the patients who received chemotherapy. The Japan Esophageal Oncology Group has developed two prospective studies on POCT versus surgery alone. One of them was based on two courses of combination chemotherapy with cisplatin and vindesine. The study revealed no significant differences in survival between the two groups ($p = 0.600$), regardless of the state of the lymph nodes.[25] Another study based on two courses of combination chemotherapy with cisplatin and fluorouracil also found no significant differences in OS between the two groups ($p = 0.130$). However, they set the DFS as the primary endpoint, and the results showed that the five-year DFS was 55% in the S group and 45% in the S + POCT group ($p = 0.037$). Therefore, POCT with cisplatin and fluorouracil was better in preventing relapses in patients with ESCC than surgery alone.[11] Xavier et al.[24] performed a multicenter randomized trial to assess the efficacy of 5-fluorouracil and cisplatin therapy after palliative surgical resection of ESCC. The results of this study suggested that postoperative chemotherapy is useless for patients who have not undergone curative resection. Lee et al.[18] conducted a prospective study using a historical surgical control group, focusing on patients with lymph node-positive ESCC. The conclusion was the same as that of the JCOG9204 study; chemotherapy can improve the DFS ($p = 0.049$) but not the OS ($p = 0.228$) of patients.

Lymphatic metastasis is the most common metastatic form of esophageal cancer. As a result of the particularity of esophageal lymphatic reflux, transverse lymphatic vessels and vertical longitudinal lymphatic vessels are present in the submucosa of the esophagus, and the number of longitudinal lymphatic vessels is considerably greater than that of transverse lymphatic vessels.[26] Thus, esophageal cancer may engage in early invasion into the submucosa and form
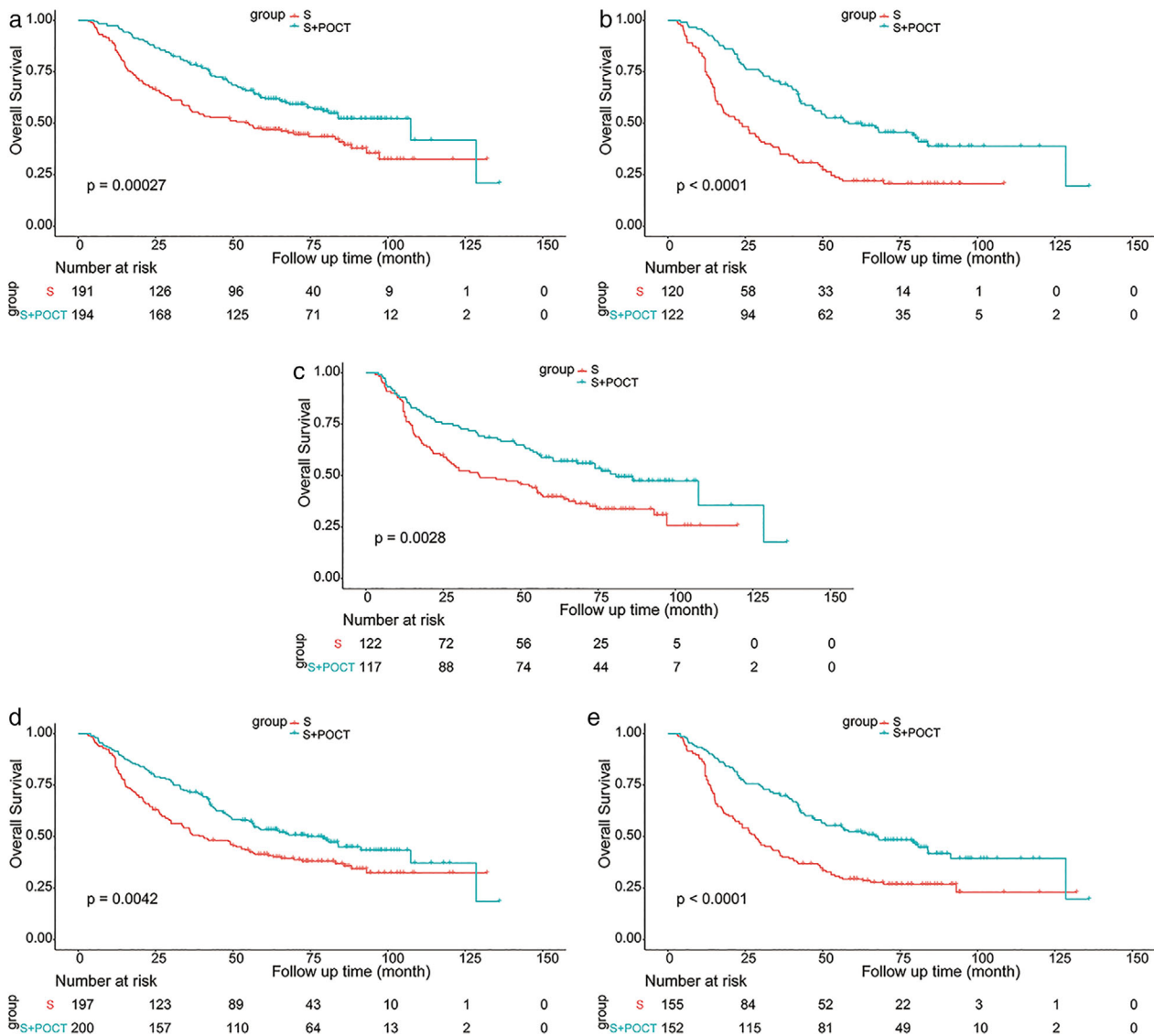
FIGURE 4 Survival curves of subgroups in the matched cohort: (a) overall survival aged younger than 65 years old, (b) overall survival with pN+, (c) overall survival with lymph nodes dissected ≤15, (d) overall survival with T3/T4a, and (e) overall survival with III/IV pStage

extensive lymph node metastases in the chest, abdomen, and neck area. Positive lymph node metastasis is often a factor indicating a poor prognosis,[27] and many trials on POCT versus surgery alone were limited to patients with lymph node positivity. Hashiguchi et al. conducted a retrospective study to explore the efficacy of DCF regimens in patients with ESCC with lymph node metastasis, and the results suggested that OS could be significantly improved.[28] A Chinese study based on cisplatin and paclitaxel chemotherapy regimens was also conducted in patients with lymph node positivity, and the results indicated that the three-year OS of patients in the surgery group was 37.5%, and that of patients in the postoperative chemotherapy group was 55% ($p = 0.013$).[29] Thus, lymph node metastasis of patients with ESCC is a key factor in determining the efficacy of chemotherapy. A subgroup analysis of lymph node metastasis was also performed in our study, and its findings are consistent

with the results of the above studies. Previous randomized controlled trials showed that POCT can improve the DFS of patients; that is, to prevent tumor relapse. Meanwhile, lymph node metastasis is the most common relapse pattern in patients with ESCC. Therefore, chemotherapy can effectively remove residual cancer cells from the body of patients with N+, thus improving their overall survival.

Due to the high incidence of lymph node metastasis of esophageal cancer, standard intraoperative lymph node dissection is an important part of radical resection of esophageal cancer. The NCCN guidelines recommend that at least 15 lymph nodes be removed for patients who have not received preoperative chemoradiotherapy to achieve adequate nodal staging.[30] Previous studies have shown that the number of lymph nodes dissected is an independent prognostic factor for patients after esophagectomy.[31,32] In the present study, patients with more than 15 lymph nodes

TABLE 3 Clinicopathological characteristics of the patients who received postoperative chemotherapy (POCT) in the matched groups (n = 296)

	Cycle		
	≤3 (*n* = 119)	>3 (*n* = 177)	*p*-value
Sex			0.174
Male	92 (77.3)	148 (83.6)	
Female	27 (22.7)	29 (16.4)	
Age (year)			0.081
≤65	71 (59.7)	123 (69.5)	
>65	48 (40.3)	54 (30.5)	
Length of tumor (cm)			0.646
<4.5	79 (66.4)	122 (68.9)	
≥4.5	40 (33.6)	55 (31.1)	
Tumor location			0.624
Upper	14 (11.8)	18 (10.2)	
Middle	70 (58.8)	114 (64.4)	
Lower	35 (29.4)	45 (25.4)	
Differentiation			0.211
Well	3 (2.5)	8 (4.5)	
Moderate	86 (72.3)	138 (78.0)	
Poor	30 (25.2)	31 (17.5)	
Pathological T stage			0.918
T1/T2	39 (32.8)	57 (32.2)	
T3/T4a	80 (67.2)	120 (67.8)	
Pathological N stage			0.053
N0	78 (65.5)	96 (54.2)	
N1–3	41 (34.5)	81 (45.8)	
No. of dissected nodes			0.473
≤15	50 (42.0)	67 (37.9)	
>15	69 (58.0)	110 (62.1)	
Eighth TNM stage			0.330
I/II	62 (52.1)	82 (46.3)	
III/IV	57 (47.9)	95 (53.7)	

Abbreviation: TNM, tumor-node-metastasis.

dissected had a better prognosis (HR = 0.621, 95% CI: 0.494–0.781, *p* < 0.001). In addition, subgroup analysis showed that patients with no more than 15 lymph nodes dissected were more likely to have a survival benefit from chemotherapy. Wang et al. also reached a similar conclusion in a retrospective study of T3N0M0 ESCC patients.[19] Other subgroup analyses showed that patients aged younger than 65 years old were more likely to benefit from POCT. This could be associated with fewer severe chronic diseases and stronger immunity in young patients.[33]

Furthermore, the chemotherapy regimen that should be adopted and the number of cycles of chemotherapy need to be identified. The classic chemotherapy regimen for ESCC is platinum-based regimens. In recent years, many drugs have been proven to be effective in ESCC patients, such as irinotecan, paclitaxel, and docetaxel.[34] However, evidence from large prospective studies is lacking, so it is difficult to determine the best first-line chemotherapy regimen for ECSS patients after curative esophagectomy. A prospective study focusing on the number of chemotherapy cycles for ESCC remains to be conducted, and whether different chemotherapy cycles affect patient survival is unclear. In our study, we performed a simple analysis of the effect of the number of chemotherapy cycles on survival. Relative to the cycle ≤3 group, the cycle >3 group had significantly better OS outcomes. Therefore, patients who can tolerate the adverse reactions of chemotherapy should receive at least four cycles of postoperative chemotherapy. In summary, large-scale randomized multicenter studies in the future should focus on a search for better chemotherapeutic drugs and determine an optimal chemotherapy cycle to unify the standard postoperative chemotherapy regimen for ESCC.

Our study still has many limitations. First, due to the retrospective nature of this study, the clinicopathological data of many patients were incomplete. In addition, we did not obtain full follow-up results from many patients because of the lack of accurate contact information, the patients' families did not cooperate and other reasons. These patients were not included in our study. Thus, selection bias was
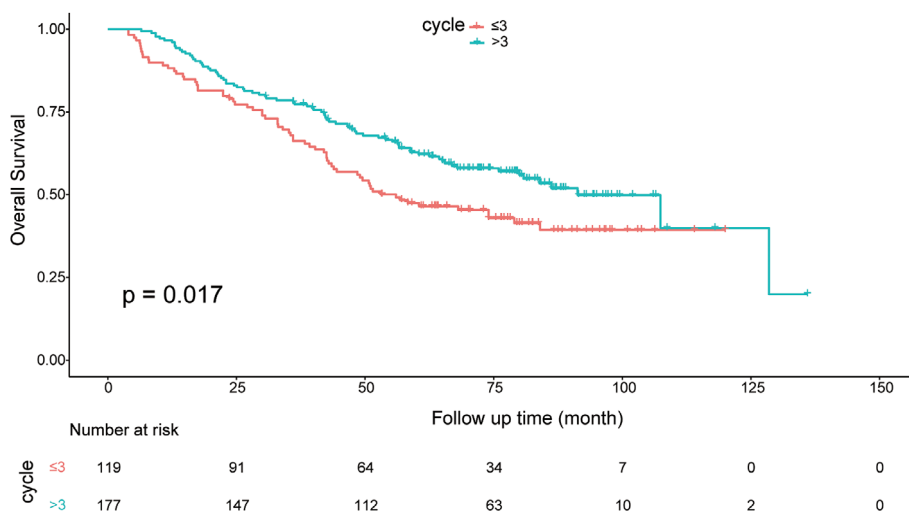

FIGURE 5 Survival curves of overall survival among the matched patients who received POCT according to chemotherapy cycles

present during the enrollment process. Second, data on DFS and toxicity of chemotherapy were not obtained. Therefore, we were unable to confirm whether POCT could improve the DFS of patients or to evaluate the safety of chemotherapy. Third, although a propensity score matching method was used to find balanced groups of patients, some potential factors that influenced survival were still present. Different physicians have different selection criteria for patients receiving chemotherapy and different choices of chemotherapeutic drugs. For example, some physicians select only patients with high-risk features for chemotherapy. This scenario possibly influenced our findings.

In conclusion, postoperative adjuvant chemotherapy conferred a strong survival benefit compared to surgery alone in this single center study. Moreover, at least four cycles of postoperative chemotherapy are necessary. The results need to be further validated in large-scale multicenter randomized controlled trials.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

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REFERENCES
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Lin Y, Totsuka Y, He Y, Kikuchi S, Qiao Y, Ueda J, et al. Epidemiology of esophageal cancer in Japan and China. J Epidemiol. 2013;23(4):233–42.
3. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381(9864):400–12.
4. van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–84.
5. Lv J, Cao XF, Zhu B, Ji L, Tao L, Wang DD. Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. World J Gastroenterol. 2010;16(13):1649–54.
6. Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, et al. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): a phase III multicenter, randomized, open-label clinical trial. J Clin Oncol. 2018;36(27):2796–803.
7. Kumagai K, Rouvelas I, Tsai JA, Mariosa D, Klevebro F, Lindblad M, et al. Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. Br J Surg. 2014;101(4):321–38.
8. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32.
9. Sohda M, Saito H, Kuriyama K, Yoshida T, Kumakura Y, Honjyo H, et al. Post-esophagectomy adjuvant chemotherapy benefits esophageal cancer patients. In Vivo. 2019;33(2):501–6.
10. Lyu X, Huang J, Mao Y, Liu Y, Feng Q, Shao K, et al. Adjuvant chemotherapy after esophagectomy: is there a role in the treatment of the lymph node positive thoracic esophageal squamous cell carcinoma? J Surg Oncol. 2014;110(7):864–8.
11. Ando N, Iizuka T, Ide H, Ishida K, Shinoda M, Nishimaki T, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study—JCOG9204. J Clin Oncol. 2003;21(24):4592–6.
12. Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer. J Thorac Oncol. 2017;12(1):36–42.
13. Visbal AL, Allen MS, Miller DL, Deschamps C, Trastek VF, Pairolero PC. Ivor Lewis esophagogastrectomy for esophageal cancer. Ann Thorac Surg. 2001;71(6):1803–8.
14. McKeown KC. Total three-stage oesophagectomy for cancer of the oesophagus. Br J Surg. 1976;63(4):259–62.
15. Sweet RH. Transthoracic resection of the esophagus and stomach for carcinoma: analysis of the postoperative complications, causes of death, and late results of operation. Ann Surg. 1945;121(3):272–84.
16. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083–107.
17. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res. 2004;10(21):7252–9.
18. Lee J, Lee K-E, Im Y-H, Kang WK, Park K, Kim K, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin in lymph node-positive thoracic esophageal squamous cell carcinoma. Ann Thorac Surg. 2005;80(4):1170–5.
19. Wang Q, Peng L, Li T, Dai W, Jiang Y, Xie T, et al. Postoperative chemotherapy for thoracic pathological T3N0M0 esophageal squamous cell carcinoma. Ann Surg Oncol. 2020;27(5):1488–95.
20. Yanagi M, Sasaki K, Uchikado Y, Omoto I, Arigami T, Kurahara H, et al. Effect of neoadjuvant chemoradiotherapy on lymph node micrometastases in thoracic esophageal cancer. Anticancer Res. 2018;38(2):893–900.
21. Ohkura Y, Shindoh J, Ueno M, Iizuka T, Udagawa H. Comparison of outcome of esophagectomy versus nonsurgical treatment for resectable esophageal cancer with clinical complete response to neoadjuvant therapy. Ann Surg Oncol. 2018;25(8):2428–33.
22. Ida S, Watanabe M, Karashima R, Imamura Y, Ishimoto T, Baba Y, et al. Changes in body composition secondary to neoadjuvant chemotherapy for advanced esophageal cancer are related to the occurrence of postoperative complications after esophagectomy. Ann Surg Oncol. 2014;21(11):3675–9.
23. Sharma S, D'Cruz AK, Kannan R, Vyas JJ. Postoperative adjuvant chemotherapy for operable esophageal cancer: a pilot clinical study. J Surg Oncol. 1992;50(2):101–4.
24. Pouliquen X, Levard H, Hay JM, McGee K, Fingerhut A, Langlois-Zantin O. 5-Fluorouracil and cisplatin therapy after palliative surgical resection of squamous cell carcinoma of the esophagus. A multicenter randomized trial. French Associations for Surgical Research. Ann Surg. 1996;223(2):127–33.
25. Ando N, Iizuka T, Kakegawa T, Isono K, Watanabe H, Ide H, et al. A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus: the Japan Clinical Oncology Group Study. J Thorac Cardiovasc Surg. 1997;114(2):205–9.
26. Wang Y, Zhu L, Xia W, Wang F. Anatomy of lymphatic drainage of the esophagus and lymph node metastasis of thoracic esophageal cancer. Cancer Manag Res. 2018;10:6295.

27. Peyre CG, Hagen JA, DeMeester SR, van Lanschot JJ, Holscher A, Law S, et al. Predicting systemic disease in patients with esophageal cancer after esophagectomy: a multinational study on the significance of the number of involved lymph nodes. Ann Surg. 2008;248(6): 979–85.

28. Hashiguchi T, Nasu M, Hashimoto T, Kuniyasu T, Inoue H, Sakai N, et al. Docetaxel, cisplatin and 5-fluorouracil adjuvant chemotherapy following three-field lymph node dissection for stage II/III N1, 2 esophageal cancer. Mol Clin Oncol. 2014;2(5):719–24.

29. Zhang L, Li W, Lyu X, Song Y, Mao Y, Wang S, et al. Adjuvant chemotherapy with paclitaxel and cisplatin in lymph node-positive thoracic esophageal squamous cell carcinoma. Chin J Cancer Res. 2017;29(2):149–55.

30. Tachimori Y. Pattern of lymph node metastases of squamous cell esophageal cancer based on the anatomical lymphatic drainage system: efficacy of lymph node dissection according to tumor location. J Thorac Dis. 2017;9(S8):S724–S30.

31. Altorki NK, Zhou XK, Stiles B, Port JL, Paul S, Lee PC, et al. Total number of resected lymph nodes predicts survival in esophageal cancer. Ann Surg. 2008;248(2):221–6.

32. Peyre CG, Hagen JA, DeMeester SR, Altorki NK, Ancona E, Griffin SM, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248(4):549–56.

33. Zou B, Tu Y, Liao D, Xu Y, Wang J, Huang M, et al. Radical esophagectomy for stage II and III thoracic esophageal squamous cell carcinoma followed by adjuvant radiotherapy with or without chemotherapy: which is more beneficial? Thorac Cancer. 2020;11(3):631–9.

34. Tomasello G, Ghidini M, Barni S, Passalacqua R, Petrelli F. Overview of different available chemotherapy regimens combined with radiotherapy for the neoadjuvant and definitive treatment of esophageal cancer. Exp Rev Clin Pharmacol. 2017;10(6):649–60.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.