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Number of Resected Lymph Nodes and Survival of Patients with Locally Advanced Esophageal Squamous Cell Carcinoma Receiving Preoperative Chemoradiotherapy

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Abstract. *Background: The association of extended lymph node (LN) dissection with improved outcomes in patients with locally advanced esophageal squamous cell carcinoma (ESCC) who received preoperative chemoradiotherapy (CRT) followed by surgery is debatable. Patients and Methods: We reviewed data from patients with esophageal cancer enrolled in three phase II clinical trials of preoperative paclitaxel and cisplatin-based CRT during 2000-2012. Patients with ESCC who underwent planned esophagectomy were enrolled. The number of resected LNs and other clinicopathological factors were analyzed regarding their impact on progression-free (PFS) and overall (OS) survival using Cox proportional hazards model. Results: In total, 139 patients were included. The median PFS and OS were 24.4 and 31.8 months, respectively. The median number of resected and positive LNs were 19 (range=2-96) and 0 (range=0-9), respectively. The mean number of positive LNs did not differ significantly among quartile groups of total resected LNs (quartile 1: 2-12, 2: 13-19, 3: 20-29, and 4: 30-96). The resected LN number analyzed as dichotomies divided by the median or as continuous variables was not associated with PFS or OS. However, in an exploratory analysis, patients of quartiles 2 and 3 had longer PFS and OS than those with quartiles of 1 and 4 in multivariate analysis (p=0.019 and 0.005, respectively). Conclusion: Although extensive LN dissection was not associated with improved survival, resection of 13-29 LNs was associated with improved survival in patients with locally advanced ESCC receiving preoperative paclitaxel and cisplatin-based CRT.*

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Esophageal cancer is a malignancy with high lethality. More than 450,000 new cases and more than 400,00 deaths were attributed to esophageal cancer worldwide in 2012. Esophageal adenocarcinoma (EAC) is major type of esophageal cancer in Western countries, whereas esophageal squamous cell carcinoma (ESCC) is predominant in Eastern countries (1). EAC and ESCC are distinct disease entities with different risk factors, genetic changes, and geographical distributions (2-4).

Preoperative chemoradiotherapy (CRT) followed by surgery has become one of the most commonly used treatment modalities for patients with locally advanced esophageal cancer (5-7). The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial, a phase III study for patients with resectable esophageal

cancer, demonstrated a significant survival benefit of preoperative paclitaxel and carboplatin-CRT followed by surgery compared to surgery alone (8). In the subgroup analysis of the CROSS trial, the median overall survival (OS) improved from 21.1 months [95% confidence interval (CI)=15.4-26.7 months] in the group treated with surgery alone to 81.6 months (95% CI=47.2-116.0 months) in the preoperative CRT group for patients with ESCC, with a hazard ratio (HR) of 0.48 (95% CI=0.28-0.83) (9).

Studies have identified several prognostic factors, including pathological complete response (pCR), pathological stage, and microscopically free surgical margin, for patients with esophageal cancer receiving preoperative CRT (10, 11). The prognostic effect of the number of resected lymph nodes (LNs) on patients with esophageal cancer has been a topic of ongoing investigation. Two retrospective studies on patients with esophageal cancer undergoing surgery alone demonstrated that the number of resected LNs is an independent prognostic factor for survival (12, 13), and one retrospective study identified at least 15 resected LNs to be required for adequate staging for patients with esophageal cancer undergoing surgery with or without preoperative CRT (14). Another retrospective study demonstrated a higher number of resected LNs (more than 30) to be associated with best outcome for patients with esophageal cancer undergoing surgery with or without adjuvant radiotherapy (15). By contrast, a retrospective study on patients with esophageal cancer receiving preoperative CRT followed by surgery, with EAC as the predominant histology, showed the number of resected LNs not to be associated with survival (16). Two recent *post hoc* retrospective analyses of CROSS trial and Francophone de Cancérologie Digestive (FFCD) 9901 trial (another phase III trial evaluating preoperative CRT focusing on patients with clinical stage I and II esophageal cancer) have demonstrated that the number of resected LNs is not associated with the survival of patients with esophageal cancer receiving preoperative CRT (17, 18). Moreover, a nationwide population-based study in Sweden indicated that more extensive lymphadenectomy during surgery for esophageal cancer does not improve survival (19).

Most of the aforementioned studies addressed the prognostic impact of the number of resected LNs in patients with esophageal cancer of both histological types, *i.e.* EAC and ESCC. To evaluate the prognostic impact of the number of resected LNs in patients with ESCC receiving preoperative CRT, we conducted the current study by reviewing a relatively large patient cohort treated with preoperative paclitaxel and cisplatin (TP)-based CRT followed by surgery.

Patients and Methods

Clinical trials for locoregional esophageal cancer. Between March 2000 and March 2012, three prospective phase II trials for locally advanced esophageal cancer patient cohort were conducted at the National Taiwan University Hospital (NTUH), Taipei, Taiwan. Patients enrolled in the three phase II trials were required to have locally advanced esophageal cancer with clinical stages of T3N0M0, T1-3N1M0, or M1a (celiac and supraclavicular lymphadenopathy for upper thoracic and lower thoracic esophageal cancer, respectively), according to the sixth edition of the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) staging system (20). In all three studies, patients underwent clinical staging workup through esophagogastroduodenoscopy (EGD), computed tomography (CT), endoscopic ultrasonography, and bronchoscopy. For clinical staging workup, fluorodeoxyglucose positron emission tomography was optional for one phase II trial initiated in March 2000, but mandatory in the other two studies.

The inclusion and exclusion criteria of the three phase II trials have been reported previously (21-23). Briefly, patients were required to have good performance status [Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2]; appropriate hematological, hepatic and renal functions; and no distant metastasis. Written informed consent had to be obtained from all participants. All three studies were approved by the Institutional Research Ethics Committee of NTUH (900603, 200707051M, and 200803088M).

Treatment and follow-up. All patients received preoperative TP-based CRT with a radiation dose of 40 Gy in 20 fractions, followed by esophagectomy planned 4-6 weeks after completing the preoperative CRT. Operative methods included open surgery or video-assisted thoracic surgery. No preplanned adjuvant therapy was administered.

All CRT regimens were based on the TP combination. For the first phase II trial, the TP-CRT regimen was the twice weekly administration of TP (35 mg/m^2 paclitaxel on Monday and Thursday and 15 mg/m^2 cisplatin on Tuesday and Friday) plus 40-Gy radiation in 20 fractions (21). For the second trial, the regimen included the aforementioned TP-CRT regimen along with cetuximab administered at a loading dose of 400 mg/m^2, followed by 250 mg/m^2/week cetuximab in four doses (22). For the third trial, the regimen included the aforementioned TP-CRT regimen, preceded by a cycle of induction chemotherapy with TP plus 24-h infusion of high-dose 5-fluorouracil and leucovorin (TP-HDFL) (23).

Follow-up after TP-based CRT and surgery was conducted as follows: During the first 3 years, patients underwent clinical follow-up every 2-3 months and imaging studies including EGD, CT, and additional studies for symptomatic lesions every 4 months; during the fourth and fifth years, patients underwent clinical follow-up every 3 months and imaging studies every 6 months.

Cohort of this study. The patient cohort of our study was retrospectively identified from the three aforementioned phase II trials (21-23). We specifically analyzed the prognostic impact of the number of resected LNs during esophagectomy only in patients with locally advanced ESCC receiving preoperative CRT; hence from the current analysis we excluded patients who were had adenocarcinoma histology, had developed progressive disease during or after preoperative CRT, did not receive planned esophagectomy, and had initial distant metastatic disease. The seventh edition of the AJCC TNM staging system was used for pathological staging (24). The present study was approved by the Institutional Research Ethics Committee of NTUH.

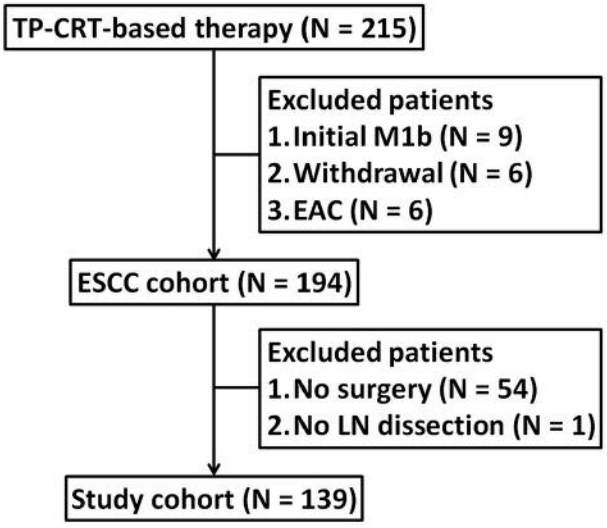

Figure 1. *Study cohort. TP-based CRT: Paclitaxel and cisplatin-based chemoradiotherapy regimen; EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; LN: lymph node.*

Statistical analysis. Follow-up data were compiled until December 31, 2015, as the cutoff date. The primary endpoint was whether the number of resected LNs predicted the prognosis of patients with locally advanced ESCC receiving preoperative TP-based CRT followed by surgery. Descriptive statistics were used for the clinicopathological characteristics. Analysis of variance (ANOVA) was used to compare the mean number of positive LNs between quartiles of the number of resected LNs. Linear regression was used to determine the correlation between the numbers of positive LNs and resected LNs. Progression-free survival (PFS) was defined from the date of enrollment to the date of progression, death from any cause, or the final follow-up date (censored). OS was defined from the date of enrollment to the date of death or final follow-up (censored). Univariate Cox proportional hazards model was used to analyze the clinicopathological factors and number of resected LNs as dichotomies divided by the median LN number of 19 or specific LN number such as 15 (14) and 23 (12), as quartiles (19), or as continuous variables (every 10 additionally resected nodes) (17) for PFS and OS according to the previously published reports. Statistically significant variables ($p \leq 0.05$) were used for multivariate analysis by Cox proportional hazards model for PFS and OS thereafter. The survival curves were analyzed using the Kaplan–Meier (KM) method and compared with log-rank test. All data analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics. In total, 215 patients were enrolled in all three studies; 139 were included in the present study (Figure 1). The clinicopathological characteristics of the study cohort are summarized in Table I. Their median age was 53.8 (range=34.3-74.3) years; 131 (94.2%) patients were men, and 132 (95.0%) had an ECOG PS of 0-1. The clinical stage, according to the sixth edition of the AJCC TNM staging system, was stage III or IVA for most patients of this study cohort (93.5%).

Table I. *Patients clinicopathological characteristics.*

Clinicopathological characteristic	(N=139)
Age, years (<65/≥65)	123/16
Median (range)	53.8 (34.3-74.3)
Gender: Male/female	131/8
ECOG PS: 0-1/2	132/7
Clinical T[a]: 2/3/4	4/133/2
Clinical N[a]: 0/1	8/131
Clinical M1a[a]: –/+	129/10
Clinical stage: IIA and IIB/III/IVA	9/120/10
Primary site: C and U/M/L	38/68/33
Albumin: <4 g/dl/≥4 g/dl/missing	23/112/4
WBC/μl: <10,000/≥10,000/missing	109/26/4
Operation method: Open/VATS	50/89
Median days from radiation completion to surgery (range)	44 (18-98)
Elective nodal irradiation: –/+/missing	26/110/3
Preoperative therapy protocol: TP-CRT/Cetuximab/TP-HDFL	56/37/46
Pathological T[b]: 0 or Tis/1/2/3/NA	57/18/29/31/4
Pathological N[b]: 0/1/2/3	100/26/12/1
Median no. of resected lymph nodes (range)	19 (2-96)
Margin: free/close (≤1 mm or involved)	126/13
Extranodal extension: Negative/positive	124/15
Lymphovascular or perineural invasion: Negative/positive	123/16
pCR: No/yes	91/48

[a]According to the 6th American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system (20); [b]according to 7th AJCC TNM staging system (24); C: cervical; U: upper thoracic; M: middle thoracic; L: lower thoracic; WBC: white cell count, VATS: video-assisted thoracoscopic surgery; TP-CRT: chemoradiotherapy with twice weekly paclitaxel and cisplatin; Cetuximab: cetuximab plus TP-CRT; TP-HDFL: one cycle induction chemotherapy with paclitaxel and cisplatin plus 24-h infusion of high-dose 5-fluorouracil and leucovorin followed by TP-CRT; pCR: pathological complete remission (no residual invasive tumor cell in primary site and resected lymph nodes).

About two-thirds of the patients underwent video-assisted thoracoscopic surgery (64.0%), whereas the remaining patients underwent open surgery. The median duration from radiation completion to surgery was 44 (range=18-98) days. R0 resection was achieved in 90.6% of the patients. Pathological staging of the resected specimens after preoperative CRT was performed according to the seventh edition of the AJCC TNM staging system. Approximately one-third of patients (34.5%) achieved pCR, defined as no residual invasive tumor cell in primary site and dissected LNs.

Number of resected and positive LNs. The distribution of the number of resected LNs is presented in Figure 2A. The

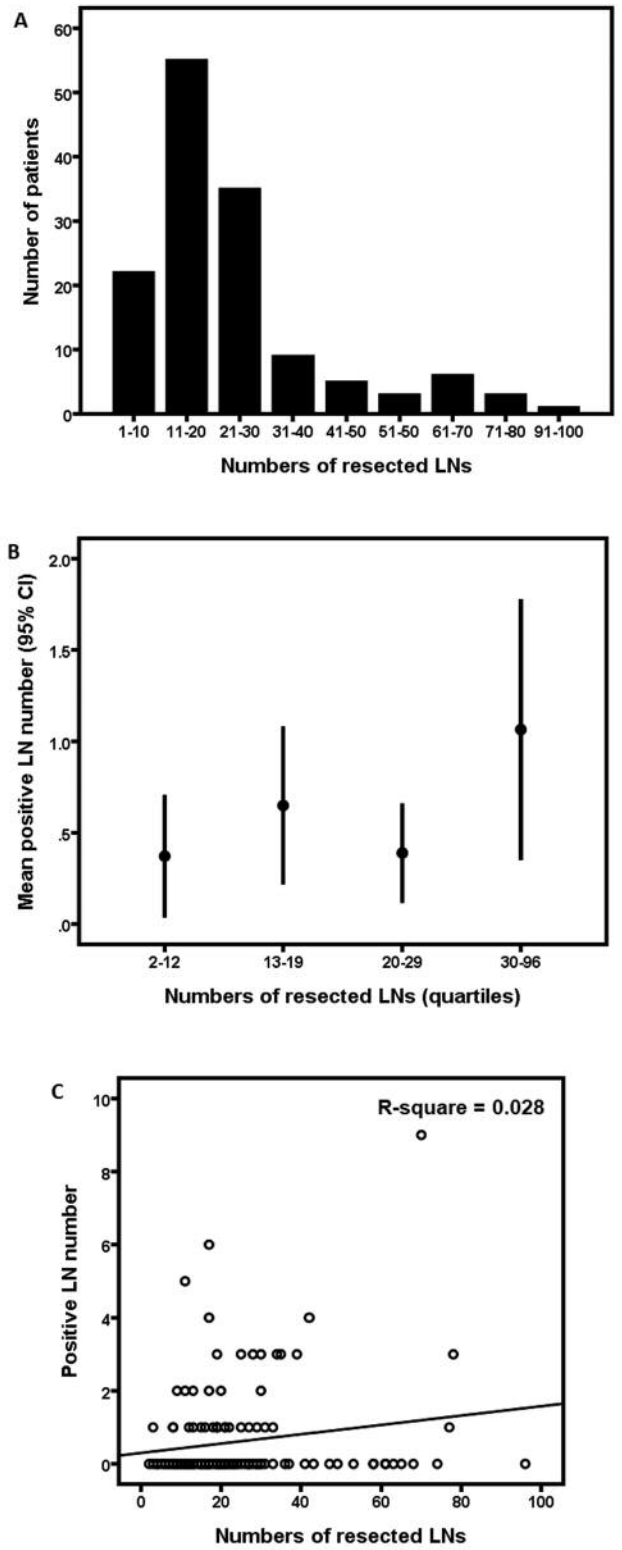

Figure 2. *A: Distribution of the number of resected lymph nodes (LNs). B: Mean positive LN number [with 95% confidence interval (CI)] in quartiles of total resected LNs. C: Association between the number of positive LNs and resected LNs through linear regression.*

median number of resected LNs was 19 (range=2-96). The mean numbers of positive LNs by quartiles are shown in Figure 2B; the numbers did not differ significantly among the four quartiles (p=0.116). Linear regression revealed extremely low positive correlation between the number of positive LNs and number of resected LNs (R2=0.028, Pearson correlation coefficient=0.168, p=0.048; Figure 2C).

Univariate analysis of the number of resected LNs and survival. The median PFS and OS of the entire study cohort were 24.4 (95% CI=16.1-32.8) and 31.8 (95% CI=21.2-42.4) months, respectively. The PFS and OS curves for the entire study cohort, assessed through the KM method, are shown in Figure 3A and B, respectively.

The univariate analysis of the association of clinicopathological factors and the number of resected LNs with PFS is summarized in Table II. Sex (p=0.045), ECOG PS (p=0.001), primary site (p=0.005), pathological T (p=0.004) and N (p<0.001) stages, extranodal extension (ENE; p<0.001), and pCR (p=0.002) were significant prognostic factors for PFS. The number of resected LNs was not associated with PFS no matter whether analyzed as dichotomies divided by the median, as dichotomies divided by a specific number of LNs such as 15 and 23 (12, 14), or as a continuous variable. Further analysis was conducted on the number of resected LNs divided into quartiles. The median PFS was 13.7, 39.9, 27.2, and 11.8 months for patients with number of resected LNs of quartile 1 to 4, respectively (p=0.123) (Figure 3C). Because patients of LN quartiles 2 and 3 had numerically longer PFS than those of quartiles 1 and 4, we thus conducted an exploratory analysis comparing quartiles 2 and 3 (LN number=13-29) as a group with quartiles 1 and 4 (LN number <13 and >29) as a group. It showed belonging to quartile 2 or 3 was associated with significantly better PFS in univariate analysis (p=0.020) (Figure 3E).

In univariate analysis on OS, ECOG PS (p=0.001), primary site (p=0.025), pathological N stage (p<0.001), ENE (p=0.011), and pCR (p=0.004) were significant prognostic factors. The number of resected LNs when analyzed as dichotomies or as continuous variables were not associated with patient OS. However, the median OS differed significantly by LNs quartile: with 20.6, 69.2, 41.2 and 19.2 months for quartiles 1 to 4, respectively (p=0.050) (Figure 3D). An additional analysis also showed that belonging to quartile 2 or 3 was statistically significantly associated with better OS in univariate analysis (p=0.006) (Figure 3F).

Multivariate analysis of the number of resected LNs and survival. The clinicopathological factors that were significantly associated with PFS or OS in univariate analysis, including the number of resected LNs in quartiles (quartiles 2 and 3 *versus* quartiles 1 and 4), were further analyzed for their prognostic significance by multivariate

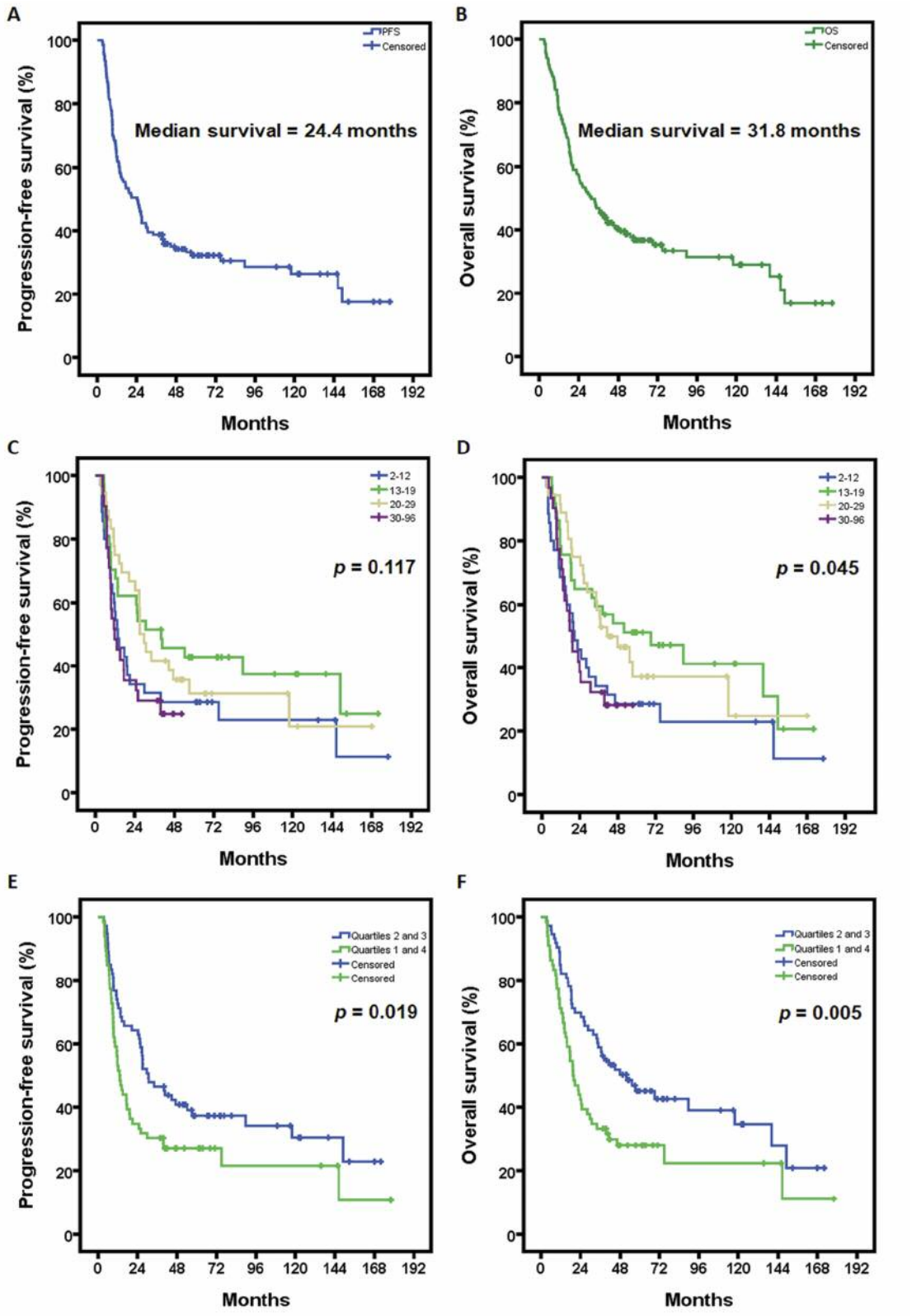

Figure 3. *Kaplan–Meier method-based curves for progression-free survival (A, C, E) and overall survival (B, D, F) for the entire study cohort (A, B), and according to number of resected lymph nodes as quartiles (1: 2-12, 2: 13-19, 3: 20-29, 4: 30-96) (C, D), and patients of quartiles 2 and 3 compared with quartiles 1 and 4 (E, F).*

Table II. *Univariate and multivariate analyses of progression-free survival and overall survival (Cox proportional hazards model).*

	Univariate						Multivariate					
	Progression-free survival			Overall survival			Progression-free survival			Overall survival		
Variable	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Gender												
Female	1.00			1.00			1.00			1.00		
Male	3.26	1.03-10.32	0.045	2.23	0.81-6.08	0.119	2.42	0.74-7.87	0.142	1.59	0.56-4.46)	0.383
ECOG PS												
0-1	1.00			1.00			1.00			1.00		
2	3.68	1.68-8.07	0.001	3.98	1.81-8.75	0.001	7.12	2.72-18.61	<0.001	6.44	2.44-17.03	<0.001
Primary site			0.005			0.025			0.017			0.117
C and U	1.00			1.00			1.00			1.00		
M	0.47	0.29-0.74	0.001	0.52	0.32-0.83	0.007	0.47	0.28-0.79	0.004	0.58	0.35-0.98	0.040
L	0.77	0.45-1.30	0.327	0.71	0.41-1.24	0.231	0.66	0.37-1.17	0.154	0.68	0.37-1.25	0.213
Pathological AJCC7th T			0.004			0.113			0.049			0.130
0 or Tis	1.00			1.00			1.00			1.00		
T1	1.29	0.68-2.44	0.441	1.30	0.68-2.49	0.420	1.25	0.64-2.43	0.518	1.31	0.67-2.56	0.427
T2	1.65	0.96-2.82	0.069	1.48	0.85-2.59	0.171	1.78	1.00-3.16	0.051	1.65	0.90-3.04	0.105
T3	2.07	1.24-3.46	0.006	1.91	1.13-3.23	0.016	2.10	1.21-3.67	0.009	1.94	1.10-3.42	0.023
Pathological AJCC7th N			<0.001			<0.001			0.130			0.026
0	1.00			1.00			1.00			1.00		
N1	1.52	0.92-2.52	0.101	1.22	0.71-2.09	0.471	1.00	0.52-1.92	0.987	0.82	0.41-1.64	0.567
N2	3.77	2.00-7.09	<0.001	4.09	2.16-7.74	<0.001	2.33	1.11-4.87	0.025	2.75	1.30-5.79	0.008
N3	7.18	0.96-53.66	0.055	9.88	1.30-75.06	0.027	0.95	0.10-8.65	0.961	2.34	0.25-22.14	0.458
Extranodal extension												
Negative	1.00			1.00			1.00			1.00		
Positive	3.30	1.87-5.81	<0.001	2.22	1.20-4.12	0.011	3.33	1.51-7.34	0.003	2.04	0.86-4.80	0.104
pCR												
Yes	1.00			1.00								
No	2.02	1.28-3.16	0.002	2.00	1.25-3.19	0.004						
No. of resected LNs (median)												
<19	1.00			1.00								
≥19	1.12	0.75-1.68	0.578	1.01	0.67-1.54	0.949						
No. of resected LNs (per 10 additionally resected)	1.03	0.91-1.16	0.702	1.03	0.90-1.17	0.664						
No. of resected LNs (by quartile)			0.123			0.050						
1	1.00			1.00								
2	0.62	0.35-1.08	0.088	0.56	0.32-0.99	0.047						
3	0.71	0.41-1.22	0.209	0.62	0.35-1.09	0.097						
4	1.14	0.65-2.00	0.653	1.12	0.63-1.99	0.689						
No. of resected LNs												
Quartiles 2 and 3	1.00			1.00			1.00			1.00		
Quartiles 1 and 4	1.60	1.08-2.39	0.020	1.78	1.18-2.68	0.006	1.83	1.16-2.89	0.009	1.83	1.15-2.92	0.011

ECOG PS: Eastern Cooperative Oncology Group Performance Status; AJCC: American Joint Committee on Cancer (24); C: cervical, U: upper thoracic, M: middle thoracic, L: lower thoracic; pCR: pathological complete remission (no residual invasive tumor cell in primary site and resected lymph nodes); LNs: lymph nodes. LN quartiles: 1: 2-12, 2: 13-19, 3: 20-29, 4: 30-96.

analysis. We found that ECOG PS ($p<0.001$), primary site ($p=0.017$), pathological T stage ($p=0.049$), ENE ($p=0.003$), and the number of resected LNs in quartiles (quartiles 2 and 3 *versus* quartiles 1 and 4) ($p=0.009$) were significant independent prognostic factors for PFS. We also found ECOG PS ($p<0.001$), pathological N stage ($p=0.026$), and the number of resected LNs in quartiles (quartiles 2 and 3 *versus* quartiles 1 and 4) ($p=0.011$) were significant independent prognostic factors for OS. The results of multivariate analysis are summarized in Table II.

Discussion

The prognostic impact of extended lymphadenectomy in patients with esophageal cancer remains debatable (25). In the current retrospective study, we analyzed a large ESCC patient cohort from three clinical studies and found that extended lymphadenectomy is not associated with the prognosis of patients with locally advanced ESCC receiving preoperative TP-based CRT followed by esophagectomy. Our findings corroborate those of recent *post hoc* analyses of the CROSS and FFCD 9901 trials, two randomized trials for preoperative CRT in patients with resectable esophageal cancer (17, 18). Thus, preoperative CRT may obviate the benefits of extended lymphadenectomy that has been demonstrated in esophageal cancer patients undergoing surgery alone.

However, in an exploratory analysis of the current study, we demonstrated that patients of LN quartiles 2 and 3 had a more favorable prognosis than those of quartiles 1 and 4 did. Our data showing that patients with fewer than 13 resected LNs had inferior survival are in line with most treatment guidelines supporting that suboptimal lymphadenectomy is not preferred. On the other hand, our data showing that patients with more than 29 resected LNs also had inferior survival imply that the prognostic benefit of extensive lymphadenectomy may plateau at certain level and even be counteracted by other poor prognostic factors associated with extended LN dissection. This inferior OS associated with extensive lymphadenectomy may be the result of the increment of postoperative complications (25, 26), but our data did not show this trend (data not shown). Another potential cause may be that extensive lymphadenectomy is potentially associated with far-advanced locoregional diseases at diagnosis (27).

In the present study, the number of positive LNs, classified as pathological N stage, demonstrated a significant effect on the survival of our patients with ESCC receiving preoperative CRT. This result is consistent with several previous reports, including ours, demonstrating that pathological N-positivity or higher pathological N-stage status is a poor prognostic factor for patients with esophageal cancer receiving preoperative CRT. It also corroborates the results of the *post hoc* analyses of the CROSS and FFCD 9901 trials (17, 18, 28).

In the analysis of the CROSS trial, more extensive lymphadenectomy was associated with a higher number of positive LNs in the group who underwent surgery alone; by contrast, this association was not observed in the preoperative CRT group (17). Our study, which focused only on patients with ESCC who were receiving preoperative CRT, revealed no significant differences in the mean number of positive LNs by quartile of resected LNs (ANOVA, p=0.116). Linear regression showed a very low positive correlation, with the corresponding low R^2 value (0.028), and the Pearson correlation coefficient was only 0.168. In other words, only 2.8% of the positive LNs could be explained by the number of LNs resected, rendering the clinical significance irrelevant.

This study has several limitations. Firstly, it was a retrospective analysis based on three consecutive clinical studies conducted at a single center. Although the three studies employed TP-based CRT as the backbone of the preoperative treatment for ESCC, the preoperative CRT regimens for the three trials varied. There was an association of CRT regimen with the number of resected LNs, *i.e.* the latest conducted TP-HDFL followed by TP-CRT regimen was associated with increased extent of LN dissection; however, the CRT regimens did not have impact on patient survival. Secondly, the enrollment period of the study cohort was long (March 2000-March 2012). During this period, diagnostic procedures, radiation therapy, surgical techniques, and postoperative care for patients with cancer have improved substantially. These differences may have subtly affected the analysis in this retrospective study. Thirdly, our analysis did not consider the extent of locoregional disease at diagnosis. For example, the dimensions of the primary esophageal tumor and extensive LN involvement identified during staging workup may have affected the surgeons' plan for extended lymphadenectomy.

This retrospective analysis found that extended lymphadenectomy was not associated with improved prognosis in patients with locally advanced ESCC receiving preoperative CRT followed by esophagectomy. However, an exploratory analysis identified that resection of 13-29 LNs was associated with improved survival in our studied patient cohort. Future studies are warranted to establish the optimal extent of lymphadenectomy in patients with locally advanced ESCC receiving preoperative CRT.

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