Postchemoradiotherapy Pathologic Stage Classified by the American Joint Committee on the Cancer Staging System Predicts Prognosis of Patients with Locally Advanced Esophageal Squamous Cell Carcinoma

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Introduction: To determine whether the postchemoradiotherapy (post-CRT) pathologic stage predicts the outcomes of patients with locally advanced esophageal squamous cell carcinoma (ESCC) undergoing preoperative CRT followed by surgery.

Methods: From three phase II trials of preoperative CRT for locally advanced ESCC, 140 patients were included. Preoperative CRT comprised twice weekly paclitaxel and cisplatin-based regimens and 40-Gy radiotherapy in 20 fractions. The post-CRT pathologic stage was classified according to the American Joint Committee on Cancer, 7th edition staging system. The prognostic effects of clinicopathologic factors were analyzed using Cox regression.

Results: With a median follow-up of 61.9 months, the median progression-free survival (PFS) and overall survival (OS) of the entire cohort were 24.5 and 30.9 months, respectively. The post-CRT pathologic stage was 0 in 34.5%, I in 12.9%, II in 29.3%, III in 13.6%, and ypT0N1-2 in 6.4% of the patients. The median PFS was 47.2, 25.9, 16.0, 9.4, and 15.1 months, and the median OS was 57.4, 34.1, 26.2, 14.1, and 17.6 months for patients with post-CRT pathologic stage 0, I, II, III, and ypT0N1-2, respectively. In multivariate analysis, performance status ($p < 0.001$), tumor location ($p = 0.016$), and extranodal extension ($p = 0.024$) were independent prognostic factors for PFS, whereas performance status ($p < 0.001$) and post-CRT pathologic stage ($p = 0.027$) were independent prognostic factors for OS.

Conclusions: The post-CRT pathologic stage classified by American Joint Committee on Cancer, 7th edition staging system predicted the survival of locally advanced ESCC patients who underwent preoperative paclitaxel and cisplatin-based CRT followed by esophagectomy.

Key Words: Esophageal neoplasms, Squamous cell carcinoma, Prognosis, Combined modality therapy.

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Esophageal cancer is a highly lethal disease that caused more than 400,000 deaths worldwide in 2008. The two major histology subtypes of esophageal cancer, adenocarcinoma and squamous cell carcinoma, exhibit distinct geographic distributions. Esophageal adenocarcinoma (EAC) is the dominant histology of esophageal cancer diagnosed in Western countries, whereas esophageal squamous cell carcinoma (ESCC) is the prominent subtype in Eastern countries.[1] EAC and ESCC have different risk factors and genetic alterations and are distinct disease entities.[2,3]

Patients with locoregional esophageal cancer have typically been treated with surgery or definitive chemoradiotherapy (CRT); however, only 15% to 25% of them experience long-term, disease-free survival.[4–6] Multimodality therapy, particularly preoperative CRT followed by surgery, has become the research focus for locoregional esophageal cancer since the 1990s. A recent meta-analysis based on 17 randomized trials evaluating the survival effect of preoperative treatment for resectable esophageal cancer revealed that the pooled hazard ratio of preoperative CRT was 0.78 (95% confidence interval [CI]: 0.70–0.88), corresponding to an absolute survival benefit at 2 years of 8.7%. The survival

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benefits for preoperative CRT were similar in EAC and ESCC subtypes.[7] The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS), a large-scale randomized phase III study comparing preoperative paclitaxel and carboplatin-CRT with surgery alone, unequivocally proved a survival benefit of preoperative CRT in locoregional esophageal cancer. The subgroup analysis of the CROSS study revealed that ESCC patients appeared to derive more overall survival (OS) benefit than did EAC patients.[8]

Several prognostic factors, such as pathologic complete response (pCR) and R0 resection, have been identified for patients who received preoperative CRT followed by surgery.[9] However, the prognostic significance of the post-CRT pathologic stage assessed by the often used American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system has been controversial. Two previous United States-based studies enrolled EAC patients predominantly and evaluated the prognostic significance of the post-CRT pathologic stage determined by the 6th edition of the AJCC (AJCC-6). The two studies reported conflicting results.[10,11] No similar studies have since been reported in ESCC patients.

To evaluate the prognostic effect of the post-CRT pathologic stage for ESCC patients, we assessed the post-CRT pathologic stages classified by the AJCC 7th edition staging system (AJCC-7), which was released in 2009 and incorporates a more sophisticated N staging, in a large cohort of ESCC patients who had been treated with preoperative paclitaxel and cisplatin-based CRT followed by surgery for their locally advanced diseases.

PATIENTS AND METHODS

Study Cohort

The study population comprised patients with locally advanced ESCC, retrospectively identified from three prospective phase II studies evaluating the efficacy of preoperative CRT based on a twice weekly paclitaxel/cisplatin regimen, followed by surgery for locally advanced esophageal cancer at National Taiwan University Hospital (NTUH), Taipei, Taiwan between 2000 and 2012. Patients enrolled into the three clinical trials were required to have treatment-naive, pathologically proven, and locally advanced esophageal cancer (stage T3N0 or T1-3N1 in AJCC-6, or selected M1a diseases with primary tumors, involving lymph nodes (LNs) that could be curatively treated using radiation and surgery). Patients underwent esophagogastroduodenoscopy, endoscopic ultrasonography, a computed tomography scan, fluorodeoxyglucose positron emission tomography which was optional for one study and was mandatory in the other two, and bronchoscopy for staging workup. The other inclusion and exclusion criteria of the three phase II studies were similar, including adequate hematological, hepatic, and renal function reserves, no distant metastases, no prior or concomitantly diagnosed malignant diseases including head and neck squamous cell carcinoma, good performance status (Eastern Cooperative Oncology Group- Performance Status [ECOG-PS] 0–2), and written informed consent. This study was approved by the Institutional Research Ethics Committee of NTUH.

Treatment and Follow-Up

The preoperative CRT regimens of the three phase II studies included (1) paclitaxel-cisplatin (TP)-CRT composed of twice weekly paclitaxel and cisplatin, administered as paclitaxel 35 mg/m^2 on Monday and Thursday and cisplatin 15 mg/m^2 on Tuesday and Friday, plus radiation with 40 Gy, administered in 20 fractions, (2) TP-CRT plus cetuximab, administered as 400 mg/m^2 3 to 5 days before the start of CRT followed by 250 mg/m^2/wk for 4 weeks, and (3) one cycle of systemic chemotherapy with TP plus weekly 24h-infusion of high-dose 5-fluorouracil and leucovorin (TP-HDFL) (administered as paclitaxel 80 mg/m^2 on day 1 and day 8, cisplatin 35 mg/m^2 on day 2 and day 9, 5-fluorouracil 2000 mg/m^2 plus leucovorin 300 mg/m^2 24-hour intravenous infusion on day 2 and day 9) followed by TP-CRT starting from day 22 of one-cycle chemotherapy. An esophagectomy plus a 2-field LN dissection was performed 4 to 6 weeks after completing CRT. No further adjuvant therapy was routinely provided. Patients were subsequently followed with regular visits every 2 to 3 months and a periodical survey by esophagogastroduodenoscopy and computed tomography every 4 to 6 months for at least 5 years. The three studies were approved by the Institutional Research Ethics Committee of NTUH and had been previously publicized on ClinicalTrial.gov. The details and results of the studies have been previously published or otherwise presented.[12–14] There are no significant differences in pCR rate, progression-free survival (PFS), and OS among patients of the three treatment groups.

Post-CRT Pathologic Stage

The post-CRT pathologic stage was classified according to the AJCC-7. The pCR was defined as no residual invasive tumor cell in the primary site and dissected LNs. We classified patients into five groups, including pathologic stage 0, stage I, stage II, stage III, and ypT0N1-2 for subsequent prognostic analyses.

Statistical Analysis

The follow-up data were compiled as of December 31, 2013. The primary objective of this study was to determine whether the post-CRT pathologic stage classified by AJCC-7 could predict the prognosis of patients with locally advanced ESCC treated by preoperative paclitaxel and cisplatin-based CRT followed by surgery. OS was defined from the first day of enrolling in clinical studies to the day of death from any cause, or the last follow-up (censored). PFS was defined from the first day of enrolling in clinical studies to the day of recurrence, death from any cause, or the last follow-up without recurrence (censored). Descriptive statistics was used for the baseline clinical characteristics and the post-CRT pathologic findings. Chi-square test was used to examine the difference of clinical factors between study cohort and all ESCC patients group. The Kaplan–Meier method was used to estimate patients' survivals. The association of clinicopathologic variables with PFS or OS was examined univariately by Cox regression. The statistically significant factors found in univariate analysis, defined by p value less than 0.05, were further evaluated for their association with PFS or OS multivariately by Cox regression. We did not

include pCR in the Cox regression model in multivariate analysis because of the inevitably high correlation with the post-CRT pathologic stage according to AJCC-7. All data analyses were performed with SPSS 20.0 (Chicago, IL).

RESULTS

Patient Characteristics

A total of 215 patients with locally advanced esophageal cancer were enrolled into the three phase II studies at our center. Excluding patients with initial M1b stage (n = 9), those who withdrew from the clinical trials (n = 6), and those who exhibited adenocarcinoma in histology (n = 6), we identified 194 patients with ESCC. Among them, 54 patients did not receive planned surgery after completing the initial preoperative CRT and were thus excluded from the analysis. Finally, 140 ESCC patients constituted the study cohort of this report (Fig. 1).

The major clinicopathologic characteristics of the study cohort patients are listed in Table 1. Their median age was 53.4 years (range, 34.3–74.3 yr). The majority were men (94.3%) with good ECOG-PS (0 or 1; 95%). At diagnosis, the clinical stage according to AJCC-6 was stage IIA-B, stage III, and stage IVA in 9 (6%), 121 (87%), and 10 patients (7%), respectively; the primary tumor was located at the cervical and upper esophagus, middle esophagus, and lower esophagus in 39 (28%), 68 (49%), and 33 (23%) patients, respectively. The median duration from completing radiation to surgery was 44 days (range, 18–98 d). No significant differences existed in clinical features between the study cohort (n = 140) and all ESCC patients enrolled in the three phase II trials (n = 194).

TABLE 1. Patient Characteristics

Characteristics	All Patients (N = 194)	Study Cohort (N = 140)	*P* Value
Age, yr (<60/≥60)	130/64	107/33	0.061
Median	55.5	53.4	
Range	34.3–79.6	34.3–74.3	
Sex (male/female)	182/12	132/8	0.858
ECOG-PS (0–1/2)	181/13	133/7	0.518
Clinical T (2/3/4)	4/185/5	4/134/2	0.695
Clinical N (0/1)	15/179	8/132	0.472
Clinical M1a (+/-)	182/12	130/10	0.728
Clinic stage (IIA and IIB/III/IVA)	15/167/12	9/121/10	0.858
Location (C and U/M/L)	60/90/44	39/68/33	0.832
Albumin, g/dL (<4/≥4/missing)	34/156/4	23/113/4	0.818
WBC (<10,000/≥10,000/missing)	156/34/4	110/26/4	0.079
Days from radiation completed to surgery			
Median		44	
Range		18–98	
Preoperative therapy protocol			
TP-CRT	90	57	0.587
Cetuximab/TP-CRT	46	37	
TP-HDFL then TP-CRT	58	46	

C, cervical; U, upper thoracic; M, middle thoracic; L, lower thoracic; WBC, white blood cell count (/μL); TP-CRT, chemoradiotherapy with twice weekly paclitaxel and cisplatin; Cetuximab/TP-CRT, cetuximab plus TP-CRT; TP-HDFL then TP-CRT, one-cycle induction chemotherapy with paclitaxel and cisplatin plus 24-hour infusion of high-dose 5-fluorouracil and leucovorin followed by TP-CRT; ECOG-PS, Eastern Cooperative Oncology Group-performance status.

Post-CRT Pathologic Stage Classified by AJCC-7

The pathologic T0 or Tis, T1, T2, and T3 were found in 41.4%, 12.9%, 20.7%, and 22.1% of the study cohort, respectively. Four patients had a residual primary tumor, but the pathologic T stage could not be classified. The median number of LN dissections was 19 (range, 2–96). One patient who underwent curative esophagectomy without LN dissection was designated as not analyzable because of the importance of pathologic N stages. The pathologic N0, N1, N2, and N3 were identified in 70.7%, 19.3%, 8.6%, and 0.7% of the study cohort, respectively. Nine percent of patients had a positive or close (≤1 mm) margin. Extranodal extension (ENE) was identified in 10.7% of the patients. Lymphovascular or perineural invasion was observed in 11.4% of the patients. The pCR to preoperative CRT (i.e., post-CRT pathologic stage ypT0 or TisN0) was observed in 48 patients (34.3%). The post-CRT pathologic findings are summarized in Table 2.

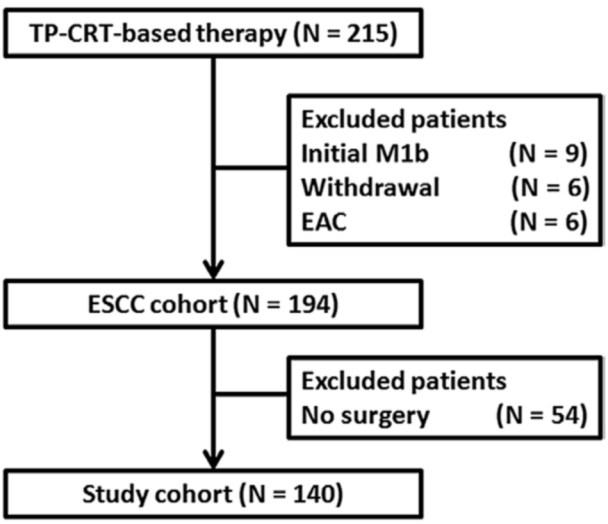

FIGURE 1. Study cohort. TP-CRT, chemoradiotherapy with twice weekly paclitaxel and cisplatin; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

Survival Analysis

After the median follow-up of 61.9 months (range, 24.7–167.8 mo), the median PFS of all patients was 24.5 months. For patients with pathologic T0 or Tis, T1, T2, and T3, the median PFS was 39.6, 29.3, 12.2, and 11.3 months, respectively ($p = 0.051$). The median PFS for patients with pathologic N0, N1, N2, and N3 was 28.3, 15.1, 8.6, and 6.9 months, respectively ($p < 0.001$). The median PFS for patients with pathologic stage 0, stage I, stage II, stage III, and ypT0N1-2 was 47.2, 25.9, 16.0, 9.4, and 15.1 months, respectively ($p = 0.001$).

The median OS of all patients was 30.9 months. The median OS for patients with pathologic T0 or Tis, T1, T2, and T3 was 41.2, 36.6, 23.9, and 18.9 months, respectively

TABLE 2. Postchemoradiotherapy Pathologic Findings

Characteristics	(N =140)	%
T		
0 or Tis	58	41.4
1	18	12.9
2	29	20.7
3	31	22.1
4	0	0
N/A	4	2.9
N		
0	99	70.7
1	27	19.3
2	12	8.6
3	1	0.7
N/A	1	0.7
Median number of total lymph nodes (range)	19 (2–96)	
AJCC 7th stage		
0	48	34.3
IA/IB	12/6	12.9
IIA/IIB	19/22	29.3
IIIA/IIIB/IIIC	14/4/1	13.6
ypT0N1/ypT0N2	5/4	6.4
N/A	5	3.6
Margin		
Free	127	90.7
Close (≤1 mm) or involved	13	9.3
Extranodal extension		
Negative	124	88.6
Positive	15	10.7
N/A	1	0.7
Lymphovascular or perineural invasion		
Negative	124	88.6
Positive	16	11.4
Pathologic complete remission (pCR)[a]		
pCR	48	34.3
Non-pCR	91	65.0
N/A	1	0.7

[a]pCR: no residual invasive tumor cell in primary site and dissected lymph nodes.
AJCC, American Joint Committee on Cancer; N/A, not available.

($p = 0.115$). For patients with pathologic N0, N1, N2, and N3, the median OS was 39.5, 23.9, 9.6, and 8.8 months, respectively ($p < 0.001$). The median OS for patients with pathologic stage 0, stage I, stage II, stage III, and ypT0N1-2 was 57.4, 34.1, 26.2, 14.1, and 17.6 months, respectively ($p = 0.002$). The PFS and OS curves for patients with distinct pathologic T, N, and M stages, estimated by the Kaplan–Meier method, are shown in Figure 2.

Prognostic Significance of Post-CRT Pathologic Staging and Other Factors

In univariate analysis, sex ($p = 0.038$), ECOG-PS ($p = 0.001$), primary tumor location ($p = 0.006$), pathologic N ($p < 0.001$), pathologic stage according to the AJCC-7 ($p = 0.002$), ENE ($p < 0.001$), and pCR ($p = 0.004$) were identified as significant factors associated with PFS. ECOG-PS ($p = 0.001$), primary tumor location ($p = 0.017$), pathologic N ($p < 0.001$), pathologic stage according to the AJCC-7 ($p = 0.004$), ENE ($p = 0.007$), and pCR ($p = 0.008$) were identified as significant factors associated with OS. The univariate analysis performed using Cox regression is summarized in Table 3.

Multivariate analysis, including all significant factors identified in the univariate analyses, indicated that ECOG-PS ($p < 0.001$), primary tumor location ($p = 0.016$), and ENE ($p = 0.024$) were independent prognostic factors for PFS. We observed a trend for pathologic stage according to the AJCC-7, for predicting PFS, although it did not reach statistical significance ($p = 0.085$).

In multivariate analysis of OS, we found that ECOG-PS ($p < 0.001$) and pathologic stage according to the AJCC-7 ($p = 0.027$) were independent prognostic factors. The multivariate analyses using Cox regression are summarized in Table 4.

DISCUSSION

Increasing data have emerged supporting the superiority of preoperative CRT followed by surgery, compared with surgery alone in treating locoregional esophageal cancer.[7,8] Although pCR has long been recognized as a crucial factor in conferring favorable outcomes in patients receiving preoperative CRT, the prognostic effect of the post-CRT pathologic stage classified by the often used AJCC TNM staging system remains uncertain. Two previous reports studying the significance of the post-CRT pathologic stage classified by the AJCC-6 in EAC patients did not achieve consistent results.[10,11] In this study, we retrospectively analyzed a large cohort of locally advanced ESCC patients who had been treated with preoperative paclitaxel/cisplatin-based CRT and found that the post-CRT pathologic stage classified by the AJCC-7 was an independent prognostic factor for patient OS. This is the first report addressing the prognostic significance of the post-CRT pathologic stage, using the AJCC system, for ESCC.

Our conclusion is consistent with previous reports that the amount of pathologic LN involvement or the pathologic node-positive status is a significant prognostic factor in ESCC patients treated with preoperative CRT.[15–17] In our patient cohort, the post-CRT pathologic N status was the most significant factor affecting prognosis in the univariate analysis. In the AJCC-7, the presence or absence of LN involvement largely differentiates the tumor staging as stage III or stage I/II, with the exception of T1-2N1, which is classified as stage IIB. However, our data also showed that patients in post-CRT stage I had better survival outcomes than did patients in post-CRT stage II, indicating that factors other than pathologic N status, such as T stages, also have a prognostic effect on ESCC patients receiving preoperative CRT.

Our analysis also indicated that PS is an independent prognostic factor for PFS and OS, and primary tumor location and ENE are additional independent prognostic factors for PFS.

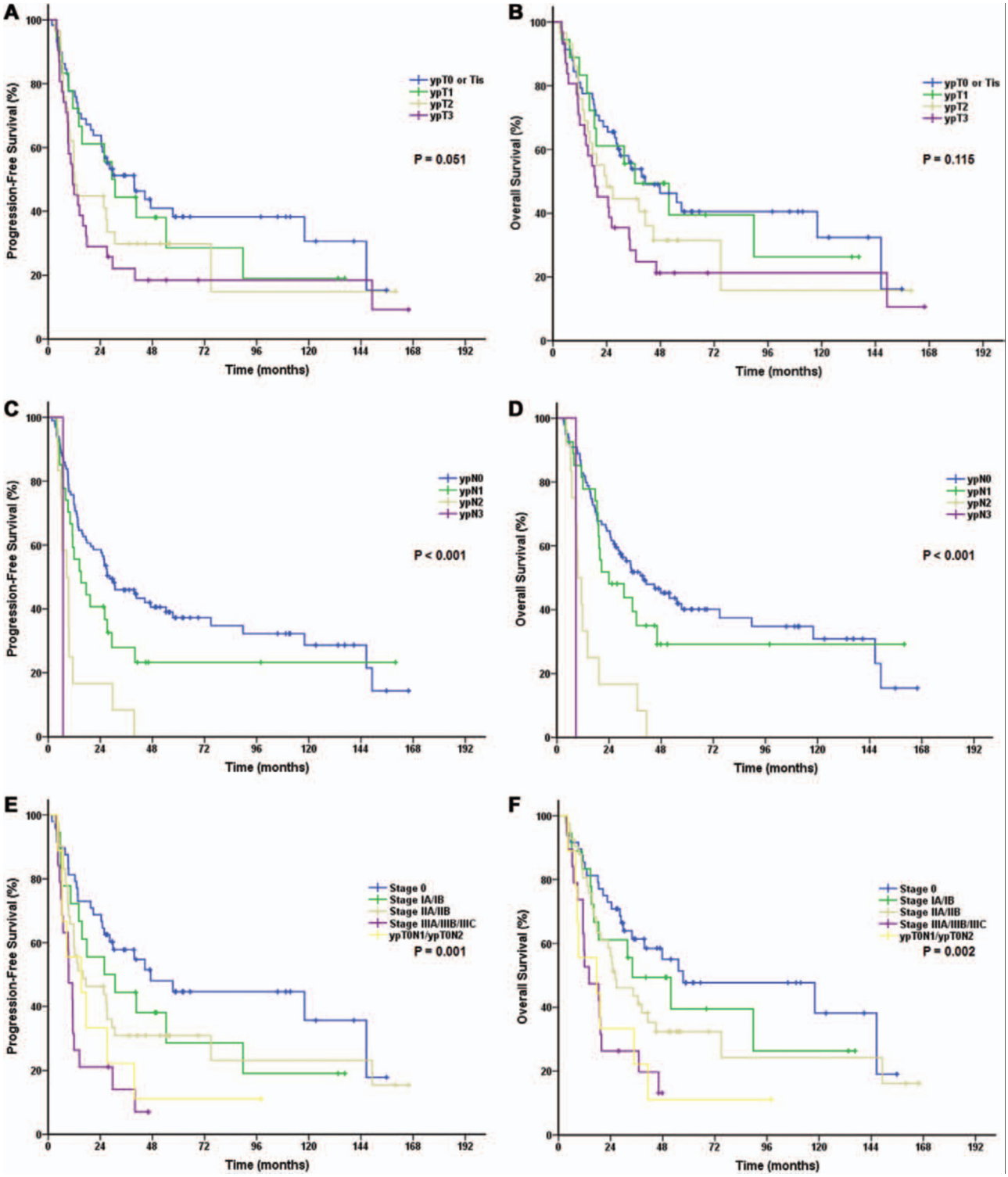

FIGURE 2. Kaplan–Meier estimates of progression-free survival (*A*, *C*, and *E*) and overall survival (*B*, *D*, and *F*) of postchemoradiotherapy pathologic stages according to the American Joint Committee on Cancer, 7th edition.

Kim et al.[18] previously reported that PS was a prognostic factor for locally advanced resectable ESCC patients who underwent preoperative CRT with a platinum/fluoropyrimidine-based regimen followed by surgery. Two other studies of ESCC patients who underwent surgery alone also revealed that ENE was an independent prognostic factor with negative survival effect.[19,20]

All patients enrolled in this analysis were treated with preoperative CRT with a paclitaxel/cisplatin-based regimen

TABLE 3. Univariate Analysis of Progression-Free Survival and Overall Survival (Cox Regression)

	Progression-Free Survival		Overall Survival	
Variable	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Age (yr)				
<60 (reference)	1.00		1.00	
≥60	1.16 (0.73,1.85)	0.522	1.22 (0.76,1.96)	0.416
Sex				
Female (reference)	1.00		1.00	
Male	3.38 (1.07,10.72)	**0.038**	3.04 (0.96,9.65)	0.059
ECOG-PS				
0–1 (reference)	1.00		1.00	
2	3.73 (1.70,8.16)	**0.001**	3.98 (1.81,8.74)	**0.001**
Clinical T		0.408		0.445
T2 (reference)	1.00		1.00	
T3	1.98 (0.49,8.04)	0.341	1.74 (0.43,7.06)	0.441
T4	3.84 (0.54,27.45)	0.180	3.55 (0.50,25.30)	0.207
Clinical N				
N0 (reference)	1.00		1.00	
N1	1.21 (0.45,3.31)	0.705	1.08 (0.39,2.94)	0.886
Clinical M1a				
(−) (reference)	1.00		1.00	
(+)	1.54 (0.74,3.18)	0.248	1.06 (0.46,2.44)	0.884
AJCC 6th stage		0.432		0.914
IIA/IIB (reference)	1.00		1.00	
III	1.32 (0.53,3.26)	0.548	1.20 (0.49,2.98)	0.689
IVA	1.99 (0.65,6.10)	0.229	1.26 (0.39,4.15)	0.699
Location		**0.006**		**0.017**
C and U (reference)	1.00		1.00	
M	0.48 (0.3,0.76)	**0.002**	0.50 (0.31,0.81)	**0.004**
L	0.76 (0.45,1.29)	0.312	0.72 (0.42,1.26)	0.251
Albumin (g/dL)				
<4 (reference)	1.00		1.00	
≥4	1.07 (0.62,1.85)	0.798	0.99 (0.57,1.71)	0.968
WBC				
<10,000 (reference)	1.00		1.00	
≥10,000	0.87 (0.52,1.46)	0.601	0.84 (0.49,1.44)	0.522
Preoperative therapy protocol		0.890		0.362
Cetuximab/TP-CRT(reference)	1.00		1.00	
TP-CRT	1.13 (0.68,1.88)	0.631	1.47 (0.86,2.52)	0.159
TP-HDFL then TP-CRT	1.07 (0.62,1.85)	0.804	1.36 (0.76,2.44)	0.302
Pathologic T		0.057		0.123
0 or Tis (reference)	1.00		1.00	
T1	1.20 (0.63,2.27)	0.578	1.07 (0.54,2.11)	0.851
T2	1.56 (0.90,2.70)	0.110	1.43 (0.82,2.50)	0.207
T3	2.00 (1.20,3.33)	**0.008**	1.84 (1.09,3.11)	**0.023**
Pathologic N		**<0.001**		**<0.001**
N0 (reference)	1.00		1.00	
N1	1.48 (0.90,2.46)	0.126	1.29 (0.76,2.19)	0.350
N2	3.71 (1.97,6.99)	**<0.001**	4.07 (2.15,7.70)	**<0.001**
N3	7.19 (0.96,53.77)	0.055	9.98 (1.31,75.85)	**0.026**

(*Continued*)

TABLE 3. (*Continued*)

	Progression-Free Survival		Overall Survival	
Variable	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Pathologic AJCC 7th stage		**0.002**		**0.004**
0 (reference)	1.00		1.00	
IA/IB	1.46 (0.75,2.85)	0.264	1.34 (0.65,2.73)	0.428
IIA/IIB	1.68 (1.00,2.85)	0.055	1.63 (0.95,2.81)	0.079
IIIA/IIIB/IIIC	3.57 (1.91,6.68)	**<0.001**	3.19 (1.67,6.07)	**<0.001**
ypT0N1/ypT0N2	2.55 (1.15,5.65)	**0.021**	2.9 (1.33,6.62)	**0.008**
Margin				
Free (reference)	1.00		1.00	
Close (≤1 mm) or involved	1.37 (0.71,2.63)	0.354	1.41 (0.73,2.72)	0.310
Extranodal extension				
Negative (reference)	1.00		1.00	
Positive	3.24 (1.80,5.82)	**<0.001**	2.33 (1.26,4.33)	**0.007**
Lymphovascular or perineural invasion				
Negative (reference)	1.00		1.00	
Positive	1.75 (0.97,3.16)	0.062	1.80 (0.98,3.33)	0.060
Pathologic complete remission (pCR)				
pCR (reference)	1.00		1.00	
non-pCR	1.93 (1.23,3.04)	**0.004**	1.88 (1.18,3.00)	**0.008**

C, cervical; U, upper thoracic; M, middle thoracic; L, lower thoracic; WBC, white blood cell count (/μL); TP-CRT, concurrent chemoradiotherapy with twice weekly paclitaxel and cisplatin; Cetuximab/TP-CRT, cetuximab plus TP-CRT; TP-HDFL then TP-CRT, one-cycle induction chemotherapy with paclitaxel and cisplatin plus 24-hour infusion of high-dose 5-fluorouracil and leucovorin followed by TP-CRT; AJCC, American Joint Committee on Cancer; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; HR, hazard ratio; CI, confidence interval.

P values less than 0.05, defined as statistically significant, are shown in bold.

TABLE 4. Multivariate Analysis of Progression-Free Survival and Overall Survival (Cox Regression)

	Progression-Free Survival		Overall Survival	
Variable	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Sex				
Female (reference)	1.00		1.00	
Male	2.81 (0.87,9.09)	0.083	2.33 (0.72,7.54)	0.160
ECOG-PS				
0–1 (reference)	1.00		1.00	
2	5.64 (2.25,14.10)	**<0.001**	6.03 (2.37,15.34)	**<0.001**
Location		**0.016**		0.077
C and U (reference)	1.00		1.00	
M	0.48 (0.29,0.80)	**0.004**	0.56 (0.34,0.93)	**0.024**
L	0.71 (0.40,1.25)	0.231	0.75 (0.42,1.35)	0.340
Pathologic AJCC 7th stage		0.085		**0.027**
0 (reference)	1.00		1.00	
IA/IB	1.53 (0.77,3.06)	0.224	1.50 (0.72,3.15)	0.281
IIA/IIB	1.80 (1.03,3.12)	**0.038**	1.81 (1.01,3.23)	**0.045**
IIIA/IIIB/IIIC	2.59 (1.26,5.32)	**0.010**	2.96 (1.45,6.04)	**0.003**
ypT0N1/ypT0N2	2.07 (0.90,4.79)	0.087	2.77 (1.18,6.51)	**0.019**
Extranodal extension				
Negative (reference)	1.00		1.00	
Positive	2.35 (1.12,4.94)	**0.024**	1.40 (0.67,2.94)	0.375

C, cervical; U, upper thoracic; M, middle thoracic; L, lower thoracic; AJCC, American Joint Committee on Cancer; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; HR, hazard ratio; CI, confidence interval.

plus a radiation dose with 40 Gy before surgery. This regimen is similar to that reported in the CROSS study, whereby patients received weekly paclitaxel/carboplatin plus a radiation dose of 41.4 Gy administered in 23 fractions before surgery. The median survival time of our patient cohort was inferior to that reported in the CROSS study (median, 30.9 versus 49.4 mo). This survival difference might have been because of patients in more advanced-stages being enrolled in our study compared with the CROSS study (clinical T3, 96% versus 84%; clinical N1, 94% versus 65%), different inclusion and exclusion criteria (e.g., patients whose tumors were longer than 8 cm or wider than 5 cm, and patients who lost more than 10% of their body weight were excluded from the CROSS study), and different patient populations regarding their primary tumor location (a higher percentage of cervical, upper, and middle thoracic primary tumors in our study than in the CROSS study). The pCR rate in our study (34.3%) was comparable with those reported in previous phase III studies.[8,21,22]

The prognosis of ypT0N1-2 patients was similar to pathologic stage III patients in this current study. A previous study revealed that the prognosis of ypT0N1 EAC patients was similar to pathologic stage II patients.[23] Another retrospective study evaluating the outcome of ESCC patients treated with preoperative CRT revealed that those with residual viable cancer cells only in the LN have similar survival outcomes as patients with pCR.[24] Our result is inconsistent with these studies. Further studies are warranted to define the prognosis of ypT0N-positive patients who are treated with preoperative CRT for locoregional esophageal cancer.

This study has several limitations. First, we did not record the differentiation of cancer cells, which has been included as a parameter to be combined with TNM status and location of the primary tumor for a complete staging of esophageal cancer according to the AJCC-7. Nevertheless, the cancer differentiation status can only affect the allocation of certain stage I or stage II cases (i.e., T2-3N0G1 of lower thoracic ESCC is classified as stage IB, whereas T2-3N0G2-3 is classified as stage IIA). Second, patients were selected from three sequential clinical trials in a single institute between 2000 and 2012. The clinical trial patient population might differ slightly from the typical patient population in actual practice, and supportive and medical care might have improved or changed significantly over this relatively long patient-enrollment period. However, the clinical trial patient population ensured that relevant clinicopathological factors were collected prospectively. Our study represents a large ESCC patient population that was treated with paclitaxel/platinum-CRT, the contemporary regimen conferring survival benefit.

In summary, our retrospective analysis indicates that post-CRT pathological staging according to the AJCC-7 is a significant prognostic factor for patients with locally advanced ESCC who underwent preoperative paclitaxel/cisplatin-based CRT followed by esophagectomy. This finding may help stratify locally advanced ESCC patients for further studies investigating novel postoperative approaches. Further studies are warranted to confirm the prognostic significance of post-CRT pathological staging and its usefulness in the treatment of ESCC.

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