# 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