Am J Cancer Res 2025;15(10):4486-4498
www.ajcr.us /ISSN:2156-6976/ajcr0168297

Original Article

Long-term clinical outcome of esophageal squamous cell carcinoma with residual disease after neoadjuvant chemoradiotherapy and surgery

Yen-Hao Chen[1,2,3,4], Hung-I Lu[5], Yu-Ming Wang[6], Chien-Ming Lo[5], Shang-Yu Chou[6], Yun-Hsuan Lin[6], Tzu-Ting Huang[6], Shau-Hsuan Li[1]

[1]Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 833, Taiwan; [2]School of Medicine, College of Medicine, Chang Gung University, Taoyuan 333, Taiwan; [3]School of Medicine, Chung Shan Medical University, Taichung 402, Taiwan; [4]Department of Nursing, School of Nursing, Fooyin University, Kaohsiung 831, Taiwan; [5]Department of Thoracic and Cardiovascular Surgery, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 833, Taiwan; [6]Department of Radiation Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 833, Taiwan

Received August 23, 2025; Accepted October 9, 2025; Epub October 25, 2025; Published October 30, 2025

Abstract: This study aimed to investigate the long-term clinical outcomes of patients with esophageal squamous cell carcinoma (ESCC) undergoing neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy with residual disease and to identify relevant clinicopathological prognostic factors. A total of 106 patients who underwent nCRT and surgery were identified. The chemotherapy regimen consisted of cisplatin plus 5-fluorouracil every 4 weeks, along with weekly carboplatin combined with paclitaxel, and the prescribed radiotherapy dose was either 41.4 Gy or 50.4 Gy. Most patients experienced tumor stage migration following nCRT and esophagectomy, such as upstaging or downstaging. Patients with ESCC undergoing trimodality therapy were categorized into three groups based on residual tumor status: ypT+N+, ypT+N0, and ypT0N+. In our cohort, the median disease-free survival (DFS) and overall survival (OS) were 8.2 months and 14.0 months, respectively. Pathological T status emerged as an independent prognostic factor associated with DFS and OS in both univariate and multivariate analyses. Patients with upstaging demonstrated inferior DFS and OS compared to those without upstaging, while patients experiencing downstaging showed superior DFS and OS compared to those without downstaging. Furthermore, DFS and OS appeared relatively worse in patients with ypT+N+ compared to those with ypT+N0 and ypT0N+. In conclusion, pathological T status serves as an independent prognostic factor for DFS and OS in ESCC patients with residual disease following nCRT and surgery, and prognosis is significantly correlated with upstaging or downstaging after nCRT. Identifying patients with the poorest prognosis is important, as additional adjuvant treatment may be necessary.

Keywords: Esophageal cancer, squamous cell carcinoma, neoadjuvant chemoradiotherapy, surgery, residual tumor, non-pathologic complete response

Introduction

Esophageal squamous cell carcinoma (ESCC) poses a significant challenge in healthcare, ranking as the ninth leading cause of cancer-related deaths in Taiwan due to its aggressive nature and poor prognosis [1]. With global life expectancy on the rise, ESCC presents an increasing burden on healthcare systems. Diagnosis often occurs at an advanced stage due to the absence of clear symptoms, necessitating a multidisciplinary approach for effective management. Definitive chemoradiotherapy is commonly employed for locally advanced ESCC and is considered a standard treatment [2]. Additionally, neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy, known as trimodality therapy, is gaining traction as it enhances surgical resectability and reduces local recurrence rates [2-5]. Recently, proton-based chemoradiotherapy revealed comparable survival outcomes with traditional chemora-

https://doi.org/10.62347/XJPA8404

diotherapy in ESCC, including trimodality therapy [6, 7]. Additionally, incorporating immunotherapy into nCRT followed by esophagectomy demonstrated safe and acceptable rates of minimally invasive surgery [8, 9]. However, despite extensive research efforts, the 5-year survival rate remains low at approximately 30% [10].

The CROSS trial, a multicenter randomized controlled trial, revealed that nCRT followed by esophagectomy significantly improved overall survival (OS) compared to surgery alone [4]. The response to nCRT, particularly achieving a pathologic complete response (pCR) where there is no evidence of disease in the resected esophagus and lymph nodes, strongly influences prognosis. Previous studies have reported pCR rates ranging from 17% to 29% after nCRT [4, 11-15]. Notably, achieving pCR has been consistently linked to prolonged OS compared to non-pCR cases [11, 12, 16]. In addition, there were some prognostic factors which were associated with poor prognosis. Hamai et al. showed that performance status 1 and ypN+ status have been identified as indicators of worse disease-free survival (DFS) and OS, in addition to pCR [12]. Another study highlighted that patients with pCR exhibited the highest 5-year OS rate, followed by those with ypT+N0, ypT0N+, and ypT+N+ statuses (62%, 49%, 47%, and 22%, respectively) [11]. Hence, ESCC patients without pCR following trimodality therapy tend to have poorer OS outcomes compared to those achieving pCR. In the CheckMate 577 trial, a global phase 3 randomized double-blind study, the role of nivolumab in the adjuvant setting following trimodality therapy was evaluated for ESCC patients with residual tumors (non-pCR). Results indicated that adjuvant nivolumab significantly improved DFS compared to placebo, representing a noteworthy clinical advancement [17, 18].

In general, achieving a pCR is recognized as a crucial prognostic indicator for both DFS and OS in patients undergoing trimodality treatment. Furthermore, adjuvant nivolumab has demonstrated significant enhancements in survival outcomes for patients who do not attain pCR. Nevertheless, the correlation between prognostic factors and clinical outcomes in ESCC patients with residual disease (non-pCR) following nCRT and esophagectomy remains uncertain. Currently, there exists inadequate evidence concerning the long-term outcomes of this specific patient cohort. Thus, the primary objective of this study is to investigate the long-term clinical outcomes of ESCC patients who underwent nCRT followed by esophagectomy and to identify pertinent clinicopathological prognostic factors.

Methods

Patient selection

The retrospective review encompassed the medical records of 2,197 patients diagnosed with ESCC and managed at Kaohsiung Chang Gung Memorial Hospital between January 2005 and December 2023. Initially, patients with a history of a second primary malignancy were excluded from the analysis. Additionally, individuals solely treated with surgery or chemoradiotherapy were not included in the study cohort. Furthermore, patients presenting with distant metastasis were also excluded from the analysis. Those undergoing alternative therapeutic modalities, such as chemotherapy alone, radiotherapy alone, or supportive care, were similarly omitted from the study cohort. Consequently, the analysis focused exclusively on ESCC patients who underwent nCRT followed by esophagectomy. Only patients with residual tumor were included, while those achieving pCR were excluded. Ultimately, a total of 106 ESCC patients meeting these stringent inclusion criteria were identified for analysis in the study. The algorithm used to identify patients who met the inclusion/exclusion criteria is shown in **Figure 1**.

Tumor stage and surgery

Prior to treatment initiation, the clinical tumor stage was evaluated using chest computed tomography (CT), endoscopic ultrasonography (EUS), and positron emission tomography (PET) scans for each patient. The tumor stages were categorized according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system [19].

Following the completion of nCRT, patients underwent surgery within 8 to 12 weeks (the mean and median duration were 69 days and 70 days, respectively, with a range of 56 to 82 days). Pathological staging was determined

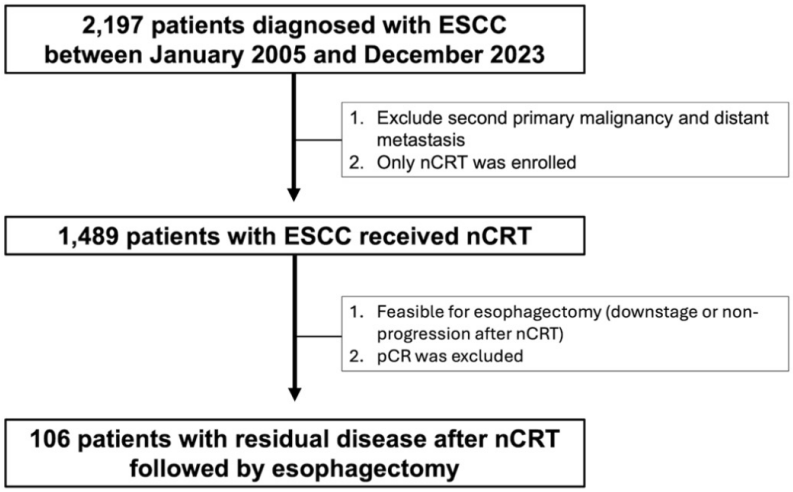

Figure 1. Flowchart of patient selection for those who received nCRT followed by esophagectomy with non-pCR. nCRT: neoadjuvant chemoradiotherapy; pCR: pathologic complete response.

based on detailed pathological reports, encompassing tumor extension, lymph node metastasis, and resection margins. In cases where no macroscopic tumor was identified, any abnormal-appearing tissue was meticulously embedded in paraffin to ensure a thorough assessment of residual tumor presence and therapy effects. pCR was defined as the absence of any evidence of viable residual tumor cells.

The distinction between clinical T status (cT) and pathological T status (pT) is as follows: the clinical T status is assessed before any treatment (such as surgery, chemotherapy, or radiotherapy) based on clinical and imaging evaluations, and it is primarily used to guide the initial treatment strategy. In contrast, the pathological T status is determined after surgical resection through histopathological examination of the excised tissue, providing a more definitive evaluation of tumor invasion.

A surgical margin is considered negative or clear when no malignant cells are detected at the resection edge, indicating complete tumor removal. Conversely, a positive or involved margin refers to the presence of cancer cells at the resection boundary, implying residual disease. The presence of positive margins has been consistently linked to poorer survival outcomes [20].

Chemotherapy

The chemotherapy protocol comprised cisplatin (75 mg/m^2) administered via a 4-hour drip on day 1, combined with 5-fluorouracil (1,000 mg/m^2) administered via continuous infusion on days 1-4, with cycles repeated every 4 weeks. In cases where the patient's creatinine clearance was less than 60 mL/min, carboplatin was utilized as a substitute for cisplatin. This chemotherapy regimen was administered concurrently with radiotherapy at a dose of 50.4 Gy. An alternative regimen involved weekly intravenous administration of carboplatin at an area under the curve of 2 mg per milliliter per minute, in conjunction with paclitaxel at a dose of 50 mg/m^2. Radiotherapy was administered concurrently with this chemotherapy regimen at a dose of 41.4 Gy. All patients received nCRT consisting of either at least two cycles of cisplatin plus 5-fluorouracil or at least five cycles of carboplatin plus paclitaxel.

Radiotherapy

Each patient was fitted with a customized thermoplastic immobilization device to ensure precise positioning. Following this, CT simulation was conducted for image acquisition. Given the treatment field encompassing the mediastinum, inverse plan intensity-modulated radiotherapy (IMRT) employing 6- or 10-MV photons was utilized for delivery. The gross target volume (GTV) included the gross tumor and gross lymph nodes visualized on CT scan and/or PET-CT images. The clinical target volume (CTV) encompassed the esophagus and the mediastinal lymph nodes. To accommodate setup uncertainties, the planning target volume (PTV) was expanded from the CTV with 0.5-1.0 cm margins in all directions. The prescribed total dose to the PTV was either 41.4 Gy administered in 23 daily fractions, or 50.4 Gy administered in 28 daily fractions.

Statistical analysis

Statistical analyses were performed using the SPSS 29 software package (IBM, Armonk, NY). The chi-square test and t-test were employed to

compare data between any two groups. DFS was defined as the duration from the date of surgery to the occurrence of tumor recurrence, distant metastasis, or death from any cause, while OS was calculated from the date of ESCC diagnosis to death from any cause or to the date of the last follow-up.

DFS and OS were estimated using the Kaplan-Meier method, with group differences assessed using the log-rank test for univariate analysis. Multivariate analyses of prognostic factors for survival were conducted utilizing the Cox proportional hazards model. Hazard ratios (HRs) along with 95% confidence intervals (CIs) and corresponding *P* values were calculated to assess the strength of associations between prognostic parameters and survival outcomes. All analyses utilized two-sided tests of significance, with $P < 0.05$ considered statistically significant.

Ethics statement

The retrospective analysis was approved by the Chang Gung Medical Foundation Institutional Review Board (approval number: 20240073-2B0), ensuring compliance with ethical standards outlined by the Institutional Research Committee and the World Medical Association Declaration of Helsinki. Given the retrospective nature of the study, the Chang Gung Medical Foundation Institutional Review Board deemed written informed consent from patients or their families unnecessary for participation in the study.

Results

Patient characteristics

This study included a cohort of 106 male patients diagnosed with locally advanced ESCC who nCRT followed by esophagectomy. Their mean age was 54 years (range: 31 to 73 years). A total of 95 patients (89.6%) had a smoking history, and 83 (78.3%) had a history of alcohol consumption. Tumor locations were distributed as follows: 18 patients (17.0%) in the upper esophagus, 47 patients (44.3%) in the middle esophagus, and 41 patients (38.7%) in the lower esophagus. The initial tumor stages (pretreatment) were as follows: clinical T1 in one patient (0.9%), T2 in six patients (5.7%), T3 in 55 patients (51.9%), T4a in six patients (5.7%), and T4b in 38 patients (35.8%). Clinical nodal status revealed N0 in 18 patients (17.0%), N1 in 37 patients (34.9%), N2 in 34 patients (32.1%), and N3 in 17 patients (16.0%). Regarding tumor staging, 16 patients (15.1%) were categorized as stage II, 35 patients (33.0%) as stage III, and 55 patients (51.9%) as stage IVA. Histological grades were distributed as follows: grade 1 in 13 patients (12.3%), grade 2 in 75 patients (70.8%), and grade 3 in 18 patients (17.0%).

Following nCRT and surgery, there were alterations in the pathological stage compared to the initial stage. Pathological T status was as follows: ypT0 in six patients (5.7%), ypT1 in 16 patients (15.1%), ypT2 in 22 patients (20.8%), ypT3 in 42 patients (39.6%), ypT4a in one patient (0.9%), and ypT4b in 19 patients (17.9%). Pathological nodal status revealed ypN0 in 64 patients (60.4%), ypN1 in 30 patients (28.3%), ypN2 in seven patients (6.6%), and ypN3 in five patients (4.7%). Pathological staging resulted in stage I for 25 patients (23.6%), stage II for 25 patients (23.6%), stage IIIA for 14 patients (13.2%), stage IIIB for 18 patients (17.0%), and stage IVA for 24 patients (22.6%). The distribution of pathological grade was as follows: grade 1 in 11 patients (10.4%), grade 2 in 71 patients (67.0%), and grade 3 in 24 patients (22.6%). Detailed clinicopathological parameters of these patients are provided in **Table 1**.

Clinical outcomes of ESCC patients receiving nCRT and surgery

Most patient experienced tumor stage migration after nCRT and esophagectomy (**Figure 2**). The median DFS and OS were 8.2 months and 14.0 months in our cohort, respectively. In our analysis of DFS, no significant differences were detected regarding age, tumor location, clinical T status, clinical N status, clinical stage, and clinical and pathological tumor grade in univariate analysis. However, 62 patients with ypT3-4 status exhibited significantly poorer DFS compared to the other 44 patients with ypT1-2 status (5.6 months versus 15.9 months, $P < 0.001$, **Figure 3A**). Additionally, the 16 patients with ypN2-3 status experienced shorter DFS compared to the remaining 90 patients with ypN0-1 status (5.0 months versus 8.6 months, $P = 0.040$). Furthermore, 56 patients with pathological stage III-IVA demonstrated worse DFS compared to the other 50 patients with pathological stage I-II (6.1 months versus 15.3

Table 1. Characteristics of 106 patients with residual esophageal squamous cell carcinoma undergoing concurrent chemoradiotherapy followed by esophagectomy

Characteristics	
Age (years)	54 years old (31-73)
Sex	
Male	106 (100%)
Cigarette smoking	
Yes	95 (89.6%)
No	11 (10.4%)
Alcohol consumption	
Yes	83 (78.3%)
No	23 (21.7%)
nCRT protocol	
Cisplatin plus 5-fluorouracil with 50.4 Gy	55 (51.9%)
Carboplatin plus paclitaxel with 41.4 Gy	51 (48.1%)
Location	
Upper	18 (17.0%)
Middle	47 (44.3%)
Lower	41 (38.7%)
Clinical status (pre-treatment)	
Clinical T status	
1	1 (0.9%)
2	6 (5.7%)
3	55 (51.9%)
4a	6 (5.7%)
4b	38 (35.8%)
Clinical N status	
0	18 (17.0%)
1	37 (34.9%)
2	34 (32.1%)
3	17 (16.0%)
Clinical tumor stage	
II	16 (15.1%)
III	35 (33.0%)
IVA	55 (51.9%)
Clinical Grade	
1	13 (12.3%)
2	75 (70.8%)
3	18 (17.0%)
Pathological status (after esophagectomy)	
Pathological T status	
0	6 (5.7%)
1	16 (15.1%)
2	22 (20.8%)
3	42 (39.6%)
4a	1 (0.9%)
4b	19 (17.9%)

months, P < 0.001). Notably, 22 patients with positive surgical margins had shorter DFS compared to the other 84 patients with negative surgical margins (4.9 months versus 9.8 months, P < 0.001). Multivariate analysis indicated that clinical T3-4 status (P = 0.026, HR: 2.82, 95% CI: 1.13-6.99), ypT3-4 (P < 0.001, HR: 2.41, 95% CI: 1.46-4.00), and pathological stage III-IVA (P = 0.003, HR: 1.99, 95% CI: 1.26-3.15) were independent prognostic factors associated with worse DFS.

In the assessment of OS, no statistically significant differences were identified concerning age, tumor location, clinical T status, clinical N status, clinical stage, and clinical and pathological tumor grade in univariate analysis. However, 62 patients with ypT3-4 status exhibited significantly shorter OS compared to the other 44 patients with ypT1-2 status (12.1 months versus 32.7 months, P = 0.002, **Figure 3B**). Similarly, 16 patients with ypN2-3 status experienced worse OS compared to the other 90 patients with ypN0-1 status (12.3 months versus 14.3 months, P = 0.038). Furthermore, 56 patients with pathological stage III-IVA had shorter OS compared to the other 50 patients with pathological stage I-II (12.1 months versus 27.3 months, P = 0.004). Additionally, 22 patients with positive surgical margins had worse OS compared to the other 84 patients with negative surgical margins (9.6 months versus 15.9 months, P < 0.001). Multivariate analysis revealed that upper-third ESCC (P = 0.026, HR: 2.01, 95% CI: 1.09-3.73), ypT3-4 (P = 0.008, HR: 2.05, 95% CI: 1.20-3.48), and positive surgical margin (P = 0.008, HR: 2.19, 95% CI: 1.23-3.91) were independent prognostic factors associated with worse OS. The univariate and multivariate analyses of DFS and OS in these 106 ESCC patients who received nCRT and surgery are presented in **Tables 2** and **3**.

Pathological N status	
0	64 (60.4%)
1	30 (28.3%)
2	7 (6.6%)
3	5 (4.7%)
Pathological tumor stage	
I	25 (23.6%)
II	25 (23.6%)
IIIA	14 (13.2%)
IIIB	18 (17.0%)
IVA	24 (22.6%)
Pathological Grade	
1	11 (10.4%)
2	71 (67.0%)
3	24 (22.6%)

nCRT: neoadjuvant chemoradiotherapy.

Comparison of survival according to tumor stage migration

Following nCRT and esophagectomy, the majority of patients exhibited tumor stage migration. "Upstage" denotes an increase in tumor stage post-trimodality therapy, with 14 patients (13.2%) demonstrating upstaging, while the remaining 92 patients (86.8%) did not. Patients experiencing upstaging showed inferior DFS (4.1 months versus 8.6 months, P = 0.001, **Figure 4A**) and OS (8.4 months versus 14.3 months, P = 0.027, **Figure 4B**) compared to those without upstaging.

Conversely, "downstage" indicates a reduction in tumor stage following trimodality treatment, with 63 patients (59.4%) undergoing downstaging and 43 patients (40.6%) not. Patients who underwent downstaging exhibited improved DFS (12.7 months versus 5.5 months, P = 0.011, **Figure 5A**) and OS (17.1 months versus 12.1 months, P = 0.019, **Figure 5B**) compared to those without downstaging.

Comparison of survival according to residual tumor status

ESCC patients who underwent nCRT and subsequent surgery were stratified into three groups based on the status of residual tumor: ypT+N+, ypT+N0, and ypT0N+. In our study, 37 patients (34.9%) were categorized as ypT+N+, 64 patients (60.4%) as ypT+N0, and 5 patients (4.7%) as ypT0N+. Although DFS appeared relatively worse in patients with ypT+N+ (6.1 months) compared to those with ypT+N0 (10.7 months) and ypT0N+ (11.0 months), no statistically significant difference was observed (**Figure 6A**). Conversely, OS was 12.2 months in patients with ypT+N+, 15.9 months in patients with ypT+N0, and 12.3 months in patients with ypT0N+, with no significant difference noted (**Figure 6B**).

Discussion

ESCC presents a significant clinical challenge due to its aggressive nature and poor prognosis, particularly in advanced stages, necessitating complex treatment strategies. nCRT followed by esophagectomy has emerged as a standard treatment approach widely adopted in clinical practice. Previous research has highlighted a pCR rate of approximately 25% following nCRT, with patients achieving pCR demonstrating improved OS compared to those without. However, there remains a dearth of studies investigating the clinical outcomes of ESCC patients who do not achieve pCR in real-world scenarios, leaving various aspects of this patient population poorly understood. Our study aimed to address this gap by examining the long-term survival outcomes of ESCC patients with residual disease following trimodality treatment. Our analysis identified pathological T status as an independent prognostic factor for both DFS and OS, surpassing other clinical parameters. While a considerable proportion of patients experienced downstaging post-nCRT, a minority still exhibited upstaging despite receiving treatment. Notably, patients achieving downstaging demonstrated improved DFS and OS, whereas those experiencing upstaging had poorer outcomes in terms of DFS and OS. Additionally, residual tumor status, particularly ypT+N+, appeared to be associated with inferior survival outcomes compared to ypT+N0 or ypT0N+, although statistical significance was not attained.

The relationship between different pathological tumor responses and clinical outcomes allows for more refined prognostic assessments tailored to individual patients. Consistent with previous findings, patients achieving pCR exhibited superior survival outcomes compared to those with residual disease [11, 12, 16]. Our

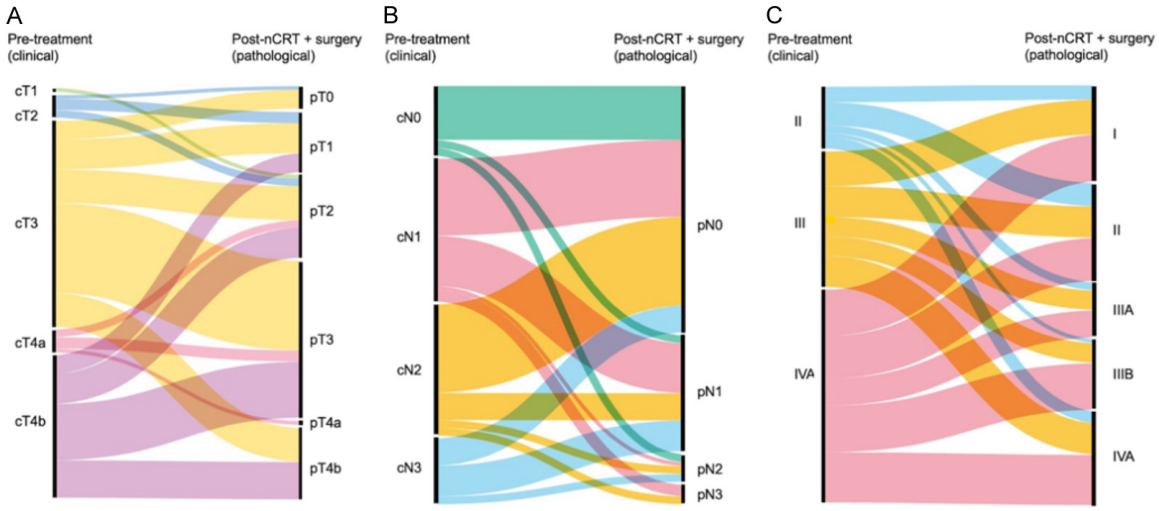

Figure 2. Tumor stage migration before and after neoadjuvant chemoradiotherapy (nCRT) and surgery. (A) T status, (B) N status, (C) tumor stage.

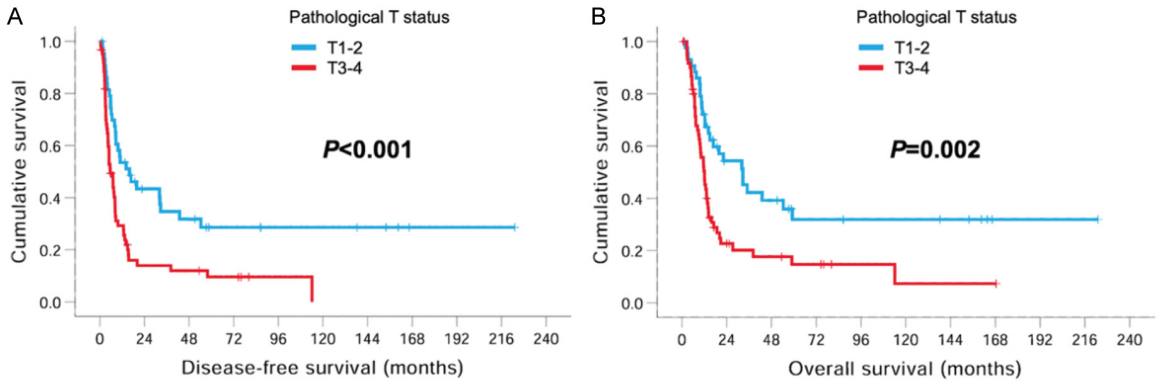

Figure 3. Comparison of Kaplan-Meier curves depicting disease-free survival (A) and overall survival (B) in patients with esophageal squamous cell carcinoma who underwent neoadjuvant chemoradiotherapy and surgery, stratified by pathological T status.

results align with those reported by Al-Kaabi et al., who observed the lowest 5-year OS rate in patients with ypT+N+ (22%), followed by ypT0N+ and ypTN0 (47% and 49%, respectively), consistent with our study's findings [11]. While statistical significance was not achieved in our analysis due to the limited sample size in the ypT0N+ group (only five patients), the discrepancy among survival curves was evident.

In contrast, Hamai et al. identified ypN+ as an independent predictor of OS, with its significance increasing with higher degrees of pathological lymph node metastasis [12]. However, in our cohort, pathological T status emerged as a more significant prognostic factor than pathological N status. This disparity may stem from differences in cohort characteristics, particularly in the extent of regression of lymph node metastasis after trimodality treatment, which was more pronounced in our cohort compared to changes in tumor invasion status. This is evidenced by the higher percentage of patients with clinical N2-3 disease (48.1%) compared to the lower percentage of patients with pathological N status (6.6% in ypN2 and 4.7% in ypN3). However, the percentage of patients with pathological T3-4 status (58.4%) remained relatively high, although significantly lower than the initial clinical T status (93.4%). In contrast, in the cohort studied by Hamai et al., there was a clear migration of clinical T status to pathological T status, with a decrease from 85.6% to 32%. Although the percentage of

Table 2. Univariate and multivariate analysis of disease-free survival (DFS) in 106 patients with residual esophageal squamous cell carcinoma undergoing concurrent chemoradiotherapy followed by esophagectomy

Characteristics	No. of patients	Univariate analysis		Multivariate analysis	
		Median DFS (months)	*P*-value	HR (95% CI)	*P*-value
Age					
< 60 years	79 (74.5%)	7.9	0.15		
≥ 60 years	27 (25.5%)	15.0			
Location					
Upper	18 (17.0%)	6.1	0.49		
Middle + Lower	88 (83.0%)	8.3			
Clinical T status					
1 + 2	7 (6.6%)	4.2	0.25		
3 + 4	99 (93.4%)	8.3		2.82 (1.13-6.99)	0.026*
Clinical N status					
0 + 1	55 (51.9%)	6.5	0.39		
2 + 3	51 (48.1%)	9.8			
Clinical tumor stage					
I + II	16 (15.1%)	6.5	0.86		
III + IVA	90 (84.9%)	8.2			
Clinical Grade					
1	13 (12.3%)	10.7	0.08		
2 + 3	93 (87.7%)	8.2			
Pathological T status					
1 + 2	44 (41.5%)	15.9	< 0.001*		
3 + 4	62 (58.5%)	5.6		2.41 (1.46-4.00)	< 0.001*
Pathological N status					
0 + 1	90 (84.9%)	8.6	0.040*		
2 + 3	16 (15.1%)	5.0			
Pathological tumor stage					
I + II	50 (47.2%)	15.3	< 0.001*		
IIIA + IIIB + IVA	56 (52.8%)	6.1		1.99 (1.26-3.15)	0.003*
Pathological Grade					
1	11 (10.4%)	8.6	0.39		
2 + 3	95 (89.6%)	8.2			
Surgical margin					
Positive	22 (20.8%)	4.9	< 0.001*		
Negative	84 (79.2%)	9.8			

HR: hazard ratio; CI: confidence interval. *Statistically significant.

patients with clinical N2-3 disease (20.8%) was similar to that of pathological N2-3 disease (15.2%), our findings suggest that in our cohort, pathological T status may hold greater prognostic significance compared to pathological N status.

Several studies have underscored the substantial extension of OS in patients achieving pCR compared to those without [11, 12, 16]. Accordingly, the development of early predictive methods to differentiate responders from non-responders may facilitate timely adjustments to treatment regimens or prompt progression to surgery. Although various studies have explored the utility of PET scans in predicting histopathological response based on changes in values pre- and post-nCRT, the heterogeneous study designs and parameters have yielded conflicting results [21-27]. Even

Table 3. Univariate and multivariate analysis of overall survival (OS) in 106 patients with residual esophageal squamous cell carcinoma undergoing concurrent chemoradiotherapy followed by esophagectomy

Characteristics	No. of patients	Univariate analysis		Multivariate analysis	
		Median OS (months)	*P*-value	HR (95% CI)	*P*-value
Age					
< 60 years	79 (74.5%)	13.2	0.39		
≥ 60 years	27 (25.5%)	19.8			
Location					
Upper	18 (17.0%)	9.2	0.24	2.01 (1.09-3.73)	0.026*
Middle + Lower	88 (83.0%)	14.2			
Clinical T status					
1 + 2	7 (6.6%)	14.9	0.77		
3 + 4	99 (93.4%)	13.6			
Clinical N status					
0 + 1	55 (51.9%)	13.2	0.62		
2 + 3	51 (48.1%)	14.2			
Clinical tumor stage					
I + II	16 (15.1%)	11.5	0.88		
III + IVA	90 (84.9%)	14.0			
Clinical Grade					
1	13 (12.3%)	16.8	0.19		
2 + 3	93 (87.7%)	14.0			
Pathological T status					
1 + 2	44 (41.5%)	32.7	0.002*		
3 + 4	62 (58.5%)	12.1		2.05 (1.20-3.48)	0.008*
Pathological N status					
0 + 1	90 (84.9%)	14.3	0.038*		
2 + 3	16 (15.1%)	12.3			
Pathological tumor stage					
I + II	50 (47.2%)	27.3	0.004*		
IIIA + IIIB + IVA	56 (52.8%)	12.1			
Pathological Grade					
1	11 (10.4%)	10.7	0.77		
2 + 3	95 (89.6%)	14.0			
Surgical margin					
Positive	22 (20.8%)	9.6	< 0.001*	2.19 (1.23-3.91)	0.008*
Negative	84 (79.2%)	15.9			

HR: hazard ratio; CI: confidence interval. *Statistically significant.

with the use of advanced diagnostic tools such as PET-CT scans combined with endoscopic assessments, the low sensitivity and positive predictive value limit their clinical applicability [28]. Moreover, Wang et al. identified gross tumor volume as a significant predictor of pCR, progression-free survival, and OS, with smaller tumor volumes associated with higher pCR rates and improved survival outcomes [29]. Conversely, failure to respond to nCRT may result in missed opportunities for curative surgery due to disease progression-related unresectability or distant metastasis, underscoring the importance of accurately predicting treatment response to mitigate such consequences.

Circulating tumor cells (CTCs) are cancer cells shed from primary or metastatic tumors into the bloodstream and are considered a promis-

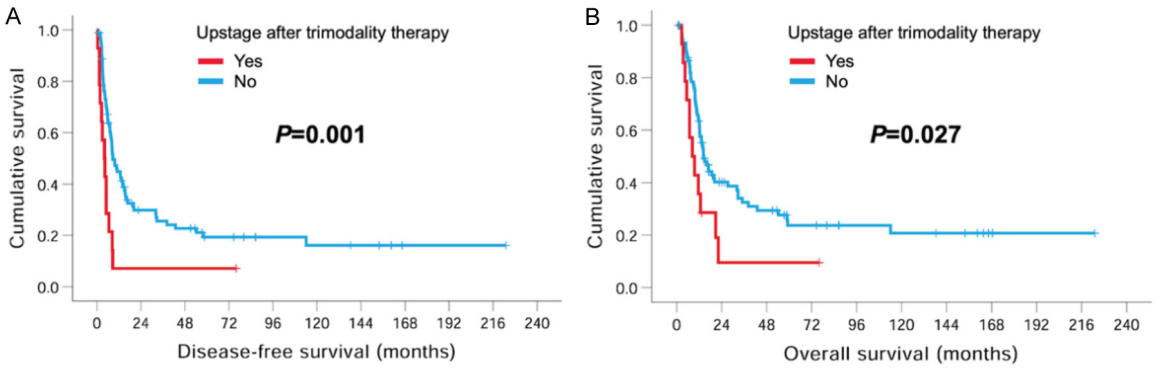

Figure 4. Kaplan-Meier survival curves illustrating disease-free survival (A) and overall survival (B) in patients with esophageal squamous cell carcinoma based on upstaging status following neoadjuvant chemoradiotherapy and surgery.

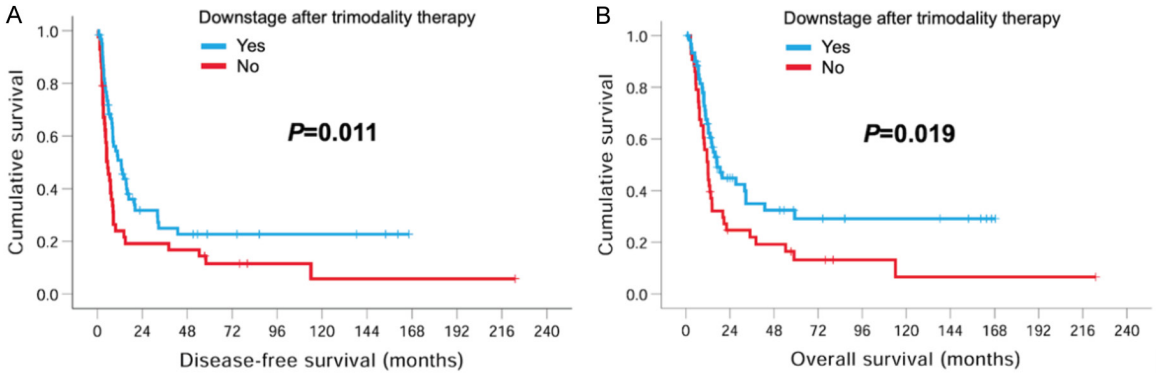

Figure 5. Kaplan-Meier survival curves demonstrating disease-free survival (A) and overall survival (B) in patients with esophageal squamous cell carcinoma based on downstaging status following neoadjuvant chemoradiotherapy and surgery.

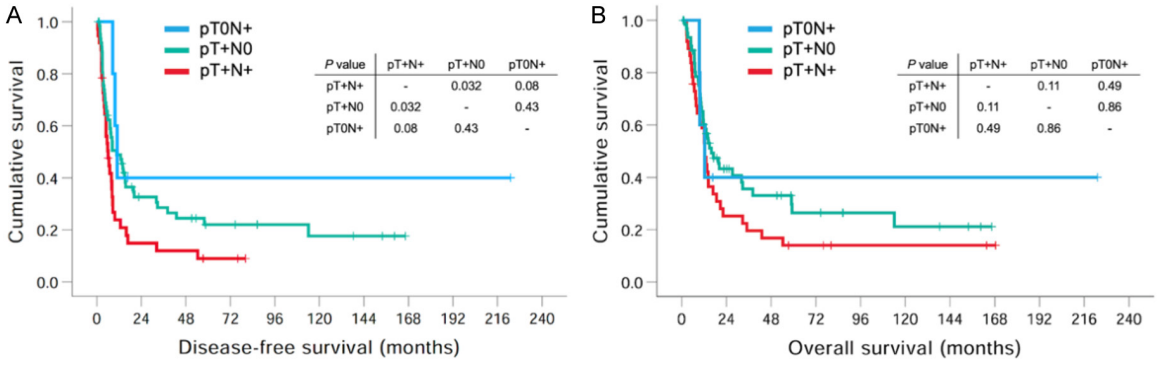

Figure 6. Comparison of Kaplan-Meier curves among patients with esophageal squamous cell carcinoma categorized by tumor response to neoadjuvant chemoradiotherapy and surgery: ypT+N+, ypT+N0, and ypT0N+. Disease-free survival (A) and overall survival (B).

ing biomarker representing a form of *"liquid biopsy"*. In patients with ESCC, CTCs have not yet become part of routine clinical practice; however, clinical studies are actively investigating their potential roles before and after surgery [30, 31]. Several studies have demonstrated that the presence or higher counts of CTCs in peripheral blood, either preoperatively or

postoperatively, may be associated with poorer outcomes, such as shorter DFS and OS [32, 33]. First, CTCs may serve as a potential tool for assessing treatment response. By analyzing the correlation between CTC counts and pathological response, it may be possible to identify whether CTCs can predict a major pathological response or even a pCR. Furthermore, the dynamic changes in CTC levels before and after surgery could represent another significant prognostic parameter, especially in patients who fail to achieve pCR after nCRT. In addition, persistent postoperative CTC positivity may indicate the need for immediate adjuvant therapy. In summary, although the clinical role of CTCs in the management of ESCC has not yet been established, larger multicenter prospective studies with standardized detection methodologies are warranted to validate their clinical utility and to integrate CTC assessment into future treatment decision-making for ESCC patients.

Our study has several limitations, including its retrospective nature and reliance on data from a single institution, which may limit generalizability. Additionally, variations in chemotherapy regimens and radiotherapy doses over the study period may introduce confounding factors. Nonetheless, our study represents one of the few investigations into the clinical outcomes of ESCC patients with residual disease following nCRT and esophagectomy, offering valuable insights into the management of this patient population in real-world settings. In summary, our findings contribute to a deeper understanding of the clinical outcomes and prognostic factors in ESCC patients with residual disease following nCRT and surgery, providing a basis for further research and informing clinical practice.

Conclusions

Our study demonstrates that the pathological T status is an independent prognostic factor for worse DFS and OS in patients with ESCC who have residual disease following nCRT and surgery. Prognosis is significantly correlated with upstaging or downstaging after nCRT, with patients exhibiting ypT+N+ status having the poorest survival outcomes. The importance of this finding is to identify patients with the poorest prognosis, suggesting that additional adjuvant treatment may be necessary.

Acknowledgements

We thank the Chang Gung Medical Foundation Kaohsiung Chang Gung Memorial Hospital Biobank & Research Specimen Processing Lab (CLRPG8L0084) for excellent technical support. This work was supported by the Chang Gung Memorial Hospital (grant numbers CORPG8L0641, CORPG8M0561 and CMRPG8N0181).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shau-Hsuan Li, Department of Hematology-Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, No. 123, Dapi Rd., Niaosong Dist., Kaohsiung 833, Taiwan. Tel: +886-7-7317123 Ext. 8303; Fax: +886-7-7322402; E-mail: lee.a0928@msa.hinet.net

References

[1] Ministry of Health and Welfare of Taiwan. Cancer Registry Annual Report 2021. Taipei City: Health Promotion Administration, Ministry of Health and Welfare, Taiwan 2021.

[2] Puhr HC, Prager GW and Ilhan-Mutlu A. How we treat esophageal squamous cell carcinoma. ESMO Open 2023; 8: 100789.

[3] Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, van Laarhoven HWM, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch ORC, Ten Kate FJW, Creemers GM, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Sangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW and van der Gaast A; CROSS study group. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015; 16: 1090-1098.

[4] van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW and van der Gaast A; CROSS Group. Preoperative

chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366: 2074-2084.
[5] Udelsman BV, Ermer T, Ely S, Canavan ME, Zhan P, Boffa DJ and Blasberg JD. Assessment of a collaborative treatment model for trimodal management of esophageal cancer. J Thorac Dis 2023; 15: 4668-4680.
[6] Hallemeier CL, Merrell KW, Neben-Wittich MA, Jethwa KR, Yoon HH, Pitot HC, Blackmon S, Shen KR, Tryggestad EJ, Giffey B, Kazemba BD, Viehman JK, Harmsen WS and Haddock MG. A prospective pilot study of pencil beam scanning proton radiation therapy as a component of trimodality therapy for esophageal cancer. Adv Radiat Oncol 2024; 9: 101547.
[7] Ogawa K, Ishikawa H, Toyozumi T, Noma K, Kono K, Hojo H, Tamamura H, Azami Y, Ishida T, Nabeya Y, Iwata H, Araya M, Tokumaru S, Maruo K, Oda T and Matsubara H. Comparison of proton-based definitive chemoradiotherapy and surgery-based therapy for esophageal squamous cell carcinoma: a multi-center retrospective Japanese cohort study. Esophagus 2024; 21: 484-494.
[8] Shen D, Chen R, Wu Q, Ji Y, van der Wilk BJ, Chen EY, Chen Q and Chen M. Safety and short-term outcomes of esophagectomy after neoadjuvant immunotherapy combined with chemotherapy or chemoradiotherapy for locally advanced esophageal squamous cell cancer: analysis of two phase-II clinical trials. J Gastrointest Oncol 2024; 15: 841-850.
[9] Wang R, Liu S, Chen B and Xi M. Recent advances in combination of immunotherapy and chemoradiotherapy for locally advanced esophageal squamous cell carcinoma. Cancers (Basel) 2022; 14: 5168.
[10] Estes NC, Stauffer J, Romberg M, Thomas JH, Jewell WR and Hermreck A. Squamous cell carcinoma of the esophagus. Am Surg 1996; 62: 573-576.
[11] Al-Kaabi A, van der Post RS, van der Werf LR, Wijnhoven BPL, Rosman C, Hulshof MCCM, van Laarhoven HWM, Verhoeven RHA and Siersema PD. Impact of pathological tumor response after CROSS neoadjuvant chemoradiotherapy followed by surgery on long-term outcome of esophageal cancer: a population-based study. Acta Oncol 2021; 60: 497-504.
[12] Hamai Y, Hihara J, Emi M, Furukawa T, Murakami Y, Nishibuchi I, Ibuki Y, Yamakita I, Kurokawa T, Nagata Y and Okada M. Evaluation of prognostic factors for esophageal squamous cell carcinoma treated with neoadjuvant chemoradiotherapy followed by surgery. World J Surg 2018; 42: 1496-1505.
[13] Hirata A, Hayano K, Ohira G, Imanishi S, Hanaoka T, Murakami K, Aoyagi T, Shuto K and Matsubara H. Volumetric histogram analysis of apparent diffusion coefficient for predicting pathological complete response and survival in esophageal cancer patients treated with chemoradiotherapy. Am J Surg 2020; 219: 1024-1029.
[14] Motoyama S, Sato Y, Sasaki T, Wakita A, Kawakita Y, Liu J, Nagaki Y, Saito H, Imai K, Konno H, Mizusawa KT and Minamiya Y. Efficacy and safety of neoadjuvant chemoradiotherapy following esophagectomy with japanese-style extended 3-field lymphadenectomy for thoracic esophageal cancer. Anticancer Res 2017; 37: 5837-5843.
[15] Wu Y and Li J. Change in maximal esophageal wall thickness provides prediction of survival and recurrence in patients with esophageal squamous cell carcinoma after neoadjuvant chemoradiotherapy and surgery. Cancer Manag Res 2021; 13: 2433-2445.
[16] Huang RW, Chao YK, Wen YW, Chang HK, Tseng CK, Chan SC and Liu YH. Predictors of pathological complete response to neoadjuvant chemoradiotherapy for esophageal squamous cell carcinoma. World J Surg Oncol 2014; 12: 170.
[17] Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, Mendez G, Feliciano J, Motoyama S, Lievre A, Uronis H, Elimova E, Grootscholten C, Geboes K, Zafar S, Snow S, Ko AH, Feeney K, Schenker M, Kocon P, Zhang J, Zhu L, Lei M, Singh P, Kondo K, Cleary JM and Moehler M; CheckMate 577 Investigators. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 2021; 384: 1191-1203.
[18] Lin Y, Liang HW, Liu Y and Pan XB. Nivolumab adjuvant therapy for esophageal cancer: a review based on subgroup analysis of CheckMate 577 trial. Front Immunol 2023; 14: 1264912.
[19] Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR. AJCC Cancer Staging Manual. 8th ed. New York: Springer. 2017.
[20] Javidfar J, Speicher PJ, Hartwig MG, D'Amico TA and Berry MF. Impact of positive margins on survival in patients undergoing esophagogastrectomy for esophageal cancer. Ann Thorac Surg 2016; 101: 1060-1067.
[21] Beukinga RJ, Hulshoff JB, Mul VEM, Noordzij W, Kats-Ugurlu G, Slart RHJA and Plukker JTM. Prediction of response to neoadjuvant chemotherapy and radiation therapy with baseline and restaging (18)F-FDG PET imaging biomarkers in patients with esophageal cancer. Radiology 2018; 287: 983-992.

[22] Cong L, Wang S, Gao T and Hu L. The predictive value of 18F-FDG PET for pathological response of primary tumor in patients with esophageal cancer during or after neoadjuvant chemoradiotherapy: a meta-analysis. Jpn J Clin Oncol 2016; 46: 1118-1126.
[23] Hammoudi N, Hennequin C, Vercellino L, Costantini A, Valverde A, Cattan P and Quero L. Early metabolic response to chemoradiotherapy by interim FDG PET/CT is associated with better overall survival and histological response in esophageal cancers. Dig Liver Dis 2019; 51: 887-893.
[24] Odawara S, Kitajima K, Katsuura T, Kurahashi Y, Shinohara H and Yamakado K. Tumor response to neoadjuvant chemotherapy in patients with esophageal cancer assessed with CT and FDG-PET/CT - RECIST 1.1 vs. PERCIST 1.0. Eur J Radiol 2018; 101: 65-71.
[25] Tandberg DJ, Cui Y, Rushing CN, Hong JC, Ackerson BG, Marin D, Zhang X, Czito BG, Willett CW and Palta M. Intratreatment response assessment with 18F-FDG PET: correlation of semiquantitative pet features with pathologic response of esophageal cancer to neoadjuvant chemoradiotherapy. Int J Radiat Oncol Biol Phys 2018; 102: 1002-1007.
[26] van Rossum PS, Fried DV, Zhang L, Hofstetter WL, van Vulpen M, Meijer GJ, Court LE and Lin SH. The incremental value of subjective and quantitative assessment of 18F-FDG PET for the prediction of pathologic complete response to preoperative chemoradiotherapy in esophageal cancer. J Nucl Med 2016; 57: 691-700.
[27] Xi M, Liao Z, Hofstetter WL, Komaki R, Ho L and Lin SH. (18)F-FDG PET response after induction chemotherapy can predict who will benefit from subsequent esophagectomy after chemoradiotherapy for esophageal adenocarcinoma. J Nucl Med 2017; 58: 1756-1763.
[28] Heneghan HM, Donohoe C, Elliot J, Ahmed Z, Malik V, Ravi N and Reynolds JV. Can CT-PET and endoscopic assessment post-neoadjuvant chemoradiotherapy predict residual disease in esophageal cancer? Ann Surg 2016; 264: 831-838.
[29] Wang R, Zhou X, Liu T, Lin S, Wang Y, Deng X and Wang W. Gross tumor volume predicts survival and pathological complete response of locally advanced esophageal cancer after neoadjuvant chemoradiotherapy. Front Oncol 2022; 12: 898383.
[30] Li Y, Wu G, Yang W, Wang X, Duan L, Niu L, Zhang Y, Liu J, Hong L and Fan D. Prognostic value of circulating tumor cells detected with the CellSearch system in esophageal cancer patients: a systematic review and meta-analysis. BMC Cancer 2020; 20: 581.
[31] Matsushita D, Arigami T, Okubo K, Sasaki K, Noda M, Kita Y, Mori S, Uenosono Y, Ohtsuka T and Natsugoe S. The diagnostic and prognostic value of a liquid biopsy for esophageal cancer: a systematic review and meta-analysis. Cancers (Basel) 2020; 12: 3070.
[32] Wang S, Du H and Li G. Significant prognostic value of circulating tumor cells in esophageal cancer patients: a meta-analysis. Oncotarget 2017; 8: 15815-15826.
[33] Zhang Y, Deng H, Chen G, Tang Z, Mao J, Mi Y, Cui S, Zhang Y, Wang N and Wang L. Clinicopathological and prognostic value of circulating tumor cells in esophageal carcinoma: a meta-analysis. Ann Palliat Med 2020; 9: 4271-4282.