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# Potential of Baseline Computed Tomography to Predict Long-Term Survival of Patients With Locally Advanced Esophageal Cancer Treated With Preoperative Chemotherapy

## *A Retrospective Cohort Study*

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**Abstract:** In this study, we evaluated the efficacy of baseline computed tomography (CT) signs and postoperative TN stages on survival of patients with advanced esophageal squamous cell carcinoma with preoperative chemotherapy. Consecutive patients (n = 130) with preoperative chemotherapy and radical esophagectomy from January 2006 to December 2011 were enrolled in this study retrospectively. Pathological T and N stages were confirmed by surgery. Baseline CT signs of tumor length, tumor thickness, outer membrane features, total number of lymph node (tLN), short diameter of the largest lymph node (SDL), and clinical T and N stages were measured. Eight-year overall survival (OS) and disease-free survival (DFS) were estimated using Kaplan–Meier and Cox proportional hazards regression analyses to determine associations between baseline CT signs and survival outcomes. Kaplan–Meier analysis showed that tLN number, largest LN short axis diameter, pT, and pN stages all correlated with OS significantly. And the total tLN number, SDL and pN stages significantly correlated with DFS. In Cox analyses, total tLN number (>6) and pN stage were significantly associated with OS (hazard ratio [HR]: 1.55 [95% CI, 1.13–2.11, $P = 0.006$] and HR: 1.49 [95% CI, 1.17–1.90, $P = 0.001$], respectively). Cox regression analysis showed that OS index was predictive of 1- to 3-year survival. Total number of lymph node in baseline CT provides equal efficiency compared to pN stages in the prediction of 8-year long-term survival outcomes for advanced esophageal squamous cell carcinoma patients with preoperative chemotherapy.

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**Abbreviations**: CT = computed tomography, DFS = disease-free survival, EUS = endoscopic ultrasound, LN = lymph node, OS = overall survival, PET = positron emission tomography, SDL = short diameter of the largest lymph node, tLN = total number of lymph nodes.

## INTRODUCTION

Esophageal cancer is one of leading causes of cancer-related deaths worldwide. Squamous cell carcinomas are significantly more common than adenocarcinomas and other malignancies in Asian patients.[1] Patients with locally advanced esophageal cancer have a poor prognosis with surgical treatment, with a median survival time of only 9 to 24 months.[2–7] Evidence from some clinical trials and meta-analyses shows that esophageal cancer patients can benefit from preoperative chemo-radiation therapy and preoperative chemotherapy.[8–10] Although the preoperative chemoradiotherapy regimen evaluated in the CROSS trial was thought to be the better preoperative combinational plan,[11–13] data from FFCD9901 suggested preoperative chemoradiotherapy increased the incidence of complications and mortality.[14] The role of preoperative chemotherapy in treating esophageal carcinoma has been gradually accepted.

Computed tomography (CT), endoscopic ultrasound (EUS), and $^{18}$F-fluorodeoxyglucose-positron emission tomography ($^{18}$F-FDG-PET)/CT are the most commonly used imaging tools for the evaluation of the baseline manifestations of esophageal cancer. EUS is considered superior for the diagnosis of T stage disease, while CT and PET-CT provide greater specificity for the diagnosis of lymph node (LN) metastasis.[15] Chest CT is inexpensive, easy to perform, and reproducible, and is therefore most commonly used in clinical practice for staging tumors, assessing treatment responses, and follow-up surveillance. Baseline CT imaging, which is a routine clinical method of initial evaluation for esophageal cancer patients, can be used to determine the tumor extent, aggressiveness, and lymphadenopathy. Baseline CT plays an important role in deciding the treatment strategy and predicting the prognosis. For the patients who have undergone surgery after neoadjuvant therapy, the postoperative pathological stage is considered to be the best prognostic factor. However, this can only be determined after surgery. Furthermore, pathological stage is also affected by the baseline condition and effect of treatment on the tumor.

There have been relatively few studies of the relationship between baseline CT signs and long-term survival for advanced esophageal squamous cell carcinoma patients with preoperative

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chemotherapy. Compared to postoperative pathological stages, the impact of baseline CT signs on long-term prognosis remains to be clearly defined. Therefore, we conducted a retrospective cohort study of esophageal squamous cell cancer patients, in which we evaluated the efficacy of baseline CT signs for the prediction of patient survival.

## METHODS

### Study Population

The retrospective cohort study was approved by the Ethics Committee of our hospital with a waiver of informed consent. This study included all esophageal squamous cell cancer patients confirmed by pathology, and received neoadjuvant chemotherapy from January, 2006 to December, 2011. All patients had pathohistological results by gastroscopy and received baseline enhanced CT scan before chemotherapy. According to the 7th edition of the UICC-AJCC TNM classification for esophageal cancer,[16] the patients were accorded with clinical stages >cT2 and/or cN+.

Patients were excluded as follows: pathologically proved other histological types of esophageal carcinoma; they underwent other preoperative therapies (e.g., radiotherapy) simultaneously; they had multiple primary esophageal cancers; they died within 30 days after surgery; their CT data could not be obtained or interpreted; and radical surgical operation could not be performed due to tumor progression or any other reasons.

### Image Interpretation

Baseline CT images obtained before chemotherapy were observed by 2 independent radiologists who were blind to the clinical data of patients. The CT imaging indicators measured as followed:

(1) Tumor length: The longest diameter obtained in sagittal image.
(2) Tumor thickness: The thickest region of tumor wall in axial image.
(3) Tumor CT value: The region of interest (ROI) was placed on the thickest region of tumor in axial image.
(4) Tumor outer membrane surface features: Smooth, coarse, or nodular convex.
(5) Total LN numbers: All visible LNs located in the cervical, thoracic, and abdominal regions according the UJCC-AJCC TNM staging.
(6) Shortest diameter of the largest regional lymph node (SDL).

The mean values of the CT indicators measured by 2 radiologists were calculated for statistical analysis. Clinical T stage was defined with these criteria: stage cT2, esophageal tumor wall thickness >5 mm with high enhancement and smooth outer membrane surface; cT3, esophageal tumor penetrated adventitia with irregular outer membrane surface; and cT4, esophageal tumor invaded adjacent structures including bronchi, aorta, pericardium, or vertebrae.[17] Clinical N stage was defined as follows: positive metastatic nodes were determined as SDL >8 mm[18] and cN stage was diagnosed by the number of positive LNs according the UJCC-AJCC TNM staging.

### Pathological Staging

Pathological staging was conducted for each patient after surgery by an experienced pathologist. The pathologist was blinded to the patient's clinical information.

### Follow-Up

All patients were followed up as part of the research study, and data were censored 8 years after CT imaging if patients were still alive. Date of death was recorded for deceased patients allowing overall survival (OS) at 8 years to be assessed. Date of disease-free survival (DFS) was noted from the baseline CT scan time to tumor progression, and patients alive and disease-free were censored at the last follow-up. Cut-off date was determined as 1st June 2014. None of patients lost to follow-up.

### Statistical Analysis

Tumor length and thickness were converted into binary variables based on the medians. The SLN was converted into a binary variable using a 10 mm cut-off value. The baseline total LN numbers were divided into 4 groups; 0 to 1, 2 to 6, 7 to 8, and ≥9. Kaplan–Meier survival estimates with log-rank tests were used to analyze the association between CT factors/pathological stages and survival outcomes. Multivariate logistic regression analysis using a stepwise backward method was conducted to find independent prognostic factors for death or recurrence and to acquire the adjusted hazard ratios (HRs). OS index was calculated according to the adjusted hazard ratios, and then a table associating OS index with 1-, 2-, and 3-year survival rates was established. $P < 0.05$ was considered to indicate statistical significance. Calculations were performed using the Statistical Package for Social Sciences Program, version 22.0 (SPSS, Chicago, IL).

## RESULTS

### Patients

There were 167 patients with esophageal squamous cell carcinoma and preoperative chemotherapy in this cohort study. According the exclusion criteria, 37 cases were excluded. Two patients died within 30 days after surgery because of serious pulmonary and mediastinal infection (Figure 1). Finally 130 patients were included in this study (Figure 1, Table 1). According to the 7th Edition of the UICC-AJCC TNM Classification for Esophageal Cancer,[16] all patients classified as >cT2 and/or cN+ were included in this study. A majority of the patients (98%; 127/130) received a platinum-based 2-drug combination, mainly paclitaxel (175 mg/m$^2$, iv, d1 Q21) and cisplatin (25 mg/m$^2$,

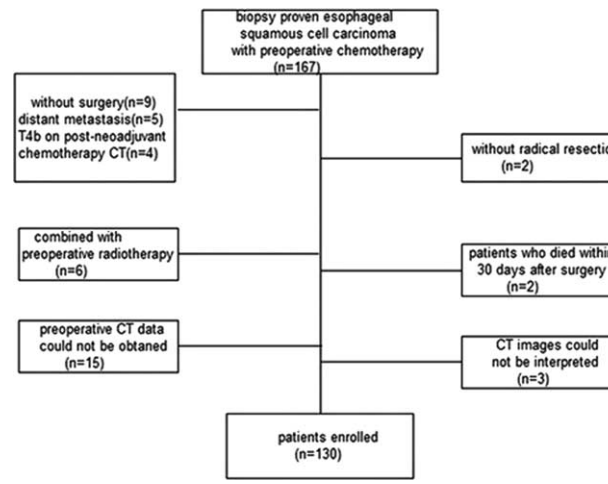


**FIGURE 1.** Flow chart of patient enrolment.

**TABLE 1.** Summary of Patient Characteristics

| Characteristics | Number | Percent |
|---|---|---|
| Sex | | |
| Male | 101 | 77.7% |
| Female | 29 | 22.3% |
| Age (median, range) | | 58 (42–75) |
| Location | | |
| Upper 1/3 | 35 | 26.9% |
| Middle 1/3 | 55 | 42.3% |
| Lower 1/3 | 40 | 30.8% |
| Surgical method | | |
| Transhiatal | 17 | 13.1% |
| Modified McKeown | 97 | 74.6% |
| Modified Ivor-Lewis | 10 | 7.7% |
| Modified Sweet | 6 | 4.6% |

iv, d1–3 Q21), with the other patients received nedaplatin (80 mg/$m^2$) combined with paclitaxel. A total of 1 to 4 chemotherapy cycles were administered before surgery at 3 to 6 weeks after neoadjuvant chemotherapy.

## Survival Analysis

Univariate Kaplan–Meier analysis showed that baseline total LN was significantly associated with OS ($P < 0.001$) and DFS ($P = 0.002$) (Table 2, Figure 2). The SDL was also significant for OS ($P = 0.039$) and DFS ($P = 0.013$) (Table 2, Figure 2). Greater baseline total LN and/or larger SDL were associated with poorer survival, while CT characteristics and clinical staging were not significant for survival.

The univariate Kaplan–Meier analysis showed that patients with higher pT showed statistically poorer OS ($P = 0.016$), but similar DFS compared with patients with lower pT ($P = 0.095$). Patients with higher pN showed statistically poorer OS ($P < 0.001$) and DFS ($P < 0.001$) (Figure 3).

Multivariate Cox regression analysis showed baseline total LN and pN were independent predictors of OS and DFS (Table 3).

## Association of OS Index With 1-, 2-, and 3-Year Survival Rates

The OS index was calculated as $1.55 \times$ total number of lymph nodes (tLN) $+ 1.49 \times$ pN according to the multivariate analysis. Baseline total LN values of 0 to 1, 2 to 6, 7 to 8, and $\geq 9$ were recorded as 1, 2, 3, and 4, respectively; pN was recorded as 0, 1, 2, and 3. Table 4 shows the association between OS index and survival rates. Higher OS index values were associated with lower survival rates.

# DISCUSSION

Esophageal cancer baseline CT signs before neoadjuvant therapy can indicate the range of tumor invasion and LN

**TABLE 2.** Univariate Analysis of Baseline CT Characteristics According to OS and DFS

| | | Overall Survival | | | Disease-Free Survival | | |
|---|---|---|---|---|---|---|---|
| Characteristics | No. | Rate | 95% CI | *P* | Rate | 95% CI | *P* |
| tLN | | | | <0.001 | | | 0.002 |
| 0–1 | 5 | 100 | / | | 100 | / | |
| 2–6 | 81 | 56 | 43 to 69 | | 69 | 58 to 80 | |
| 7–8 | 25 | 37 | 17 to 57 | | 67 | 46 to 88 | |
| ≥9 | 19 | 8 | 0 to 22 | | 10 | 0 to 28 | |
| cT | | | | 0.738 | | | 0.062 |
| T2 | 16 | 46 | 17 to 75 | | 87 | 70 to 100 | |
| T3 | 53 | 45 | 22 to 58 | | 49 | 34 to 64 | |
| T4 | 61 | 46 | 29 to 63 | | 66 | 50 to 82 | |
| cN | | | | 0.251 | | | 0.503 |
| N0 | 11 | 70 | 42 to 98 | | 62 | 26 to 98 | |
| N1 | 64 | 50 | 49 to 79 | | 69 | 57 to 81 | |
| N2 | 38 | 35 | 17 to 53 | | 48 | 28 to 68 | |
| N3 | 12 | 23 | 0 to 61 | | 27 | 0 to 68 | |
| Outer membrane surface | | | | 0.082 | | | 0.164 |
| Smooth | 69 | 47 | 28 to 66 | | 65 | 51 to 79 | |
| Coarse and/or nodular convex | 61 | 37 | 19 to 55 | | 54 | 38 to 70 | |
| Tumor length, cm | | | | 0.838 | | | 0.488 |
| >7 | 72 | 41 | 33 to 49 | | 60 | 43 to 77 | |
| ≤7 | 58 | 49 | 34 to 64 | | 61 | 45 to 77 | |
| Tumor thickness, mm | | | | 0.652 | | | 0.593 |
| >17 | 66 | 40 | 23 to 57 | | 64 | 49 to 79 | |
| ≤17 | 64 | 44 | 22 to 66 | | 56 | 42 to 70 | |
| SDL | | | | 0.039 | | | 0.013 |
| >10 | 73 | 29 | 15 to 43 | | 46 | 30 to 62 | |
| ≤10 | 57 | 59 | 42 to 66 | | 76 | 64 to 88 | |

CI = confidence interval, CT = computed tomography, DFS = disease-free survival, LN = lymph node, OS = overall survival, SDL = short diameter of the largest lymph node, tLN = total number of lymph node.

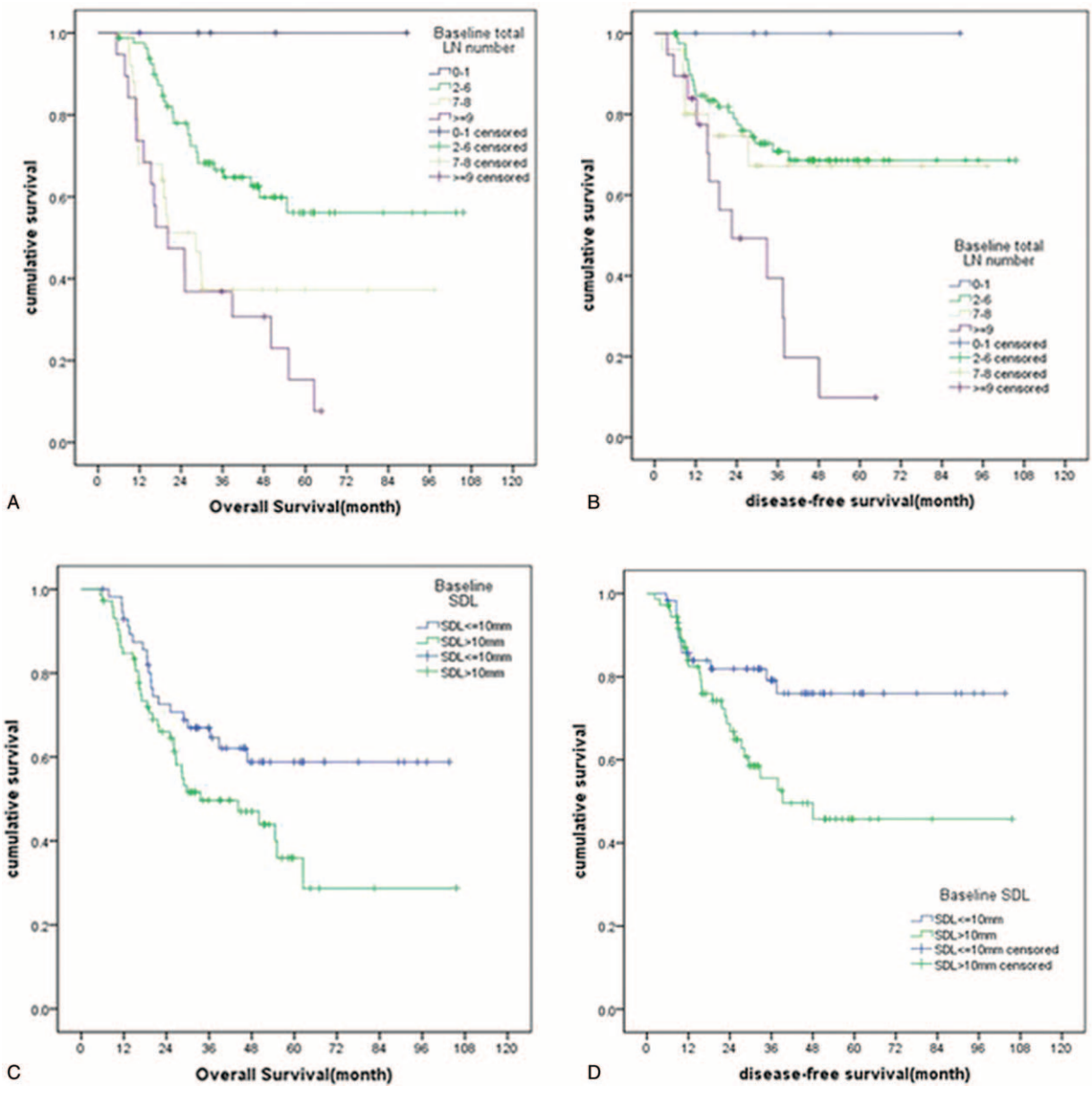


**FIGURE 2.** (A–D) Kaplan–Meier curves of correlation of baseline computed tomography characteristics with survival outcomes. (A) Total LN number and OS ($P < 0.001$); (B) total LN number and DFS ($P < 0.001$); (C) short diameter of the largest LN and OS ($P = 0.039$); and (D) short diameter of the largest LN and DFS ($P = 0.039$). DFS = disease-free survival, LN = lymph node, OS = overall survival.

dissemination. Compared with postoperative pathological stages, the impact of baseline CT signs on long-term survival remains to be established. Many North American institutions continue to adopt preoperative chemoradiotherapy (CROSS trial) in the treatment of esophageal cancer patients that demonstrate more locally advanced disease.[11] But FFCD9901 trial indicated preoperative chemoradiotherapy increased the incidence of complications and mortality.[14] Surgeons should consider the influence to the surgery caused by the radiation. Meanwhile, our cohort study began to observe the patients from 2006. At that time in early 2006, preoperative chemoradiotherapy and chemotherapy still had some controversial issues to become the approved standard therapy. So, we opted to only include the patients with neoadjuvant chemotherapy to observe and analyze.

An important finding of our study was that the tLNs detected in baseline CT examinations showed a strong association with the long-term survival of esophageal cancer patients with neoadjuvant chemotherapy and surgery. When we divided the baseline total LN values into 4 groups (0–1, 2–6, 7–8, and ≥9), the results indicated that a higher baseline total LN number was associated with poorer OS and DFS survival, with a statistically significant difference observed in comparisons of the OS between any 2 of the groups.

Previous studies have shown that higher total numbers of resected LNs and higher numbers of negative LN are associated

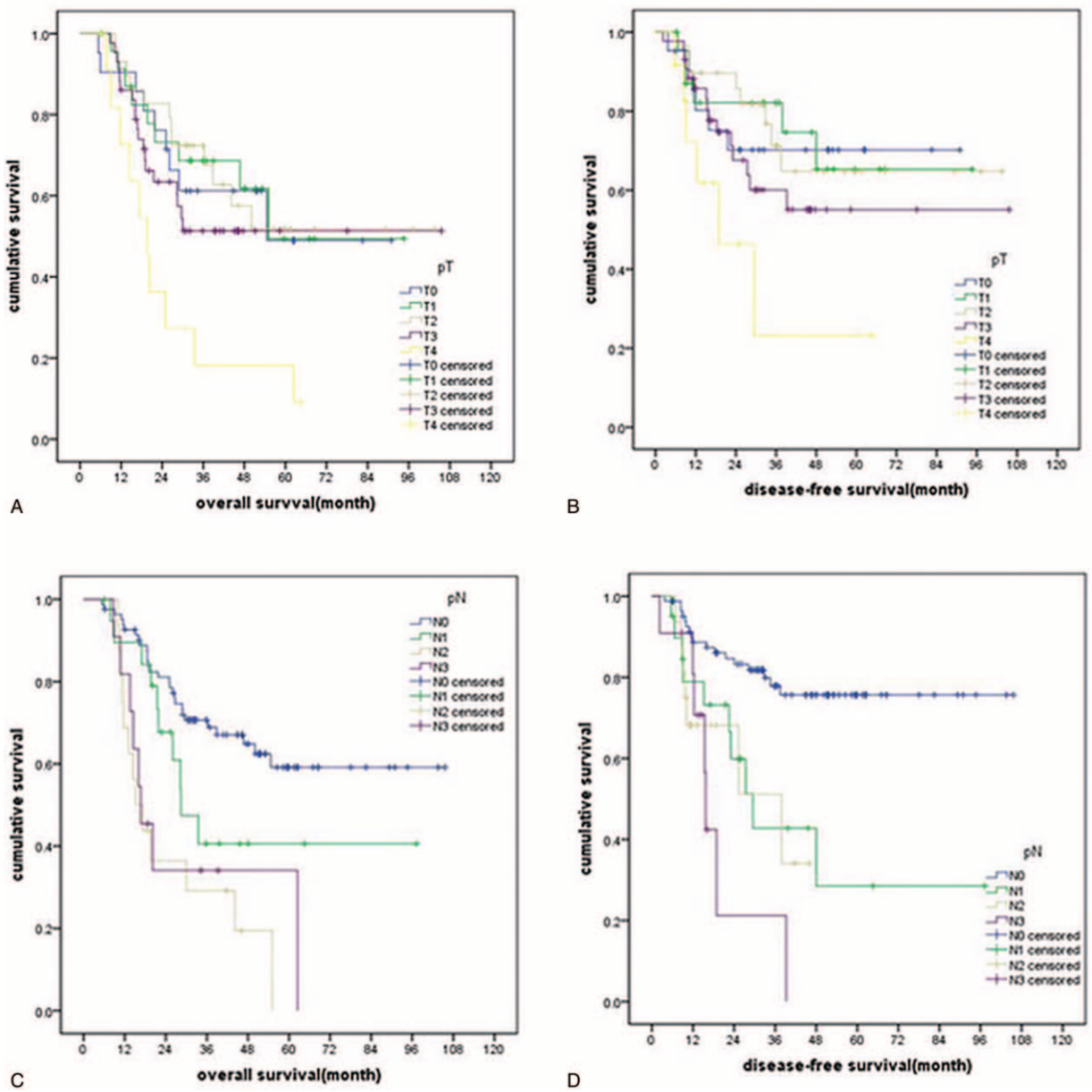


**FIGURE 3.** (A–D) Kaplan–Meier curves of correlation of pT and pN stages with survival outcomes. (A) pT stages and OS ($P = 0.016$); (B) pT stages and DFS ($P = 0.095$); (C) pN stages and OS ($P < 0.001$); and (D) pN stages and DFS ($P < 0.001$). DFS = disease-free survival, LN = lymph node, OS = overall survival.

with better OS of esophageal cancer patients.[19] Due to the poor diagnostic power of CT in differentiating positive or negative metastatic LN status (sensitivity, 30%–60%; specificity, 60%–80%),[20,21] it is very difficult to determine the number of metastatic lymph nodes accurately before surgery. Metastatic LNs exhibit morphological changes, which are typically larger in size and irregular in shape. Furthermore, as the fat inside the metastatic LN is replaced by tumor cells, the LN density increases. The tLNs detected by CT increases with these changes; therefore, to some extent, the tLNs detected by CT indirectly reflects the total number of metastatic LNs. The results of our study also confirmed that the total LN number detected in baseline CT examinations influences the long-term prognosis of patients with neoadjuvant chemotherapy and surgery.

We also found that SDL was related to prognosis. Larger SDL (>10 mm) was associated with poorer OS and DFS. The largest LN detected in CT examinations indicated a higher probability of metastasis than other smaller LNs. As the largest LN is not always completely removed by neoadjuvant chemotherapy, the potential tumor activity might have an impact to the long-term prognosis of patients. However, in the multivariate analysis, the SDL had a mild influence to long-term survival compared to the influence of the tLNs and pN stage.

**TABLE 3.** Results of Multivariate Cox Regression Analysis

| Items | HR | 95% CI | *P* |
|---|---|---|---|
| OS | | | |
| tLN | 1.55 | 1.13–2.11 | 0.006 |
| pN | 1.49 | 1.17–1.90 | 0.001 |
| DFS | | | |
| tLN | 1.55 | 1.08–2.21 | 0.017 |
| pN | 1.71 | 1.28–2.28 | <0.001 |

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, OS = overall survival, tLN = total number of lymph node.

In accordance with previous studies, the pT and pN stages were associated with OS of esophageal squamous cancer patients with neoadjuvant chemotherapy, while the pN stage was associated with DFS. This indicates that the extent of LN metastasis has an important impact on patient prognosis in that patients with a higher number of metastatic LNs, the tumor tends to disseminate to more distant sites by the lymphatic channels, and the probability of tumor recurrence and metastasis is increased.

Multivariate Cox regression analysis showed that the baseline total LN number and pN were independent predictors of OS and DFS. The HRs for the baseline total LN number and pN in predicting OS were 1.55 and 1.49, respectively, while the values for DFS were 1.55 and 1.71, respectively (Table 5). These values indicate that baseline total LN number and pN stage are important in long-term survival prognosis and the impact of these factors should be considered in evaluating the prognosis of patients with esophageal squamous cancer after neoadjuvant chemotherapy.

OS index can be calculated according to the HRs obtained in Cox regression analysis. We used the calculated OS indexes to predict 1-, 2-, and 3-year survival rates of patients. This approach provides objective data for clinicians to evaluate patient prognosis. Nomogram, another statistical method, has been reported to predict survival outcomes after neoadjuvant chemoradiotherapy for esophageal cancer,[22] although these reports are rare.

**TABLE 4.** OS Index and Survival Rates

| OS Index | 1-year, % | 2-year, % | 3-year, % |
|---|---|---|---|
| 1.55 | 100 | 100 | 100 |
| 3.10 | 83 | 78 | 75 |
| 4.59 | 91 | 71 | 28 |
| 4.65 | 71 | 64 | 56 |
| 6.08 | 75 | 47 | 23 |
| 6.14 | 75 | 50 | 25 |
| 6.20 | 71 | 43 | 14 |
| 7.57 | 80 | 40 | NA |
| 7.63 | 50 | 25 | 0 |
| 7.69 | 50 | NA | NA |
| 9.12 | 50 | NA | NA |
| 9.18 | 50 | 25 | 0 |
| 10.67 | 50 | 25 | 0 |

NA = not available, OS = overall survival

**TABLE 5.** Univariate Analysis of pT and pN According to OS and DFS

| | | Overall Survival | | | Disease-Free Survival | | |
|---|---|---|---|---|---|---|---|
| Characteristics | No. | Rate | 95% CI | *P* | Rate | 95% CI | *P* |
| pT | | | | 0.016 | | | 0.095 |
| T0 | 21 | 49 | 22 to 76 | | 70 | 50 to 90 | |
| T1 | 24 | 49 | 21 to 77 | | 65 | 40 to 90 | |
| T2 | 29 | 52 | 32 to 72 | | 65 | 45 to 85 | |
| T3 | 43 | 51 | 35 to 67 | | 55 | 37 to 73 | |
| T4 | 12 | 9 | 0 to 27 | | 23 | 0 to 59 | |
| pN | | | | <0.001 | | | <0.001 |
| N0 | 82 | 59 | 46 to 72 | | 76 | 66 to 86 | |
| N1 | 20 | 41 | 17 to 65 | | 29 | 0 to 58 | |
| N2 | 16 | 0 | / | | 34 | 0 to 69 | |
| N3 | 11 | 0 | / | | 0 | / | |

CI = confidence interval, DFS = disease-free survival, OS = overall survival.

Previous studies showed that esophageal tumor length determined by endoscopy was associated with patient prognosis,[23] and CT multiplanar reconstruction of coronary and sagittal images could be used to measure tumor length. CT estimates of tumor length made with multiplanar reformatted images were more accurate than those made with axial scans alone.[24] Our study showed that tumor length measured by baseline CT had no correlation with DFS and OS. We speculated that this was because tumor length does not necessarily reflect the depth of invasion because of the nonuniform growth of tumors.

Swisher et al[25] reported that postchemoradiation therapy esophageal wall thickness in CT examination correlated with pathologic response for esophageal cancer patients but not with 3-year survival. We also found that baseline CT examinations did not correlate with prognosis. It can be speculated that, because tumor thickness is influenced by gross tumor type, greater thickness does not always correlate with depth of invasion in some tumors.

Recently, other imaging modalities including EUS and PET are performed before surgery to assess resectability.[26] EUS provides accurate initial staging of locoregional esophageal cancer. EUS-FNA is more sensitive than CT and more accurate than CT or EUS for nodal staging.[27] Some studies have reported PET scan could predict histopathologic complete response and outcome after definitive or preoperative chemoradiotherapy in patients with esophageal cancer.[28–30] Unfortunately, at the time early 2006, our hospital did not own the PET/CT and EUS-FNA facilities. In future study, we propose to compare the role of these different baseline imaging modalities for the long-term survival of esophageal cancer patients.

Our study had several limitations. First, although this study contained a relatively large cohort of patients sample size, it was a single-center's retrospective study. However, no definite prognostic factors obtained in baseline CT examinations have been reported previously. We were unable to determine suitable signs to divide into groups to perform the prospective study; therefore, we conducted a retrospective study to identify prognostic factors among the baseline CT signs, which provides the

basis of future research. Second, we did not add the CT value after enhancement into the data analysis because the CT value measurement was sometimes influenced by blood circulation and instability. Third, the majority of patients included in this study were male (77%). Gender factors may challenge the external validity of this study.

## CONCLUSIONS

This study provides evidence that the tLNs identified in baseline CT examinations can be used to predict 8-year OS and DFS of patients with esophageal cancer who received preoperative chemotherapy with similar accuracy compared with postoperative pathological N stages. According to the HRs from Cox regression analysis, the calculated OS index can be used to predict the 1 to 3-year survival rates of patients. This information is important in improving individualized treatment programs.

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