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# The long-term impact of tumor burden in pT3N0M0 esophageal squamous cell carcinoma

## A propensity score-matched analysis

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**Abstract**

The purpose of this study was to assess the impact of tumor burden on the survival of patients with pathologic T3N0M0 (pT3N0M0) esophageal squamous cell carcinoma (ESCC).

A total of 84 patients with pathologic T3N0M0 ESCC treated with radical esophagectomy and 3-field lymphadenectomy (3-FL) from January 2008 to December 2009 in our center were analyzed. Receiver-operating characteristic (ROC) curve analysis was performed to calculate the optimal cutoff value. The Kaplan–Meier method and log-rank test were used to assess the overall survival (OS) differences between groups. A regression model was applied to identify prognostic factors for OS. Propensity score matching (PSM) was performed to adjust for the imbalance and indication biases in the 2 groups.

The median follow-up time was 62 months (range, 1–84 months), and the 5-year OS rate was 62% (95% confidence interval, 52.2–71.8%). According to the ROC curve analysis, the optimal cutoff values for the maximal esophageal wall thickness, tumor length, and tumor volume were 1.3 cm, 5.9 cm, and 18.6 cc, respectively. Univariate analysis revealed that maximal esophageal wall thickness >1.3 cm ($P = .014$), tumor volume >18.6 cc ($P < .001$), and vascular invasion ($P < .001$) were significantly associated with OS. The multivariate Cox regression model identified tumor volume and vascular invasion as factors affecting OS. After propensity matching, patients with a tumor volume ≤18.6 cc had a better OS than those with a tumor volume >18.6 cc (5-year OS, 85% vs 50%, $P = .008$).

Tumor volume may serve as a good prognostic factor for patients with pT3N0M0 ESCC treated with radical esophagectomy and 3-FL. Larger-scale studies are warranted to validate these findings.

**Abbreviations:** 3-FL = 3-field lymphadenectomy, AJCC = American Joint Committee on Cancer, AUC = area under concentration-time curve, CT = computed tomography, ESCC = esophageal squamous cell carcinoma, GTV = gross tumor volume, GTV-P = planning target volume, LE = lower 3rd ESCC, M = distant metastasis, ME = middle 3rd ESCC, N = lymph node metastasis, OS = overall survival, PFS = progression-free survival, PSM = propensity score matching, pT3N0M0 = pathologic T3N0M0, ROC = receiver-operating characteristic, T = primary tumor invasion, UE = upper 3rd ESCC.

**Keywords:** esophageal squamous cell carcinoma, prognosis, propensity score matching, tumor volume

## 1. Introduction

The incidence of esophageal cancer and number of esophageal cancer-related deaths in China are the highest in the world, and the main pathologic type is squamous cell carcinoma. Despite significant improvements in diagnostic accuracy and treatment methods for esophageal squamous cell carcinoma (ESCC), the prognosis of ESCC remains unsatisfactory, with a 5-year survival rate of patients with ESCC in China of only 30.3%.[1,2]

Preoperative risk factor assessment plays a crucial role in decision-making regarding the optimal treatment regimens in ESCC. In addition to primary tumor invasion (T), the number of regional lymph nodes with metastasis (N), and distant metastasis (M), the 8th TNM staging system issued by American Joint Committee on Cancer (AJCC) also recommends the histologic type, tumor location, and tumor grade as prognostic factors for patients with esophageal carcinoma. Among pathologic T3N0M0 (pT3N0M0) ESCC cases, cases with grade 2 and 3 tumors in the lower one-third of the esophagus are classified as stage IIa, while cases in which the tumors are located in the upper and middle 3rds of the esophagus are classified as stage IIb.[3–5]

In addition to the influencing factors mentioned earlier, measurements of tumor burden, such as the thickness of the esophageal wall, tumor length, and tumor volume, have also been

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evaluated as the possible prognostic factors.[6–8] However, these studies mainly focused on the influence of tumor burden in cases of locally advanced ESCC treated with definitive radiotherapy. Here, we analyzed the impact of tumor burden on the long-term prognosis of patients with pT3N0M0 ESCC treated with radical esophagectomy and 3-field lymphadenectomy (3-FL).

## 2. Materials and methods

### 2.1. Patients

This study was approved by the Ethics Committee of the Fujian Provincial Tumor hospital (No. KT2018-013-01). All patients provided written informed consent prior to treatment, and all information was anonymized before analysis. Eighty-four consecutive ESCC cases who meet the following criteria were included in the study: Karnofsky score ≥70 points, histologically confirmed ESCC, treatment with radical esophagectomy and 3-FL with at least 15 lymph nodes resected, classified as pT3N0M0, and without a history of malignant disease. The patients who received neoadjuvant radiotherapy and/or chemotherapy were excluded. All patients were restaged according to the 8th TNM staging system issued by the AJCC.[9] For patients with pT3N0M0 ESCC, G1 and lower 3rd G2/3 cases were classified as stage IIa, and upper and middle 3rd G2/3 cases were classified as IIb.

### 2.2. Tumor burden evaluation

Patients underwent computed tomography (CT) scanning with Toshiba Asteionmulisice instruments in supine position with the arms above the head. The scan area ranged from the skull base to the 5th lumber spine. The following scan parameters were used: collimation, slice width 5 mm; 120 kVp; and 230 mAs. Multiplanar reformation was performed at the Sun Ultra AW 4.0 workstation, with a slice width of 1 mm. Two experienced imaging specialists in our hospital reviewed the pretreatment thoracic CT scans. Measurements of maximal esophageal wall thickness were performed retrospectively. The diameter of the thickest part of the primary tumor on the CT image was identified as the maximal esophageal wall thickness.

Barium sulfate mixed with water was instilled into the gastrointestinal tract, and https://en.wikipedia.org/wiki/X-ray was used and X-ray imaging was performed to obtain radiographs of the regions of interest. The barium enhances the visibility of the relevant parts of the esophagus by coating the inside wall of the tract to identify the length of esophageal carcinoma.

Imaging data from a prior CT scan were imported to the radiotherapy treatment planning system (Pinnacle, version 9.2; Philips Radiation Oncology System, Fitchburg, WI), and the primary tumor area was delineated on each image by 2 thoracic radiation oncologists independently in our hospital. The system was operated to reconstruct 3-dimensional (3D) images and calculate the tumor volume automatically.

The values of tumor burden mentioned above were calculated by 2 independent observers, with the data recorded. The maximal esophageal wall thickness, tumor length, and tumor volume were then calculated as the mean of the 2 independently calculated values.

### 2.3. Follow-up

Regular follow-up examination was conducted every 3 months the 1st year, every 6 months the next 2 years, and once per year thereafter. The routine examination included physical examination, routine blood tests, biochemical examination, thoracic and upper abdominal CT scanning, barium meal radiography, etc. December 2014 was the last censoring date for evaluating survival time. Survival time was defined as the interval between the date of surgery and death or last follow-up. The median follow-up time was 62 months (range, 1–84 months).

### 2.4. Statistical analysis

All recorded data were analyzed using SPSS (version 23.0; IBM Corp, Armonk, NY). Receiver-operating characteristic (ROC) curve analysis was performed to calculate the optimal cutoff value for predicting prognosis in ESCC. The Kendall test was used to determine the linear correlation between tumor volume and patients' clinicopathologic characteristics. The survival rate was calculated using the Kaplan–Meier method, and a log-rank test was used to assess the survival differences between groups. Cox proportional hazards regression analysis was performed to identify independent variables that were correlated with the patients' 5-year survival. Propensity score matching (PSM) was employed to create 2 balanced groups according to the cutoff values for each measurement of tumor burden. After matching, the influencing factors were compared using Chi-squared test. Kaplan–Meier methods were used to analyze overall survival (OS) in the matched groups. All tests were 2-sided, and a $P$-value $<.05$ was considered statistically significant.

## 3. Results

### 3.1. Patients' characteristics

A total of 84 patients (65 males and 19 females) meeting the inclusion criteria were enrolled (Table 1). The median patient age was 59 years (range, 34–80 years). The numbers of patients with tumors located in the upper 3rd (UE), middle 3rd (ME), and lower 3rd (LE) of the esophagus were 11 (13.1%), 46 (54.8%), and 27 (32.1%), respectively. The numbers of cases with tumor cell differentiation of G1, G2, and G3 were 15 (17.9%), 63 (75.0%), and 6 (7.1%), respectively. All the clinicopathologic characteristics were comparable between patients grouped by tumor volume, as shown in Table 2. Our study showed that tumor volume was associated with gender ($P<.001$). In addition, there was a positive correlation between the tumor volume and thickness of the esophageal wall ($r=0.535$, $P<.001$) and tumor length ($r=0.228$, $P<.038$). Also, there was a negative correlation between the tumor volume and gender ($r=-0.394$, $P<.001$).

### 3.2. Overall survival of the whole cohort

Among the 84 ESCC cases, the 1-year, 3-year, and 5-year OS rates were 88% (95% confidence interval [CI], 87.9–88.1%), 77% (95% CI, 76.9–77.1%), and 62% (95% CI, 61.9–62.1%), respectively. For the stage IIa cases, the 1-year, 3-year, and 5-year OS rates were 85% (95% CI, 84.9–85.1%), 69% (95% CI, 71.9–72.1%), and 61% (95% CI, 60.8–61.2%), respectively. For stage IIb cases, the 1-year, 3-year, and 5-year OS rates were 91% (95% CI, 90.9–91.1%), 84% (95% CI, 83.9–84.1%), and 64% (95% CI, 63.9–64.1%), respectively. There were no significant differences in the OS rates between the stage IIa and IIb cases ($\chi^2=0.001$, $P=.978$).

**Table 1**

**Characteristics of 84 patients with pT3N0M0 esophageal squamous cell carcinoma.**

| Characteristics | n (%) |
|---|---|
| Gender | |
| Male | 65 (77.4) |
| Female | 19 (22.6) |
| Age, yr | |
| ≤60 | 46 (54.8) |
| >60 | 38 (45.2) |
| Vascular invasion | |
| Yes | 77 (91.7) |
| No | 7 (8.3) |
| Tumor cell differentiation | |
| G1 | 15 (17.9) |
| G2, G3 | 69 (82.1) |
| Tumor location | |
| Upper and middle 3rd | 57 (67.9) |
| Lower 3rd | 27 (32.1) |
| Thickness of esophageal wall, cm | |
| ≤1.3 | 29 (34.5) |
| >1.3 | 55 (65.5) |
| Tumor length, cm | |
| ≤5.9 | 60 (71.4) |
| >5.9 | 24 (28.6) |
| Tumor volume, cc | |
| ≤18.6 | 36 (42.9) |
| >18.6 | 48 (57.1) |

### 3.3. Impact of maximal esophageal wall thickness on overall survival

The average maximal esophageal wall thickness for the whole cohort was 1.54 ± 0.47 cm (range, 0.7–2.6 cm). From the ROC curve analysis, the area under concentration-time curve (AUC) for the maximal esophageal wall thickness was 0.625 (95% CI, 0.506–0.744), and the sensitivity and specificity were 0.806 and 0.542, respectively. Based on the Jorden index (sensitivity + specificity − 1), the optimal cutoff value was 1.3 cm (Fig. 1A). For cases with a maximal esophageal wall thickness ≤1.3 cm (n = 29), the 1-year, 3-year, and 5-year OS rates were 97% (95% CI, 96.9–97.1%), 90% (95% CI, 89.9–90.1%), and 83% (95% CI, 82.9–83.1%), respectively. For ESCC cases with a maximal esophageal wall thickness >1.3 cm (n = 55), the 1-year, 3-year, and 5-year OS rates were 83% (95% CI, 82.9–83.1%), 70% (95% CI, 69.9–70.1%), and 51% (95% CI, 50.9–51.1%). From these results, the OS was significantly better for patients with a maximal esophageal wall thickness ≤1.3 cm ($\chi^2 = 6.064$, $P = .014$; Fig. 2A).

### 3.4. Impact of tumor length on overall survival

The average tumor length for the whole cohort was 4.73 ± 1.42 cm (range, 1.0–9.0 cm), and from the ROC curve analysis, the AUC for tumor length was 0.525 (95% CI, 0.390–0.657). Based on the Jorden index, the optimal cutoff value for tumor length was 5.9 cm (Fig. 1B). For ESCC cases with a tumor length ≤5.9 cm (n = 60), the 1-year, 3-year, and 5-year OS rates were 88% (95% CI, 87.9–88.1%), 77% (95% CI, 77.9–78.1%), and 65% (95% CI, 65.9–66.1%), respectively. For ESCC cases with a tumor length >5.9 cm (n = 24), the 1-year, 3-year, and 5-year OS rates were 85% (95% CI, 87.9–88.1%), 75% (95% CI, 74.8–75.2%), and 60% (95% CI, 53.8–54.2%), respectively. Statistical analysis showed no significant difference in the OS according to tumor length ($\chi^2 = 2.452$, $P = .117$). The survival curves for tumor length for the 2 groups are shown in the Figure 2B.

### 3.5. Impact of tumor volume on overall survival

The average tumor volume among all cases was 23.04 ± 8.10 cc (range, 11.0–36.0 cc). From the ROC curve analysis, the AUC for tumor volume was 0.75 (95% CI, 0.648–0.853), and the sensitivity and specificity were 0.806 and 0.604, respectively. Based on the Jorden index, the optimal cutoff value for tumor volume was 18.6 cc (Fig. 1C). For ESCC cases with a tumor volume ≤18.6 cc (n = 36), the 1-year, 3-year, and 5-year OS rates were 97% (95% CI, 96.9–97.1%), 92% (95% CI, 91.9–92.1%), and 83% (95% CI, 82.9–83.1%), respectively. For ESCC cases

**Table 2**

**Characteristics of patients with a tumor volume ≤18.6 cc and those with a tumor volume >18.6 cc before and after PSM.**

| | Before matching | | | | After matching | | | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | Tumor volume ≤18.6 cc n (%) | Tumor volume >18.6 cc n (%) | $\chi^2$ | *P*-value | Tumor volume ≤18.6 cc n (%) | Tumor volume >18.6 cc n (%) | $\chi^2$ | *P*-value |
| Gender | | | 13.059 | <.001 | | | 0.000 | 1.000* |
| Male | 21 (58.3) | 44 (91.7) | | | 21 (80.8) | 22 (84.6) | | |
| Female | 15 (41.7) | 4 (8.3) | | | 5 (19.2) | 4 (15.4) | | |
| Age, yr | | | 1.025 | .246 | | | 0.000 | 1.000 |
| ≤60 | 22 (61.1) | 24 (50.0) | | | 13 (61.5) | 13 (61.5) | | |
| >60 | 14 (38.9) | 24 (50.0) | | | 10 (38.5) | 10 (38.5) | | |
| Vascular invasion | | | 1.430 | .231* | | | 0.000 | 1.000* |
| No | 35 (97.2) | 42 (87.5) | | | 25 (96.2) | 25 (96.2) | | |
| Yes | 1 (2.8) | 6 (12.5) | | | 1 (3.8) | 1 (3.8) | | |
| Tumor cell differentiation | | | 0.676 | .411 | | | 0.000 | 1.000* |
| G1 | 5 (13.9) | 10 (20.8) | | | 2 (7.7) | 1 (3.8) | | |
| G2/G3 | 31 (86.1) | 38 (79.2) | | | 24 (92.3) | 25 (96.2) | | |
| Tumor location | | | 0.455 | .500 | | | 0.081 | .776* |
| Upper and middle | 23 (63.9) | 34 (70.8) | | | 17 (65.4) | 15 (57.7) | | |
| Lower | 13 (36.1) | 14 (29.2) | | | 9 (34.6) | 11 (42.3) | | |

* If n ≥ 40 and 1≤ theoretical frequency (T) < 5, the Fisher exact test was used to compare the influencing factors.

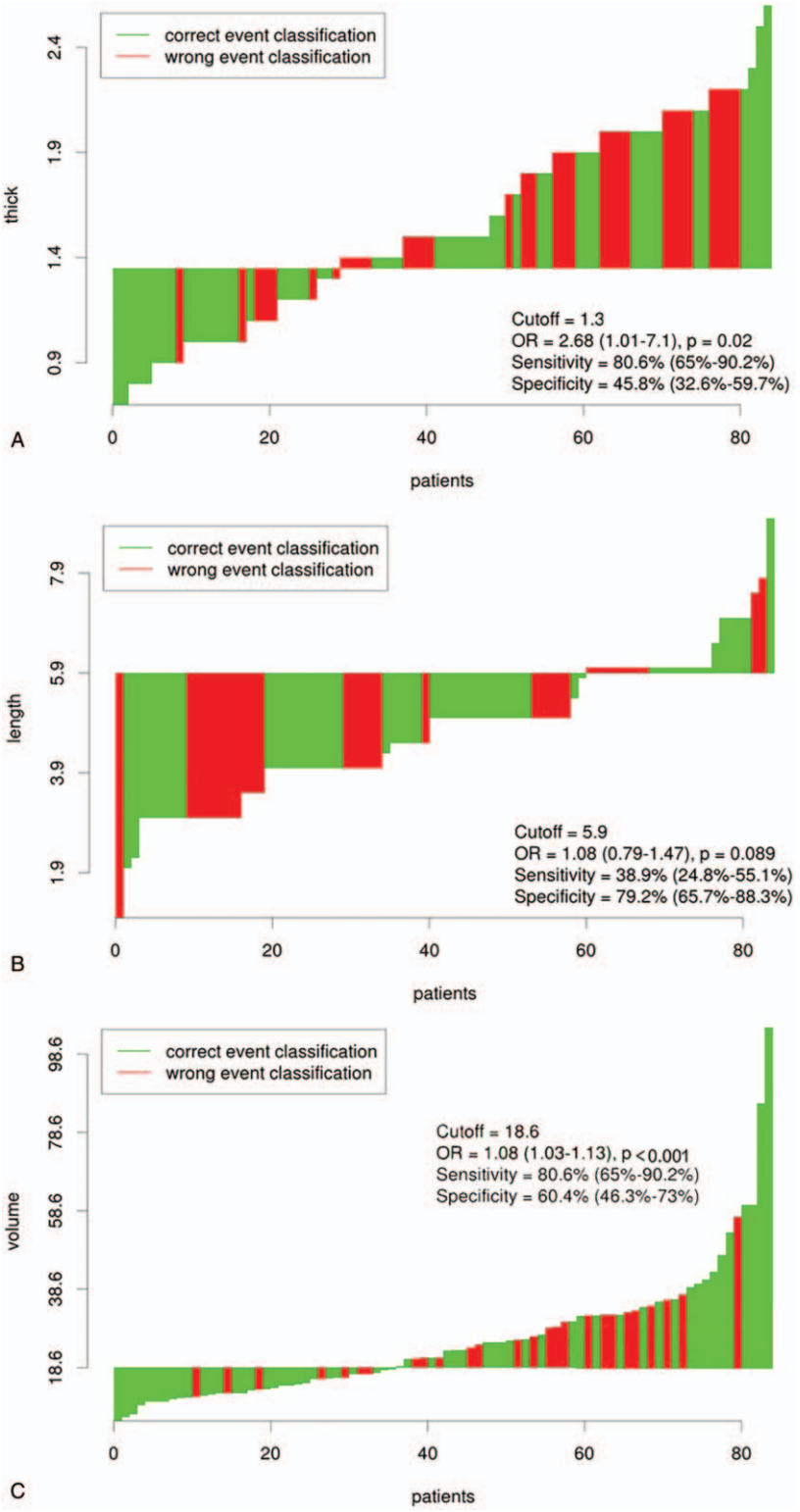


**Figure 1.** Waterfall plot of optimal dichotomization for 84 patients with esophageal squamous cell carcinoma. Optimal cutoff was evaluated for the events of death. Classification was performed using (A) the maximal esophageal wall thickness, (B) tumor length, and (C) tumor volume before propensity score matching.

with a tumor volume >18.6 cc (n = 48), the 1-year, 3-year, and 5-year OS rates were 81% (95% CI, 80.9–81.1%), 66% (95% CI, 65.9–66.1%), and 46% (95% CI, 45.9–46.1%), respectively. From these results, the OS was significantly better for patients with a tumor volume ≤18.6 cc ($\chi^2 = 13.433$, $P < .001$; Fig. 2C).

For G1 patients, the average tumor volume was 23.04 ± 8.17 cc (range, 11.0–36.0 cc), and tumor volume did not show any significant influence on the survival curve between according to the cutoff value of 18.6 cc ($P = .551$). For G2/3 cases, for which the average tumor volume was 25.91 ± 18.02 cc

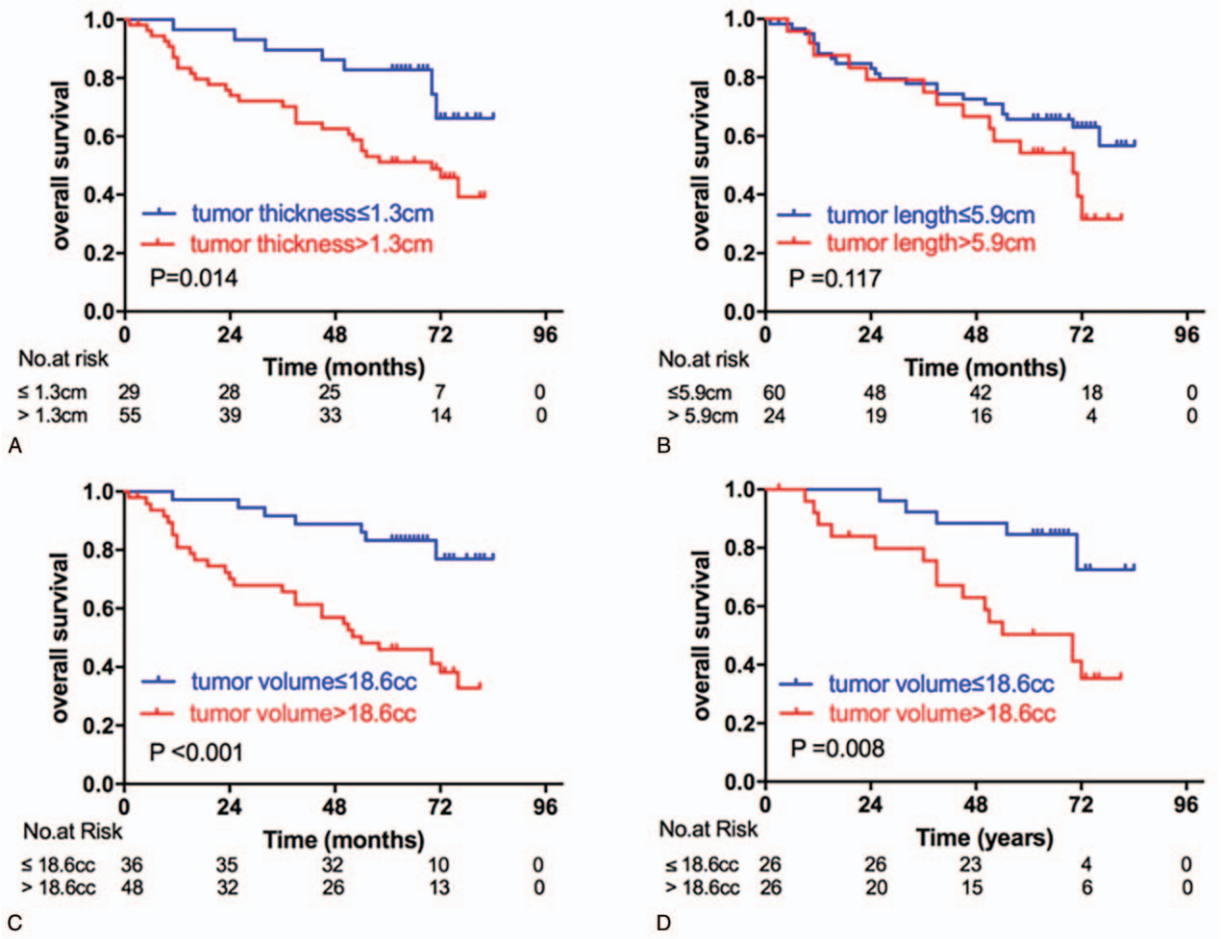


**Figure 2.** Kaplan–Meier survival curves for overall survival of 84 patients with esophageal squamous cell carcinoma, according to the (A) maximal esophageal wall thickness, (B) tumor length, (C) tumor volume before propensity score matching (PSM), and (D) tumor volume after PSM.

(range, 5.0–106.9 cc), patients with a tumor volume ≤18.6 cc had a better OS than those with a tumor volume >18.6 cc ($\chi^2=14.467$, $P<.001$).

### 3.6. Prognostic factors affecting overall survival in the whole cohort

Univariate analysis demonstrated that vascular invasion ($P<.001$), maximal esophageal wall thickness ($P=.014$), and tumor volume ($P<.001$) were significantly associated with OS among the patients with pT3N0M0 ESCC. Multivariate analysis confirmed that vascular invasion ($P=.003$) and tumor volume ($P=.043$) were independent prognostic factors in ESCC (Table 3).

### 3.7. Influence of tumor volume on overall survival with propensity score matching

Twenty-six pairs consisting of 26 patients each from the tumor volume ≤18.6 cc group and the tumor volume >18.6 cc group were matched 1-to-1 by PSM. The clinical characteristics of the 2 groups did not differ significantly after PSM (Table 2). Among the matched samples, patients with ESCC with a tumor volume ≤18.6 cc had a longer 5-year OS than those with a tumor volume >18.6 cc (85% vs 50%, $\chi^2=7.137$, $P=.008$; Fig. 2D).

## 4. Discussion

Staging factors including the depth of the primary invasion, tumor cell grade, and tumor location may not be sufficient to comprehensively predict the prognosis of patients with ESCC. Measurements of tumor burden such as the thickness of the esophageal wall, tumor length, and tumor volume have been evaluated as possible prognostic factors for locally advanced ESCC with definitive radiotherapy in recent studies.[10–12] In the present study, we demonstrated that patients with pT3N0M0 ESCC with a small tumor burden based on a maximal esophageal wall thickness ≤1.3 cm and tumor volume ≤18.6 cc had a better OS than those with a larger tumor volume. All of the patients in our study accepted radical esophagectomy and 3-FL, which eliminated the impact of surgical mode on the prognosis, and the other indication biases were adjusted by performing the PSM analysis to create 2 balanced groups. Among the matched samples, the patients with ESCC with a tumor volume ≤18.6 cc had a longer 5-year OS than those with a tumor volume >18.6 cc (85% vs 50%, $P=.008$).

For patients with pT3N0M0 ESCC, tumor cell grade and tumor location were recommended as staging factors in the 8th AJCC guideline but were found to not be sufficient to predict the prognosis in some studies. Situ et al[13] studied 302 patients with pT3N0M0 ESCC and found that the 5-year OS did not differ among cases with G1 tumor cell differentiation G1 vs G2/3. In

**Table 3**

**Univariate and multivariate analysis of 5-year overall survival (OS).**

| Variables | Univariate | | | | Multivariate | | |
|---|---|---|---|---|---|---|---|
| | n | 5-yr OS, % | $\chi^2$ | *P*-value | Hazard ratio | 95% CI | *P*-value |
| Gender | | | 2.903 | .088 | | | .387 |
| Male | 65 | 59 | | | 1 | | |
| Female | 19 | 74 | | | 0.614 | 0.203–1.855 | |
| Age, yr | | | 0.003 | .955 | | | .873 |
| ≤60 | 46 | 63 | | | 1 | | |
| >60 | 38 | 61 | | | 1.062 | 0.508–2.23 | |
| Vascular invasion | | | 14.153 | <.001 | | | .003 |
| No | 7 | 67 | | | 1 | | |
| Yes | 77 | 14 | | | 4.573 | 1.650–12.673 | |
| Tumor cell differentiation | | | 1.012 | .314 | | | .082 |
| G1 | 15 | 67 | | | 1 | | |
| G2, G3 | 69 | 61 | | | 2.531 | 0.887–7.221 | |
| Tumor location | | | 1.137 | .286 | | | .144 |
| Upper and middle 3rd | 57 | 65 | | | 1 | | |
| Lower 3rd | 27 | 57 | | | 1.832 | 0.831–4.131 | |
| Thickness of esophageal wall, cm | | | 6.064 | 0.014 | | | .059 |
| ≤1.3 | 29 | 83 | | | 1 | | |
| >1.3 | 55 | 51 | | | 2.947 | 0.960–9.048 | |
| Tumor length, cm | | | 2.452 | 0.117 | | | .578 |
| ≤5.9 | 60 | 65 | | | 1 | | |
| >5.9 | 24 | 60 | | | 1.650 | 0.283–9.603 | |
| Tumor volume, cc | | | 13.433 | <0.001 | | | .043 |
| ≤18.6 | 36 | 83 | | | 1 | | |
| >18.6 | 48 | 46 | | | 2.968 | 1.036–8.503 | |

CI = confidence interval.

addition, the tumor location was not associated with the long-term survival. Yang et al[14] retrospectively studied 1220 patients with ESCC and found that the 5-year survival rates for patients with tumors in the UE, ME, and LE were 44.8%, 50.5%, and 45.6%, respectively. These results showed that different tumor locations and tumor cell grades in ESCC did not affect prognosis. Similarly, in our study, we classified the pT3N0M0 ESCC cases as stage IIa to IIb based on the tumor location and tumor cell grade and found no statistically significant differences in the survival curves between the stage IIa and IIb groups (61% vs 64%). Thus, no significant difference in OS was observed among patients with ESCC with tumors of different grades and locations who underwent radical esophagectomy and 3-FL.

Many clinical studies have demonstrated that the tumor burden significantly influences the outcomes in cases of carcinomas such as nasopharyngeal carcinoma, melanoma, and breast carcinoma.[15–19] For patients with ESCC, measurements of the tumor burden, such as the thickness of the esophageal wall, tumor length, and tumor volume, were also shown to be relevant factors for prognosis in recent studies. The maximal esophageal wall thickness was found to significantly affect the OS of the patients with ESCC in the present study. In 1981, Moss et al[20] first proposed that the esophagus wall thickness could be used as a staging criterion for primary tumor invasion. Li et al[11] studied 96 patients with T3-4 ESCC receiving neoadjuvant chemoradiotherapy and radical esophagectomy and found that the pretreatment maximal esophageal carcinoma wall thickness >20 mm was associated with a significantly worse 5-year OS than a smaller wall thickness. Also, the maximal tumor thickness was an independent adverse predictor of disease-free survival and 5-year OS in their study. These results were similar to those of our present study. Our ROC curve analysis results showed that the best cutoff value for the maximal esophageal wall thickness was 1.3 cm. For patients with T3N0M0 ESCC, a maximal esophageal wall thickness >1.3 cm was an adverse prognostic factor for OS. In another retrospective study, Zhang et al[21] demonstrated that a tumor size >3.5 cm conferred a significantly worse prognosis than a tumor size <3.5 cm (23.9% vs 43.2%), and their further analysis showed that tumor size was an independent prognostic factor for node-negative ESCC.

In addition to the maximal esophageal wall thickness, tumor length was also studied as a prognostic factor in ESCC. Wu et al[10] studied 1435 patients with ESCC treated with radical resection and showed that tumor length was an independent prognostic factor, which is similar to the findings of Ma et al,[6] who studied 362 patients with ESCC who received surgical resection and demonstrated that the tumor length independently influenced patient survival. Patients with a tumor length >4 cm had worse OS than those with a shorter tumor length. In our present study, the best cutoff value for tumor length calculated from the ROC curve was 5.9 cm. The patients with pT3N0M0 ESCC with a tumor length ≤5.9 cm appeared to show a survival benefit, but the difference was not statistically significant.

Many studies have focused on investigating the relationship between tumor volume and OS in ESCC. Chen et al[22] studied 187 patients with ESCC who received definitive radiotherapy and found that a gross tumor volume (GTV) >39.16 cc and planning target volume (GTV-P) >28.30 cc were significantly associated with both OS and progression-free survival (PFS; $P < 0.05$). In addition, the GTV was shown to be an independent prognostic factor. In another study, Yamashita et al[23] conducted a multivariate Cox analysis of 63 patients with ESCC who received intensity-modulated radiotherapy combined with concurrent chemotherapy and found that a tumor volume >60 cc was an independent predictor of OS. Similarly, Chen et al[24] studied 153 patients with ESCC who received 3D conformal

radiotherapy and found that the 5-year survival rates for patients with tumor volumes <20 cc, 20–40 cc, and >40 cc were 41.5%, 18.1%, and 15.4%, respectively. Thus, tumor volume has been treated as a crucial prognostic factor in esophageal carcinoma. However, recent publications mainly analyzed this relationship with long-term survival in patients with locally advanced ESCC treated with intensity modulated radiotherapy. Our study focused on the postoperative survival of patients with pT3N0M0 ESCC and found that the best cutoff value for tumor volume was 18.6 cc. The patients with a tumor volume >18.6 cc had a better 5-year OS than those with a tumor volume <18.6 cc (83% vs 46%). Further subgroup analyses found that for patients with ESCC with tumor cell differentiation G2/G3, the tumor volume ≤18.6 cc was associated with a better OS than a tumor volume >18.6 cc. However, for cases with tumor differentiation G1, no significant difference in the 5-year OS as observed according to tumor volume. Moreover, we performed PSM to adjust for the indication biases in the 2 groups. After PSM, the patients with a tumor volume ≤18.6 cc had a longer 5-year OS than those with a tumor volume >18.6 cc.

Based on the current NCCN guideline, the survival benefit of postoperative radiotherapy for patients with pT3N0M0 ESCC remains controversial. Yang et al[25] retrospectively studied 678 patients with pT3N0M0 ESCC and found that the 5-year OS rates of those treated with radical surgery only and those treated with radical surgery plus postoperative radiotherapy were 58.8% vs 75.2%, respectively. Thus, the postoperative radiotherapy showed a survival benefit for patients with pT3N0M0 ESCC. Conversely, Xiao et al[26] and Worni et al[27] found that postoperative radiotherapy did not provide a survival benefit in patients with ESCC. Moreover, Wong et al[28] demonstrated that postoperative chemoradiotherapy did not increase the OS of patients with lymph node-negative esophageal cancer. Additionally, no consensus has been reached regarding the benefit of neoadjuvant chemoradiotherapy. Some studies[29,30] have reported that neoadjuvant chemoradiotherapy before surgery significantly increases the OS and PFS of patients with ESCC. Conversely, Mariette et al[31] studied 195 patients with stage I or II ESCC and found that the patients who received neoadjuvant chemoradiotherapy did not have a longer OS than the patients treated with surgery only, but instead, greater mortality was observed among those who received neoadjuvant chemoradiotherapy. Short et al[32] also reported that for stage IIa and IIb ESCC, surgical resection via esophagectomy should be the main treatment method. In another study by Huang and Yu,[33] neoadjuvant chemoradiotherapy improved the OS of patients with lymph node-positive esophageal carcinoma. However, the benefit for patients with lymph node-negative ESCC was unclear in that study. In our present study, a tumor volume >18.6 cc significantly decreased the OS of patients with pT3N0M0 ESCC. Further studies of the value of the postoperative and/or neoadjuvant chemoradiotherapy in pT3N0M0 ESCC cases with a tumor volume >18.6 cc are warranted to provide guidance for the treatment planning for patients with pT3N0M0 ESCC.

Previous studies showed that tumor burden is a prognostic factor for locally advanced ESCC treated with definitive radiotherapy. However, to the best of our knowledge, no studies have focused on this relationship in early stage ESCC treated with radical esophagectomy and 3-FL. The present study demonstrates that a tumor volume >18.6 cc was associated with a significantly decreased OS in the propensity score-matched cases. However, this study has some limitations. The number of included postoperative pT3N0M0 cases was limited, and a larger amount of data will be required to verify our results. Moreover, the number of pT3N0M0 patients treated with postoperative radiotherapy was limited, and the role of the postoperative radiotherapy in patients with pT3N0M0 ESCC with a large tumor volume needs to be elucidated in further studies.

In conclusion, our study confirmed that the tumor volume is an independent prognostic factor for pT3N0M0 ESCC. The optimal cutoff value for tumor volume was 18.6 cc for predicting survival of patients with pT3N0M0 ESCC treated with radical esophagectomy. Larger-scale studies are needed to validate these findings.

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