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Research Article

# Prognostic Variables for Patients with T2N0M0 Esophageal Squamous Cell Carcinoma

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## 1. Abstract

**1.1. Aims:** To explore the variables which could predict the prognosis and might be considered as staging factors in patients with T2N0M0 Esophageal Squamous Cell Carcinoma (ESCC).

**1.2. Methods:** Records of 525 patients with pathologic T2N0M0 ESCC who underwent surgical resection were reviewed. The T2 category was further subdivided into T2a (circular muscle layers) and T2b (longitudinal muscle layers) based on the invasion depth. The differences in clinic pathologic characteristics between patients with T2a and T2b diseases were compared with the $\chi^2$ test. Univariate and multivariate analyses were conducted to investigate prognostic factors.

**1.3. Results:** The 1-, 3- and 5-year Overall Survival (OS) rates for the whole group were 96.0%, 79.3% and 67.0%, respectively. Age, histologic grade, and T2 subcategory were found to affect OS, while histologic grade, T2 subcategory, and number of lymph nodes resected were found to affect Disease-Free Survival (DFS). Sex, tumor location and tumor length were not correlated with survival. In subgroup analyses for histologic grade, patients with well and moderately differentiated tumors had similar survival, and the survival of these patients groups was better than that of patients with poorly differentiated tumors.

**1.4. Conclusions:** T2 subcategory by invasion depth was an independent prognostic factor and maybe considered as a staging factor for T2N0M0 ESCC. Histologic grade, age, and number of lymph nodes resected were also correlated with the outcome of these patients.

**2. Keywords:** Esophageal neoplasm; Factor; Prognosis; Squamous cell carcinoma; Stage

## 3. Introduction

Esophageal carcinoma is a highly aggressive cancer that occurs worldwide [1]. Esophagectomy with appropriate lymphadenectomy remains the major component of therapy for resectable cases and provides accurate pathologic staging information. Previous editions of the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) staging system for esophageal cancer were simply determined by the anatomical extent (T, N, and M). Since the seventh edition, which was published in 2010, other factors, such as the histopathologic type, histologic grade, and tumor location, have been incorporated into this new staging system [2]. The seventh edition TNM staging system had significant changes compared with the previous versions, especially for T2-3N0M0 Esophageal Squamous Cell Carcinoma (ESCC), which was defined as stage IIA in the sixth edition but might now be sub classified into stages IB, IIA, or IIB based on different histologic grades and tumor locations.

However, the impact of histologic grade and tumor location on the prognostic prediction of patients with ESCC is controversial [3-10]. In the latest eighth edition of the AJCC pathologic TNM (pTNM) stage, only histologic grade but not tumor location was incorporated into the stage for T2N0M0 ESCC [11]. PT2N0M0G1 disease is now sub classified into stage IB, and pT2N0M0G2-3 is now sub classified into stage IIA. Moreover, previous studies also showed that other factors such as age, sex, tumor length, number of lymph nodes resected, and T2 subcategory based on the inva-

sion depth to circular (T2a) or longitudinal (T2b) muscle layers might predict prognosis for patients with ESCC [12-20]. We think that it is important to investigate the prognostic factors for accurate staging and treatment decision-making in patients with T2N0M0 ESCC.

In this study, we evaluated the clinic pathologic features and outcome data of 525 patients with T2N0M0 ESCC who underwent esophagectomy and explored the prognostic factors for these patients.

## 4. Patients and Methods

### 4.1. Patients

The records of patients with ESCC who underwent esophagectomy at the Cancer Hospital of Shantou University Medical College between January 1995 and December 2016 were reviewed. Only the patients who met the following criteria were included in this study: (1) histopathological diagnosis of T2 category ESCC; (2) no lymph node metastasis; (3) radical resection; and (4) no neoadjuvant therapy to surgery. Patients who had previous malignancies or died of surgery were excluded. This project was approved by our Ethics Committee, and informed consent was waived from all participants.

To evaluate whether the subdivision of the T2 category by invasion depth was associated with survival, we further defined tumors invading the circular muscle layer as T2a and tumors invading the longitudinal muscle layer as T2b.

### 4.2. Surgery

Esophagectomy with lymphadenectomy was performed via a left thoracotomy for most patients before 2010, while a right thoracotomy was routinely performed for all patients after 2011; thoracoscopic esophagectomy was also performed after 2011. The details of the surgical procedures were described in our previous study [21].

### 4.3. Follow-up

The follow-up procedures were also described in our previous study [22]. Briefly, the patients had a visit to our outpatient department for examinations every 3 months for the first year, every 6 months for the second year and every 6 to 12 months thereafter.

### 4.4. Statistical Analysis

Statistical analysis was completed with SPSS 20.0 software (IBM, Armonk, New York, USA). The differences in clinic pathologic features between patients with T2a and T2b diseases were compared with the $\chi^2$ test. Survival was determined by the Kaplan-Meier method, and the differences between groups were calculated by the log-rank test. Multivariate analyses were conducted to investigate independent prognostic factors using the variables that were significant in the univariate analyses. $P < 0.05$ was set as significant.

## 5. Results

### 5.1. Patient Characteristics

A total of 525 patients were included in this study for analysis (Table 1). The median age was 58 years (range, 32 to 82 years). Males were the predominant sex (356 patients, 67.7%). The mean number of lymph nodes resected was 15.1 (range, 1-66). Two hundred ninety-six patients had fewer than 15 lymph nodes resected, and 229 patients had 15 or more lymph nodes resected. One hundred ninety-six patents had T2a disease, and 329 patients had T2b disease. The patients with T2b disease had significantly longer tumor lengths than patients with T2a disease (P=0.002), while other factors, such as sex, age, tumor location, histologic grade, and number of lymph nodes resected, were comparable in these two groups (P>0.05).

**Table 1**: Comparison of the clinicopathologic features between patients with T2a and T2b subcategory

| Variable | No. patients (%) | T subcategory | | $\chi^2$ | *P* value |
|---|---|---|---|---|---|
| | | T2a (%) | T2b (%) | | |
| Sex | | | | 0.031 | 0.861 |
| Male | 356(67.8) | 132(67.3) | 224(68.1) | | |
| Female | 169(32.2) | 64(32.7) | 105(31.9) | | |
| Age (yr) | | | | 2.491 | 0.115 |
| ≤60 | 320(61.0) | 128(65.3) | 192(61.0) | | |
| >60 | 205(39.0) | 68(34.7) | 137(39.0) | | |
| Tumor location | | | | 4.064 | 0.131 |
| Upper third | 71(10.0) | 34(17.3) | 37(11.2) | | |
| Middle third | 377(73.8) | 133(67.9) | 244(74.2) | | |
| Lower third | 77(16.2) | 29(14.8) | 48(14.6) | | |
| Tumor length | | | | 9.933 | 0.002 |
| ≤4cm | 272(67.5) | 119(60.7) | 153(46.5) | | |
| >4 cm | 253(32.5) | 77(39.3) | 176(53.5) | | |
| Histologic grade | | | | 2.447 | 0.294 |
| Well | 195(32.9) | 68(34.7) | 127(38.6) | | |
| Moderately | 281(54.2) | 113(57.7) | 168(51.1) | | |
| Poorly | 49(12.9) | 15(7.7) | 34(10.3) | | |
| Number of lymph nodes resected | | | | <0.001 | 0.983 |
| <15 | 297(49.7) | 111(56.6) | 186(56.5) | | |
| ≥15 | 228(6.0) | 85(43.4) | 143(43.5) | | |

### 5.2. Prognostic Factors

The mean follow-up time for the entire group was 85.0 months (range, 5-255 months). Two hundred and four patients died, and 15 patients were lost to follow-up (2.9%). The 1-, 3- and 5-year Overall Survival (OS) rates were 96.0%, 79.3% and 67.0%, respectively. The variables related to OS and Disease-Free Survival (DFS) are shown in (Table 2). Age, histologic grade, and T2 subcategory were found to affect OS (Figure 1), (P<0.05), while histologic grade, T2 subcategory, and number of lymph nodes resected were found to affect DFS (Figure 2), (P<0.05). Sex, tumor location and tumor length were not correlated with survival. In subgroup analyses for histologic grade, the OS (P=0.622) and DFS (P=0.523) between patients with well- and moderately differentiated tumors were not significantly different; however, patients with poorly differentiated tumors had significantly worse survival than the other two groups (P<0.001).

Multivariate analyses were conducted to investigate independent prognostic factors using the variables that were significant in the univariate analyses (age, histologic grade, T2 subcategory in OS, and histologic grade, T2 subcategory, number of lymph nodes resected in DFS). We found that all of these factors were significantly associated with survival in multivariate analyses (Table 3), (P<0.05). Advanced age, poor histologic grade, and T2b subcategory were correlated with poor OS, while poor histologic grade, T2b subcategory, and fewer lymph nodes resected adversely affected DFS.

**Table 2:** Univariate analysis in regard to overall survival and disease-free survival according to patient and tumor characteristics

| Variable | No. patients | 5-yr OS (%) | $\chi^2$ | *P* value | 5-yr DFS (%) | $\chi^2$ | *P* value |
|---|---|---|---|---|---|---|---|
| Sex | | | 2.927 | 0.087 | | 3.085 | 0.079 |
| Male | 356 | 64.3 | | | 65.3 | | |
| Female | 169 | 72.7 | | | 73.3 | | |
| Age (yr) | | | 7.015 | 0.008 | | 2.795 | 0.095 |
| ≤60 | 320 | 69.8 | | | 69.8 | | |
| >60 | 205 | 62.4 | | | 64.6 | | |
| Tumor location | | | 2.203 | 0.332 | | 1.483 | 0.476 |
| Upper third | 71 | 62.1 | | | 63.8 | | |
| Middle third | 377 | 65.8 | | | 66.6 | | |
| Lower third | 77 | 77.1 | | | 77.1 | | |
| Tumor length | | | 0.193 | 0.661 | | 0.094 | 0.759 |
| ≤4cm | 272 | 66 | | | 67.2 | | |
| >4 cm | 253 | 68.1 | | | 68.6 | | |
| Histologic grade | | | 14.531 | 0.001 | | 14.707 | 0.001 |
| Well | 195 | 72 | | | 73.1 | | |
| Moderately | 281 | 67.1 | | | 67.9 | | |
| Poorly | 49 | 45.6 | | | 45.6 | | |
| T2 subcategory | | | 7.764 | 0.005 | | 7.083 | 0.008 |
| T2a | 196 | 73.8 | | | 74.3 | | |
| T2b | 329 | 63 | | | 64 | | |
| Number of lymph nodes resected | | | 3.263 | 0.071 | | 4.928 | 0.026 |
| <15 | 297 | 63.9 | | | 64.3 | | |
| ≥15 | 228 | 70.8 | | | 72.3 | | |
| DFS, disease-free survival; MST, median survival time; OS, overall survival | | | | | | | |

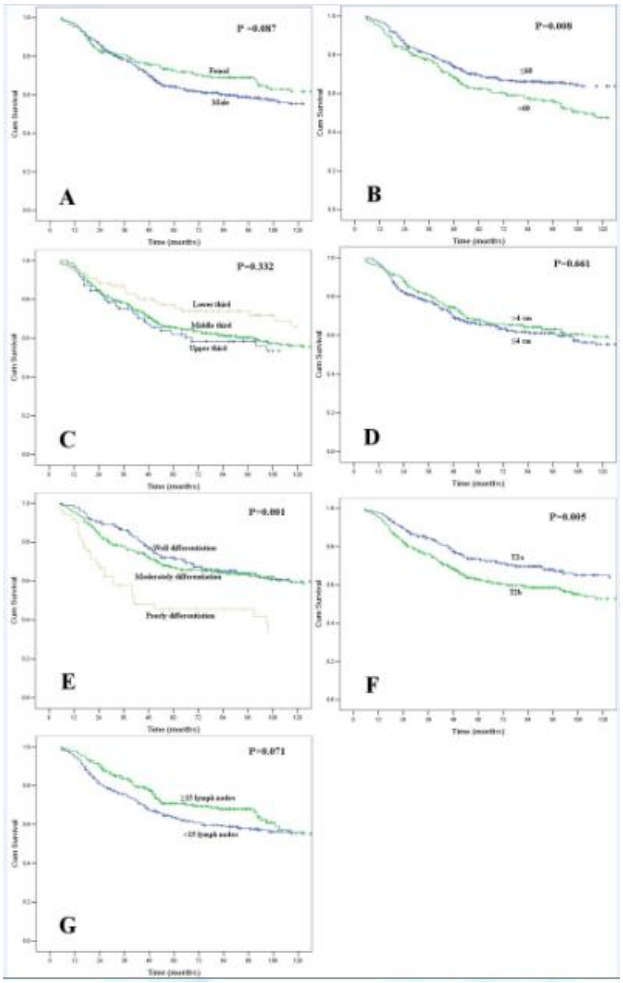


**Figure 1:** Kaplan-Meier curves for overall survival according to sex (Figure 1A), age (Figure 1B), tumor location (Figure 1C), tumor length (Figure 1D), histologic grade (Figure 1E), T2 subcategory (Figure 1F), and number of lymph nodes resected (Figure 1G). The survival differences were significant in age, histologic grade and T2 subcategory (P<0.001).

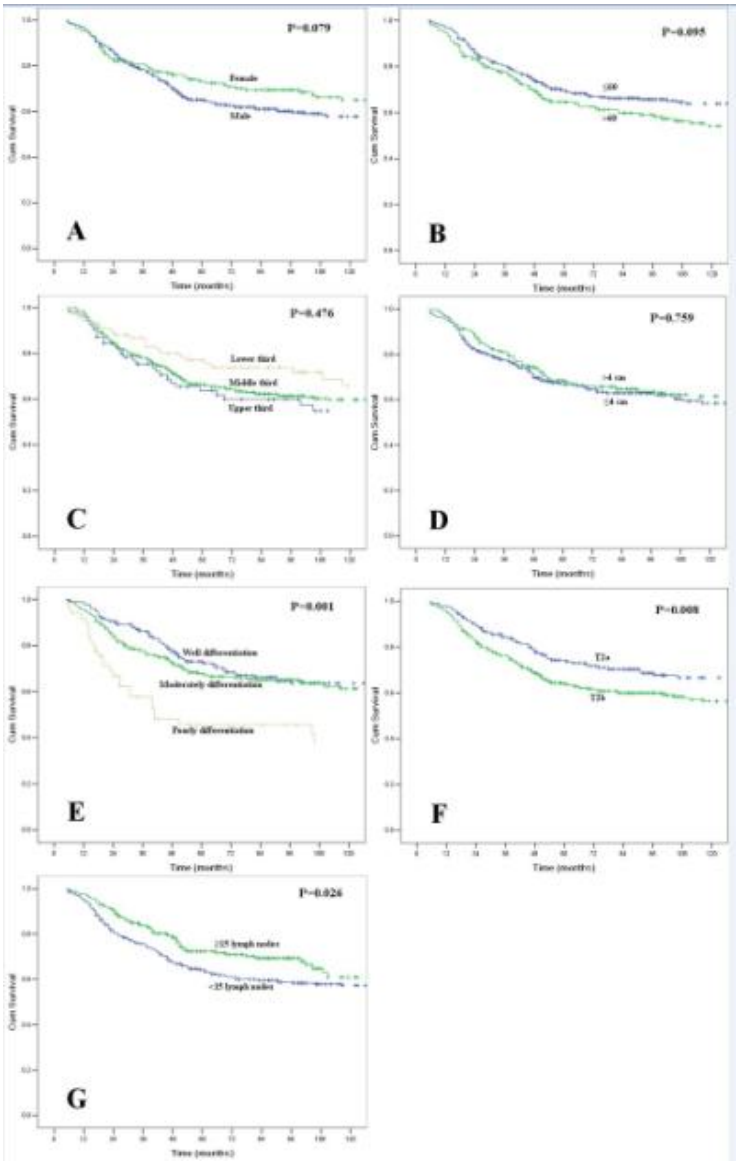


**Figure 2:** Kaplan-Meier curves for disease-free survival according to sex (Figure 2A), age (Figure 2B), tumor location (Figure 2C), tumor length (Figure 2D), histologic grade (Figure 2E), T2 subcategory (Figure 2F), and number of lymph nodes resected (Figure 2G). The survival differences were significant in histologic grade, T2 subcategory, and number of lymph nodes resected (P<0.001).

**Table 3**: Multivariate Cox regression analysis in regard to overall survival and disease-free survival of the 525 patients with T2N0M0 esophageal squamous cell carcinoma.

| Prognostic factor | Hazard Ratio | 95% CI | *P* value |
|---|---|---|---|
| Overall survival | | | |
| Age | 1.411 | 1.071-1.859 | 0.014 |
| Histologic grade | 1.351 | 1.084-1.684 | 0.007 |
| T2subcategory | 1.491 | 1.105-2.014 | 0.009 |
| Disease-free survival | | | |
| Histologic grade | 1.395 | 1.108-1.757 | 0.005 |
| T2subcategory | 1.519 | 1.117-2.066 | 0.008 |
| Number of lymph nodes resected | 0.705 | 0.522-0.951 | 0.024 |
| CI, confidence interval. | | | |

## 6. Discussion

Locally advanced ESCC is now treated preferably with induction therapy followed by surgery [23]. However, for patients who chose surgery as their initial therapy and were confirmed as T2N0M0 stage

in pathological examination, no adjuvant treatments after surgery were always recommended. However, nearly half of these patients developed metastatic diseases after surgery, [3] which indicated that a more reliable staging system is needed to select patients with a high risk of metastasis, and postoperative therapy might be recommended to improve their prognosis.

The AJCC TNM staging system for esophageal cancer was simply determined by the anatomical extent (T, N, and M) in editions prior to the seventh and these previous editions defined a single stage for all patients with T2N0M0 ESCC. However, previous studies found that factors other than this anatomical extent, such as age, sex, histologic grade, tumor length, tumor location, and number of resected lymph nodes, might also influence the outcome of patients with ESCC. [3-10], [12-20]. Whether these factors should be incorporated into the TNM staging system is still controversial. Histologic grade and tumor location were incorporated into the sub classification of T2N0M0 disease in the seventh edition of TNM stage for ESCC [2]. T2N0M0G1 disease in the lower esophagus was defined as stage IB, T2N0M0G1 disease in the middle or upper esophagus and T2N0M0G2-3 disease in the lower esophagus were defined as stage IIA, and T2N0M0G2-3 disease in the middle or upper esophagus was defined as stage IIB. However, in the latest eighth edition of pTNM stage, tumor location is not considered a staging factor for T2N0M0 ESCC [11]. In this edition, T2N0M0 disease is only sub classified into different stages by histologic grade (stage IB for T2N0M0G1 and stage IIA for T2N0M0G2-3).

In the current study, we explored the prognostic variables for T2N0M0 ESCC in a large patient cohort. We found that both the histologic grade and T2 subcategory were correlated with OS and DFS. Moreover, age was found to be correlated with OS but not with DFS, and the number of lymph nodes resected was correlated with DFS but not with OS. Other factors, such as sex, tumor location, and tumor length, did not significantly affect survival.

The data from the Worldwide Esophageal Cancer Collaboration (WECC), which were used to construct the seventh and eighth editions of the AJCC TNM staging system for esophageal cancer, showed that men and advanced age had worse survival [16, 17]. In our current study, we found that age was correlated with OS but not with DFS. Younger patients had significantly better OS than older patients. Although the differences in OS and DFS were not statistically significant between males and females in our study, the survival curves indicated that females tended to have better survival than males. We think that further studies with larger patient cohorts should be conducted to investigate the prognostic value of age and sex in patients with T2N0M0 ESCC.

Our study did not support the addition of tumor location to the staging system for T2N0M0 ESCC, which would be similar to the eighth edition of the TNM stage. The impact of tumor location on the prognostic prediction of patients with ESCC is controversial [3-6, 18, 21]. Yang et al. [4] found that tumor location was not correlated with survival in patients with operable thoracic ESCC, even in subgroup analyses of T2N0M0 and T3N0M0 diseases. Situ et al. [3, 18] also found that tumor location was not an independent prognostic factor for patients with T2N0M0 and T3N0M0 ESCC. However, some other studies found that tumor location might be correlated with the outcome of patients with ESCC, [5, 6] but none of these studies conducted subgroup analyses for T2N0M0 disease. Our findings in this study supported the exclusion of tumor location as a staging variable for T2N0M0 ESCC in the eight edition of the TNM staging system.

The prognostic value of tumor length on esophageal cancer is also controversial [14, 24-26]. The T category in the TNM staging system is defined by the invasion depth of the tumor but not the tumor size, which is always calculated according to the maximum length of the tumor. Previous studies showed that tumor length might affect the survival of patients with ESCC and could be combined with the current T category to increase the prediction precision [14, 25]. However, these studies had variable methodologies and patients in different stages. As tumor length is always correlated with other tumor-related factors, it might reduce its prognostic value. Hollis et al [24]. found that after accounting for other tumor-related factors, tumor length only resulted in a marginal improvement in predictive accuracy in patients with esophageal cancer. Our data showed that tumor length was not an independent prognostic factor for patients with T2N0M0 ESCC and that it should not be included in the staging system for these patients.

Our results supported that histologic grade, which is included in the seventh and eight editions of the TNM staging system, should be incorporated into the staging system for T2N0M0 ESCC. However, in the eighth edition of pTNM stage for ESCC, T2N0M0G2 and T2N0M0G3 diseases were combined into a single stage IIA, while T2N0M0G1 disease was classified as stage IB. In our study, we found that patients with well (G1) and moderately differentiated (G2) tumors had similar survival, which was significantly better than that of patients with poorly differentiated (G3) tumors, indicating that T2N0M0G1 and T2N0M0G2 diseases should be combined into the same stage and that T2N0M0G3 disease should be classified as a different stage. The findings were similar when staging tumors according to the eighth edition pTNM staging system for esophageal adenocarcinoma, which classified T2N0M0G1-2 as stage IC and T2N0M0G3 as stage IIA [11].

We also found that the T2 subcategory was an independent prognostic factor for patients with T2N0M0 ESCC. Patients with tumors invading the circular muscle layer had significantly better survival than those with tumors invading the longitudinal muscle layer. Previous studies also found that the T2 subcategory might improve the prediction of survival for patients with ESCC, [19, 20] while Tian et al.

[27] found it did not affect survival. However, all of these studies included patients with positive lymph nodes. As patients with T2b tumors might have a higher risk of lymph node involvement, the worse survival for patients with T2b tumors might partly contribute to the higher rate of lymph node metastasis. To the best of our knowledge, our study was the first to compare the prognosis of T2 subcategory patients with negative lymph nodes. Our findings supported a subdivision of T2N0M0 ESCC by invasion depth in the further staging system.

Our data also showed that the number of lymph nodes resected was correlated with DFS in patients with T2N0M0 ESCC. Patients with 15 or more lymph nodes resected had significantly better survival than those with fewer than 15 lymph nodes resected. It is easy to understand that the extent of lymphadenectomy will impact the accuracy of the nodal stage. When the number of examined lymph nodes is small, stage migration may occur, leading to an under stage of nodal status. However, the number of lymph nodes resected and the benefits of lymphadenectomy in patients with esophageal cancer are still controversial. [15, 28-31] Peyre et al. [15] found that the number of lymph nodes resected was an independent predictor of survival for patients with esophageal cancer who underwent surgery and recommended that at least 23 lymph nodes be resected to maximize survival benefit. However, their study included patients with positive lymph nodes and different T categories. Greenstein et al. [28] found that the number of lymph nodes resected was independently associated with DFS for patients with lymph node-negative esophageal cancer and recommended at least 18 lymph nodes to be removed. However, Hsu et al. [29] showed that the number of resected lymph nodes was not a prognostic factor for recurrence in patients with ESCC after surgery. Our study showed that the number of lymph nodes resected can impact the DFS for patients with T2N0M0 ESCC and that it is important to perform an adequate oncologic procedure with sufficient lymphadenectomy for these patients.

In conclusion, our study supported the exclusion of tumor location for the sub stages of T2N0M0 ESCC in the eighth edition TNM staging system. Moreover, T2N0M0G1 and T2N0M0G2 diseases should be combined into a same stage while T2N0M0G3 disease should be classified into another stage. Furthermore, T2 subcategory by invasion depth was an independent prognostic factor and maybe incorporated into a further staging system for T2N0M0 ESCC. Further studies are required to examine our findings and investigate the possibility of adding these factors into the future staging system for T2N0M0 ESCC.

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