Predictors of Lymph Node Metastasis in Siewert Type II T1 Adenocarcinoma of the Esophagogastric Junction: A Population-Based Study

Liubo Chen, MD1,2, Kejun Tang, PhD3, Sihan Wang, PhD4, Dongdong Chen, MM4, and Kefeng Ding, PhD, MD1,2

Abstract

Background: Endoscopic resection has been introduced as an alternative treatment for superficial adenocarcinoma of the esophagogastric junction (AEG), but is limited by positive nodal status. We aimed to investigate the predictors of lymph node metastasis (LNM) in patients with Siewert type II T1 AEG.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify eligible patients with Siewert type II T1 AEG. The prevalence of LNM was assessed. Logistic regression analysis with multivariable adjustment was used to determine predictors of LNM. We also performed Cox regression analysis to examine the prognostic value of LNM, which was further confirmed by competing risk analysis and cumulative incidence function (CIF).

Results: In total, 2651 patients with T1 AEG were included, with a median age of 69 years and a median follow-up of 28 months. The overall prevalence of LNM was 17.2% in T1 AEG. When stratified by tumor invasion depth, the prevalence of LNM was 8.5% for intramucosal tumors and 22.6% for submucosal tumors. Adjusted logistic regression analysis showed that age, sex, tumor grade, tumor size and tumor infiltration depth were independent predictors of LNM in T1 AEG. Multivariate Cox regression analysis revealed that positive nodal status was significantly associated with worse overall survival and cancer-specific survival (CSS). Subgroup analysis consistently demonstrated that patients with LNM had significantly poorer CSS than those without LNM in most subgroups. Finally, the CIF was calculated, showing that patients with LNM had a significantly higher cancer-specific death rate than those without LNM.

Conclusions: This population-based study identified age, sex, tumor grade, tumor infiltration depth and tumor size as independent predictors of LNM in T1 AEG. Considering the high prevalence of LNM in T1 AEG, endoscopic resection for curative aims may only be introduced in patients without high risks of LNM.

Keywords
esophagogastric junction, adenocarcinoma, lymph node metastasis, predictor, SEER

Received November 28, 2020. Received revised April 30, 2021. Accepted for publication May 30, 2021.
Introduction

Although adenocarcinoma of the esophagogastric junction (AEG) is uncommon, its incidence has been rapidly increasing over time globally.\(^1\)-\(^4\) The incidence of AEG increased by approximately 2.5-fold from the early 1970s to the early 1990s according to the statistics from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program.\(^2\) Similarly, a Japanese cohort of consecutive patients with gastric adenocarcinoma revealed that the overall proportion of AEG increased from 2.3\% (1962-1965) to 10.0\% (2001-2005).\(^3\) The survival of AEG patients is generally poor and might vary greatly depending on regional lymph node involvement and distant metastasis.\(^5\)

AEG is commonly considered as a separate tumor entirety of digestive tract cancer.\(^6\),\(^7\) Due to its special anatomical location, the classification of AEG has been historically complicated. Siewert classified AEG into 3 subgroups based on the anatomical location of the tumor epicenter relative to the esophagogastric junction (EGJ): Siewert type I (5 to 1 cm above the EGJ), type II (1 cm above to 2 cm below the EGJ), and type III (2 to 5 cm below the EGJ).\(^8\),\(^9\) Among the 3 subtypes, Siewert type II is generally considered as the true cardia carcinoma arising from EGJ.\(^9\),\(^10\)

Despite the overall poor survival of patients with AEG, the prognosis of patients with superficial lesions is relatively favorable if curative resection is performed. Superficial AEG has been traditionally managed with surgical resection in most cases,\(^11\) mainly including radical esophagectomy and lymphadenectomy.\(^12\) Although radical surgery is conventionally linked with secure long-term outcomes, it also has several drawbacks.\(^13\) First, the surgical procedure may increase the risk of overtreatment in mucosal or submucosal tumor lesions without high risks of local recurrence and distant metastasis. Additionally, the in-hospital mortality rate of esophagectomy is reported to be as high as 5.0\%,\(^5\) and operative resection of the gastric cardia and postoperative complications can diminish the quality of life of patients.\(^14\)

Endoscopic resection, a minimally invasive technique, has been increasingly propagated as a reliable treatment option for superficial AEG when properly adopted based on rigorous indication criteria.\(^15\),\(^16\) In a retrospective study enrolling 53 patients with superficial AEG who underwent endoscopic submucosal dissection (ESD), Yamada et al reported that the cause-specific survival rate was 100\%, without recurrence or metastasis among patients after curative resection (median follow-up: 6.1 years).\(^17\) Another retrospective Japanese study from 13 centers revealed similar findings, showing that the 5-year cause-specific survival rate was 100\% among superficial AEG patients with a low risk of lymph node metastasis (LNM).\(^18\) Endoscopic resection can eliminate superficial cancer that is confined to the primary site, while it cannot be used to cure cancers with regional lymph node involvement or even distant metastasis.\(^18\) Among patients with superficial AEG who were treated with endoscopic mucosal resection (EMR) or ESD, the 5-year overall survival (OS) was 93.9\% in patients with a low risk of LNM, which sharply dropped to approximately 80\% among those with a high risk of LNM.\(^15\) Therefore, the accurate prediction of lymph node involvement is an essential prerequisite for the success of endoscopic resection, which is also of great significance in pretreatment decision making.

The SEER database, an authoritative source of cancer data in the US, records and reports cancer incidence and survival data by covering approximately 28\% of the total US population.\(^19\),\(^20\) By providing information on patient-specific and tumor-specific characteristics, the SEER database is particularly useful for studying uncommon malignant tumors.

In the present study, the SEER database was used to assess the prevalence of LNM in T1 AEG (mucosal and submucosal tumor lesions) and to identify the predictors of LNM in T1 AEG.

Materials and Methods

Patient Selection

We performed this retrospective study by retrieving relevant data from the SEER database. Although detailed information on the Siewert classification of AEG (type I, II or III) was not directly available in the SEER database, we were still able to specifically identify Siewert type II AEG according to 2 parameters. Cancers simultaneously satisfying 2 conditions (“TNM 7/CS v0204 + Schema” encoded 28 (Esophagus GE Junction) and “Primary Site-Labeled” encoded 160 (Cardia, NOS)) were extracted and classified as Siewert type II AEG.\(^2\),\(^21\),\(^22\)

We downloaded the data of patients diagnosed with AEG from 2004 to 2015 from the SEER database. For this analysis, the inclusion criteria were as follows: 1) age at diagnosis of 18 years or older (in consideration of the extremely small proportion of patients under 18 years and the large proportion of older patients); 2) pathologically diagnosed T1 Siewert Type II AEG; 3) available lymph node status; 4) active follow-up; and 5) first or the only 1 primary malignancy. Patients were excluded if they had in situ cancer. Moreover, patients with distant metastasis and those with survival times less than 1 month were also excluded. The details of patient selection are depicted in Figure 1.

Patient demographics (age, sex, race, year of diagnosis and marital status), tumor characteristics (tumor grade, tumor size, T stage, N stage and number of lymph nodes examined), treatment regimens and patient survival were collected from the SEER database for subsequent analysis. Since the SEER database is publicly available and the data are de-identified, the requirement for approval was waived by the local ethics committee.
Eligible patients were divided into N-negative and N-positive groups according to their regional lymph node status. The Chi-square test or Fisher’s exact test was used to test the independence of the clinicopathological categorical variables. Predictors of LNM were assessed and identified by unadjusted and adjusted logistic regression models as well as backward logistic regression model. Odds ratios (ORs) along with 95% confidence intervals (CIs) were calculated. Afterward, a nomogram model was generated based on the independent LNM predictors identified from the adjusted logistic regression analysis. The performance of the nomogram-based prediction of LNM risk was evaluated by a calibration curve. A receiver operating characteristic (ROC) curve was plotted to assess the predictive accuracy of the nomogram model.

In this study, the primary endpoints included OS and cancer-specific survival (CSS). The former was defined as the duration from the cancer diagnosis to death from any cause, while the latter referred to the period between the date of diagnosis and the date of death attributed to this type of cancer. Survival curves for both OS and CSS were generated by the Kaplan-Meier method. The difference between survival curves was evaluated by the log-rank test. We further applied a Cox regression model to identify independent prognostic factors for OS and CSS. Finally, in consideration of both oncological and non-oncological risks among tumor patients, competing risk analysis was performed, and the cumulative incidence function (CIF) was calculated.23,24

SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) and R software for Mac version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used to analyze data and to plot figures. The level of statistical significance was set at 2-sided $P$ values < 0.05.

**Results**

**Demographic and Clinicopathological Characteristics of Patients**

The detailed process of patient selection was shown in Figure 1. Among the 21482 patients with Siewert II AEG diagnosed between 2004 and 2015, 2651 eligible patients were finally enrolled based on the inclusion and exclusion criteria. The median age was 69 years [interquartile range (IQR), 60-78], and the median follow-up was 28 months (IQR, 11-63). Most patients were male (76.8%) and white (88.8%). Overall, 457 of 2651 patients (17.2%) had LNM. Table 1 summarized the patient demographics and clinicopathological characteristics.

**Independent Predictors of Lymph Node Metastasis**

Adjusted multivariable logistic regression was performed to identify the risk factors for LNM. The results showed that age, sex, tumor grade, depth of tumor invasion and tumor size were significant predictive factors for LNM in T1 AEG (Table 2). Interestingly, a decreased LNM risk was detected in older patients [OR = 0.64 (age: 66-80 years), OR = 0.40 (age: over 80 years), both $P$ < 0.05]. The risk of LNM was attenuated in female patients [OR = 0.59 (0.44-0.79), $P$ < 0.001]. Regarding oncological factors, patients with moderately-differentiated [OR = 1.62 (1.02-2.70), $P$ = 0.049] and poorly-differentiated [OR = 3.10 (1.96-5.11), $P$ < 0.001] AEG had a higher risk of LNM than those with well-differentiated lesions. Tumor invasion depth was also significantly associated with LNM risk. Patients with submucosal tumors had a 2.28-fold higher risk of LNM than those with mucosal lesions. Compared with patients with small tumor lesions sized $\leq$ 1 cm, the risk of LNM was significantly increased in those with tumor sizes exceeding 1 cm [OR = 2.22 (1.1-2.4 cm), OR = 4.48 (2.1-4 cm), OR = 5.81 (> 4 cm), all $P$ < 0.05]. Moreover, the backward logistic regression model robustly showed that age, sex, tumor grade, tumor invasion and tumor size were independent predictors of LNM in T1 AEG (Table 2).

To better visualize and present the risk factors of LNM, we further constructed a nomogram model (Supplementary Figure 1A), which could be used to estimate the numerical probability for a specific individual by integrating these parameters. To assess the performance of the nomogram
A calibration curve was constructed and showed good agreement between the nomogram-predicted risks and the actual risks of LNM (C index: 0.742) (Supplementary Figure 1B). In addition, to assess the predictive capacity of the nomogram for predicting LNM risk, a ROC curve was plotted. As shown in Supplementary Figure 1C, the area under the curve (AUC) of the ROC curve was 0.742 (95% CI: 0.718-0.765).

### Table 1. Clinicopathological Characteristics of Patients.

|                        | Total (N = 2651) | N negative (N = 2194) | N positive (N = 457) | P     |
|------------------------|------------------|----------------------|----------------------|-------|
| **Age**                |                  |                      |                      |       |
| ≤50                    | 189 (7.13)       | 147 (6.70)           | 42 (9.19)            | 0.002 |
| 51-65                  | 849 (32.03)      | 686 (31.27)          | 163 (35.67)          |       |
| 66-80                  | 1133 (42.74)     | 938 (42.75)          | 195 (42.67)          |       |
| >80                    | 480 (18.11)      | 423 (19.28)          | 57 (12.47)           | 0.646 |
| **Race**               |                  |                      |                      |       |
| Black                  | 135 (5.09)       | 115 (5.24)           | 20 (4.38)            |       |
| White                  | 2353 (88.76)     | 1947 (88.74)         | 406 (88.84)          |       |
| Other                  | 152 (5.73)       | 124 (5.65)           | 28 (6.13)            |       |
| Unknown                | 11 (0.41)        | 8 (0.36)             | 3 (0.66)             |       |
| **Sex**                |                  |                      |                      | < 0.001 |
| Male                   | 2035 (76.76)     | 1645 (74.98)         | 390 (85.34)          |       |
| Female                 | 616 (23.24)      | 549 (25.02)          | 67 (14.66)           |       |
| **Marital status**     |                  |                      |                      | 0.032 |
| Married                | 1630 (61.49)     | 1326 (60.44)         | 304 (66.52)          |       |
| Unmarried              | 880 (33.19)      | 744 (33.91)          | 136 (29.76)          |       |
| Unknown                | 141 (5.32)       | 124 (5.65)           | 17 (3.72)            |       |
| **Tumor grade**        |                  |                      |                      | < 0.001 |
| Well differentiated     | 286 (10.79)      | 264 (12.03)          | 22 (4.81)            |       |
| Moderately differentiated | 971 (36.63)    | 827 (37.69)          | 144 (31.51)          |       |
| Poorly differentiated/undifferentiated | 916 (34.55) | 670 (30.54)          | 246 (53.83)          |       |
| Unknown                | 479 (18.03)      | 433 (19.74)          | 45 (9.85)            |       |
| **Tumor invasion**     |                  |                      |                      | < 0.001 |
| Intramucosa            | 998 (37.65)      | 913 (41.61)          | 85 (18.60)           |       |
| Submucosa              | 807 (30.44)      | 625 (28.49)          | 182 (39.82)          |       |
| Not specified          | 846 (31.91)      | 656 (29.90)          | 190 (41.58)          |       |
| **Tumor size (cm)**    |                  |                      |                      | < 0.001 |
| ≤1                     | 457 (17.24)      | 432 (19.69)          | 25 (5.47)            |       |
| 1.1-2                  | 453 (17.09)      | 388 (17.68)          | 65 (14.22)           |       |
| 2.1-4                  | 469 (17.69)      | 341 (15.54)          | 128 (28.01)          |       |
| >4                     | 283 (10.68)      | 187 (8.52)           | 96 (21.01)           |       |
| Unknown                | 989 (37.31)      | 846 (38.56)          | 143 (31.29)          |       |
| **N stage**            |                  |                      |                      | < 0.001 |
| N0                     | 2194 (82.76)     | 2194 (100)           | 0 (0)                |       |
| N1                     | 427 (16.11)      | 0 (0)                | 427 (93.44)          |       |
| N2                     | 23 (0.87)        | 0 (0)                | 23 (5.03)            |       |
| N3                     | 7 (0.26)         | 0 (0)                | 7 (1.53)             |       |
| **Local treatment**    |                  |                      |                      | < 0.001 |
| No/unknown             | 1039 (39.19)     | 824 (37.56)          | 215 (47.05)          |       |
| Endoscopic resection   | 427 (16.11)      | 422 (19.23)          | 5 (1.09)             |       |
| Surgery                | 1185 (44.70)     | 948 (43.21)          | 237 (51.86)          |       |
| **Radiation**          |                  |                      |                      | < 0.001 |
| No/unknown             | 1859 (70.12)     | 1671 (76.16)         | 188 (41.14)          |       |
| Yes                    | 792 (29.88)      | 523 (23.84)          | 269 (58.86)          |       |
| **Chemotherapy**       |                  |                      |                      | < 0.001 |
| No/unknown             | 1727 (65.15)     | 1599 (72.88)         | 128 (28.01)          |       |
| Yes                    | 924 (34.85)      | 595 (27.12)          | 329 (71.99)          |       |
| **Cause of death**     |                  |                      |                      | < 0.001 |
| Alive                  | 1168 (44.06)     | 1039 (47.36)         | 129 (28.23)          |       |
| Dead from cancer       | 1057 (39.87)     | 785 (35.78)          | 272 (59.52)          |       |
| Dead not from cancer   | 411 (15.5)       | 361 (16.45)          | 50 (10.94)           |       |
| Unknown                | 15 (0.57)        | 9 (0.41)             | 6 (1.31)             |       |
| **Total number of lymph nodes [Median (IQR)]** | 0 (0, 12) | 0 (0, 11) | 5 (0, 17) | < 0.001 |
| **Follow-up time (months) Median (IQR)** | 28 (11.63) | 31 (12.68) | 18 (8.41) | < 0.001 |

Abbreviation: IQR, interquartile range.
Lymph Node Metastasis and Patient Survival

Unadjusted and adjusted Cox regression models were adopted to investigate the prognostic significance of LNM. Our findings showed that age, marital status, tumor grade, tumor size, lymph node status, local treatment and radiation were significant prognostic factors for both OS (Table 3) and CSS (Table 4) in patients with T1 AEG. Tumor invasion was significantly associated with CSS but not OS in the adjusted Cox regression analysis. Kaplan-Meier curves were further plotted to depict the survival in patients stratified by lymph node status. As shown in Figure 2A and B, OS and CSS rates were significantly decreased in patients with positive LNM compared with those without LNM (both \( P < 0.0001 \)).

We further performed survival analysis in subsets of patients according to different clinicopathological features. As shown in Figure 2C, patients with positive lymph node status had significantly poorer CSS than those without LNM in most subgroups. Therefore, subgroup analysis further demonstrated that LNM was an independent prognostic factor for patients with T1 AEG.

Competing Risk Analysis

The long-term survival outcomes of cancer patients are affected by oncological factors and non-oncological factors. During follow-up, patients might die from other causes, such as cardiovascular disease and car accidents, before the occurrence of cancer-specific death. \(^{24,25}\) To accurately reveal the prognostic value of LNM in T1 AEG, a competing risk model was applied for a direct and exact interpretation of the effects of risk factors on the cause-specific cumulative incidence of death. \(^{26}\) Multivariate analysis showed that age over 80 years (subdistribution hazard ratio (SHR) = 1.51, \( P = 0.006 \)), unmarried status (SHR = 1.26, \( P < 0.001 \)), poorly differentiated/undifferentiated tumor grade (SHR = 1.31, \( P = 0.045 \)), submucosal lesion (SHR = 1.23, \( P = 0.037 \)), tumor size over 2 cm, positive nodal status (SHR = 1.51, \( P < 0.001 \)) and the administration of local treatment were all significant prognostic factors for CSS (Table 5). Finally, the CIF was calculated to elucidate the probability of cancer-specific death and death.

### Table 2. Logistic Regression Analysis of Risk Factors for Lymph Node Metastasis in T1 AEG.

|                        | Unadjusted logistic regression | Adjusted logistic regression | Adjusted selection from adjusted logistic regression |
|------------------------|-------------------------------|-------------------------------|-----------------------------------------------|
|                        | OR (95% CI) \( P \)          | OR (95% CI) \( P \)          | OR (95% CI) \( P \)                          |
| **Age**                |                               |                               |                                               |
| \( \leq 50 \)          | Reference                      | Reference                      | Reference                                    |
| 51-65                  | 0.83 (0.57-1.23) \( 0.346 \)  | 0.77 (0.51-1.17) \( 0.210 \)  | 0.77 (0.51-1.17) \( 0.213 \)                |
| 66-80                  | 0.73 (0.50-1.07) \( 0.097 \)  | 0.64 (0.43-0.97) \( 0.032 \)  | 0.65 (0.43-0.98) \( 0.035 \)                |
| >80                    | 0.47 (0.30-0.74) \( < 0.001 \) | 0.40 (0.25-0.65) \( < 0.001 \) | 0.40 (0.20-0.64) \( < 0.001 \)              |
| **Race**               |                               |                               |                                               |
| Black                  | Reference                      | Reference                      | Reference                                    |
| White                  | 1.20 (0.75-2.01) \( 0.465 \)  |                               |                                               |
| Other                  | 1.30 (0.79-2.46) \( 0.415 \)  |                               |                                               |
| Unknown                | 2.16 (0.44-8.19) \( 0.285 \)  |                               |                                               |
| **Sex**                |                               |                               |                                               |
| Male                   | Reference                      | Reference                      | Reference                                    |
| Female                 | 0.51 (0.39-0.67) \( < 0.001 \) | 0.59 (0.44-0.79) \( < 0.001 \) | 0.57 (0.43-0.76) \( < 0.001 \)              |
| **Marital status**     |                               |                               |                                               |
| Married                | Reference                      | Reference                      | Reference                                    |
| Unmarried              | 0.80 (0.64-0.99) \( 0.045 \)  | 0.90 (0.70-1.15) \( 0.392 \)  |                                               |
| Unknown                | 0.60 (0.34-0.98) \( 0.054 \)  | 0.62 (0.35-1.05) \( 0.091 \)  |                                               |
| **Tumor grade**        |                               |                               |                                               |
| Well differentiated    | Reference                      | Reference                      | Reference                                    |
| Moderately differentiated | 2.09 (1.33-3.43) \( 0.002 \)  | 1.62 (1.02-2.70) \( 0.049 \)  | 1.59 (0.99-2.65) \( 0.060 \)                |
| Poorly differentiated / undifferentiated | 4.41 (2.85-7.16) \( < 0.001 \) | 3.10 (1.96-5.11) \( < 0.001 \) | 3.05 (1.94-5.03) \( < 0.001 \)              |
| Unknown                | 1.25 (0.74-2.16) \( 0.416 \)  | 1.26 (0.73-2.22) \( 0.414 \)  | 1.23 (0.71-2.17) \( 0.466 \)                |
| **Tumor invasion**     |                               |                               |                                               |
| Intramucosa            | Reference                      | Reference                      | Reference                                    |
| Submucosa              | 3.13 (2.38-4.14) \( < 0.001 \) | 2.28 (1.69-3.09) \( < 0.001 \) | 2.29 (1.70-3.11) \( < 0.001 \)              |
| Not specified          | 3.11 (2.37-4.11) \( < 0.001 \) | 2.27 (1.69-3.07) \( < 0.001 \) | 2.25 (1.67-3.04) \( < 0.001 \)              |
| **Tumor size (cm)**    |                               |                               |                                               |
| \( \leq 1 \)           | Reference                      | Reference                      | Reference                                    |
| 1.1-2                  | 2.90 (1.81-4.76) \( < 0.001 \) | 2.22 (1.37-3.71) \( 0.002 \)  | 2.20 (1.36-3.67) \( 0.002 \)                |
| 2.1-4                  | 6.49 (4.20-10.40) \( < 0.001 \) | 4.48 (2.85-7.28) \( < 0.001 \) | 4.42 (2.82-7.19) \( < 0.001 \)              |
| >4                    | 8.87 (5.62-14.49) \( < 0.001 \) | 5.81 (3.57-9.72) \( < 0.001 \) | 5.72 (3.52-9.57) \( < 0.001 \)              |
| Unknown                | 2.92 (1.91-4.64) \( < 0.001 \) | 2.45 (1.56-3.98) \( < 0.001 \) | 2.40 (1.53-3.91) \( < 0.001 \)              |

Abbreviations: AEG, adenocarcinoma of the esophagogastric junction; OR, odds ratio; 95% CI, 95% confidence intervals.
attributable to other causes. The results showed that patients with LNM had a significantly higher cancer-specific death rate than those without LNM ($P < 0.01$) (Figure 3).

**Discussion**

Endoscopic resection of early-stage AEG based on rigorous indication criteria and complete resection of the tumor is advantageous. In addition to the comparable long-term clinical outcomes between endoscopic resection and surgical resection, endoscopic treatment has been widely introduced due to the dramatically decreased post-operative morbidity and significantly increased quality of life.

Our population-based analysis revealed that the overall risk of LNM in patients with T1 AEG was relatively high (17.2%). In addition, the prevalence of LNM in patients with
Intramucosal cancer was 8.5% (85 out of 998), which sharply rose to 22.6% in those with submucosal tumors (182 out of 807). Consistent with our findings, by analyzing 453 patients with T1 AEG who underwent surgical resection between 2004 and 2010, Dubeicz et al\textsuperscript{12} previously reported that the prevalence of LNM was 9.5% for T1a tumors and 22.9% for T1b tumors. Similarly, the proportion of LNM was 22.2% in patients with T1 adenocarcinoma of the esophagus and EGJ, according to an Australian study from 1985 to 2003.\textsuperscript{5}

In consideration of the decisive role of LNM in choosing endoscopic or surgical resection, we further examined the predictors of LNM in patients with T1 AEG. Age, sex, tumor grade, depth of tumor infiltration and tumor size were identified as significant predictors of lymph node involvement in T1 AEG. In a previous population-based study, Dubeicz et al

### Table 4. Cox Regression Analysis of Prognostic Factors for Cancer-Specific Survival in T1 AEG.

| Variable                      | Unadjusted analysis | Adjusted analysis | Variable selection |
|-------------------------------|---------------------|-------------------|--------------------|
|                               | HR (95% CI)         | P                 | HR (95% CI)        | P                 | HR (95% CI)        | P                 |
| Age                           |                     |                   |                    |                   |                    |                   |
| ≤50                           | Reference           |                   | Reference          |                   | Reference          |                   |
| 51-65                         | 1.11 (0.83-1.47)    | 0.483             | 1.06 (0.80-1.41)   | 0.687             | 1.06 (0.80-1.42)   | 0.669             |
| 66-80                         | 1.53 (1.16-2.01)    | 0.002             | 1.29 (0.98-1.71)   | 0.072             | 1.30 (0.98-1.72)   | 0.066             |
| >80                           | 3.38 (2.55-4.49)    | < 0.001           | 1.80 (1.34-2.42)   | < 0.001           | 1.83 (1.36-2.45)   | < 0.001           |
| Race                          |                     |                   |                    |                   |                    |                   |
| Black                         | Reference           |                   | Reference          |                   | Reference          |                   |
| White                         | 0.62 (0.49-0.79)    | < 0.001           | 0.92 (0.72-1.18)   | 0.530             |                    |                   |
| Other                         | 0.63 (0.45-0.89)    | 0.009             | 0.90 (0.64-1.28)   | 0.566             |                    |                   |
| Unknown                       | 0.55 (0.20-1.50)    | 0.241             | 1.05 (0.38-2.92)   | 0.918             |                    |                   |
| Sex                           |                     |                   |                    |                   |                    |                   |
| Male                          | Reference           |                   | Reference          |                   | Reference          |                   |
| Female                        | 1.06 (0.92-1.23)    | 0.399             |                    |                   |                    |                   |
| Marital status                |                     |                   |                    |                   |                    |                   |
| Married                       | Reference           |                   | Reference          |                   | Reference          |                   |
| Unmarried                     | 1.64 (1.44-1.86)    | < 0.001           | 1.34 (1.17-1.53)   | < 0.001           | 1.34 (1.18-1.53)   | < 0.001           |
| Unknown                       | 1.34 (1.02-1.76)    | 0.034             | 1.00 (0.76-1.31)   | 0.980             | 1.01 (0.77-1.33)   | 0.946             |
| Tumor grade                   |                     |                   |                    |                   |                    |                   |
| Well differentiated           | Reference           |                   | Reference          |                   | Reference          |                   |
| Moderately differentiated     | 1.30 (1.02-1.67)    | 0.037             | 1.05 (0.81-1.34)   | 0.729             | 1.04 (0.81-1.34)   | 0.739             |
| Poorly differentiated/undifferentiated | 2.46 (1.94-3.12) | < 0.001           | 1.40 (1.10-1.79)   | 0.006             | 1.40 (1.09-1.78)   | 0.007             |
| Unknown                       | 1.40 (1.07-1.84)    | 0.014             | 0.91 (0.69-1.20)   | 0.502             | 0.91 (0.69-1.20)   | 0.499             |
| Tumor invasion                |                     |                   |                    |                   |                    |                   |
| Intramucosa                   | Reference           |                   | Reference          |                   | Reference          |                   |
| Submucosa                     | 1.09 (0.91-1.30)    | 0.361             | 1.23 (1.01-1.50)   | 0.037             | 1.23 (1.01-1.50)   | 0.039             |
| Not specified                 | 4.16 (3.58-4.83)    | < 0.001           | 1.72 (1.46-2.02)   | < 0.001           | 1.71 (1.46-2.01)   | < 0.001           |
| Tumor size (cm)               |                     |                   |                    |                   |                    |                   |
| ≤1                            | Reference           |                   | Reference          |                   | Reference          |                   |
| 1.1-2                         | 2.01 (1.48-2.73)    | < 0.001           | 1.38 (1.01-1.88)   | 0.045             | 1.38 (1.01-1.88)   | 0.044             |
| 2.1-4                         | 3.73 (2.81-4.96)    | < 0.001           | 1.98 (1.48-2.66)   | < 0.001           | 1.97 (1.47-2.65)   | < 0.001           |
| >4                            | 6.58 (4.92-8.80)    | < 0.001           | 2.24 (1.65-3.04)   | < 0.001           | 2.23 (1.64-3.02)   | < 0.001           |
| Unknown                       | 5.51 (4.24-7.16)    | < 0.001           | 2.13 (1.62-2.81)   | < 0.001           | 2.12 (1.61-2.80)   | < 0.001           |
| N stage                       |                     |                   |                    |                   |                    |                   |
| N negative                    | Reference           |                   | Reference          |                   | Reference          |                   |
| N positive                    | 2.02 (1.76-2.32)    | < 0.001           | 1.60 (1.38-1.87)   | < 0.001           | 1.59 (1.37-1.84)   | < 0.001           |
| Local treatment               |                     |                   |                    |                   |                    |                   |
| No/unknown                    | Reference           |                   | Reference          |                   | Reference          |                   |
| Endoscopic resection          | 0.09 (0.07-0.12)    | < 0.001           | 0.16 (0.12-0.21)   | < 0.001           | 0.16 (0.12-0.21)   | < 0.001           |
| Surgery                       | 0.16 (0.14-0.19)    | < 0.001           | 0.25 (0.21-0.30)   | < 0.001           | 0.25 (0.21-0.30)   | < 0.001           |
| Radiation                     |                     |                   |                    |                   |                    |                   |
| No/unknown                    | Reference           |                   | Reference          |                   | Reference          |                   |
| Yes                           | 2.11 (1.86-2.38)    | < 0.001           | 0.83 (0.70-0.97)   | 0.021             | 0.79 (0.69-0.91)   | < 0.001           |
| Chemotherapy                  |                     |                   |                    |                   |                    |                   |
| No/unknown                    | Reference           |                   | Reference          |                   | Reference          |                   |
| Yes                           | 2.09 (1.85-2.36)    | < 0.001           | 0.93 (0.79-1.10)   | 0.422             |

Abbreviations: AEG, adenocarcinoma of the esophagogastric junction; HR, hazard ratio; 95% CI, 95% confidence intervals.
investigated the predictors of LNM in patients with pT1 carcinoma of the esophagus and the gastric cardia who underwent surgical resection. Similarly, their study revealed that tumor infiltration of the submucosa, large tumor size (exceeding 1 cm) and poor tumor differentiation were independent predictors of LNM.

In our study, we showed that poorly differentiated or undifferentiated tumor grades increased the LNM risk by 3 times, compared to well-differentiated tumor grade. In a Chinese cohort involving 393 AEG patients who underwent radical resection and lymphadenectomy, tumor differentiation was also an independent influencing factor for LNM. Poor differentiation indicates higher tumor heterogeneity, resulting in more aggressive biological characteristics compared to well and moderately differentiated tumors. Tumor size has also been considered to be associated with LNM risk in AEG. Gross tumor volume detected by multidetector computed tomography is an independent risk factor for LNM. In addition, gross tumor volume can also be used to differentiate negative lymph nodes from positive lymph nodes, which can also assist preoperative clinical decision making. Tumor infiltration depth is another important predictor of lymph node positivity in superficial esophageal carcinoma.

As expected, we also found that tumor infiltration depth was an independent predictor of LNM in T1 AEG. Intriguingly, we found that the LNM risk was significantly decreased in older patients. Specifically, the risk of LNM in patients aged 66-80 years and over 80 years significantly dropped to 0.64 and 0.40 (both P < 0.05), respectively, compared to that in patients aged 50 years or under. In a single-center study involving 137 AEG patients, the rate of LNM was slightly but not significantly higher in younger patients (71.9%) than in older patients (64.8%). The insignificant statistical outcomes might be due to the relatively small sample size. Similarly, several studies have reported decreased LNM risk in older populations with other malignancies of the digestive system, but not in AEG. Although relevant studies have indicated that the overall poor prognosis of young patients might be due to a more aggressive biological process of the tumor, the underlying causes for the decreased LNM risk in older patients still remain elusive. Further studies are warranted to explore the intrinsic associations between age and LNM in AEG. Our findings indicate for the first time that endoscopic resection might be the optimal option for low-risk older T1 AEG patients who are at high risk of perioperative and postoperative complications if surgically treated. In addition, we also showed that female patients had a significantly lower risk of LNM than male patients (OR = 0.59, P < 0.001). The incidence of AEG shows a male predominance. Siewert and Stein reported that the male-to-female ratio was 4.9 in Siewert type II AEG. Similarly, the male-to-female ratio was 3.1 in patients with Siewert type II T1 AEG in our study. Although there are few studies investigating the male predominance and its possible role on patient prognosis in AEG, several studies have shown longer survival in females than in males with esophageal cancer, which is caused by both sex itself (sex hormones and reproductive factors) and other extrinsic risk factors for mortality. Thus, it is intriguing to examine the possible underlying causes of sex differences in the incidence and prognosis of AEG in the future.

In the survival analysis, we found that age, marital status, tumor grade, tumor size, lymph node status, local treatment and radiation were significant prognostic factors for both OS and CSS. The cancer-specific death rate was 35.8% in patients without LNM, which dramatically increased to 59.5% in nodal-positive patients. The above findings indicate that lymph node status definitively plays a vital role in the outcomes attributable to cancer.

A distinctive feature of follow-up in cancer patients is that their survival is threatened by both oncological and non-oncological factors. For instance, a patient who dies of a car accident is no longer at risk of death attributable to cancer. These non-oncological events are called competing events. In our study, we performed competing risk analysis and calculated the CIF to accurately determine the
prognostic significance of lymph node status. Consequently, lymph node involvement was robustly associated with poor survival in T1 AEG.

We investigated the predictors of LNM in T1 AEG by enrolling 2651 eligible patients from the SEER database. With a median follow-up of 28 months and a relatively large sample size, our findings can achieve a high degree of statistical power. However, certain limitations still exist. In addition to the studied predictors of LNM, lymphovascular invasion has been reported as an independent predictor of LNM. However, we could not assess these factors due to the limited data available in the SEER database.

Table 5. Competing Risk Analysis for Cancer-Specific Death.

|                        | Univariate analysis | Multivariate analysis |
|------------------------|---------------------|-----------------------|
|                        | SHR (95% CI)        | P                     |
|                        | Reference           | Reference             |
| Age                    |                     |                       |
| ≤50                    | Reference           | Reference             |
| 51-65                  | 1.07 (0.81-1.41)    | 0.640                 |
| 66-80                  | 1.37 (1.05-1.80)    | 0.021                 |
| >80                    | 2.76 (2.08-3.65)    | < 0.001               |
| Race                   |                     |                       |
| Black                  | Reference           | Reference             |
| White                  | 0.63 (0.50-0.81)    | < 0.001               |
| Other                  | 0.65 (0.46-0.91)    | 0.012                 |
| Unknown                | 0.60 (0.23-1.59)    | 0.310                 |
| Sex                    |                     |                       |
| Male                   | Reference           | Reference             |
| Female                 | 0.94 (0.81-1.08)    | 0.360                 |
| Marital status         |                     |                       |
| Married                | Reference           | Reference             |
| Unmarried              | 1.55 (1.37-1.75)    | < 0.001               |
| Unknown                | 1.34 (1.02-1.78)    | 0.037                 |
| Tumor grade            |                     |                       |
| Well differentiated    | Reference           | Reference             |
| Moderately differentiated | 1.27 (0.99-1.63)   | 0.55                  |
| Poorly differentiated / undifferentiated | 2.33 (1.83-2.95) | < 0.001               |
| Unknown                | 1.34 (1.02-1.75)    | < 0.001               |
| Tumor invasion         |                     |                       |
| Intramucosa            | Reference           | Reference             |
| Submucosa              | 1.10 (0.92-1.31)    | 0.28                  |
| Not specified          | 3.72 (3.20-4.32)    | < 0.001               |
| Tumor size (cm)        |                     |                       |
| ≤1                     | Reference           | Reference             |
| 1.1-2                  | 1.99 (1.48-2.68)    | < 0.001               |
| 2.1-4                  | 3.62 (2.74-4.77)    | < 0.001               |
| >4                     | 6.07 (4.55-8.10)    | < 0.001               |
| Unknown                | 5.12 (3.96-6.62)    | < 0.001               |
| N stage                |                     |                       |
| N negative             | Reference           | Reference             |
| N positive             | 1.99 (1.74-2.27)    | < 0.001               |
| Local treatment        |                     |                       |
| No/unknown             | Reference           | Reference             |
| Endoscopic resection   | 0.11 (0.08-0.14)    | < 0.001               |
| Surgery                | 0.21 (0.18-0.24)    | < 0.001               |
| Radiation              |                     |                       |
| No/unknown             | Reference           | Reference             |
| Yes                    | 2.03 (1.80-2.29)    | < 0.001               |
| Chemotherapy           |                     |                       |
| No/unknown             | Reference           | Reference             |
| Yes                    | 2.07 (1.84-2.33)    | < 0.001               |

Abbreviations: SHR, subdistribution hazard ratio; 95% CI, 95% confidence intervals.
Conclusions

In summary, in this population-based study, we report that the prevalence of LNM is as high as 17.2% among patients with T1 AEG. Age, sex, tumor grade, depth of tumor infiltration and tumor size are independent predictors of LNM in T1 AEG. Despite the obvious advantage of endoscopic resection, decision making in the treatment of T1 AEG should be cautiously approached according to the individualized conditions of patients. Endoscopic resection might be reasonably performed among T1 nodal-negative AEG patients with well-differentiated, small-size and mucosa-confined lesions, especially in the elder population, for curative aims.

Abbreviations

AEG, adenocarcinoma of esophagogastric junction; CI, confidence interval; CIF, cumulative incidence function; CSS, cancer-specific survival; EGJ, esophagogastric junction; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; IQR, interquartile range; LNM, lymph node metastasis; OR, odd ratio; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results; SHR, subdistribution hazard ratio.

Authors’ Note

Liubo Chen, MD, Kejun Tang, PhD, and Sihan Wang, PhD contributed equally to this work. Since SEER database is publicly available and de-identified, the requirement for approval was waived by the local ethics committee in this retrospective study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by Key Technology Research and Development Program of Zhejiang Province (No.2017C03017), National Natural Science Foundation of China (No. 81802750) and Zhejiang Provincial Natural Science Foundation of China (No. LQ19H160043).

ORCID iD

Liubo Chen, MD https://orcid.org/0000-0002-5582-7203
Kejun Tang, PhD https://orcid.org/0000-0002-9461-3646

Supplemental Material

Supplemental material for this article is available online.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.
2. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. Semin Radiat Oncol. 2013;23(1):3-9.
3. Kusano C, Gotoda T, Khor CJ, et al. Changing trends in the proportion of adenocarcinoma of the esophagogastric junction in a large tertiary referral center in Japan. J Gastroenterol Hepatol. 2008;23(11):1662-1665.
4. Hatta W, Tong D, Lee YY, Ichihara S, Uedo N, Gotoda T. Different time trend and management of esophagogastric junction adenocarcinoma in three Asian countries. Dig Endosc. 2017;29(Suppl 2):18-25.
5. Zhang X, Watson DI, Jamieson GG, Lally C, Bessell JR, Devitt PG. Outcome of oesophagectomy for adenocarcinoma of the oesophagus and oesophagealgastric junction. ANZ J Surg. 2005;75(7):513-519.
6. Turkington RC, Parkes E, Kennedy RD, et al. Clinical tumour staging of adenocarcinoma of the esophagus and esophagogastric junction. J Clin Oncol. 2015;33(9):1088.
7. Zheng Z, Yin J, Wu HW, et al. Explored risk factors for lymph node metastasis with Siewert II/III adenocarcinoma of the gastroesophageal junction. Anticancer Res. 2017;37(8):4605-4610.
8. Siewert JR, Stein HJ. Classification of adenocarcinoma of the esophagogastric junction. Br J Surg. 1998;85(11):1457-1459.
9. Rudiger Siewert J, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. Ann Surg. 2000;232(3):353-361.
10. von Rahden BH, Feith M, Stein HJ. Carcinoma of the cardia: classification as esophageal or gastric cancer? Int J Colorectal Dis. 2005;20(2):89-93.
11. Nakagawa K, Koike T, Iijima K, et al. Comparison of the long-term outcomes of endoscopic resection for superficial squamous cell carcinoma and adenocarcinoma of the esophagus in Japan. Am J Gastroenterol. 2014;109(3):348-356.
12. Dubecz A, Kern M, Solymosi N, Schweigert M, Stein HJ. Predictors of lymph node metastasis in surgically resected T1 esophageal cancer. Ann Thorac Surg. 2015;99(6):1879-1885. Discussion 86.
13. Sugita S, Kinoshita T, Kuwata T, et al. Long-term oncological outcomes of laparoscopic versus open transhiatal resection for
patients with Siewert type II adenocarcinoma of the esophagogastric junction. *Surg Endosc.* 2021;35(1):340-348.

14. Lagarde SM, de Boer JD, ten Kate FJ, Busch OR, Obertop H, van Lanschot JJ. Postoperative complications after esophagectomy for adenocarcinoma of the esophagus are related to timing of death due to recurrence. *Ann Surg.* 2008;247(1):71-76.

15. Abe S, Ishihara R, Takahashi H, et al. Long-term outcomes of endoscopic resection and metachronous cancer after endoscopic resection for adenocarcinoma of the esophagogastric junction in Japan. *Gastrointest Endosc.* 2019;89(6):1120-1128.

16. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett’s esophagus: European Society of Gastrointestinal Endoscopy (ESGE) position statement. *Endoscopy.* 2017;49(2):191-198.

17. Yamada M, Oda I, Nonaka S, et al. Long-term outcome of endoscopic resection of superficial adenocarcinoma of the esophagogastric junction. *Endoscopy.* 2013;45(12):992-996.

18. Nakamura T, Ide H, Eguchi R, Ota M, Shimizu S, Isono K. Adenocarcinoma of the esophagogastric junction: a summary of responses to a questionnaire on adenocarcinoma of the esophagus and the esophagogastric junction in Japan. *Dis Esophagus.* 2002;15(3):219-225.

19. Engels EA, Pfeiffer RM, Ricker W, Wheeler W, Parsons R, Warren JL. Use of surveillance, epidemiology, and end results-Medicare data to conduct case-control studies of cancer among the US elderly. *Am J Epidemiol.* 2011;174(7):860-870.

20. Daly MC, Paquette IM. Surveillance, Epidemiology, and End Results (SEER) and SEER-Medicare databases: use in clinical research for improving colorectal cancer outcomes. *Clin Colon Rectal Surg.* 2019;32(1):61-68.

21. Miccio JA, Oladeru OT, Yang J, et al. Neoadjuvant vs. adjuvant treatment of Siewert type II gastroesophageal junction cancer: an analysis of data from the Surveillance, Epidemiology, and End Results (SEER) registry. *J Gastrointest Oncol.* 2016;7(3):403-410.

22. Chen K, Deng X, Yang Z, et al. Survival nomogram for patients with metastatic Siewert type II adenocarcinoma of the esophagogastric junction: a population-based study. *Expert Rev Gastroenterol Hepatol.* 2020;14(8):757-764.

23. Dignam JJ, Zhang Q, Kocherginsky M. The use and interpretation of competing risks regression models. *Clin Cancer Res.* 2012;18(8):2301-2308.

24. de Glas NA, Kiderlen M, Vandenbergroucke JP, et al. Performing survival analyses in the presence of competing risks: a clinical example in older breast cancer patients. *J Natl Cancer Inst.* 2016;108(5):djv366.

25. Gao H, He X, Du J, et al. Competing risk analysis of primary tracheal carcinoma based on SEER database. *Cancer Manag Res.* 2019;11:1059-1065.

26. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation.* 2016;133(6):601-609.

27. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res.* 2007;13(2 Pt 1):559-565.

28. Hirasawa K, Kokawa A, Oka H, et al. Superficial adenocarcinoma of the esophagogastric junction: long-term results of endoscopic submucosal dissection. *Gastrointest Endosc.* 2010;72(5):960-966.

29. Kim HJ, Chung H, Shin SK, et al. Comparison of long-term clinical outcomes between endoscopic and surgical resection for early-stage adenocarcinoma of the esophagogastric junction. *Surg Endosc.* 2018;32(8):3540-3547.

30. Zhang YJ, Wang J, Zhang XL, et al. Patterns and influencing factors of lymph node metastasis of adenocarcinoma of the esophagogastric junction in 393 patients. *Zhonghua Zhong Liu Za Zhi.* 2016;38(9):672-676.

31. Li R, Chen TW, Hu J, et al. Tumor volume of resectable adenocarcinoma of the esophagogastric junction at multidetector CT: association with regional lymph node metastasis and N stage. *Radiology.* 2013;269(1):130-138.

32. Ancona E, Rampado S, Cassaro M, et al. Prediction of lymph node status in superficial esophageal carcinoma. *Ann Surg Oncol.* 2008;15(11):3278-3288.

33. Yoon HY, Kim CB. Gastroesophageal junction adenocarcinoma of young patients who underwent curative surgery: a comparative analysis with older group. *Surg Today.* 2011;41(2):203-209.

34. Xu X, Zhang C, Ni X, et al. Population-based analysis on predictors for lymph node metastasis in T1 colon cancer. *Surg Endosc.* 2020;34(9):4030-4040.

35. Ahmadi O, Stringer MD, Black MA, McCall JL. Influence of age and site of disease on lymph node yield in colorectal cancer. *N Z Med J.* 2014;127(1395):31-40.

36. Pyo JH, Lee H, Min YW, et al. Young age and risk of lymph node metastasis in differentiated type early gastric cancer. *Ann Surg Oncol.* 2018;25(9):2713-2719.

37. Hasegawa S, Yoshikawa T. Adenocarcinoma of the esophagogastric junction: incidence, characteristics, and treatment strategies. *Gastric Cancer.* 2010;13(2):63-73.

38. Siewert JR, Stein HJ, Feith M. Adenocarcinoma of the esophagogastric junction. *Scand J Surg.* 2006;95(4):260-269.

39. Xie SH, Lagergren J. The male predominance in esophageal cancer. *Circulation.* 2007;136(2 Pt 1):318-320.

40. Corley DA, Buffler PA. Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the cancer incidence in five continents database. *Int J Epidemiol.* 2001;30(6):1415-1425.

41. Hidaka H, Hotokezaka M, Nakashima S, Uchiyama S, Maehara N, Chijiwa K. Sex difference in survival of patients treated by surgical resection for esophageal cancer. *World J Surg.* 2007;31(10):1982-1987.

42. Bohanes P, Yang D, Chhibar RS, et al. Influence of sex on the survival of patients with esophageal cancer. *J Clin Oncol.* 2012;30(18):2265-2272.

43. Gockel I, Domeyer M, Sgourakis GG, et al. Prediction model of lymph node metastasis in superficial esophageal adenocarcinoma and squamous cell cancer including D2-40 immunostaining. *J Surg Oncol.* 2009;100(3):191-198.