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

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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

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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).[15] 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.

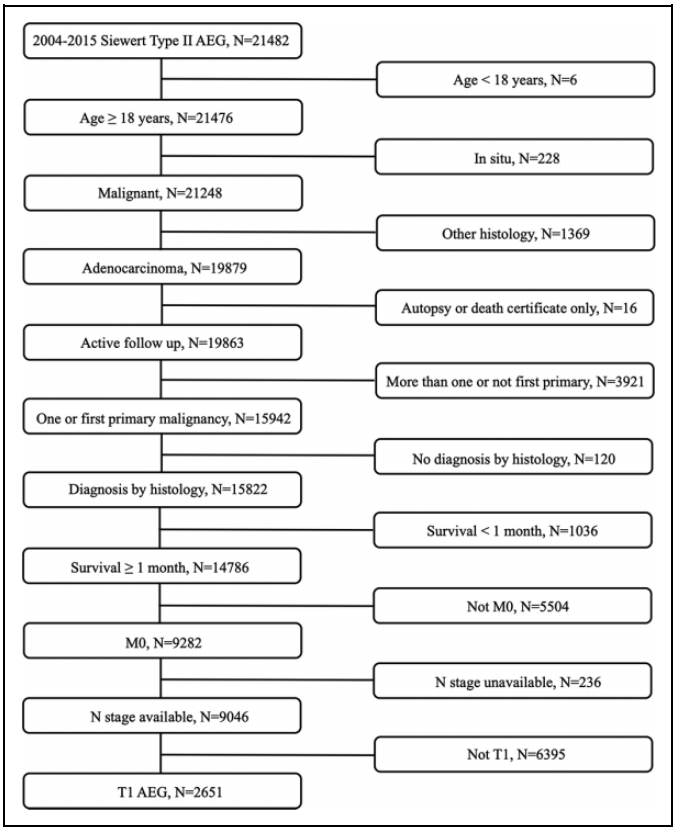

Figure 1. Flowchart of patient selection.

Statistical Analysis

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 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

Table 1. Clinicopathological Characteristics of Patients.

	Total (N = 2651)	N negative (N = 2194)	N positive (N = 457)	*P*
Age				0.002
≤50	189 (7.13)	147 (6.70)	42 (9.19)	
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)	
Race				0.646
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	478 (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.

model, 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 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						
≤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					
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			
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)						
≤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.

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 3. Cox Regression Analysis of Prognostic Factors for Overall Survival in T1 AEG.

	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	1.23 (0.95-1.59)	0.118	1.20 (0.92-1.55)	0.174	1.20 (0.93-1.56)	0.167
66-80	2.05 (1.60-2.62)	< 0.001	1.80 (1.40-2.31)	< 0.001	1.81 (1.41-2.33)	< 0.001
>80	4.38 (3.39-5.66)	< 0.001	2.48 (1.90-3.24)	< 0.001	2.52 (1.94-3.29)	< 0.001
Race						
Black	Reference		Reference			
White	0.67 (0.54-0.83)	< 0.001	0.98 (0.79-1.22)	0.851		
Other	0.67 (0.51-0.92)	0.013	0.95 (0.70-1.28)	0.730		
Unknown	0.42 (0.16-1.15)	0.093	0.72 (0.26-1.96)	0.521		
Sex						
Male	Reference					
Female	1.04 (0.92-1.17)	0.526				
Marital status						
Married	Reference		Reference		Reference	
Unmarried	1.60 (1.43-1.77)	< 0.001	1.32 (1.18-1.47)	< 0.001	1.32 (1.18-1.48)	< 0.001
Unknown	1.23 (0.97-1.56)	0.085	0.96 (0.75-1.22)	0.710	0.96 (0.75-1.21)	0.709
Tumor grade						
Well differentiated	Reference		Reference		Reference	
Moderately differentiated	1.32 (1.08-1.61)	0.007	1.12 (0.92-1.38)	0.260	1.12 (0.91-1.37)	0.286
Poorly differentiated / undifferentiated	2.14 (1.76-2.61)	< 0.001	1.39 (1.14-1.71)	0.001	1.38 (1.13-1.69)	0.002
Unknown	1.42 (1.14-1.77)	0.002	0.98 (0.79-1.23)	0.890	0.98 (0.79-1.23)	0.881
Tumor invasion						
Intramucosa	Reference		Reference		Reference	
Submucosa	1.00 (0.87-1.15)	0.994	1.17 (0.99-1.37)	0.050	1.17 (1.00-1.37)	0.049
Not specified	3.27 (2.88-3.68)	< 0.001	1.55 (1.36-1.78)	< 0.001	1.55 (1.35-1.77)	< 0.001
Tumor size (cm)						
≤1	Reference		Reference		Reference	
1.1-2	1.53 (1.23-1.90)	< 0.001	1.18 (0.94-1.48)	0.145	1.17 (0.94-1.46)	0.167
2.1-4	2.37 (1.93-2.91)	< 0.001	1.51 (1.21-1.87)	< 0.001	1.49 (1.21-1.85)	< 0.001
>4	3.98 (3.21-4.94)	< 0.001	1.72 (1.37-2.17)	< 0.001	1.70 (1.35-2.14)	< 0.001
Unknown	3.41 (2.84-4.10)	< 0.001	1.54 (1.27-1.87)	< 0.001	1.53 (1.26-1.86)	< 0.001
N stage						
N negative	Reference		Reference		Reference	
N positive	1.70 (1.50-1.92)	< 0.001	1.49 (1.30-1.71)	< 0.001	1.47 (1.29-1.68)	< 0.001
Local treatment						
No/unknown	Reference		Reference		Reference	
Endoscopic resection	0.19 (0.16-0.22)	< 0.001	0.28 (0.23-0.35)	0.403	0.29 (0.24-0.35)	< 0.001
Surgery	0.18 (0.16-0.21)	< 0.001	0.26 (0.22-0.31)	< 0.001	0.26 (0.23-0.31)	< 0.001
Radiation						
No/unknown	Reference		Reference		Reference	
Yes	1.89 (1.70-2.10)	< 0.001	0.85 (0.73-0.98)	0.026	0.80 (0.71-0.90)	< 0.001
Chemotherapy						
No/unknown	Reference		Reference			
Yes	1.77 (1.59-1.96)	< 0.001	0.90 (0.78-1.05)	0.178		

Abbreviations: AEG, adenocarcinoma of the esophagogastric junction; HR, hazard ratio; 95% CI, 95% confidence intervals.

attributable to other causes.[27] 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,[15,17,28,29] endoscopic treatment has been widely introduced due to the dramatically decreased postoperative 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

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

	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			
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					
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			
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			
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			
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			
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.

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, Dubecz et al[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.[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, Dubecz et al

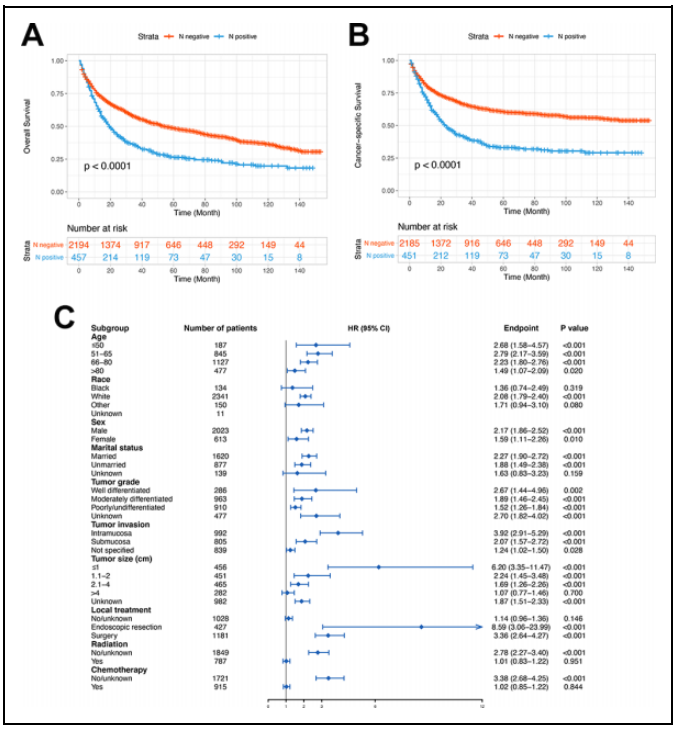

Figure 2. Prognostic value of lymph node metastasis in T1 AEG. Kaplan Meier curves for (A), Overall survival and (B), cancer-specific survival in patients stratified by lymph node status. (C) Forest plot for subgroup analysis. The patients were divided into subgroups according to different clinicopathological characteristics. Patients with Lymph Node Metastasis (LNM) had significantly worse CSS than those without LNM in most subgroups.

investigated the predictors of LNM in patients with pT1 carcinoma of the esophagus and the gastric cardia who underwent surgical resection.[12] 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.[30] Poor differentiation indicates higher tumor heterogeneity, resulting in more aggressive biological characteristics compared to well and moderately differentiated tumors.[7] 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.[31] In addition, gross tumor volume can also be used to differentiate negative lymph nodes from positive lymph nodes,[31] which can also assist preoperative clinical decision making. Tumor infiltration depth is another important predictor of lymph node positivity in superficial esophageal carcinoma.[12,32] 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%).[33] 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,[34,35] 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,[36] 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.[37] Siewert and Stein reported that the male-to-female ratio was 4.9 in Siewert type II AEG.[38] 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,[39-42] which is caused by both sex itself (sex hormones and reproductive factors) and other extrinsic risk factors for mortality.[39] 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 (Table 1). The above findings indicate that lymph node status definitely 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.[25] In our study, we performed competing risk analysis and calculated the CIF to accurately determine the

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

	Univariate analysis		Multivariate analysis	
	SHR (95% CI)	*P*	SHR (95% CI)	*P*
Age				
≤50	Reference		Reference	
51-65	1.07 (0.81-1.41)	0.640	1.03 (0.79-1.35)	0.82
66-80	1.37 (1.05-1.80)	0.021	1.13 (0.86-1.47)	0.39
>80	2.76 (2.08-3.65)	< 0.001	1.51 (1.13-2.01)	0.006
Race				
Black	Reference		Reference	
White	0.63 (0.50-0.81)	< 0.001	0.84 (0.65-1.09)	0.18
Other	0.65 (0.46-0.91)	0.012	0.85 (0.59-1.21)	0.36
Unknown	0.60 (0.23-1.59)	0.310	1.11 (0.51-2.41)	0.79
Sex				
Male	Reference			
Female	0.94 (0.81-1.08)	0.360		
Marital status				
Married	Reference		Reference	
Unmarried	1.55 (1.37-1.75)	< 0.001	1.26 (1.10-1.44)	0.001
Unknown	1.34 (1.02-1.78)	0.037	1.07 (0.81-1.42)	0.63
Tumor grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.27 (0.99-1.63)	0.55	0.98 (0.75-1.28)	0.88
Poorly differentiated / undifferentiated	2.33 (1.83-2.95)	< 0.001	1.31 (1.01-1.70)	0.045
Unknown	1.34 (1.02-1.75)	< 0.001	0.86 (0.65-1.15)	0.31
Tumor invasion				
Intramucosa	Reference		Reference	
Submucosa	1.10 (0.92-1.31)	0.28	1.23 (1.01-1.50)	0.037
Not specified	3.72 (3.20-4.32)	< 0.001	1.57 (1.33-1.86)	< 0.001
Tumor size (cm)				
≤1	Reference		Reference	
1.1-2	1.99 (1.48-2.68)	< 0.001	1.33 (0.97-1.81)	0.073
2.1-4	3.62 (2.74-4.77)	< 0.001	1.94 (1.45-2.58)	< 0.001
>4	6.07 (4.55-8.10)	< 0.001	2.05 (1.50-2.79)	< 0.001
Unknown	5.12 (3.96-6.62)	< 0.001	2.04 (1.56-2.68)	< 0.001
N stage				
N negative	Reference		Reference	
N positive	1.99 (1.74-2.27)	< 0.001	1.51 (1.28-1.78)	< 0.001
Local treatment				
No/unknown	Reference		Reference	
Endoscopic resection	0.11 (0.08-0.14)	< 0.001	0.19 (0.14-0.26)	< 0.001
Surgery	0.21 (0.18-0.24)	< 0.001	0.31 (0.26-0.37)	< 0.001
Radiation				
No/unknown	Reference		Reference	
Yes	2.03 (1.80-2.29)	< 0.001	0.89 (0.75-1.05)	0.16
Chemotherapy				
No/unknown	Reference		Reference	
Yes	2.07 (1.84-2.33)	< 0.001	1.05 (0.88-1.25)	0.57

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

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.[43] However, we could not assess these factors due to the limited data available in the SEER database.

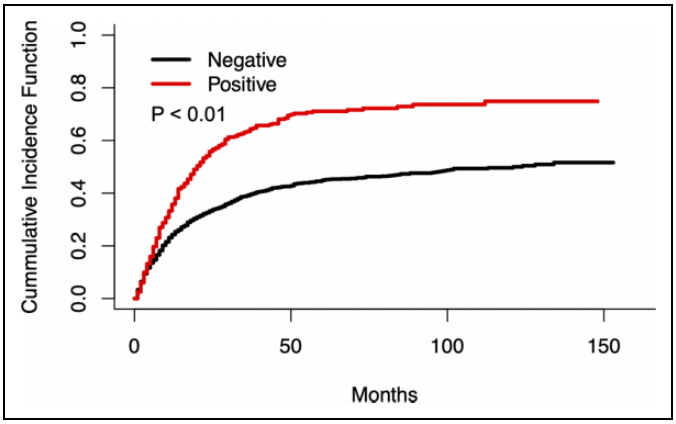

Figure 3. Cumulative incidence function for cancer-specific death in T1 AEG. The red curve indicates the cancer-specific death in patients with Lymph Node Metastasis (LNM), and the black curve suggests the cancer-specific death in patients without LNM.

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

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Supplemental Material

Supplemental material for this article is available online.

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