



Treatment Options for T1 Stage Adenocarcinoma of Esophagogastric Junction: A Real-World Retrospective Cohort Study

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Abstract

Background: The number of patients diagnosed with T1 stage adenocarcinoma of esophagogastric junction (AEGJ) has been increasing. This study was conducted to investigate the effect of different treatment options (surgery, chemoradiation, and surgery+chemoradiation) on long-term survival in patients with T1-stage AEGJ.

Methods: We searched the Surveillance, Epidemiology, and End Results (SEER) database to identify the records of patients with T1-stage AEGJ between 2010 and 2018. Patient demographics and cancer parameters were compared among the three groups. The Kaplan–Meier method and Cox proportional hazard modeling were used to compare long-term survival.

Results: Data from 925 T1 stage AEGJ patients (surgery: n=516, surgery+chemoradiation: n=206, chemoradiation: n=203) were collected. We found that the OS and CSS rates of three treatment options had significant difference. Besides, positive nodal status also showed lower OS and CSS rate. Multivariate Cox regression analysis showed that surgery group has much lower risk of death compared with chemoradiation group and similar risk of death compared with surgery+chemoradiation group. Subgroup analysis suggested that in patients with N1–N3 status had higher OS and CSS rates in surgery+chemoradiation group.

Conclusion: Using SEER data, we identified a significant survival advantage with the use of surgery compared to chemoradiation in patients with T1-stage AEGJ while the long-term survival of patients after surgery+chemoradiation group was not significantly different and low risk of death in positive nodal status.

Keywords

adenocarcinoma of esophagogastric junction, T1 stage, Surveillance, Epidemiology, and End Results (SEER), treatment options

Introduction

The incidence of adenocarcinoma of esophagogastric junction (AEGJ) has increased rapidly over the last few decades.¹ Its prevalence in Asia, including China and Japan, is expected to rise as a consequence of the decrease in the rate of *Helicobacter pylori* infection² and the high prevalence of gastroesophageal reflux disease³ and obesity.⁴ Although AEGJ is now regarded and staged as an esophageal cancer according to the 7th American Joint Committee on Cancer (AJCC) staging system, this approach remains a subject of disagreement, confusion,

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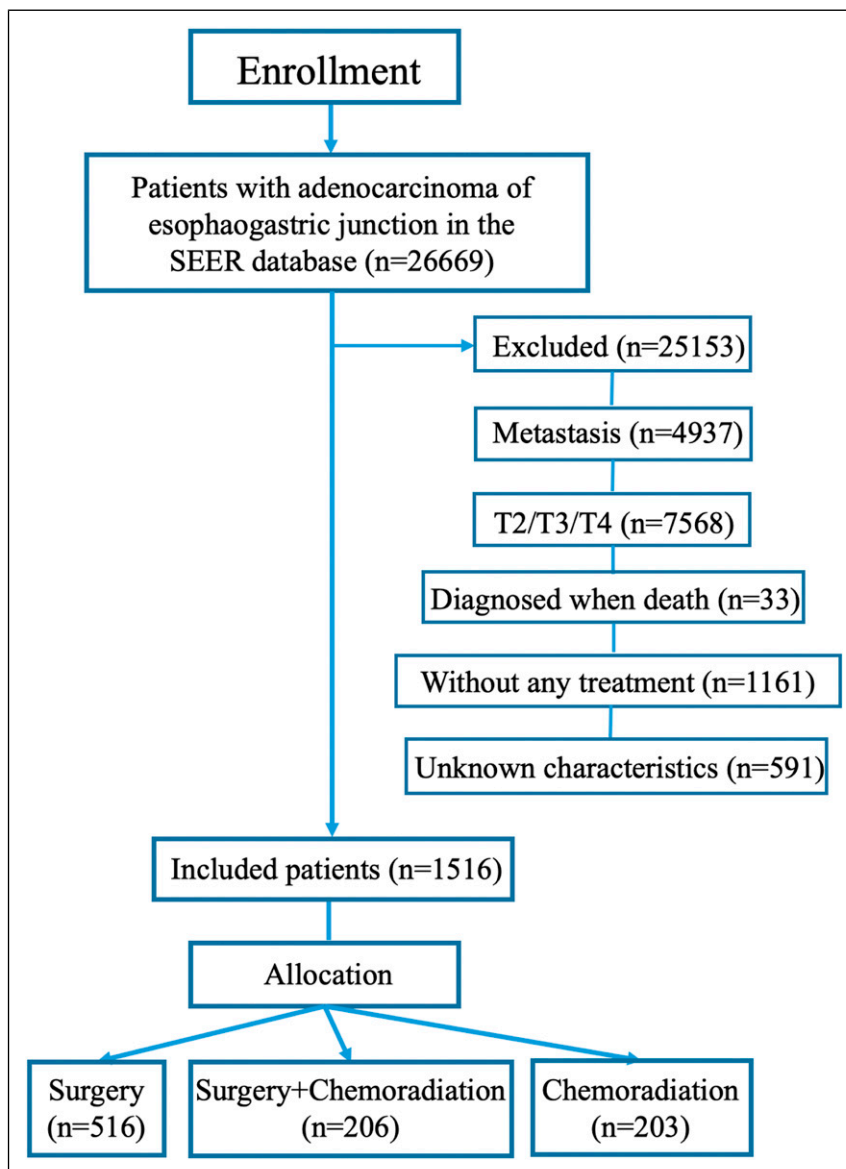


Figure 1. The flowchart of study population selection.

and debate.⁵ Therefore, the National Comprehensive Cancer Network (NCCN) still recommends adopting an individualized therapeutic approach.⁶

Surgery remains the primary curative modality for AEGJ, especially in T1 stage.⁷ However, overall prognosis of this disease remains poor because of distant and locoregional recurrence of disease, with 5-year survival rates averaging around 30% with surgery alone.⁸ This low rate may be due to inadequate staging.⁹ Consequently, neoadjuvant or perioperative multimodality strategies incorporating chemotherapy, radiation, or the combination of both have emerged over the past few decades, with the goal of eradicating occult micrometastatic disease and improving both surgical and survival outcomes.¹⁰⁻¹²

However, no studies for now specifically addressed the relatively stage-specific roles of chemoradiation alone, and

combined chemoradiation with surgery in AEGJ, especially in early stage. Hence, in our study, we used the Surveillance, Epidemiology, and End Results (SEER) database to conduct a national descriptive epidemiological study to compare the effect of different treatment options on long-term survival in patients with T1 stage AEGJ by using conventional and propensity score matching (PSM) approaches.

Methods

Study Population and Data Source

A retrospective study was performed by using “SEER research Plus Data, 18 registries, Nov 2020 sub (2000–2018) database” in this study (<https://seer.cancer.gov/>). Eligible patients included:

Table 1. Baseline characteristics of the three groups.

Variables	Surgery	Surgery+chemoradiation	Chemoradiation	P
Age (years)				
<65	192 (55.7%)	103 (29.9%)	50 (14.5%)	<.001
≥65	324 (55.9%)	103 (17.8%)	153 (26.4%)	
Sex				
Male	386 (53.8%)	170 (22.8%)	169 (22.7%)	.272
Female	130 (62.8%)	36 (20%)	34 (18.9%)	
Race				
Non-API	477 (56.1%)	191 (22.5%)	182 (21.4%)	.414
API	39 (52.0%)	15 (20.0%)	21 (28.0%)	
Tumor size				
<3 cm	425 (70.1%)	117 (19.3%)	64 (10.6%)	<.001
3–5 cm	64 (32.2%)	60 (30.2%)	75 (37.7%)	
>5 cm	27 (22.5%)	29 (24.2%)	64 (53.3%)	
Histological grade				
Grade I	102 (74.5%)	23 (16.8%)	12 (8.8%)	<.001
Grade II	264 (58.9%)	91 (20.3%)	93 (20.8%)	
Grade III	145 (44.1%)	88 (26.7%)	96 (29.2%)	
Grade IV	5 (45.5%)	4 (36.4%)	2 (18.2%)	
Nodal status				
N0	478 (67.3%)	89 (12.6%)	139 (19.7%)	<.001
N1–3	38 (17.4%)	117 (53.4%)	64 (29.2%)	
T Stage				
T1a	184 (70.2%)	33 (12.6%)	45 (17.2%)	<.001
T1b	313 (64.8%)	132 (27.3%)	38 (7.9%)	
T1-unclassified	19 (10.6%)	41 (22.8%)	120 (66.7%)	
Histology				
Intestinal type	47 (62.7%)	17 (22.7%)	11 (14.7%)	.447
Diffuse type	6 (50%)	4 (33.3%)	2 (16.7%)	
Unclassified	463 (55.3%)	185 (22.1%)	190 (22.7%)	

Note: Node status: N0 represented negative node status. N1 Metastasis in 1–2 regional lymph nodes, N2: Metastasis in 3–6 regional lymph nodes, N3: Metastasis in 7 or more regional lymph nodes, N3a: Metastasis in 7–15 regional lymph nodes N3b: Metastasis in 16 or more regional lymph nodes.

(1) patients with T1M0 adenocarcinoma of the esophagogastric junction (no invasion beyond the submucosa); (2) patients treated with surgery, radiotherapy, chemotherapy, chemoradiotherapy or surgery, and chemoradiotherapy. Exclusion criteria include the following: (1) other histological types of carcinoma; (2) metastatic cancer; (4) age less than 18 years; (5) tumor was diagnosed solely on autopsy or death certificate; (6) patients with missing or unknown information. The 7th edition American Joint Committee on Cancer (AJCC) TNM system was applied. Sample size calculation was conducted by the survival module in the PASS 15 software. Log-rank test (Freedman method) with $\alpha=.05$, $\beta=.2$, one-sided hypothesis was applied. The expected survival rate of surgery, surgery+chemoradiation, and chemoradiation was .6, .7, and .9, respectively. The study duration was 11 years. The maximum calculated sample size was 137 required for each group. In our study, we initially enrolled in 516, 206, and 203 in surgery, surgery+chemoradiation, and chemoradiation groups, respectively. Demographics (age, sex, race, and year

of diagnosis), clinical and histological characteristics (tumor size, lymph node metastasis, grade, TNM stage, and therapy methods), survival months and status, cancer-specific survival (CSS), or overall survival (OS) were recorded. We selected AEGJ patients with true carcinoma of the cardia (“C16.0 Cardia” of ICD-O-3) into analysis, which is defined as Siewert II type based on the latest NCCN guideline of cancer of esophagogastric junction. Patients were divided into three groups according to the treatment modality: surgery alone, chemoradiation alone, and surgery+chemoradiation. The detailed flowchart of study population selection is listed in [Figure 1](#).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The SEER Program collects data from population-based cancer registries with anonymous information. The SEER database has public-use data,

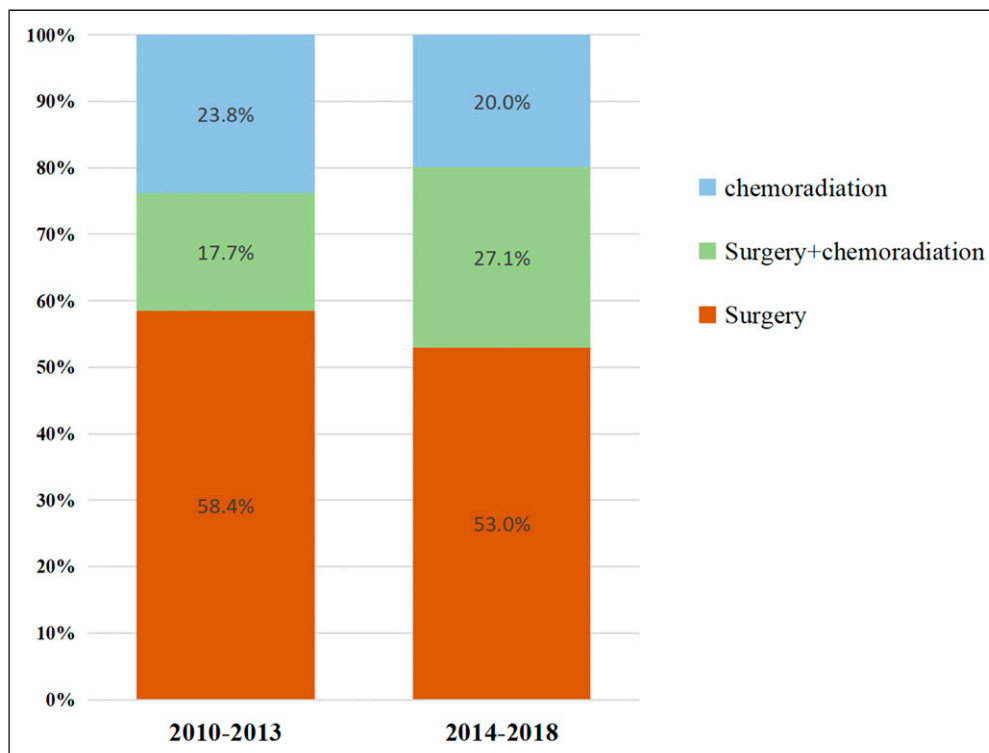


Figure 2. Changes in use of surgery ($P = .268$), chemoradiation ($P = .208$), and surgery+chemoradiation ($P = .002$) from 2010–2014 to 2015–2018.

and our study did not require approval or a declaration of local ethics.

Statistical Analysis

Data were extracted by using SEER*Stat program version 8.3.9. Statistical analysis was performed by using Statistics, Version 20.0 (SPSS, Chicago, IL) and R software (version 3.5.1, <http://www.R-project.org/>). Propensity score matching was conducted to calibrate the effects of the baseline of clinicopathological differences. The R*C chi-square test was applied for comparison of categorical characteristics. The Kaplan–Meier method and the log-rank test were applied for survival analysis. Multivariate Cox proportional hazard test was then used by including variables with P -values $< .1$. The 3-year and 5-year OS and CSS were calculated. Tests were two-sided with a significance level of $P < .05$.

Results

Baseline Characteristics

The SEER database included data of 925 patients (surgery: $n = 516$, 55.8%; surgery+chemoradiation: $n = 206$, 22.3%; chemoradiation: $n = 203$, 21.9%). The patients older than 65 years account for 62.7%. The majority of patients were non-API (91.9%) and male (78.4%). There are 137 patients with Grade I histology, 448 patients with Grade II, 329 patients

with Grade III, and 11 with Grade IV. In nodal status, most patients were in N0 status ($n = 706$, 76.3%). The detailed patient demographics and tumor parameters are listed in Table 1. We found that there were significant differences in age, tumor size, histological grade, nodal status, and T stage among the three groups ($P < .001$). Consequently, in order to minimize this confounding bias, we performed PSM analysis to generate balanced cohorts in surgery group vs chemoradiation group and surgery group vs surgery+ chemoradiation group.

There was an increase in the proportion of patients who underwent surgery+chemoradiation from the year of diagnosis in 2010–2013 (17.7%, 84/474) to 2014–2018 (27.1%, 122/451), $P = .002$. The number of cases treated via chemoradiation (23.8% vs 20.0%, $P = .208$) and surgery only (58.4% vs 53.0%, $P = .268$) remained relatively stable over the two time periods (Figure 2).

The OS and CSS rates of the three groups are shown in Figure 3A and Figure 3B. We found that the OS and CSS rates of three treatment options had significant difference ($P < .0001$). Besides, positive nodal status also showed lower OS and CSS rates ($P < .0001$) (Figure 3C and 3D).

Surgery Group vs. Chemoradiation Group

We generated two balanced cohorts of surgery and chemoradiation groups. After PSM analysis, there were no differences in age ($P = .340$), sex ($P = .249$), race ($P = .653$), tumor size ($P = .157$),

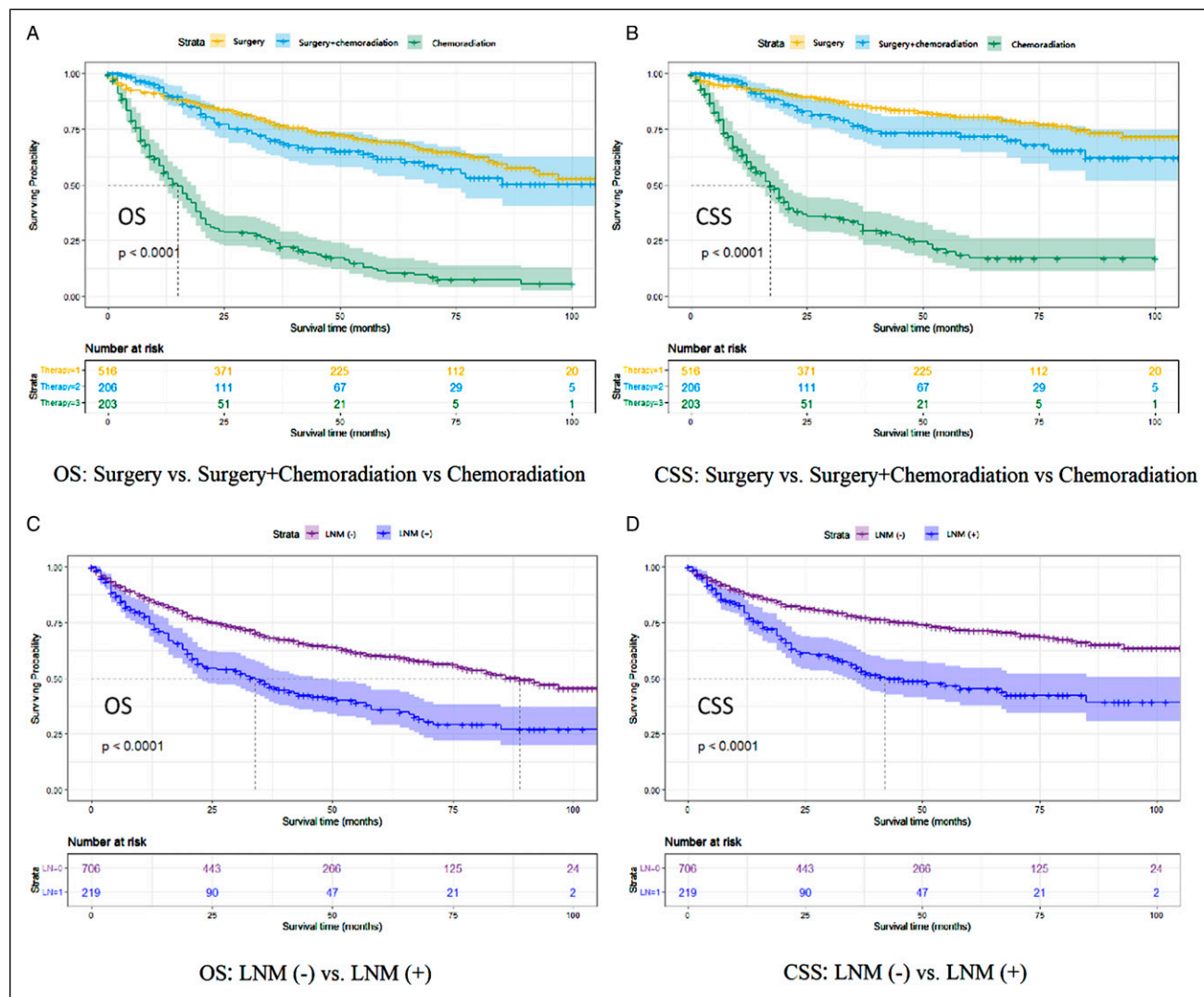


Figure 3. The OS and CSS rates in all the three treatments ($P < .0001$) and in positive nodal status patients ($P < .0001$).

histological grade ($P = .929$), nodal status ($P = .082$), and histology ($P = .084$) (Supplementary Table 1). The OS and CSS rates in surgery group were significantly higher than those in chemoradiation group ($P < .0001$) (Figure 4A and 4B).

In univariate analysis, we found that positive nodal status (HR: 2.086 [1.366–3.185], $P = .001$) and treatment options (surgery) (HR: .213 [.133–.342], $P < .001$) were significant prognostic factors of CSS. In multivariate Cox regression, only treatment options (surgery) were significant prognostic factors of CSS, that is, surgery has much lower risk of death (HR: .242 [.162–.360], $P < .001$).

In univariate analysis, we found that positive nodal status (HR: 1.936 [1.330–2.817], $P = .010$), T1b stage (HR: .468 [.311–.705], $P < .001$) and treatment options (surgery) (HR: .242 [.162–.360], $P < .001$) were significant prognostic factors of OS. In multivariate Cox regression, only treatment options (surgery) were significant prognostic factors of CSS, that is surgery has much lower risk of death (HR: .265 [.164–.425], $P < .001$) (Supplementary Table 2).

Surgery Group vs. Surgery+Chemoradiation Group

Another two balanced cohorts of surgery and surgery+chemoradiation groups. After PSM analysis, there were no differences in age ($P = .274$), sex ($P = .476$), race ($P = .060$), tumor size ($P = .850$), histological grade ($P = .901$), nodal status ($P = .773$), T stage ($P = .913$), and histology ($P = .883$) (Table 2). The OS and CSS rates in surgery group were similar compared with those in surgery+chemoradiation group (OS: $P = .12$; CSS: $P = .39$) (Figure 4C and 4D).

In univariate analysis, we found that age (HR: 2.622 [1.407–4.888], $P = .002$), sex (HR: 3.093 [1.116–8.572], $P = .030$), and nodal status (HR: 3.028 [1.781–5.150], $P < .001$) were significant prognostic factors of CSS. In multivariate Cox regression, only nodal status was significant prognostic factor of CSS, that is, patients with N1–N3 status have much lower risk of death (HR: 2.584 [1.427–4.678], $P = .002$).

In univariate analysis, we found that age (HR: 2.254 [1.367–3.715], $P = .001$), sex (HR: 2.216 [1.065–4.612], $P = .033$), and

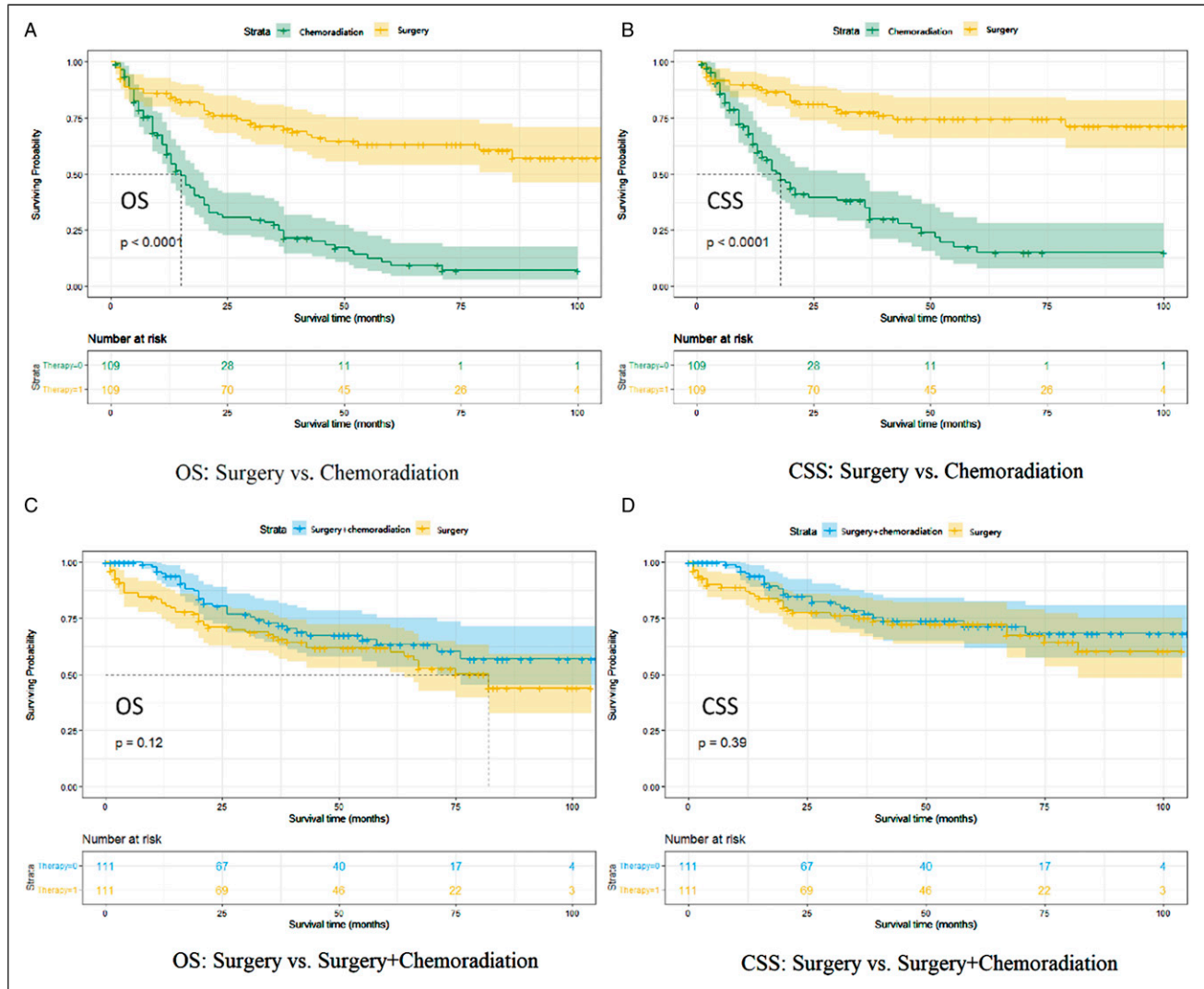


Figure 4. The OS (A) and CSS (B) rates in surgery group vs chemoradiation group; The OS (C) and CSS (D) in surgery group vs surgery+chemoradiation group.

nodal status (HR:2.209 [1.415–3.449], $P < .001$) were significant prognostic factors of OS. In multivariate Cox regression, only nodal status was significant prognostic factor of OS, that is, patients with N1–N3 status have much higher risk of death (HR: 1.849 [1.121–3.047], $P = .016$) (Table 3). Subgroup analysis suggested that in patients with N1–N3 status, the OS and CSS rates in surgery+chemoradiation group were significantly higher when compared with those in surgery group (OS: $P = .000093$; CSS: $P = .017$) (Figure 5A and B).

Discussion

Adenocarcinomas of the GEJ are often lumped in therapeutic trials and analyzed with either esophageal cancer or gastric cancer.¹³ To our knowledge, this is the first large-scale retrospective study to report survival data after 3 different treatment options. Early stage AEGJ is classified into mucosal

carcinoma (T1a), submucosal carcinoma (T1b), and carcinoma in situ (Tis).¹⁴ We explored the preferred treatment options for T1 stage of AEGJ in this study. Surgery remains the cornerstone of treatment for resectable AEGJ.¹⁵ However, the role of chemotherapy and radiotherapy in early stage of AEGJ remains controversial. In NCCN guidelines, AEGJ patients with T1b stage were recommended with chemoradiotherapy, with an improved survival rate.⁶ Consequently, we performed this population-based study to explore factors associated with survival rate.

In our study, we found that basic clinical characteristics differed among the three groups. Consequently, we performed propensity score matching to eliminate the confounding factors.¹⁶ Univariate and multivariate analyses of OS and CSS in patients with T1 stage AEGJ treated with surgery and chemoradiation after propensity score matching showed that surgery could significantly lower the risk of death compared

Table 2. Characteristics of patients treated with surgery and surgery+chemoradiation for T1 stage AEGJ.

Variables	Unmatched cohort			Matched cohort		
	Surgery, n = 516 n (%)	Surgery+chemoradiation, n = 206 n (%)	P	Surgery, n = 111 n (%)	Surgery+chemoradiation, n = 111 n (%)	P
Age at diagnosis (y)						
< 65	192 (65.1)	103 (34.9)	.002	41 (45.6)	49 (54.4)	.274
≥65	324 (75.9)	103 (24.1)		70 (53.0)	62 (47.0)	
Sex						
Female	110 (75.3)	36 (24.7)	.246	21 (55.3)	17 (44.7)	.476
Male	406 (70.5)	170 (29.5)		90 (48.9)	94 (51.1)	
Race						
Non-API	477 (71.4)	191 (28.6)	.898	93 (47.4)	103 (52.6)	.060
API	39 (72.2)	15 (27.8)		18 (69.2)	8 (30.8)	
Tumor size						
<3 cm	425 (78.4)	117 (21.6)	<.001	68 (48.6)	72 (51.4)	.850
3–5 cm	64 (51.6)	60 (48.4)		27 (51.9)	25 (48.1)	
>5 cm	27 (48.2)	29 (51.8)		16 (53.3)	14 (46.7)	
Histological grade						
Grade I	102 (81.6)	23 (18.4)	<.001	13 (46.4)	15 (53.6)	.901
Grade II	264 (74.4)	91 (25.6)		48 (48.5)	51 (51.5)	
Grade III	145 (62.2)	88 (37.8)		49 (52.7)	44 (47.3)	
Grade IV	5 (55.6)	4 (44.4)		1 (50.0)	1 (50.0)	
Nodal status						
N0	478 (84.3)	89 (15.7)	<.001	75 (49.3)	77 (50.7)	.773
N1–3	38 (24.5)	117 (75.5)		36 (51.4)	34 (48.6)	
T Stage						
T1a	184 (84.4)	33 (15.2)	<.001	24 (51.1)	23 (48.9)	.913
T1b	313 (71.3)	132 (29.7)		75 (50.3)	74 (49.7)	
T1-unclassified	19 (31.7)	41 (68.3)		12 (46.2)	14 (53.8)	
Histology						
Intestinal type	47 (73.4)	17 (26.6)	.661	10 (52.6)	9 (47.4)	.883
Diffuse type	6 (60.0)	4 (40.0)		3 (60.0)	2 (40.0)	
Unclassified	463 (71.5)	185 (28.5)		98 (49.5)	100 (50.5)	

with patients who received chemoradiation alone. However, univariate and multivariate analyses of OS and CSS in patients with T1 stage AEGJ treated with surgery and surgery+chemoradiation after propensity score matching showed similar risk of death, which suggested that chemoradiation before or after surgery could not improve patients' survival rate. In subgroup analysis, we found that patients with positive nodal status (N1–N3) had higher OS and CSS rates when treated with surgery+chemoradiation. Chemoradiation has the advantage of organ preservation and compensate for the lack of regional/nodal control in surgery.¹⁷ However, with a relapse rate up to 30% and radiotherapy-associated side effects, this strategy remains highly controversial.¹⁸ Additionally, we found that nodal status was significantly associated with OS and CSS. Lymphatic node metastases appear early in this disease, which is explained by the abundant lymphatic drainage in the esophageal submucosa.¹⁹ Lymph node metastases in intramucosal adenocarcinomas (pT1a) vary between 0% and 15% in the literature.^{20,21} In adenocarcinomas with submucosal invasion (pT1b), lymph node metastases

are found in 4.1–50% of the cases.^{22,23} Similar to our study, the research group of Lorenz and Ell showed that in early cancers in Barrett's esophagus treated by radical surgical resection, lymph node status is the only independent prognostic factor for recurrence and survival rates.²⁴ Another study on the prevalence and topography of lymph node metastases in early carcinomas revealed a lymph node involvement of 0% for pT1a adenocarcinomas of the esophagogastric junction (AEG) and a lymph node involvement of 18% for pT1b adenocarcinomas.²⁵ The risk of lymph node metastases in early cancers cannot be reliably evaluated preoperatively, and there is always a residual risk for lymph node metastases in surgery.²⁶ This is in accordance with our study that chemoradiation before or after surgery could improve the survival rate of patients with positive nodal status.²⁷ The survival benefit of adjuvant therapy observed might be explained by microscopic metastases present at the time of surgical resection, receptive for chemoradiation.²⁸

There are several advantages to using SEER data for this study. Specifically, large sample sizes and long-term follow-up

Table 3. Univariate and multivariate analyses of OS and CSS in patients with T1-stage AEGJ treated with surgery and surgery+chemoradiation after propensity score matching.

Variables	Univariate Analysis			Multivariate Analysis		
	CSS		OS	CSS		OS
	HR (95% CI)	P-Value	HR (95% CI)	HR (95% CI)	P-Value	P-Value
Age (years)						
<65	Ref	1.0	Ref	Ref	1.0	1.0
≥65	2.622 (1.407–4.888)	.002	2.254 (1.367–3.715)	1.899 (.974–2.703)	.060	1.702 (.994–2.915)
Sex						
Female	Ref	1.0	Ref	Ref	1.0	1.0
Male	3.093 (1.116–8.572)	.030	2.216 (1.065–4.612)	2.510 (.880–7.163)	.085	1.961 (.918–4.186)
Race						
Non-API	Ref	1.0	Ref	Ref	1.0	1.0
API	.748 (.319–1.751)	.503	.572 (.262–1.246)	1.086 (.441–2.674)	.857	.709 (.313–1.606)
Tumor size						
<3 cm	Ref	1.0	Ref	Ref	1.0	1.0
1–2 cm	1.505 (.833–2.719)	.176	1.363 (.826–2.249)	1.372 (.728–2.585)	.328	1.137 (.661–1.958)
2–3 cm	.954 (.419–2.172)	.911	.890 (.448–1.768)	1.023 (.441–2.375)	.958	.907 (.451–1.824)
Histological grade						
Grade I	Ref	1.0	Ref	Ref	1.0	1.0
Grade II	1813 (.542–6.062)	.334	1.055 (.463–2.403)	1.367 (.396–4.722)	.621	.936 (.398–2.199)
Grade III	3.912 (.972–10.485)	.056	2.006 (.899–4.476)	2.324 (.682–7.915)	.178	1.664 (.724–3.821)
Grade IV	3.792 (.393–36.563)	.249	1.730 (.212–14.112)	2.710 (.361–38.108)	.270	1.769 (.206–15.182)
Nodal status						
N0	Ref	1.0	Ref	Ref	1.0	1.0
N1–3	3.028 (1.781–5.150)	<.001	2.209 (1.415–3.449)	2.584 (1.427–4.678)	.002	1.849 (1.121–3.047)
T Stage						
T1a	Ref	1.0	Ref	Ref	1.0	1.0
T1b	1.276 (.639–2.550)	.490	1.249 (.708–2.203)	1.372 (.728–2.585)	.328	.981 (.532–1.810)
T1-unclassified	.788 (.247–2.513)	.687	.652 (.237–1.795)	1.023 (.441–2.375)	.958	.796 (.281–2.254)
Treatment option						
Surgery+chemoradiation	Ref	1.0	Ref	Ref	1.0	1.0
Surgery	1.264 (.741–2.154)	.390	1.422 (.907–2.230)	1.360 (.786–2.351)	.272	1.565 (.985–2.486)

Abbreviations: CI, confidence interval; CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio.

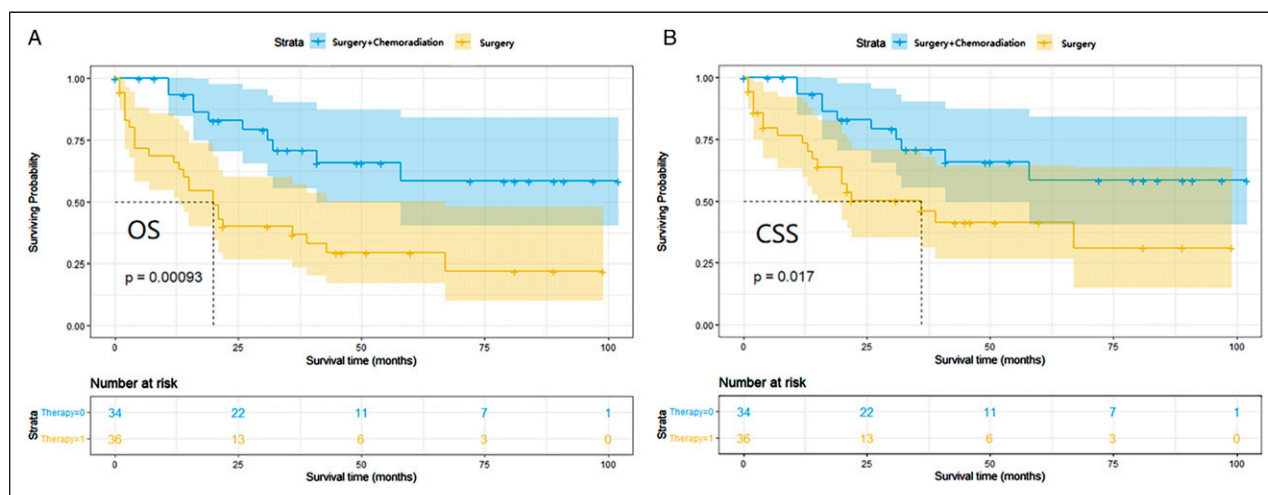


Figure 5. The OS (A) and CSS (B) rates in surgery+chemoradiation group vs surgery group in patients with N1–N3 status.

enable reporting of survival outcomes and provide evidence to compare different treatments. To minimize interference from baseline differences in each treatment group, we used PSM to analyze treatment outcomes and used OS and CSS as the primary treatment outcomes. The interpretation of our results, however, is restricted by several limitations. Firstly, because of the retrospective nature of the study, patient characteristics were not comparable. T1a and T1b cohorts are different in terms of prognosis and choice of treatment. PSM could not overcome all of these problems in this study. The current SEER database lacks information on medical history, such as comorbidities, complications, operation details (open or minimally invasive), medical center information (hospital volume, surgical, and endoscopic experience), lymph node involvement, postoperative nutrition status (e.g., hemoglobin), and subsequent therapy (e.g., chemoradiotherapy before or after surgery, hormonal therapy, or biotherapy).

Conclusion

Our population-based study demonstrated better OS and CSS outcomes of surgery compared to chemoradiation and similar OS and CSS outcomes of surgery+chemoradiation compared to surgery alone in T1 stage of AEGJ. Patients with N1–N3 status had higher OS and CSS rates in surgery+chemoradiation group. Further prospective randomized controlled studies are needed to be performed to investigate the efficacy of surgery and adjuvant chemoradiation for the treatment of early stage AEGJ.

Authors' Contributions

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. Conception and design: Xiaoying Zhou and Guoxin Zhang; development of methodology: Han Chen and Shuo Li; acquisition of data: Han Chen and

Jie Hua; analysis and interpretation of data: Weifeng Zhang and Xueliang Li; writing, review, and/or revision of the manuscript: Xiaoying Zhou and Han Chen; study supervision: Xueliang Li, Xinmin Si, and Guoxin Zhang.

Declaration of Conflicting Interest

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

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Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki.

Informed Consent

Institutional review board approval and informed consent were not required in the current study because SEER research data are publicly available and all patient data are de-identified.

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