Endoscopic versus surgical therapy for early esophagogastric junction adenocarcinoma based on lymph node metastasis risk: a population-based analysis

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Research

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Abstract

Background

In this study, we aimed to compare the prognosis and lymph node metastasis (LNM) risk in patients with early-stage esophagogastric junction (EGJ) adenocarcinoma after endoscopic treatment (ET) or radical surgery.

Methods

We collected data from eligible patients based on Surveillance, Epidemiology, and End Results database between 2004 and 2016. Logistic regression analysis was used to determine independent predictors of LNM (examination of at least 16 lymph nodes). Cox regression analysis and propensity score-matched (PSM) analysis were subsequently utilized to compare overall survival (OS) and cancer-specific survival (CSS) of patients treated with ET or radical surgery.

Results

In total, 5266 patients were identified. Among them, 856 patients had greater than or equal to 16 examined lymph nodes (LNs) (LNE ≥ 16). The LNM rates were 18.8% in all patients, 8.3% in T1a patients, and 24.6% in T1b patients. Independent predictors of LNM were submucosal invasion, tumor size ≥ 3cm, and decreasing differentiation (P < 0.05). The LNM rate decreased to approximately 5.3% in T1b tumors with well differentiation and tumor size < 3cm. However, the LNM incidence increased to 17.9% or 33.3% in T1a tumors with poor differentiation or with both tumor size ≥ 3cm and poor differentiation. Cox regression analysis demonstrated CSS was not significantly different in early-stage EGJ adenocarcinoma patients undergoing ET and those treated with radical surgery (HR = 0.830, P = 0.062), which were robustly validated after PSM analysis. Moreover, subgroup analysis stratified by T1a and T1b showed similar results.

Conclusions

Consequently, our findings indicated ET as an alternative to radical surgery in early EGJ adenocarcinoma.

Introduction

Nowadays, great changes have been made in the clinical intervention for early malignant and precancerous lesions of the upper gastrointestinal (GI) tract, from radical surgery to endoscopic treatment. The incidence of esophagogastric junction (EGJ) adenocarcinoma has been rapidly rising in Western countries in the last decades [1]. A similar trend has been observed in Asia, probably due to the available eradication therapy for Helicobacter pylori (H.pylori), a high prevalence of gastroesophageal reflux disease and obesity, and dietary factors [2], and partly shared with those of gastric adenocarcinoma, i.e. H.pylori infection and dietary factors [3]. As a minimally invasive approach, endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) is also curative for superficial GI malignancies, including esophageal, gastric and colonic lesions [4]. Moreover, due to the varied incidence of lymph node metastasis (LNM) in esophageal and gastric cancer, there are also difference of the curative resection criteria of ESD / EMR between esophageal and gastric cancer [5, 6]. However, it is unknown which curative resection criteria are better for EGJ adenocarcinoma, since the incidence of metastatic EGJ adenocarcinoma remains unknown. Of note, inaccessible assessment of pathologic lymph node (LN) has been considered as the main drawback of endoscopic treatment (ET), which can significantly affect patients' survival in the case of metastatic LNs. Therefore, clinical decision-making in early-stage EGJ adenocarcinoma can be optimized by better pretreatment LNM risk stratification according to both patient and tumor features.

In this study, eligible patients from Surveillance, Epidemiology, and End Results (SEER) database were utilized to determine preoperative predictors of LNM, followed by comparison of the effects of radical surgery, ET, and radiotherapy (RT) on long-term survival in early-stage EGJ adenocarcinoma. Finally, an early-stage EGJ adenocarcinoma therapeutic algorithm was proposed for patients at acceptable risk for ET.
Materials And Methods

Origins of materials

The National Cancer Institute (NCI) supported SEER database, records data on tumor incidence and survival by covering almost 28% of population in the USA from diverse geographic regions (18 cancer registries) from 2004 to 2016. The collection and recoding of SEER data were performed using data items and codes on the basis of North American Association of Central Cancer Registries (NAACCR)[7]. Access to SEER database was obtained, and our study gained institutional approval.

Inclusion and exclusion criteria

In total, 5266 patients were enrolled. The inclusion criteria were as follows: (1) year of diagnosis (from 2004 to 2016); (2) patients were 18 years or older; (3) histological type included adenocarcinoma (8140), mucinous adenocarcinoma (MAC) (8480), and signet ring cell cancer (SRCC) (8490); (4) available active follow-up data. (5) patients with T1 EGJ adenocarcinoma (site codes, C15.5, C16.0, C16.1 and C16.2) and treated with either ET, radical surgery or RT. According to the records in SEER database, ET referred to endoscopic treatment for local tumor excision with pathology specimen. In addition, the definition of radical surgery was all forms of partial esophagus removal along with partial or total gastrectomy. RT was defined as ionizing radiation-based therapy. (6) At least 16 regional lymph nodes (LNs) were examined after surgical resection. The exclusion criteria were as follows: (1) distant metastasis; (2) patients who received neoadjuvant therapy (3) patients had more than one primary malignancies, except those with EGJ as the first diagnosed; (4) patients died within 1 month, which was mostly caused by surgical complications; (5) patients undergoing local tumor destruction without pathological specimen.

Statistical analysis

Age at diagnosis, race, year of diagnosis, marital status, gender, tumor size, differentiation grade, survival (months), number of examined LNs, LNM, histology and death cause were collected from SEER database. The main endpoints included overall survival (OS) and cancer-specific survival (CSS).

For comparisons among group, categorical variables were analyzed by Fisher's exact test or Pearson's test. Risk factors for LNM were determined by both univariate and multivariate logistic regression models, shown as odd ratios (ORs) along with 95% confidence intervals (CIs). Moreover, adjusted hazard ratios (HRs) along with 95% CIs were calculated by both univariate and multivariate Cox regression models. Additionally, PSM analysis was performed by using the 1:1 "nearest neighbor" match paradigm, aiming at further adjustment of variations in general data and bias minimization. The following covariates histology, grade, race, gender, age, T stage, tumor size, year of diagnosis, and marital status were used in PSM analysis. After matching, we compared two groups with control for covariate balance and similarity in baseline covariates between groups, and two matched groups were compared according to the study objectives. Statistical analysis was performed by R software version R-3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria) as well as SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). GraphPad Prism 6.0 (GraphPad Software, San Diego, CA) was employed to plot survival curves. A two-sided P value < 0.05 suggested statistical significance.

Results

Patient Characteristics

In total, 5266 eligible patients were included (surgical therapy: n = 2418, 45.9%; ET: n = 1290, 24.5%; RT: n = 1558, 29.6%). Among them, 4389 patients were male and the remaining 877 were females. The median age at diagnosis was 68 years, ranging from 22 to 99 years (mean ± SD: 68.16 ± 11.24 years). The median follow-up was 32 months, ranging between 1 and 155 months. The detailed data on patient demographics as well as tumor characteristics were shown in Table 1.
Table 1
The characteristics of 5266 patients with early-stage esophagogastric junction cancer

| Characteristic   | Surgery | ET          | RT          | Statistic | p       |
|------------------|---------|-------------|-------------|-----------|---------|
| Gender           |         | N = 2418,% | N = 1290,%  | N = 1558,%|         |
| Female           |         | 376(15.6)  | 234(18.1)   | 267(17.1) | 0.109   |
| Male             |         | 2042(84.4) | 1056(81.9)  | 1291(82.9)|         |
| Age(years)       |         |             |             |           |         |
| Up to 49         |         | 170(7.0)   | 39(3.0)     | 49(3.1)   | < 0.001 |
| 50–64            |         | 985(40.7)  | 360(27.9)   | 338(21.7) |         |
| 65–79            |         | 1114(46.1) | 650(50.4)   | 664(42.6) |         |
| 80+              |         | 149(6.2)   | 241(18.7)   | 507(32.5) |         |
| Race             |         |             |             |           | 0.046   |
| White            |         | 2270(93.9) | 1221(94.7)  | 1445(92.7)|         |
| Black            |         | 56(2.3)    | 32(2.5)     | 58(3.7)   |         |
| Others*          |         | 92(3.8)    | 37(2.9)     | 55(3.5)   |         |
| T stage          |         |             |             |           | < 0.001 |
| T1a              |         | 979(40.5)  | 927(71.9)   | 336(21.6) |         |
| T1b              |         | 1226(50.7) | 226(17.5)   | 147(9.4)  |         |
| T1x              |         | 213(8.8)   | 137(10.6)   | 1075(69.0)|         |
| Tumor size(cm)   |         |             |             |           | < 0.001 |
| < 1              |         | 511(21.1)  | 351(27.2)   | 30(1.9)   |         |
| 1–2              |         | 571(23.6)  | 211(16.4)   | 96(6.2)   |         |
| 2–3              |         | 420(17.4)  | 86(6.7)     | 111(7.1)  |         |
| 3+               |         | 431(17.8)  | 70(5.4)     | 550(35.3) |         |
| Not stated       |         | 485(20.1)  | 572(44.3)   | 771(49.5) |         |
| Year of diagnosis|         |             |             |           | < 0.001 |
| 2004–2006        |         | 577(23.9)  | 116(9.0)    | 399(25.6) |         |
| 2007–2009        |         | 675(27.9)  | 189(14.7)   | 408(26.2) |         |
| 2010–2012        |         | 555(23.0)  | 315(24.4)   | 342(22.0) |         |
| 2013–2016        |         | 611(25.3)  | 670(51.9)   | 409(26.3) |         |
| Marital status   |         |             |             |           | < 0.001 |
| Married          |         | 1687(69.8) | 819(63.5)   | 884(56.7) |         |

Abbreviation: ET, Endoscopic therapy ; RT, Radiotherapy; pT, pathologic tumor; T1a ,tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa; T1x, unknown T1a or T1b.

*American Indian/Alaska Native, Asian/Pacific Islander.
LNM Risks in Early-Stage EGJ adenocarcinoma

In total, 856 patients with EGJ adenocarcinoma diagnosed between 2004 and 2016 with at least 16 LNs examined who received surgical resection were collected. The overall LNM rate was 18.8% (161/856). When stratified by pT stage, LNM rates were 8.3% (25/300) and 24.6% (122/496) in T1a and T1b patients, respectively. LNM rate decreased to 5.3% (2/38) in well-differentiated T1b tumors with tumor size < 3cm; while LNM incidence increased to 17.9% (12/67) in poorly-differentiated T1a tumors, and rose to as high as 33.3% (5/15) in poorly-differentiated tumors exceeding 3cm in size. We further employed univariate and multivariate logistic regression analyses to identify risk factors for LNM. Consequently, we robustly found that tumor size, tumor grade and pT stage were significant predictive indicators for LNM. LNM rate was significantly higher in T1b than T1a tumors (OR: 2.162, 95% CI: 1.311–3.565, P = 0.003). Compared with small tumors less than 1cm in size, the risk of LNM was increased in tumor sizes exceeding 3 cm (OR = 5.524, 95% CI: 2.716–11.234, P < 0.001). The incidence of LNM was also significantly higher in tumors with poor/moderate differentiation or undifferentiation than those with well differentiation (OR 4.325, 95% CI: 1.774–10.544, P = 0.001; OR 5.15, 95% CI 1.81–14.63, P = 0.002, respectively). The detailed patient characteristics were summarized in Table 2. According to the present NCCN guidelines, ET is recommended for T1a tumors but is less definitive for T1b tumors.
| Characteristic       | Univariate analysis | Multivariate analysis |
|---------------------|---------------------|-----------------------|
|                     | OR (95% CI)         | P         | OR (95% CI)         | P         |
| Gender              |                     |           |                     |           |
| Female              | Reference           |           |                     |           |
| Male                | 1.216 (0.762–1.942) | 0.412     |                     |           |
| Age (years)         |                     |           |                     |           |
| Up to 49            | Reference           |           |                     |           |
| 50–64               | 0.904 (0.455–1.794) | 0.773     |                     |           |
| 65–79               | 0.946 (0.480–1.865) | 0.872     |                     |           |
| 80+                 | 1.910 (0.737–4.948) | 0.183     |                     |           |
| Race                |                     |           |                     |           |
| White               | Reference           |           |                     |           |
| Black               | 0.236 (0.031–1.785) | 0.162     |                     |           |
| Others*             | 1.135 (0.510–2.525) | 0.756     |                     |           |
| Tumor size (cm)     |                     |           |                     |           |
| < 1                 | Reference           |           | Reference           |           |
| 1–2                 | 2.556 (1.256–5.201) | 0.010     | 1.699 (0.813–3.554) | 0.159     |
| 2–3                 | 3.403 (1.638–7.070) | 0.001     | 1.930 (0.896–4.156) | 0.093     |
| 3+                  | 8.868 (4.496–17.490)| <0.001    | 5.524 (2.716–11.234)| <0.001    |
| Not stated          | 1.350 (0.576–3.166) | 0.490     | 1.130 (0.466–2.738) | 0.787     |
| pT stage            |                     |           |                     |           |
| T1a                 | Reference           |           | Reference           |           |
| T1b                 | 3.588 (2.271–5.670) | <0.001    | 2.162 (1.311–3.565) | 0.003     |
| T1x                 | 3.348 (1.622–6.912) | 0.001     | 2.729 (1.234–6.035) | 0.013     |
| Year of diagnosis   |                     |           |                     |           |
| 2004–2006           | Reference           |           |                     |           |
| 2007–2009           | 1.410 (0.830–2.397) | 0.204     |                     |           |
| 2010–2012           | 1.174 (0.690–1.998) | 0.553     |                     |           |
| 2013–2016           | 0.986 (0.586–1.661) | 0.959     |                     |           |
| Marital status      |                     |           |                     |           |
| Married             | Reference           |           |                     |           |
| Single/widowed      | 1.258 (0.789–2.006) | 0.335     |                     |           |

Abbreviation: LNE, Number of examined lymph nodes; OR, odd ratio; 95% CI, 95% confidence intervals; pT, pathologic tumor; T1a, tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa.

* American Indian/Alaska Native, Asian/Pacific Islander.
| Characteristic          | Univariate analysis | Multivariate analysis |
|------------------------|---------------------|-----------------------|
| Other/unknown          | 0.881(0.517–1.501)  | 0.640                 |

**Grade**

| Grade                        | Univariate analysis | Multivariate analysis |
|------------------------------|---------------------|-----------------------|
| Well-differentiated         | Reference           | Reference             |
| Moderately differentiated    | 3.614(1.518–8.602)  | 0.004                 |
| Poorly/Undifferentiated      | 7.558(3.202–17.840) | < 0.001               |
| Unknown                      | 1.158(0.341–3.932)  | 0.814                 |

**Histology**

| Histology                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
| Adenocarcinoma                   | Reference           | Reference             |
| Mucinous carcinoma               | 1.332(0.274–6.480)  | 0.723                 |
| Signet ring cell carcinoma       | 2.331(1.322–4.110)  | 0.003                 |

Abbreviation: LNE, Number of examined lymph nodes; OR, odd ratio; 95% CI, 95% confidence intervals; pT, pathologic tumor; T1a, tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa.

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**LNM Rates in T1a Tumors**

The rate of LNM in T1a tumor sizes exceeding 3 cm was 23.8% (10/42) compared with 6.1% (12/197) in tumors < 3 cm in size. Compared with small tumors less than 1 cm in size, the risk of LNM was increased in tumor sizes exceeding 3 cm (OR = 4.673, 95% CI: 1.421–15.371, P = 0.011) in multivariate analysis. The presence of LNM was 4.8% (3/62), 7.0% (8/115) and 17.9% (12/67) in well-differentiated, moderately differentiated and poorly/undifferentiated T1a tumor, respectively. The incidence of LNM was higher in poorly differentiated T1a cancer than compared with well-differentiated one (OR4.291, 95% CI:1.149–16.021, P = 0.030) in univariate analysis. The details of other tumor features were shown in Table 3.
Table 3
Logistic regression analysis of the risk factors for lymph node metastasis in T1a esophagogastric junction cancer (LNE ≥ 16)

| Characteristic          | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | OR (95% CI)         | P         | OR (95% CI) | P         |
| Gender                  | Reference           |           | Reference   |           |
| Female                  |                     |           | Male        | 1.710(0.493–5.930) | 0.398 |
| Age (years)             | Reference           |           | Reference   |           |
| Up to 49                |                     |           | 50–64       | 0.687(0.207–2.276) | 0.539 |
|                         |                     |           | 65–79       | 0.433(0.121–1.548) | 0.198 |
|                         |                     |           | 80+         | Omitted    |           |
| Race                    | Reference           |           | Reference   |           |
| White                   |                     |           | Black       | Omitted    |           |
|                         | 1.067(0.131–8.691)  | 0.952    | Others*     | Omitted    |           |
| Tumor size (cm)         | Reference           |           | Reference   |           |
| < 1                     |                     |           | 1.516(0.422–5.446) | 0.524 |
| 1–2                     | 1.617(0.295–8.846)  | 0.580    | 1.342(0.364–4.943) | 0.658 |
| 2–3                     | 6.062(1.928–19.060) | 0.002    | 4.673(1.421–15.371) | 0.011 |
| 3+                      | 1.003(0.231–4.355)  | 0.996    | 0.984(0.219–4.423) | 0.983 |
| Year of diagnosis       | Reference           |           | Reference   |           |
| 2004–2006               |                     |           | 2007–2009   | 0.486(0.128–1.851) | 0.290 |
| 2010–2012               | 0.736(0.254–2.132)  | 0.573    | 2013–2016   | 0.623 (0.216–1.796) | 0.381 |
| Marital status          | Reference           |           | Reference   |           |
| Married                 |                     |           | Single/widowed | 0.597(0.170–2.092) | 0.420 |
|                         | Other/unknown       | 0.531(0.119–2.370) | 0.406 |
| Grade                   | Reference           |           | Reference   |           |
| Well-differentiated     |                     |           | Moderately differentiated | 1.470(0.376–5.754) | 0.580 |
|                         | 1.543(0.380–6.259)  | 0.544    |             |           |

Abbreviation: LNE, Number of examined lymph nodes; OR, odd ratio; 95% CI, 95% confidence intervals; T1a, tumor invades the lamina propria or muscularis mucosa.

* American Indian/Alaska Native, Asian/Pacific Islander.
### Characteristic

| Characteristic          | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
| Poorly/Undifferentiated | 4.291(1.149–16.021) | 0.030                 |
|                         | 0.055               |                       |
| Unknown                 | 0.728(0.117–4.527)  | 0.734                 |
|                         | 0.835               |                       |

### Histology

| Histology                     | Reference          | Reference          |
|-------------------------------|--------------------|--------------------|
| Adenocarcinoma                | Reference          | Reference          |
| Mucinous carcinoma            | 11.727(0.709-193.969) | 0.085               |
|                               | 0.327              |                     |
| Signet ring cell carcinoma    | 1.466(0.316–6.791) | 0.625               |
|                               | 0.755              |                     |

Abbreviation: LNE, Number of examined lymph nodes; OR, odd ratio; 95% CI, 95% confidence intervals; T1a, tumor invades the lamina propria or muscularis mucosa.

* American Indian/Alaska Native, Asian/Pacific Islander.

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**LNM Rates in T1b Tumors**

We further compared the LNM rate in T1b tumors between tumor size exceeding 3 cm and tumors < 3 cm, which was 42.7% (56/131) versus 19.3% (61/316). The incidence of LNM was higher in poorly/undifferentiated tumors (OR 4.944, 95% CI: 1.440–16.970, P = 0.011) than well-differentiated tumors. Compared with small tumors less than 1 cm in size, the risk of LNM was increased in tumor sizes exceeding 3 cm (OR = 6.091, 95% CI: 2.239–16.570, P < 0.001). The presence of LNM was 6.4% (3/47), 21.4% (47/220) and 32.9% (70/213) in well-differentiated, moderately differentiated and poorly/undifferentiated T1b tumors, respectively. LNM incidence was higher in poorly-differentiated than well-differentiated T1b tumors (OR 4.944, 95% CI: 1.44–16.97, P = 0.011) in multivariate analysis. The details of other tumor features were shown in Table 4.
Table 4
Logistic regression analysis of the risk factors for lymph node metastasis in T1b esophagogastric junction cancer (LNE ≥ 16)

| Characteristic          | Univariate analysis |          |          | Multivariate analysis |          |
|-------------------------|---------------------|----------|----------|-----------------------|----------|
|                         | OR (95% CI)         | P        | OR (95% CI) | P                      |
| **Gender**              |                     |          |          |                       |          |
| Female                  | Reference           |          |          |                       |          |
| Male                    | 1.216 (0.706–2.095) | 0.481    |          |                       |          |
| **Age (years)**         |                     |          |          |                       |          |
| Up to 49                | Reference           |          |          |                       |          |
| 50–64                   | 1.029 (0.390–2.716) | 0.954    |          |                       |          |
| 65–79                   | 1.076 (0.413–2.801) | 0.881    |          |                       |          |
| 80+                     | 1.875 (0.551–6.379) | 0.314    |          |                       |          |
| **Race**                |                     |          |          |                       |          |
| White                   | Reference           |          |          |                       |          |
| Black                   | 1.053 (0.410–2.699) | 0.915    |          |                       |          |
| Others*                 | 0.352 (0.037–3.374) | 0.365    |          |                       |          |
| **Tumor size (cm)**     |                     |          |          |                       |          |
| < 1                     | Reference           |          |          |                       |          |
| 1–2                     | 2.410 (0.882–6.587) | 0.086    | 2.036 (0.732–5.666) | 0.173    |
| 2–3                     | 2.686 (0.969–7.447) | 0.058    | 2.292 (0.809–6.490) | 0.118    |
| 3+                      | 7.019 (2.622–18.791)| < 0.001 | 6.091 (2.239–16.570)| < 0.001 |
| Not stated              | 1.068 (0.289–3.943) | 0.921    | 1.042 (0.277–3.921) | 0.951    |
| **Year of diagnosis**   |                     |          |          |                       |          |
| 2004–2006               | Reference           |          |          |                       |          |
| 2007–2009               | 1.611 (0.850–3.053) | 0.144    |          |                       |          |
| 2010–2012               | 1.239 (0.655–2.344) | 0.511    |          |                       |          |
| 2013–2016               | 0.974 (0.526–1.806) | 0.934    |          |                       |          |
| **Marital status**      |                     |          |          |                       |          |
| Married                 | Reference           |          |          |                       |          |
| Single/widowed          | 1.759 (1.012–3.055) | 0.045    | 1.780 (0.981–3.232) | 0.058    |
| Other/unknown           | 0.888 (0.469–1.681) | 0.715    | 0.879 (0.448–1.724) | 0.707    |
| **Grade**               |                     |          |          |                       |          |
| Well-differentiated     | Reference           |          |          |                       |          |
| Moderately differentiated| 3.985 (1.184–13.404)| 0.026    | 3.005 (0.872–10.359)| 0.081    |

Abbreviation: LNE, Number of examined lymph nodes; OR, odd ratio; 95% CI, 95% confidence intervals; T1b, tumor invades the submucosa.

* American Indian/Alaska Native, Asian/Pacific Islander.
### Characteristic

| Characteristic                  | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
| Poorly/Undifferentiated        | 7.179(2.154–23.931) | 4.944(1.440–16.970)   |
| Unknown                        | 2.095(0.317–13.835) | 1.496(0.207–10.794)   |

### Histology

- **Adenocarcinoma**
  - Reference
- **Mucinous carcinoma**
  - 0.667(0.077–5.776)
  - 0.713
  - 0.497(0.053–4.627)
  - 0.539
- **Signet ring cell carcinoma**
  - 2.578(1.320–5.037)
  - 0.006
  - 2.025(0.980–4.184)
  - 0.057

*American Indian/Alaska Native, Asian/Pacific Islander.*

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**Patient survival**

The mean OS in the surgical therapy, ET, and RT groups was 105 months (95% CI 103–108), 97 months (95% CI 93–102), and 27 months (95% CI 25–29), respectively. Log-rank test showed that survival was similar in patients treated by surgical therapy and ET ($p = 0.064$). The survival was significantly better in patients treated by surgical therapy than those treated by RT ($p < 0.001$). Survival curves of the three groups were displayed in Fig. 1a. The mean CSS was 121 months (95% CI 118–123), 126 months (95% CI 122–131), and 36 months (95% CI 33–39) in the surgical therapy, ET, and RT groups, respectively. Log-rank test revealed that the survival of patients treated by surgical therapy was significantly worse than those treated by ET ($p < 0.001$) and the survival of patients treated by surgical therapy was significantly better than those treated by RT ($p < 0.001$). The survival curves of the three groups were displayed in Fig. 1b. The multivariate Cox regression models showed that OS (ET: HR 1.220, 95% CI: 1.059–1.406, $p = 0.006$; RT: HR 3.700, 95% CI: 3.271–4.185, $p < 0.001$) and CSS (ET: HR 0.830, 95% CI: 0.682–1.010, $p = 0.062$; RT: HR 4.024, 95% CI: 3.483–4.649, $p < 0.001$) compare with surgical therapy group. The survival was significantly higher in ET and surgical therapy groups than RT group. Moreover, univariate and multivariate Cox regression models consistently revealed that tumor size ($\geq 2\text{cm}$), marital status, pT stage, LNM, Grade (Poorly/Undifferentiated), histology (Mucinous carcinoma) and old age ($\geq 65\text{years}$) were significant prognostic indicators for both OS and CSS (Table 5).
Table 5
Cox regression analysis of OS and CSS in patients with early-stage esophagogastric junction cancer.

| Characteristic | OS                      | CSS                      |
|----------------|-------------------------|--------------------------|
|                | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|                | HR (95% CI) | P         | HR (95% CI) | P         | HR (95% CI) | P         | HR (95% CI) | P         |
| Gender         |             |           |             |           |             |           |             |           |           |
| Female         | Reference   |           | Reference   |           | Reference   |           | Reference   |           |           |
| Male           | 0.998(0.896–1.112) | 0.975      | 0.968(0.855–1.097) | 0.612      |           |           |           |           |
| Race           |             |           |             |           |             |           |             |           |           |
| White          | Reference   |           | Reference   |           | Reference   |           | Reference   |           |           |
| Black          | 1.353(1.084–1.689) | 0.007      | 1.187(0.949–1.484) | 0.133      | 1.351(1.044–1.748) | 0.022      | 1.104(0.851–1.431) | 0.457      |
| Others*        | 0.830(0.656–1.049) | 0.119      | 0.818(0.646–1.036) | 0.095      | 0.918(0.705–1.195) | 0.523      | 0.908(0.696–1.185) | 0.477      |
| Tumor size(cm) |             |           |             |           |             |           |             |           |           |
| < 1            | Reference   |           | Reference   |           | Reference   |           | Reference   |           |           |
| 1–2            | 1.507(1.257–1.807) | < 0.001    | 1.144(0.952–1.375) | 0.152      | 1.879(1.474–2.394) | < 0.001    | 1.284(1.004–1.641) | 0.046      |
| 2–3            | 2.115(1.762–2.538) | < 0.001    | 1.309(1.084–1.579) | 0.005      | 2.778(2.183–3.537) | < 0.001    | 1.469(1.146–1.882) | 0.002      |
| 3+             | 4.139(3.531–4.851) | < 0.001    | 1.564(1.317–1.856) | < 0.001    | 6.456(5.224–7.979) | < 0.001    | 1.906(1.521–2.390) | < 0.001    |
| Not stated     | 2.943(2.525–3.430) | < 0.001    | 1.389(1.180–1.635) | < 0.001    | 4.176(3.392–5.141) | < 0.001    | 1.682(1.349–2.096) | < 0.001    |
| Year of diagnosis |             |           |             |           |             |           |             |           |           |
| 2004–2006      | Reference   |           | Reference   |           | Reference   |           | Reference   |           |           |
| 2007–2009      | 0.868(0.784–0.962) | 0.007      | 0.900(0.812–0.997) | 0.044      | 0.887(0.786–1.001) | 0.051      | 0.942(0.834–1.063) | 0.333      |
| 2010–2012      | 0.690(0.616–0.773) | < 0.001    | 0.741(0.660–0.831) | < 0.001    | 0.697(0.611–0.795) | < 0.001    | 0.793(0.694–0.907) | 0.001      |
| 2013–2016      | 0.659(0.582–0.747) | < 0.001    | 0.770(0.677–0.875) | < 0.001    | 0.630(0.545–0.727) | < 0.001    | 0.807(0.697–0.935) | 0.004      |
| Marital status |             |           |             |           |             |           |             |           |           |
| Married        | Reference   |           | Reference   |           | Reference   |           | Reference   |           |           |
| Single/widowed | 1.436(1.306–1.578) | < 0.001    | 1.191(1.080–1.312) | < 0.001    | 1.530(1.371–1.707) | < 0.001    | 1.249(1.116–1.398) | < 0.001    |
| Other/unknown  | 1.142(1.016–1.284) | 0.027      | 1.182(1.050–1.332) | 0.006      | 1.232(1.077–1.409) | 0.002      | 1.252(1.092–1.435) | 0.001      |

Abbreviation: ET, Endoscopic therapy; RT, Radiotherapy; LNM, lymph node metastasis; HR, Hazard ratio; 95% CI, 95% confidence intervals; T1a ,tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa; T1x, unknown T1a or T1b.

*American Indian/Alaska Native, Asian/Pacific Islander.
|                | OS                        |                  | CSS                        |                  |
|----------------|---------------------------|------------------|---------------------------|------------------|
| **T1a**        | Reference                 |                  | Reference                 |                  |
| **T1b**        | 1.205(1.083– 1.340)       | 0.001            | 1.192(1.061– 1.340)       | 0.003            |
|                |                           |                  | 1.403(1.229– 1.601)       | < 0.001          |
|                |                           |                  |                           | 1.313(1.137– 1.517) | < 0.001 |
| **T1x**        | 3.905(3.553– 4.292)       | < 0.001          | 1.443(1.292– 1.612)       | < 0.001          |
|                |                           |                  | 5.153(4.594– 5.779)       | < 0.001          |
|                |                           |                  |                           | 1.596(1.400– 1.818) | < 0.001 |
| **Treatment**  |                           |                  |                           |                  |
| **Surgery**    | Reference                 |                  | Reference                 |                  |
| **ET**         | 1.092(0.960– 1.241)       | 0.180            | 1.220(1.059– 1.406)       | 0.006            |
|                |                           |                  | 0.693(0.578– 0.831)       | < 0.001          |
|                |                           |                  |                           | 0.830(0.682– 1.010) | 0.062 |
| **RT**         | 6.111(5.573– 6.702)       | < 0.001          | 3.700(3.271– 4.185)       | < 0.001          |
|                |                           |                  | 7.031(6.311– 7.834)       | < 0.001          |
|                |                           |                  |                           | 4.024(3.483– 4.649) | < 0.001 |
| **LNM**        |                           |                  |                           |                  |
| **No**         | Reference                 | Reference        | Reference                 | Reference        |
| **Yes**        | 2.275(2.066– 2.504)       | < 0.001          | 1.507(1.361– 1.668)       | < 0.001          |
|                |                           |                  | 2.728(2.453– 3.035)       | < 0.001          |
|                |                           |                  |                           | 1.614(1.443– 1.805) | < 0.001 |
| **Grade**      |                           |                  |                           |                  |
| **Well-differentiated** | Reference | Reference | Reference | Reference |
| **Moderately differentiated** | 1.573(1.349– 1.834) | < 0.001 | 1.084(0.928– 1.267) | 0.310 |
|                |                           |                  | 1.780(1.466– 2.162)       | < 0.001          |
|                |                           |                  |                           | 1.097(0.900– 1.336) | 0.358 |
| **Poorly/Undifferentiated** | 2.368(2.031– 2.761) | < 0.001 | 1.245(1.060– 1.461) | 0.007 |
|                |                           |                  | 3.122(2.577– 3.783)       | < 0.001          |
|                |                           |                  |                           | 1.393(1.141– 1.700) | 0.001 |
| **Unknown**    | 1.216(1.026– 1.440)       | 0.024            | 0.873(0.734– 1.037)       | 0.121            |
|                |                           |                  | 1.325(1.069– 1.642)       | 0.010            |
|                |                           |                  |                           | 0.898(0.722– 1.116) | 0.332 |
| **Histology**  |                           |                  |                           |                  |
| **Adenocarcinoma** | Reference | Reference | Reference | Reference |
| **Mucinous carcinoma** | 2.136(1.574– 2.899) | < 0.001 | 1.792(1.319– 2.435) | < 0.001 |
|                |                           |                  | 2.262(1.602– 3.194)       | < 0.001          |
|                |                           |                  |                           | 1.796(1.270– 2.540) | 0.001 |
| **Signet ring cell carcinoma** | 1.779(1.531– 2.068) | < 0.001 | 1.191(1.018– 1.393) | 0.029 |
|                |                           |                  | 1.960(1.657– 2.319)       | < 0.001          |
|                |                           |                  |                           | 1.184(0.994– 1.410) | 0.059 |
| **Age(years)** |                           |                  |                           |                  |
| **Up to 49**   | Reference                 |                  | Reference                 |                  |
| **50–64**      | 1.192(0.943– 1.505)       | 0.141            | 1.161(0.918– 1.467)       | 0.213            |
|                |                           |                  | 1.038(0.803– 1.343)       | 0.774            |
|                |                           |                  |                           | 1.006(0.776– 1.303) | 0.966 |
| **65–79**      | 1.908(1.521– 2.394)       | < 0.001          | 1.659(1.320– 2.085)       | < 0.001          |
|                |                           |                  | 1.514(1.180– 1.943)       | 0.001            |
|                |                           |                  |                           | 1.298(1.009– 1.670) | 0.043 |
| **80+**        | 4.358(3.452– 5.502)       | < 0.001          | 2.447(1.929– 3.106)       | < 0.001          |
|                |                           |                  | 3.669(2.841– 4.737)       | < 0.001          |
|                |                           |                  |                           | 1.937(1.491– 2.518) | < 0.001 |

Abbreviation: ET, Endoscopic therapy; RT, Radiotherapy; LNM, lymph node metastasis; HR, Hazard ratio; 95% CI, 95% confidence intervals; T1a, tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa; T1x, unknown T1a or T1b.

*American Indian/Alaska Native, Asian/Pacific Islander.
In total, 920 patient pairs were included in the PSM analysis. Patient features and tumor characteristics of both surgical therapy and ET groups after propensity matching were displayed in Table 6. As a result, all matched variables were balanced between two groups (all P > 0.05). Survival analysis and log-rank test revealed worse OS in ET group than surgical therapy group (Fig. 1c). There was no significant difference in CSS (Fig. 1d). Moreover, Cox proportional hazards regression revealed significant differences in OS (HR = 1.488, 95% CI 1.240–1.786; P < 0.001) and no significant differences in CSS (HR = 1.112, 95% CI: 0.866–1.429; P = 0.405) between surgical therapy and ET groups. The details of other tumor features were shown in Table 7.
### Table 6
Baseline characteristics of patients treated with ES and ET for early-stage esophageal cancer before and after the propensity score-matched (1:1 matching).

| Characteristic          | Before matched | After matched | Statistic | p     | Statistic | p     |
|-------------------------|----------------|---------------|-----------|-------|-----------|-------|
|                         | ES  | ET    | Surgery   | ES  | ET    | Surgery   | ET    |
|                         | N=2418 | N=1290 | Statistic | p    | N=920 | N=920 | Statistic | p    |
| Gender                  |     |       |           |     |       |           |       |
| Female                  | 376(15.6) | 234(18.1) | χ² = 4.104 | 0.043 | χ² = 0.434 | 0.510 |
| Male                    | 2042(84.4) | 1056(81.9) |           |       |         |       |
| Age( years)             |     |       |           |     |       |           |       |
| Up to 49                | 170(7.0)   | 39(3.0)   | χ² = 190.802 | < 0.001 | χ² = 5.161 | 0.160 |
| 50–64                   | 985(40.7)  | 360(27.9)  |           |       |         |       |
| 65–79                   | 1114(46.1) | 650(50.4)  |           |       |         |       |
| 80+                     | 149(6.2)   | 241(18.7)  |           |       |         |       |
| Race                    |     |       |           |     |       |           |       |
| White                   | 2270(93.9) | 1221(94.7) | χ² = 2.270 | 0.321 | χ² = 3.222 | 0.200 |
| Black                   | 56(2.3)    | 32(2.5)    |           |       |         |       |
| Others*                 | 92(3.8)    | 37(2.9)    |           |       |         |       |
| Tumor size(cm)          |     |       |           |     |       |           |       |
| < 1                     | 511(21.1)  | 351(27.2)  | χ² = 374.707 | < 0.001 | χ² = 4.393 | 0.355 |
| 1–2                     | 571(23.6)  | 211(16.4)  |           |       |         |       |
| 2–3                     | 420(17.4)  | 86(6.7)    |           |       |         |       |
| 3+                      | 431(17.8)  | 70(5.4)    |           |       |         |       |
| Not stated              | 485(20.1)  | 572(44.3)  |           |       |         |       |
| Year of diagnosis       |     |       |           |     |       |           |       |
| 2004–2006               | 577(23.9)  | 116(9.0)   | χ² = 337.009 | < 0.001 | χ² = 2.772 | 0.428 |
| 2007–2009               | 675(27.9)  | 189(14.7)  |           |       |         |       |
| 2010–2012               | 555(23.0)  | 315(24.4)  |           |       |         |       |
| 2013–2016               | 611(25.3)  | 670(51.9)  |           |       |         |       |
| Marital status          |     |       |           |     |       |           |       |
| Married                 | 1687(69.8) | 819(63.5)  | χ² = 15.807 | < 0.001 | χ² = 5.671 | 0.059 |
| Single/widowed          | 402(16.6)  | 270(20.9)  |           |       |         |       |

Abbreviation: ET, Endoscopic therapy; T1a, tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa; T1x, unknown T1a or T1b.*American Indian/Alaska Native, Asian/Pacific Islander.
|                         | Before matched | After matched |
|-------------------------|----------------|---------------|
| Other/unknown           | 329(13.6)      | 201(15.6)     |
|                         |                | 138(15.0)     |
|                         |                | 157(17.1)     |
| **T stage**             |                |               |
| T1a                     | 979(40.5)      | 927(71.9)     |
|                         | 592(64.3)      | 595(64.7)     |
| T1b                     | 1226(50.7)     | 226(17.5)     |
|                         | 235(25.5)      | 217(23.6)     |
| T1x                     | 213(8.8)       | 137(10.6)     |
|                         | 93(10.1)       | 108(11.7)     |
| **Grade**               |                |               |
| Well-differentiated     | 346(14.3)      | 210(16.3)     |
|                         | 160(17.4)      | 134(14.6)     |
| Moderately differentiated| 1019(42.1)    | 438(34.0)     |
|                         | 352(38.3)      | 338(36.7)     |
| Poorly/Undifferentiated | 726(30.0)      | 191(14.8)     |
|                         | 167(18.2)      | 182(19.8)     |
| Unknown                 | 327(13.5)      | 451(35.0)     |
|                         | 241(26.2)      | 266(28.9)     |
| **Histology**           |                |               |
| Adenocarcinoma          | 2270(93.9)     | 1255(97.3)    |
|                         | 887(96.4)      | 887(96.4)     |
| Mucinous carcinoma      | 25(1.0)        | 8(0.6)        |
|                         | 8(0.9)         | 8(0.9)        |
| Signet ring cell cancer | 123(5.1)       | 27(2.1)       |
|                         | 25(2.7)        | 25(2.7)       |

χ² = 400.549 < 0.001
χ² = 1.844 0.398
χ² = 279.570 < 0.001
χ² = 4.461 0.216
χ² = 21.284 < 0.001
χ² = 0 1.0

Abbreviation: ET, Endoscopic therapy; T1a, tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa; T1x, unknown T1a or T1b.*American Indian/Alaska Native, Asian/Pacific Islander.
Table 7
Cox regression analysis of OS and CSS in patients with early-stage esophagogastric junction cancer after propensity score matching

| Characteristic | OS | | | CSS | | |
|----------------|----|---|---|----|---|---|
|                | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|                | HR (95% CI) | P  | HR (95% CI) | P  | HR (95% CI) | P  |
| Gender         |                |    |              |    |              |    |
| Female         | Reference     |    | Reference     |    | Reference     |    |
| Male           | 1.029 (0.819–1.293) | 0.807 | 1.031 (0.751–1.414) | 0.851 | |
| Race           |                |    |              |    |              |    |
| White          | Reference     |    | Reference     |    | Reference     |    |
| Black          | 1.182 (0.667–2.098) | 0.567 | 0.720 (0.268–1.934) | 0.515 | |
| Others*        | 0.901 (0.508–1.598) | 0.722 | 0.693 (0.286–1.680) | 0.417 | |
| Tumor size(cm) |                |    |              |    |              |    |
| < 1            | Reference     |    | Reference     |    | Reference     |    |
| 1–2            | 1.369 (1.028–1.822) | 0.031 | 1.115 (0.833–1.491) | 0.465 | 1.360 (0.908–2.038) | 0.136 | 1.046 (0.692–1.581) | 0.831 |
| 2–3            | 1.685 (1.190–2.386) | 0.003 | 1.159 (0.811–1.657) | 0.418 | 2.029 (1.277–3.223) | 0.003 | 1.324 (0.822–2.134) | 0.248 |
| 3+             | 2.157 (1.507–3.087) | < 0.001 | 1.489 (1.029–2.153) | 0.035 | 2.658 (1.664–4.245) | < 0.001 | 1.652 (1.016–2.687) | 0.043 |
| Not stated     | 1.318 (1.033–1.681) | 0.026 | 1.085 (0.841–1.400) | 0.529 | 1.385 (0.982–1.955) | 0.063 | 1.126 (0.785–1.614) | 0.520 |
| Year of diagnosis |    |    |              |    |              |    |
| 2004–2006      | Reference     |    | Reference     |    | Reference     |    |
| 2007–2009      | 0.780 (0.614–0.990) | 0.041 | 0.733 (0.575–0.933) | 0.012 | 0.785 (0.561–1.099) | 0.158 | 0.705 (0.502–0.992) | 0.045 |
| 2010–2012      | 0.578 (0.443–0.755) | < 0.001 | 0.564 (0.428–0.742) | < 0.001 | 0.560 (0.389–0.806) | < 0.001 | 0.517 (0.355–0.752) | 0.001 |
| 2013–2016      | 0.615 (0.459–0.823) | 0.001 | 0.558 (0.412–0.756) | < 0.001 | 0.560 (0.379–0.827) | < 0.001 | 0.476 (0.317–0.714) | < 0.001 |
| Marital status |                |    |              |    |              |    |
| Married        | Reference     |    | Reference     |    | Reference     |    |
| Single/widowed | 1.219 (0.986–1.508) | 0.068 | 1.226 (0.914–1.645) | 0.174 | |
| Other/unknown  | 0.849 (0.644–1.119) | 0.245 | 0.852 (0.583–1.244) | 0.406 | |
| T stage        |                |    |              |    |              |    |

Abbreviation: ET, Endoscopic therapy; HR, Hazard ratio; 95% CI, 95% confidence intervals; T1a, tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa; T1x, unknown T1a or T1b.

*American Indian/Alaska Native, Asian/Pacific Islander.
|          | OS                    | CSS                    |
|----------|-----------------------|------------------------|
| **T1a**  | Reference             | Reference              |
| T1b      | 1.920 (1.567−2.351)   | < 0.001                |
|          | 1.494 (1.203−1.857)   | < 0.001                |
|          | 2.310 (1.755−3.041)   | < 0.001                |
|          | 1.705 (1.270−2.289)   | < 0.001                |
| **T1x**  | 2.082 (1.618−2.680)   | < 0.001                |
|          | 1.784 (1.374−2.316)   | < 0.001                |
|          | 2.499 (1.778−3.512)   | < 0.001                |
|          | 2.087 (1.464−2.976)   | < 0.001                |

**Treatment**

| Variable | OS          | CSS          |
|----------|-------------|--------------|
| **ES**   | Reference   | Reference    |
| **ET**   | 1.599 (1.337−1.913) | < 0.001 | 1.488 (1.240−1.786) | < 0.001 | 1.229 (0.962−1.570) | 0.099 | 1.112 (0.866−1.429) | 0.405 |

**Grade**

| Grade                        | OS          | CSS          |
|------------------------------|-------------|--------------|
| **Well-differentiated**      | Reference   | Reference    |
| **Moderately differentiated**| 1.246 (0.941−1.649) | 0.124 | 1.148 (0.875−1.506) | 0.822 | 1.251 (0.851−1.839) | 0.254 | 1.025 (0.693−1.514) | 0.903 |
| **Poorly/Undifferentiated**  | 1.668 (1.233−2.258) | 0.001 | 1.196 (0.874−1.636) | 0.264 | 1.937 (1.292−2.903) | 0.001 | 1.323 (0.868−2.017) | 0.193 |
| **Unknown**                  | 0.788 (0.584−1.063) | 0.118 | 0.752 (0.554−1.021) | 0.067 | 0.664 (0.432−1.021) | 0.062 | 0.621 (0.401−0.962) | 0.033 |

**Histology**

| Histology                   | OS          | CSS          |
|------------------------------|-------------|--------------|
| **Adenocarcinoma**           | Reference   | Reference    |
| **Mucinous carcinoma**       | 1.855 (0.829−4.152) | 0.133 | 1.116 (0.488−2.550) | 0.795 | 3.031 (1.249−7.353) | 0.014 | 1.810 (0.725−4.517) | 0.204 |
| **Signet ring cell carcinoma** | 2.042 (1.304−3.199) | 0.002 | 1.297 (0.808−2.082) | 0.281 | 2.413 (1.379−4.220) | 0.002 | 1.373 (0.759−2.486) | 0.295 |

**Age**

| Age (years) | OS          | CSS          |
|-------------|-------------|--------------|
| Up to 49    | Reference   | Reference    |
| 50−64       | 0.982 (0.526−1.834) | 0.956 | 1.024 (0.547−1.916) | 0.941 | 0.559 (0.283−1.105) | 0.094 | 0.574 (0.289−1.141) | 0.113 |
| 65−79       | 1.796 (0.982−3.286) | 0.057 | 1.685 (0.918−3.095) | 0.092 | 0.980 (0.514−1.868) | 0.952 | 0.881 (0.459−1.692) | 0.704 |
| 80+         | 4.969 (2.687−9.188) | < 0.001 | 3.821 (2.051−7.118) | < 0.001 | 3.078 (1.593−5.948) | 0.001 | 2.158 (1.102−4.226) | 0.025 |

Abbreviation: ET, Endoscopic therapy; HR, Hazard ratio; 95% CI, 95% confidence intervals; T1a, tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa; T1x, unknown T1a or T1b.

*American Indian/Alaska Native, Asian/Pacific Islander.

Subgroup Analysis

The 920 patient pairs were further categorized into T1a and T1b groups. After adjustment of both patient demographics and tumor variables, surgical therapy and ET related CSS (HR = 1.085, 95% CI 0.760−1.550; P = 0.653), (HR = 1.335, 95% CI: 0.856−2.083; P = 0.203) were not significantly different in T1a and T1b patients (shown in Table 8).
Table 8  Cox regression analysis of CSS in patients with T1a and T1b esophagogastric junction cancer after propensity score matching

| Characteristic | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|----------------|---------------------|-----------------------|---------------------|-----------------------|
|                | HR (95% CI)         | P                     | HR (95% CI)         | P                     |
| **Gender**     |                     |                       |                     |                       |
| Female         | Reference           |                       | Reference           |                       |
| Male           | 1.005 (0.640–1.579) | 0.982                 | 1.252 (0.706–2.219) | 0.442                 |
| **Race**       |                     |                       |                     |                       |
| White          | Reference           |                       | Reference           |                       |
| Black          | Omitted             |                       | 0.697 (0.097–5.011) | 0.720                 |
| Others*        | 1.310 (0.536–3.205) | 0.554                 | Omitted             |                       |
| **Tumor size(cm)** |                 |                       |                     |                       |
| < 1            | Reference           | 0.680                 | Reference           |                       |
| 1–2            | 1.126 (0.642–1.975) | 0.680                 | 1.038 (0.589–1.829) | 0.897                 |
| 2–3            | 1.815 (0.912–3.612) | 0.089                 | 1.546 (0.767–3.115) | 0.223                 |
| 3+             | 2.167 (1.062–4.425) | 0.034                 | 2.184 (1.056–4.517) | 0.035                 |
| Not stated     | 1.234 (0.792–1.921) | 0.353                 | 1.248 (0.788–1.976) | 0.346                 |
| **Year of diagnosis** |          |                       |                     |                       |
| 2004–2006      | Reference           | 0.290                 | Reference           |                       |
| 2007–2009      | 0.781 (0.494–1.234) | 0.290                 | 0.835 (0.525–1.330) | 0.448                 |
| 2010–2012      | 0.611 (0.369–1.011) | 0.055                 | 0.615 (0.363–1.042) | 0.070                 |
| 2013–2016      | 0.458 (0.249–0.842) | 0.012                 | 0.449 (0.238–0.848) | 0.014                 |
| **Marital status** |           |                       |                     |                       |
| Married        | Reference           | 0.465                 | Reference           |                       |
| Single/widowed | 1.171 (0.767–1.790) | 0.465                 | 1.446 (0.897–2.331) | 0.130                 |
| Other/unknown  | 0.916 (0.542–1.546) | 0.741                 | 0.798 (0.379–1.678) | 0.551                 |
| **Treatment**  |                     |                       |                     |                       |

Abbreviation: ET, Endoscopic therapy; RT, Radiotherapy; LNM, lymph node metastasis; HR, Hazard ratio; 95% CI, 95% confidence intervals; T1a, tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa;

*American Indian/Alaska Native, Asian/Pacific Islander.
|                | T1a                          | T1b                          |
|----------------|------------------------------|------------------------------|
| surgery        | Reference                    | Reference                    |
| ET             | 1.083 (0.764–1.536)          | 1.085 (0.760–1.550)          |
|                | 0.654                        | 0.653                        |
| Grade          | Reference                    | Reference                    |
| Moderately     | 1.059 (0.636–1.764)          | 1.072 (0.580–1.629)          |
| differentialed | 0.824                        | 0.915                        |
| Poorly         | 1.505 (0.848–2.669)          | 1.117 (0.614–2.031)          |
| /Undifferentiated | 0.162                      | 0.717                        |
| Unknown        | 0.627 (0.367–1.072)          | 0.536 (0.309–0.929)          |
| Histology      | Reference                    | Reference                    |
| Adenocarcinoma | Reference                    | Reference                    |
| Mucinous       | 3.494 (0.863–14.140)         | 4.054 (0.989–16.618)         |
| carcinomama    | 0.079                        | 0.052                        |
| Signet ring    | 2.826 (1.240–6.441)          | 1.876 (0.770–4.571)          |
| cell carcinoma | 0.013                        | 0.166                        |
| Age (years)    | Reference                    | Reference                    |
| Up to 49       | Reference                    | Reference                    |
| 50–64          | 0.858 (0.303–2.431)          | 0.801 (0.282–2.280)          |
| 65–79          | 1.270 (0.461–3.497)          | 1.050 (0.378–2.913)          |
| 80+            | 4.341 (1.537–12.257)         | 3.060 (1.061–8.827)          |

**Abbreviation:** ET, Endoscopic therapy; RT, Radiotherapy; LNM, lymph node metastasis; HR, Hazard ratio; 95% CI, 95% confidence intervals; T1a, tumor invades the lamina propria or muscularis mucosa; T1b, tumor invades the submucosa.

*American Indian/Alaska Native, Asian/Pacific Islander.*

**Discussion**

Accumulative studies have demonstrated EGJ adenocarcinoma as a separate entity from gastric or esophageal malignancies due to the unique clinicopathological characteristics and patient survival [8, 9]. The majority of EGJ carcinomas are handled by surgical intervention, including esophagectomy along with total or proximal gastrectomy, which, however, greatly attenuates postoperative living quality and is accompanied with high risk of complications. To be specific, the rate of postoperative complications is reported to be 33–39% according to a systematic review[10]. ESD is particularly suitable for patients with early-stage proximal gastric cancer, who, otherwise, are generally treated with total gastrectomy. If patients are managed with ESD, the whole stomach can be preserved, along with better life quality [11]. Due to the unknown incidence of LNM in EGJ adenocarcinoma, there is no consensus on the indication of endoscopic resection for superficial EGJ adenocarcinoma.

To our knowledge, our study is the largest one concerning LNM rates in early-stage EGJ adenocarcinoma after eliminating patients with less than 16 examined LNs. We found that the LNM rate in early-stage EGJ adenocarcinoma was as high as 18.8% (161/856). LNM rates stratified by pT stage were 8.3% (25/300) in T1a, and 24.6% (122/496) in T1b. Moreover, the rate of LNM decreased to 5.3% (2/38) in well-differentiated T1b tumors with tumor size < 3cm; and LNM rate increased to 17.9% (12/67) in poorly differentiated T1a tumors, and to 33.3% (5/15) in poorly differentiated T1a tumors with tumor size > 3cm. Overall, there is limited...
information concerning LNM rate in superficial EGJ adenocarcinoma. According to the study by Gertler, LNM was only detectable in pT1b tumors (18%) but not in pT1a among superficial EGJ adenocarcinoma[12], which was also similarly reported by Stein[13]. Moreover, Koufuji, et al. reported no LNM in T1 EGJ carcinoma [14]. Of the above studies, the relatively inadequate sample size might be the most significant drawbacks. Zhu, et al. reported that the overall LNM rate of superficial EGJ carcinoma was 21.75%, which is 11.41% and 26.50% in mucosal cancer and submucosal cancer, respectively. The results of the above study are consistent with our findings and another study concerning surgically resected pT1 EGJ carcinoma [15, 16].

Previous studies have shown that tumor size, pathological differentiation, lymphovascular invasion and infiltration depth are risk factors for LNM in gastric and esophageal cancer [12, 16]. In our study, similar predictors of LNM involvement were revealed, including tumor size, differentiation type, and depth of invasion. To be specific, poor tumor differentiation (including moderately/poorly differentiated and undifferentiated) and tumor sizes exceeding 3 cm increased LNM risk. It is clear that tumor differentiation is the most potent predictor. Therefore, endoscopic intervention might be proper for low-risk patients, while, high-risk patients should be managed by surgical resection in consideration of the high risk of LNM.

Previous researches have revealed that age, T stage and tumor differentiation are independently correlated with poor prognosis [17–19] Due to the bias caused these parameters which can interfere with the comparison of ET and surgical therapy, multivariate Cox regression analysis and PSM were performed. ET and surgical therapy were associated with similar CSS in patients with early-stage EGJ adenocarcinoma. Additionally, subgroup analysis stratified by T stage also showed similar outcomes. PSM analysis also revealed consistent outcomes, which could decrease selection bias associated with diverse clinical features of ET and surgical therapy. The authors found that patients with sm1 cancers, classified by submucosal invasion of < 500µm, and tumors smaller than 3 cm had no LNMs. Nevertheless, with deep submucosal invasion of ≥ 500µm stratified by sm2 and sm3, the incidence of LNM increased to 28.6%, irrespective of tumor size. The above outcomes suggest that ESD can be safely used to treat patients with sm1 and tumor size < 3 cm, which is beyond the proposed guidelines [6, 20]. Most patients with T1b tumors should be treated by surgical intervention in consideration of high LNM rate (24.6%). Nevertheless, LNM incidence in T1b cancer with all low-risk tumor characteristics was only 5.3%. Hence, definitive ET must be cautiously determined on submucosal cancers without other high-risk characteristics. The multivariate Cox regression models showed that CSS (ET: HR 0.830, 95% CI:0.682–1.010, P = 0.062; RT: HR 4.024, 95% CI: 3.483–4.649, P < 0.001) compared with surgical therapy group. Moreover, Cox proportional hazards regression revealed no significant differences in CSS (HR = 1.112, 95% CI: 0.866–1.429; P = 0.405) between surgical therapy and ET groups after PSM. Therefore, ET might be a valid alternative to surgical therapy to treat early EGJ adenocarcinoma, especially in elderly patients.

Diagnostic ER is considered as potentially curative and also has more accurate evaluation of invasion depth than endoscopic ultrasonography (EUS)[21], which is a feasible and reasonable final step in all early-stage EGJ adenocarcinoma. Pathologic assessment on ER samples could assist further therapeutic strategies, which should simultaneously consider patient-related parameters. Moreover, multidisciplinary team involving surgeons, medical oncologists and endoscopists is necessary for clinical decision-making. For patients with older age or multiple comorbidities, a higher probability of leaving positive LNs may be acceptable for a lower morbidity procedure. Conversely, aggressive surgical therapy should be considered among young patients even with low risks of LNM.

In this population-based study, our findings are mainly based on real-world outcomes. Nevertheless, certain limitations must be acknowledged, Firstly, relevant data on lymphovascular invasion, the deep distance of submucosal invasion and macroscopic type are inaccessible in SEER database, which are potential risk factors for LNM. The absence of these variables might affect the accurate assessment of LNM. Secondly, the applied models are simplified and only use available and accepted measures, which clearly do not adequately account for all variables associated with subject outcomes. Additionally, selection biases are unavoidable in the retrospective analysis. Finally, although PSM was further performed in this study, the results must be cautiously interpreted due to the fraction of unmatched patients.

**Conclusion**

This population-based study reveals that LNM risk is significantly increased in submucosal than intramucosal tumors. In subgroup analysis, patients with poorly-differentiated T1a cancers with size > 3 cm had an increased LNM rate than those with T1b cancers without other high-risk factors. These data suggest disease heterogeneity among patients with early-stage EGJ.
adenocarcinomawhich must be identified to select the optimal resection strategy. Therefore, we believe that national guidelines for management of early-stage EGJ adenocarcinoma should include all high risk-features for LNM and stage-specific surgery therapy mortality. Therefore, ET is a valid alternative to surgery for early EGJ adenocarcinoma.

**Declarations**

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**Competing Interests**

The authors have declared that no competing interest exists.

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**Availability of data and materials**

The datasets analyzed in this study are collected from SEER repository

(https://seer.cancer.gov/).

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

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Figures
Figure 1
Kaplan-Meier curves for OS and CSS. Panels A and B depict the overall and CSS of the three groups in the original data set, and panels C and D depict the OS and CSS of the two group after propensity score matching.