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Endoscopic therapy versus esophagectomy for T1bN0M0 esophageal cancer: A population-based study using propensity score matching

Jiamin Zhu [a,1], Xiao Liang [a,1], Shusen Chen [b,1], Ya Qin [a], Dong Shen [a,*], Xi Yang [c,**]

[a] Department of Oncology, the Affiliated Jiangyin Hospital of Southeast University Medical College, 163 Shoushan Road, Jiangyin, 214400, China
[b] Department of Radiation Oncology, Nantong Tumor Hospital, Affiliated Tumor Hospital of Nantong University, Nantong, 226321, China
[c] Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai Clinical Research Center for Radiation Oncology, Shanghai Key Laboratory of Radiation Oncology, Shanghai 200032, China

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ABSTRACT

Background: Endoscopic therapy is an optional strategy for the treatment of esophageal cancer (EC) under an early stage, especially stage T1a. However, its efficacy in the treatment of T1b EC has not been thoroughly assessed. We investigated the efficacy of esophagectomy, endoscopic therapy, as well as chemoradiotherapy in patients with T1bN0M0 EC.

Methods: The Surveillance, Epidemiology, and End Results database (SEER) was employed to identify patients diagnosed with T1bN0M0 EC. Patient demographics were compared among the endoscopic therapy, esophagectomy, and chemoradiotherapy groups. Our study employed Kaplan-Meier analysis and Cox regression model to evaluate patient outcomes and long-term survival rates. The overall survival (OS) and cancer-specific survival (CSS) rates were compared among patients with EC who underwent endoscopic therapy or esophagectomy, employing propensity score matching (PSM).

Results: A total of 820 patients diagnosed with T1bN0M0 EC were identified. The number of patients who received endoscopic therapy, esophagectomy, and chemoradiotherapy was 173, 556, and 91, respectively. Patients subjected to endoscopic therapy and esophagectomy had greatly longer OS and CSS than those who underwent chemoradiotherapy. Patients treated with esophagectomy had longer OS than endoscopic therapy patients, but there were no differences in CSS between the two groups. PSM generated 153 patient pairs among T1bN0M0 patients, demonstrating that both the esophagectomy and endoscopic therapy groups exhibited comparable OS and CSS rates.

Conclusion: Endoscopic therapy and esophagectomy were associated with a significant survival advantage compared with chemoradiotherapy in patients with T1bN0M0 EC. In contrast, after PSM, among the EC patients with stage T1bN0M0, OS and CSS did not differ after endoscopic therapy or esophagectomy. These results indicate that endoscopic therapy could be a viable alternative to esophagectomy in patients diagnosed with T1bN0M0 EC.

* Corresponding author. Department of Oncology, the Affiliated Jiangyin Hospital of Southeast University Medical College, 163 Shoushan Road, Jiangyin, 214400, China.
** Corresponding author.
E-mail addresses: sdshendong@126.com (D. Shen), ntgeorge@qq.com (X. Yang).
[1] Theses authors contributed equally to this work.

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1. Introduction

In recent years, the incidence of EC has been steadily increasing globally. EC is associated with a grim prognosis, exhibiting a mere 40 % 5-year survival rate for cases at the localized disease stage [1]. Patients with early-stage cancer are more commonly identified because of advancements in endoscopic approaches and diagnostic strategies. Early ECs, which account for about 20 % of patients, are confined to the mucosa or submucosa [2,3]. Based on the tumor node metastasis (TNM) staging, T1a ECs are identified as tumors confined to the lamina propria or mucous membrane. ECs with the T1b stage are confined to the submucosa and do not invade the muscular layer of the esophagus [4,5]. According to its depth of infiltration, Japanese guidelines subdivide T1b tumors into SM1, SM2, and SM3 [6]. SM1 lesions are confined to the superficial submucosa, with a restricted depth of 200 mm for esophageal squamous cell carcinoma (ESCC) and 500 mm for esophageal adenocarcinoma (EAC). In contrast, SM2 and SM3 tumors extend into the submucosa, with depths exceeding 200 mm for ESCC or surpassing 500 mm for EAC [7].

According to the guidelines, the most basic therapy for EC patients with early-stage remains esophagectomy [8]. The standard treatment for stage I EC with submucosal invasion (T1b) is esophagectomy. However, esophagectomy has high morbidity and mortality rates. Endoscopic therapy allows resection of the entire tumor, regardless of the size or specific histology of the specimen [9]. The specimens obtained are meticulously sectioned with a tumor-free lateral basal margin, mitigating the risk of residual disease and local recurrence. Thus, encompassing both endoscopic resection and ablative techniques, has generated substantial interest as a viable alternative to surgical interventions for treating early EC [10].

Previous research assessing endoscopic therapy in patients with T1bN0M0 EC has not compared the effectiveness of this approach with that of esophagectomy [11]. Patients with T1bN0M0 EC are expected to experience higher quality of life from endoscopic therapy than esophagectomy, if endoscopic therapy is as effective as surgical resection [12,13]. However, if endoscopic therapy is not as effective as esophagectomy for patients with T1bN0M0 EC, then it should not be recommended as a primary therapy for these patients.

Consequently, in this investigation, we employed the SEER database to scrutinize the impacts of endoscopic therapy, esophagectomy, and chemoradiotherapy on survival time in patients diagnosed with T1bN0M0 EC.

2. Methods

2.1. Data source

A retrospective analysis was conducted using data retrieved from the SEER database spanning the years 2006–2015. The SEER 18 database encompasses about 28 % of the of the United States population. Patients with T1bN0M0 EC were included in the study. The study cohort comprised patients who received a primary diagnosis of EC, as categorized by the International Classification of Diseases for Oncology (ICD-*O*-3 codes): C15.0-C15.5, C15.8-C15.9. TNM staging was performed in accordance with the 6th edition of the American Joint Committee on Cancer (AJCC) TNM staging system. Tumor depth was classified into two categories: T1a, signifying invasion into the lamina propria or muscularis mucosae, and T1b, denoting invasion into the submucosa. Cases with unclear therapy data or unknown survival statuses were ruled out. The study encompassed data related to gender, age at diagnosis, race, marital status, site of cancer, cause of death, tumor differentiation, and histological type, were collected.

2.2. Classification of treatment modalities

The EC patients with T1bN0M0 stage were grouped by the three treatments including esophagectomy, endoscopic therapy, and chemoradiotherapy. Endoscopic treatment group refers to the basic treatment is endoscopy. Endoscopic treatment involves endoscopic approaches to local tumor destruction and resection. Tumor eradication methods encompass photodynamic therapy, laser ablation and cryotherapy. Excisional procedures include mucosal excision or polypectomy, laser excision and excisional biopsy. Esophagectomy entailed various types of resections, including partial or complete esophageal removal, gastrectomy, or laryngectomy. Chemoradiotherapy was defined as a combination of chemotherapy and ionizing radiation.

2.3. Propensity score matching (PSM)

Because of the unmatched dataset of demographic and clinical features in SEER, selection bias is prevalent. In this study, we used PSM to eliminate bias caused by various factors. A matched dataset was applied using propensity scores for age at diagnosis, race, gender, marital status, site of cancer, tumor grade, and histology. Subsequent to performing PSM, statistical significance of the differences in these categorical clinical characteristics was assessed using chi-square tests. Propensity score values were between the range of 0 and 1, and patients with similar propensity scores from the treatment and control groups were paired until all patients in the smaller group had been successfully matched.

2.4. Statistical analysis

The study cohort was categorized into endoscopic therapy, esophagectomy, and chemoradiotherapy groups. OS is the period from randomization until death from any cause. According to the CSS definition, only death due to EC is considered an event, and survival or death from other causes is considered a survival. Survival curves was generated by Kaplan-Meier method. OS and CSS among the three

treatments were compared by log-rank tests. We used Multivariate Cox proportional hazards models to assess the multivariate survival analysis. Statistical analyses were carried out with SPSS version 24.0. All analyses were two-sided, and statistical significance was defined by P values < 0.05. Graphs and figures were produced using GraphPad Prism version 6.02.

3. Results

3.1. Patient characteristics

In the SEER database, from 2006 to 2015, a total of 39,284 patients received a diagnosis of EC, with 1056 of these individuals specifically diagnosed with T1bN0M0 stage. (Fig. 1). Of these 1056 patients, 1038 had ESCC and EAC. Among them, 556 patients underwent esophagectomy, 173 patients received endoscopic therapy as the primary method of treatment, and 91 patients received chemoradiotherapy. Table 1 offers a comprehensive overview of patients baseline demographics and pathological characteristics for the complete sample. Considerable differences were observed in age at diagnosis, gender, race, marital status, site of cancer, tumor differentiation, and histological type.

3.2. Survival analysis before and after PSM

We first compared OS and CSS among the three treatments for patients with T1bN0M0 ESCC and EAC before PSM. The OS and CSS times in the endoscopic therapy and esophagectomy cohorts were significantly longer than those in the chemoradiotherapy group (OS: endoscopic therapy versus chemoradiotherapy, 101 versus 21 months, respectively, $P < 0.001$; and esophagectomy versus chemoradiotherapy, 58 versus 21 months, respectively, $P < 0.001$; CSS: endoscopic therapy versus chemoradiotherapy, 111 versus 60 months, respectively, $P < 0.001$; and esophagectomy versus chemoradiotherapy, 108 versus 60 months, respectively, $P < 0.001$). In contrast to endoscopic therapy, patients who received esophagectomy exhibited superior OS times (101 versus 58 months, $P = 0.003$) and similar CSS times (111 versus 108 months, $P = 0.437$) (Fig. 2A and B). The 5-year OS rates for the endoscopic therapy, esophagectomy, and chemoradiotherapy groups were 48.2 %, 65.2 %, and 21.3 %, respectively. Additionally, the 5-year CSS rates for endoscopic therapy, esophagectomy, and chemoradiotherapy cohorts were 94.5 %, 94.8 %, and 57.0 %, respectively.

Our study conducted a 1:1 PSM, producing 153 patient pairs. The characteristics of the patients and the variables associated with cancer after PSM are listed in Table 2. The matching variables were well-balanced between both treatment groups. Following PSM,

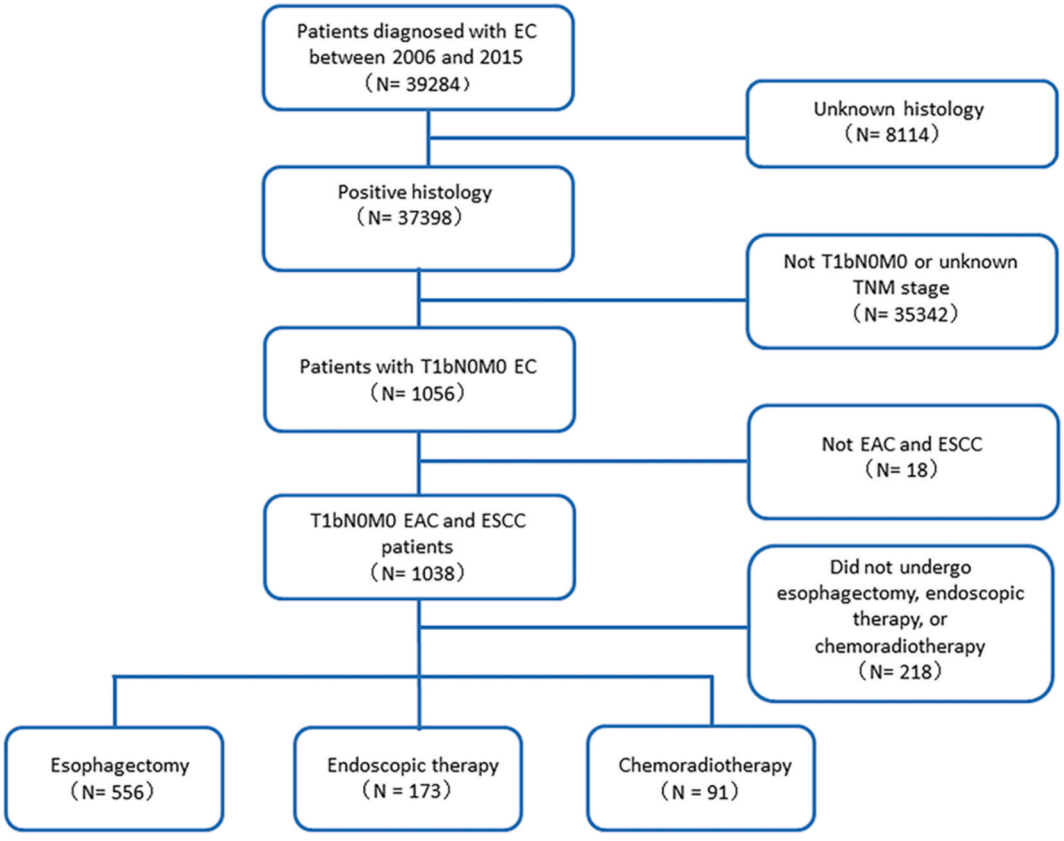

Fig. 1. Flow diagram of patient enrollment. EC, esophageal cancer; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

Table 1
Baseline and tumor characteristics.

Characteristic	Esophagectomy (n = 556)	Endoscopic therapy (n = 173)	Chemoradiotherapy (n = 91)	P value
Age (years)				< 0.001
<70	355 (63.8 %)	57 (32.9 %)	46 (50.5 %)	
70–79	83 (14.9 %)	28 (16.2 %)	11 (12.1 %)	
≥80	118 (21.3 %)	88 (50.9 %)	34 (37.4 %)	
Gender				0.948
Female	101 (18.2 %)	33 (19.1 %)	16 (17.6 %)	
Male	455 (81.8 %)	140 (80.9 %)	75 (82.4 %)	
Race				0.019
White	505 (90.8 %)	157 (90.8 %)	74 (81.3 %)	
other/unknown	51 (9.2 %)	16 (9.2 %)	17 (18.7 %)	
Marital status				0.005
Married	379 (68.2 %)	98 (56.6 %)	51 (56.0 %)	
other/unknown	177 (31.8 %)	75 (43.4 %)	40 (44.0 %)	
Site of cancer				< 0.001
Upper esophagus	16 (2.9 %)	10 (5.8 %)	15 (16.5 %)	
Middle esophagus	62 (11.2 %)	22 (12.7 %)	16 (17.6 %)	
Lower esophagus	421 (75.7 %)	119 (68.8 %)	47 (51.6 %)	
Other	57 (10.2 %)	22 (12.7 %)	13 (14.3 %)	
Grade				< 0.001
I/II	338 (60.8 %)	117 (67.6 %)	44 (48.4 %)	
III/IV	193 (34.7 %)	37 (21.4 %)	29 (31.9 %)	
Unknown	25 (4.5 %)	19 (11.0 %)	18 (19.8 %)	
Histology				< 0.001
Adenocarcinoma	456 (82.0 %)	137 (79.2 %)	54 (59.3 %)	
Squamous cell carcinoma	100 (18.0 %)	36 (20.8 %)	37 (40.7 %)	

Kaplan-Meier curves and log-rank testing demonstrated the comparable OS rates between the esophagectomy and endoscopic therapy cohorts ($P = 0.490$) (Fig. 3A). Moreover, no significant difference was observed in the CSS time between the two treatment groups. (esophagectomy versus endoscopic therapy, 111 versus 108 months, respectively, $P = 0.661$) (Fig. 3B).

Our study conducted univariate and multivariate Cox regression analyses on the entire study population. Age ($P < 0.001$) surfaced as a noteworthy predictor of OS, as indicated in Table 3. No significant differences were observed for race, marital status, gender, site of cancer, tumor grade, histology, or treatment group. Multivariate analyses revealed that patients 80 years old or older had a higher OS mortality risk than patients less than 70 years of age (HR: 2.568, $P < 0.001$). Therefore, age was an independent predictor of OS. For CSS, univariate analyses revealed that tumor grade ($P = 0.079$) was a significant predictor of CSS (Table 4). No significant differences were observed for age, race, marital status, gender, site of cancer, histology, or treatment group. According to the results of the multivariate analysis, patients with tumor grades III/IV exhibited a heightened risk of cancer-specific mortality in comparison to patients with tumor grades I/II (HR: 2.105, $P = 0.028$). Tumor grade was an important predictor of CSS.

To stratify the patients by age at diagnosis, race, gender, marital status, tumor grade, histology, and treatment group, a forest plot of HRs for OS time and CSS time were performed to demonstrate exploratory subgroup analysis (Fig. 4A and B). The results showed no significant difference in either OS or CSS for age groups 70–79 years or ≥80 years, black or other race, female gender, grade III/IV or unknown stage, and the ESCC subgroup.

4. Discussion

Endoscopic therapy is an endoscopic resection method for the treatment of EC patients with early stage. Endoscopic therapy has been conducted for many years and is considered a practical and crucial curative therapy for early EC. This method has been widely popularized in Asia and Western countries. In accordance with the Japanese guidelines, the definitive criterion for endoscopic therapy is the presence of intramucosal carcinoma that primarily encompasses the epithelium and lamina propria, and occupies less than two-thirds of the esophageal lumen. In addition, the relative indication is involvement of the musculature mucosa or invasion of tumors smaller than 200 μm in the submucosa [14]. As outlined in the guidelines, the primary treatment for pathological T1a disease is endoscopic resection, either with or without ablation. Endoscopic resection is also an option for surgically fit patients with superficial pathological T1b stage, and for all patients with pathological T1b stage who are not candidates for surgery [15]. In the USA, for patients with T1b EC, endoscopic therapy rates increased from 6.6 % in 2004 to 20.9 % in 2010 [16]. Thus, a large proportion of patients with T1b stage received endoscopic therapy without the support of specific guidelines. Therefore, it is crucial to analyze the curative effects of endoscopic therapy in patients with T1b EC.

Based on our data, we found significant differences in age among the treatment groups, with older patients tending to choose endoscopic therapy. Furthermore, both OS and CSS rates were notably elevated in the endoscopic therapy and esophagectomy groups in comparison to the chemoradiotherapy group. Notably, CSS exhibited a similarity between the endoscopic therapy and esophagectomy groups. Before PSM, patients treated with esophagectomy had longer OS than those in the endoscopic therapy group. After PSM, EC patients with T1bN0M0 stage treated endoscopically had OS rates comparable to those treated by esophagectomy. Since patients in the esophagectomy groups were younger than those in the endoscopic therapy group, age may have been a factor affecting

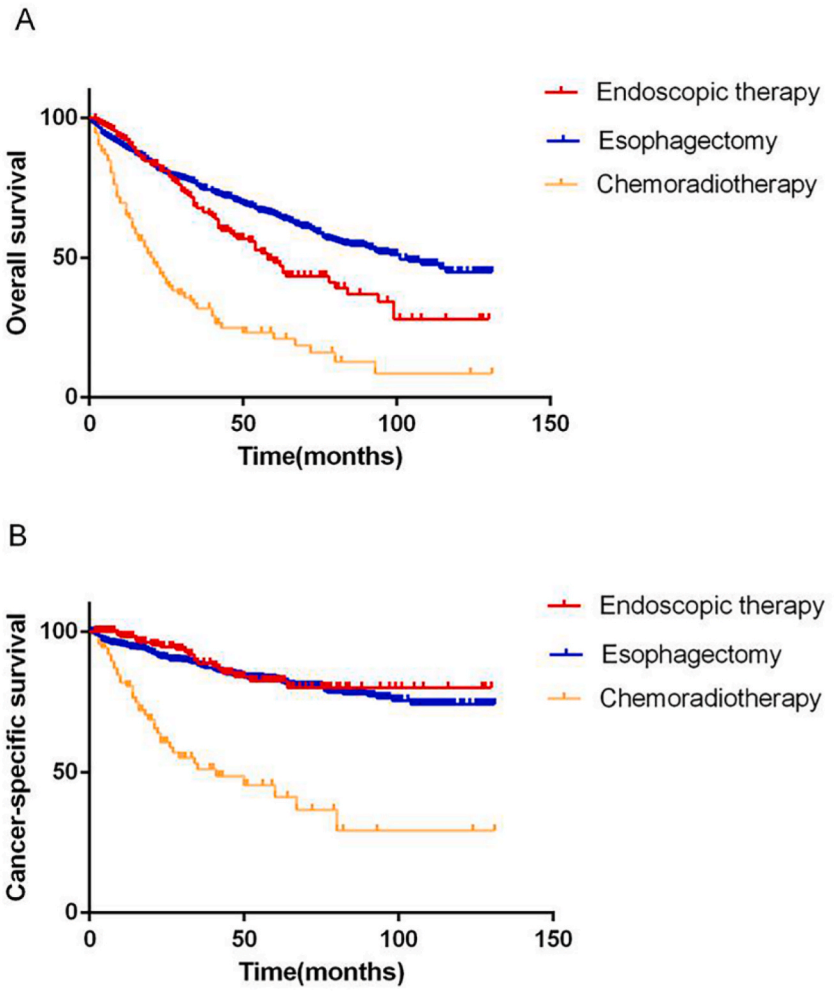

Fig. 2. Kaplan-Meier curves for overall survival (A) and cancer-specific survival (B) in patients with T1bN0M0 esophageal cancer receiving esophagectomy, endoscopic therapy, and chemoradiotherapy before propensity score matching. $P < 0.05$ represents significant differences. (overall survival: endoscopic therapy versus chemoradiotherapy, $P < 0.001$; esophagectomy versus chemoradiotherapy, $P < 0.001$; endoscopic therapy versus esophagectomy, $P = 0.003$; cancer specific survival: endoscopic therapy versus chemoradiotherapy, $P < 0.001$; endoscopic therapy versus esophagectomy, $P = 0.437$).

OS and thus resulting in bias. Through PSM, bias in patient age and other aspects was reduced, and the populations of the two treatment groups was more balanced, yielding more objective and convincing OS data. Patients ≥80 years of age had a higher OS mortality risk than patients <70 years of age. Therefore, age was an independent predictor of OS. Our data also showed that CSS rates were similar in the esophagectomy and endoscopic therapy groups both before and after PSM. Moreover, individuals with tumor grades III/IV experienced a heightened risk of cancer-specific mortality when compared to those with tumor grades I/II. Tumor grade could also be used to predict CSS. Collectively, the results of our support the use of endoscopic therapy in patients with T1bN0M0 EC to some extent.

In the context of T1a EC, a substantial proportion of patients can achieve a cure through endoscopic resection alone, obviating the need for supplementary therapy. However, for T1b EC, characterized by a heightened propensity for lymph node metastasis, it is imperative to consider additional treatment, particularly for patients with local esophageal tumors or concealed regional lymph node metastasis [17,18]. Moreover, once lymph node metastasis develops macroscopically, the efficacy of this treatment becomes significantly worse. Prior research has underscored the substantial risk of lymph node involvement, reaching up to 7 % in cases of T1a EC and 20 % for T1b EC [19,20]. The key to the success of endoscopic therapy is that lies in the absence of lymph node metastasis among most individuals with superficial EC. As was demonstrated in this study, endoscopic therapy is a superior choice to esophagectomy for individuals with low-risk T1b lesions. Low risk in this context was characterized by the absence of lymph node invasion, restricted submucosal invasion limited to the SM1 layer, and good-to-moderate differentiation [21]. Therefore, before implementing endoscopic therapy in patients with T1b EC, a comprehensive assessment encompassing the risk of lymph node dissemination, the extent of submucosal invasion, and the degree of tumor differentiation need to be fully assessed. When deemed essential, diagnostic

Table 2
Patient baseline demographics and pathological characteristics of endoscopic therapy and esophagectomy before and after PSM.

Characteristic	Before PSM			After PSM		
	Esophagectomy (n = 556)	Endoscopic therapy (n = 173)	*P* value	Esophagectomy (n = 153)	Endoscopic therapy (n = 153)	*P* value
Age at diagnosis			<0.001			0.992
<70	355 (63.8 %)	57 (32.9 %)		55 (35.9 %)	56 (36.6 %)	
70–79	83 (14.9 %)	28 (16.2 %)		25 (16.3 %)	25 (16.3 %)	
≥80	118 (21.3 %)	88 (50.9 %)		73 (47.8 %)	72 (47.1 %)	
Gender			0.787			0.560
Female	101 (18.2 %)	33 (19.1 %)		31 (20.3 %)	27 (17.6 %)	
Male	455 (81.8 %)	140 (80.9 %)		122 (79.7 %)	126 (82.4 %)	
Race			0.976			1.000
White	505 (90.8 %)	157 (90.8 %)		141 (92.2 %)	141 (92.2 %)	
Other/unknown	51 (9.2 %)	16 (9.2 %)		12 (7.8 %)	12 (7.8 %)	
Marital status			0.005			0.814
Married	379 (68.2 %)	98 (56.6 %)		58 (37.9 %)	60 (39.2 %)	
Other/unknown	177 (67.9 %)	75 (43.4 %)		95 (62.1 %)	93 (60.8 %)	
Site of cancer			0.172			0.427
Upper esophagus	16 (2.9 %)	10 (5.8 %)		4 (2.6 %)	8 (5.2 %)	
Middle esophagus	62 (11.2 %)	22 (12.7 %)		16 (10.5 %)	16 (10.5 %)	
Lower esophagus	421 (75.7 %)	119 (68.8 %)		118 (77.1 %)	108 (70.6 %)	
Other	57 (10.2 %)	22 (12.7 %)		15 (9 %)	21 (13.7 %)	
Tumor grade			<0.001			0.809
I/II	338 (60.8 %)	117 (67.6 %)		106 (69.3 %)	104 (68.0 %)	
III/IV	193 (34.7 %)	37 (21.4 %)		37 (24.2 %)	36 (23.5 %)	
Unknown	25 (4.5 %)	19 (11.0 %)		10 (6.5 %)	13 (8.5 %)	
Histology			0.405			0.883
Adenocarcinoma	456 (82.0 %)	137 (79.2 %)		125 (81.7 %)	124 (81.0 %)	
Squamous cell carcinoma	100 (18.0 %)	36 (20.8 %)		28 (18.3 %)	29 (19.0 %)	

methodologies including positron emission tomography/computed tomography or endoscopic ultrasonography (EUS) may be employed [22].

The utilization of the SEER database in our study conferred several advantages. In particular, the substantial sample sizes and the inclusion of long-term follow-up data afforded us reliable survival outcomes and compelling evidence for diverse treatment strategies. The number of patients with T1bN0M0 EC is small and it is difficult to enroll patients in prospective studies; furthermore, the follow-up span is long. Our data were based on a relatively large sample size, which may therefore be more representative of real-world data. However, this study did have some limitations. For example, the lack of information on clinical prognostic factors for survival and some oncological relevant data, such as operation details, lymph node involvement, tumor status after surgery, neoadjuvant therapy before endoscopic therapy or esophagectomy, and the type of chemotherapy, may have led to biased interpretations of the findings. In addition, the performance status of patients could also be considered since it might affect treatment modality and survival. The notable limitation of the SEER database lies in its absence of data on comorbidities, a factor that has the potential to introduce selection bias. It is conceivable that patients undergoing esophagectomy may exhibit a relatively healthier baseline. Incorporating randomized, controlled trials that juxtapose endoscopic therapy and esophagectomy would be of great value. Considering the similarity in OS and CSS durations, the absence of this information is likely to have had a negligible impact on the overall outcomes. The SEER database does not specify whether the stage is based on the pathological stage or clinical stage. However, even endoscopic treatment cannot achieve complete pathology as seen with esophagectomy, and staging is not as accurate as with esophagectomy. Patients who are treated by radiotherapy and chemotherapy receive clinical staging, but they have been fully evaluated. Moreover, because of the unmatched dataset of demographic and clinical features in SEER, selection bias could have occurred. Therefore, in our study, we used PSM to reduce the impact of selection bias. Endoscopic therapy and esophagectomy have been used and developed at different times, and because the SEER database analysis was retrospective, our results were biased owing to the uneven use of endoscopic therapy or esophagectomy in patients in the past. Finally, the assessment of treatment responses and recurrence rates remained elusive, as the data within the SEER database did not provide this information.

In summary, endoscopic therapy and esophagectomy showed similar benefits for CSS in all patients with T1bN0M0 EC. Our data showed that in all of the mass analysis of the retrospective SEER database, after PSM, no discernible distinctions in OS and CSS were detected between endoscopic therapy and esophagectomy. Moreover, our findings substantiate endoscopic therapy as a viable alternative to esophagectomy for individuals with T1bN0M0 stage. At the same time, we also realized that for data in the SEER database, the TNM stage had not been fully and accurately assessed, particularly with regard to pathological analysis. We advocate for thorough pre-operative evaluations to be performed when identifying suitable candidates for endoscopic treatment, with the aim of mitigating the need for unnecessary esophagectomy. Consequently, there is a requirement for additional randomized controlled trials to further scrutinize the effectiveness of endoscopic therapy in patients diagnosed with T1bN0M0 EC.

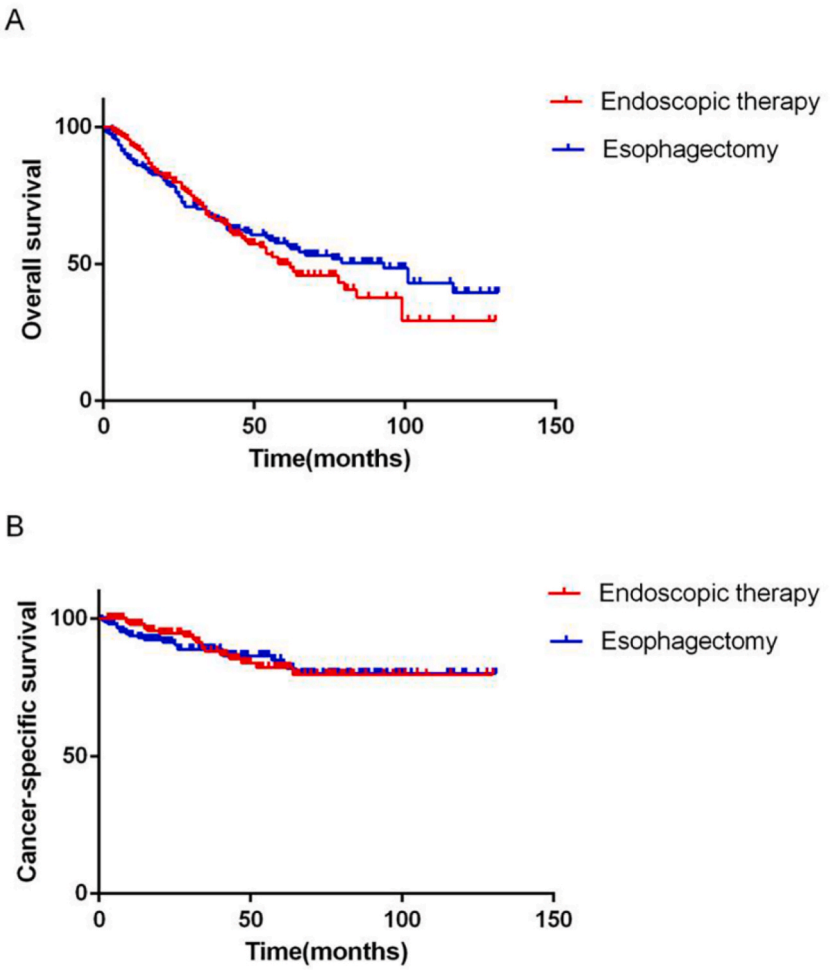

Fig. 3. Overall survival (A) and cancer specific survival (B) in patients with T1bN0M0 esophageal cancer receiving esophagectomy and endoscopic therapy after propensity score matching. $P < 0.05$ represents significant differences (overall survival: esophagectomy versus endoscopic therapy, $P = 0.490$; cancer specific survival: esophagectomy versus endoscopic therapy, $P = 0.661$).

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None.

Data availability statement

The data utilized in this study were extracted from the freely accessible SEER database (https://seer.cancer.gov/seerstat/).

Ethical approval

Not applicable.

CRediT authorship contribution statement

Jiamin Zhu: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Xiao Liang:** Validation, Supervision, Investigation, Formal analysis. **Shusen Chen:** Visualization, Project administration, Methodology, Investigation. **Ya Qin:** Visualization, Resources, Project administration, Methodology. **Dong Shen:** Visualization, Validation, Resources, Conceptualization. **Xi Yang:** Validation, Supervision, Investigation, Funding acquisition, Formal analysis.

Table 3
Univariate and multivariate analyses for OS of patients.

Characteristics	Univariable		Mutivirable	
	Log-rank test	P value	HR (95%CI)	P value
Age	27.418	P < 0.001		
<70			Ref.	
70–79			1.224 (0.674–2.225)	0.507
≥80			2.648 (1.755–3.997)	P < 0.001
Gender	0.666	0.415		
Female				
Male				
Race	0.008	0.931		
White				
Other/unknown				
Marital status	0.055	0.814		
Married				
Other/unknown				
Site of cancer	3.168	0.366		
Upper esophagus				
Middle esophagus				
Lower esophagus				
Other				
Tumor grade	3.232	0.199		
I/II			Ref.	
III/IV			1.213 (0.833–1.765)	0.314
Unknown			0.723 (0.363–1.442)	0.357
Histology	2.709	0.100		
Adenocarcinoma			Ref.	
Squamous cell carcinoma			1.477 (0.988–2.209)	0.057
Treatment group	0.477	0.490		
Endoscopic therapy			Ref.	
Esophagectomy			0.868 (0.620–1.217)	0.412

Table 4
Univariate and multivariate analyses for cancer-specific survival of patients.

Characteristics	Univariable		Mutivirable	
	Log-rank test	P value	HR (95%CI)	P value
Age	1.927	0.382		
<70				
70–79				
≥80				
Gender	0.674	0.412		
Female			.	
Male				
Race	0.259	0.610		
White				
Other/unknown				
Marital status	0.883	0.347		
Married			.	
Other/unknown				
Site of cancer	1.836	0.607		
Upper esophagus				
Middle esophagus				
Lower esophagus				
Other				
Tumor grade	5.066	0.079		
I/II			Ref.	
III/IV			2.105 (1.085–4.086)	0.028
Unknown			1.514 (0.518–4.425)	0.448
Histology	1.588	0.208		
Adenocarcinoma				
Squamous cell carcinoma				
Treatment group	0.192	0.661		
Endoscopic therapy			Ref.	
Esophagectomy			1.167 (0.624–2.181)	0.629

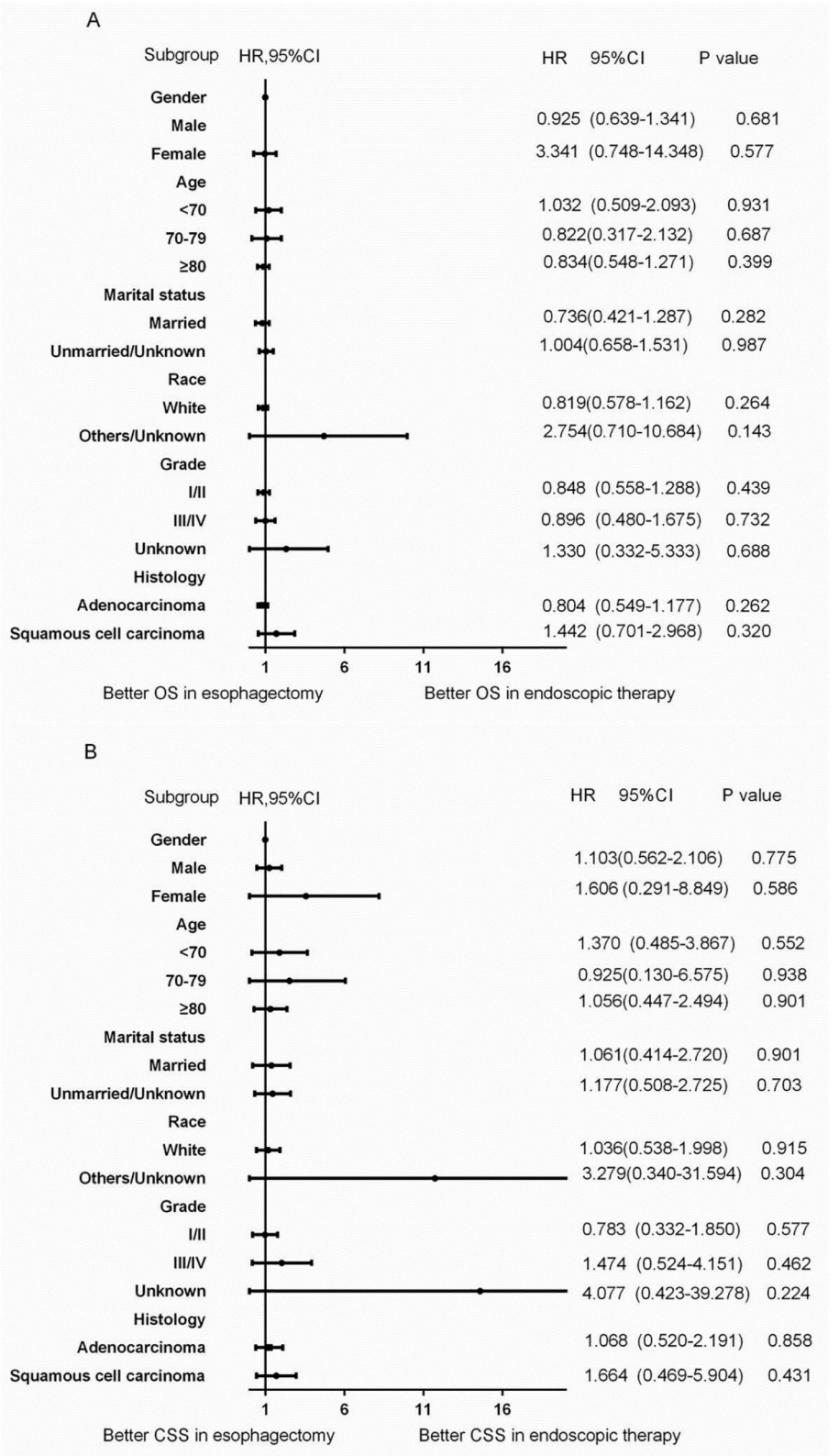

Fig. 4. Forest plot of hazard ratios (HRs) for overall survival (A) and cancer specific survival (B) between endoscopic therapy and esophagectomy in the subgroup analysis. The spot on the X-axis indicates the HR and the 95 % confident interval (CI) of each subgroup.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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