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Comparison of LNM and survival in T1 stage esophageal cancer patients based on histological classification

A large population-based study

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Abstract

Limited evidence and contradictory results have been reported regarding the impact of squamous cell carcinoma (SCC) and adenocarcinoma (AC) classification on lymph node metastasis (LNM) and prognosis in esophageal cancer (EC). We aimed to compare 2 histology types in terms of LNM and prognosis using a comprehensive statistical analysis of a large population. The Surveillance, Epidemiology, and End Results (SEER) database was used to extract patient information. Univariate and multivariate logistic or Cox regression, a multivariate competing risk model and propensity score matching (PSM) were used to explore the association between LNM or survival and the 2 histology types. Information for 4764 patients, including 1712 SCC and 3052 AC patients, was extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Multivariate logistic regression analysis revealed a correlation between LNM and histology (odds ratio [OR] = 0.654, $P = .037$). We found that patients with AC had a better prognosis than SCC patients through both the multivariate Cox regression (hazard ratio [HR] = 0.866) and the multivariate competing risk model (subdistribution hazard ratio [SHR] = 0.704). However, no positive relation was found between LNM and histology type ($P = .844$) based on propensity score matching (PSM), and the prognosis remained poorer for the patients with SCC ($P < .001$). T1-stage EC with a histology of SCC may have a comparable risk of LNM as the AC type, while SCC has a poorer prognosis than the AC type.

Abbreviations: AC = adenocarcinoma, CI = confidence interval, CSS = cancer-specific survival, EC = esophageal cancer, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal desection, LNM = lymph node metastasis, OR = odds ratio, OS = overall survival, PSM = propensity score matching, SCC = squamous cell carcinoma, SEER = Surveillance, Epidemiology, and End Results.

Keywords: esophageal cancer, lymph node metastasis, SEER, survival

1. Introduction

Esophageal cancer (EC) is a disease with very high mortality and ranks as the seventh leading cancer. According to the latest statistics, in 2018, EC was a highly malignant tumor worldwide, with 572,034 new cases, accounting for 3.2% of all cancers, and with 508,585 deaths, accounting for 5.3% of all cancer mortality.[1] Most ECs are categorized into 2 histopathological types: squamous cell carcinoma (SCC) and adenocarcinoma (AC). SCC is predominant in patients from the USA, the UK, other western European countries and China, while AC is found to be rapidly increasing.[2] The major risk factors for SCC include consumption of tobacco and alcohol, whereas the chronic reflux of gastric acid, including Barrett esophagus, is a risk factor for AC.[3] For the treatment of EC, current options include surgery, endoscopic therapy such as endoscopic submucosal desection (ESD), radiation and chemotherapy.[4] According to a recently released large follow-up study, the 1-year overall survival (OS) rate of patients after surgery with SCC was approximately 45%, while the OS rate was 43% for patients with AC.[5] More seriously, the 5-year survival rate for both types were low, at <15%.[5]

Fortunately, with advancements and advocation in endoscopy technology, early diagnosis and treatment of early EC has created a paradigm shift.[6] The 5-year survival rate of patients with superficial EC is approximately 85% to 100%, while that of patients with submucosal EC is 64% to 78%.[7–9] Some studies have found no difference in OS or cancer recurrence or metastasis in patients with T1 EC treated with ESD or esophagectomy; moreover, ESD is recommended for patients with T1a EC due

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All methods were carried out in accordance with relevant guidelines and regulations of Jiangxi Provincial People's Hospital. Ethics approval and consent was obtained from SEER database (https://seer.cancer.gov/).

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to its fewer adverse events and lower cost.[10,11] For endoscopic therapy such as endoscopic mucosal resection (EMR) and ESD, the presence of lymph node metastasis (LNM) is one of the most important determinants of long-term prognosis for patients with T1 EC.[12,13] Understanding and predicting the presence of LNM allows a determination of whether endoscopic treatment and esophagectomy is the optimal method of management.[8,14] Early studies showed that the rate of LNM for SCC (17%) was higher than that for AC (16.6%)[15]; in contrast, the results of a propensity score-matched study showed that patients with AC had a higher risk of LNM than those with SCC.[16] A recent retrospective study showed that the rate and patterns of LNM between SCC and AC did not statistically differ.[17,18] With respect to survival of T1 EC, previous analyses have provided limited evidence to assess differences in survival of SCC and AC. In addition, due to the small number of samples involved in retrospective studies, it is necessary to reanalyze the differences in LNM and survival for SCC compared with those of AC with a large population-based study with various statistical methods.

In our study, to investigate the LNM rate and prognosis of SCC and AC, we extracted the information of 4764 patients from the Surveillance, Epidemiology, and End Results (SEER) database to perform comprehensive analysis by multivariate regression analysis, constructing a competing risk model and conducting propensity score matching (PSM) to provide evidence for endoscopic treatment and follow-up of SCC and AC in the T1 stage.

2. Methods

2.1. Patients

All patients with T1 EC were retrieved from the SEER database with the National Cancer Institute's SEER*Stat software (version 8.3.6). The patients did not give informed consent because the SEER database is free for public use. According to the International Classification of Diseases in Oncology (ICD-O-3), tumors with codes 8070, 8071, 8072, 8073, 8074, 8075, 8076, and 8078 are identified as SCC, while those with codes 8140, 8144 and 8145 are considered as AC.[19,20] In our study, patients with EC were included according to the following criteria:

(1) patients older than 20 who were diagnosed as EC by positive histology from 1979 through 2015,
(2) patients with a histopathology of squamous carcinoma or AC,
(3) patients who were classified as T1 stage, and
(4) patients with detailed information, including race, grade, regional nodes examined, tumor size, historic stage, N stage and M stage.

Informed consent was obtained from the patient for the purpose of publication. All methods were carried out in accordance with relevant guidelines and regulations of Jiangxi Provincial People's Hospital.

2.2. Clinicopathological factors

The clinicopathological variables extracted from the SEER database in our study included age, race, sex, pathology grade, LNM, M stage, tumor size, N stage, historic stage, regional nodes examined and primary site. The patients were divided into 2 age groups: <60 years and ≥60 years. Race was classified into 3 types: white, black and other. Sex included male and female. Pathology grade was categorized as well/moderately differentiated type and poorly differentiated/undifferentiated type. Historic stage was recorded as localized, regional and distant.

Table 1

Patients' demographics, clinical characteristics at diagnosis.

Variables	Total (%)	Squamous cell carcinoma	Adenocarcinoma	*P*-value
n	4764	1712	3052	
Age				.008
<60	1124 (23.6%)	357 (20.85%)	767 (25.13%)	
≥60	3640 (76.4%)	1355 (79.15%)	2285 (74.87%)	
Race				<.001
White	4017 (84.32%)	1097 (64.08%)	2920 (95.67%)	
Black	490 (10.28%)	423 (24.71%)	67 (2.2%)	
Other	257 (5.4%)	192 (11.21%)	65 (2.13%)	
Sex				<.001
Male	3737 (78.44%)	1091 (63.73%)	2646 (86.7%)	
Female	1027 (21.56%)	621 (36.27%)	406 (13.3%)	
Pathology grade				.084
Well/Moderately differentiated	2756 (57.85%)	962 (56.19%)	1794 (58.78%)	
Poorly and undifferentiated	2008 (42.15%)	750 (43.81%)	1258 (41.22%)	
Lymph node metastasis				.0036
No	3356 (70.45%)	1162 (67.87%)	2194 (71.89%)	
Yes	1408 (29.55%)	550 (32.13%)	858 (28.11%)	
Metastasis				.196
No	3563 (74.79%)	1299 (75.88%)	2264 (74.18%)	
Yes	1201 (25.21%)	413 (24.12%)	788 (25.82%)	
Tumor size				<.001
≤2 cm	1586 (33.29%)	375 (21.9%)	1211 (39.68%)	
≤3 cm	732 (15.37%)	297 (17.35%)	435 (14.25%)	
≤5 cm	1200 (25.19%)	509 (29.73%)	691 (22.64%)	
>5 cm	1246 (26.15%)	531 (31.02%)	715 (23.43%)	
Regional nodes examined				<.001
≤13	4097 (85%)	1577 (92.11%)	2520 (82.57%)	
>13	667 (14%)	135 (7.89%)	532 (17.43%)	
Historic stage				.013
Localized	2857 (59.97%)	987 (57.65%)	1870 (61.27%)	
Regional	608 (12.76%)	247 (14.43%)	361 (11.83%)	
Distant	1299 (27.27%)	478 (27.92%)	821 (26.9%)	

Table 2

Univariate and multivariate logistic regression model for exploring the potential risk factors for lymph node metastasis in patients.

Variables	Univariate analysis	*P*-value	Multivariate analysis	*P*-value
Age		.000		<.001
<60	Reference	-	Reference	-
≥60	0.686 (0.595–0.792)	.000	0.62 (0.541–0.792)	
Race				
White	Reference	-		
Black	1.010 (0.822–1.24)	.922		
Other	1.354 (1.04–1.76)	.025		
Sex				.06
Male	Reference	-	Reference	-
Female	0.835 (0.715–0.975)	.023	0.923 (0.723–1.12)	
Pathology grade				.018
Well/Moderately differentiated	Reference	-	Reference	-
Poorly and undifferentiated	1.832 (1.615–2.077)	.000	1.528 (1.32–1.743)	
Tumor size				<.001
≤2 cm	Reference	-	Reference	-
≤3 cm	2.16 (1.742–2.678)	.000	1.644 (1.4–2.341)	<.001
≤5 cm	2.977 (2.470–3.578)	.000	2.23 (2.015–3.63)	<.001
>5 cm	5.043 (4.218–6.028)	.000	4.55 (3.79–5.721)	<.001
Regional nodes examined				.749
≤13	Reference	-	Reference	-
>13	0.661 (0.545–0.802)	.000	0.816 (0.725–1.126)	.749
Histology				.037
Squamous cell carcinoma	Reference	-	Reference	-
Adenocarcinoma	0.826 (0.727–0.94)	.004	0.654 (0.574–0.747)	.037

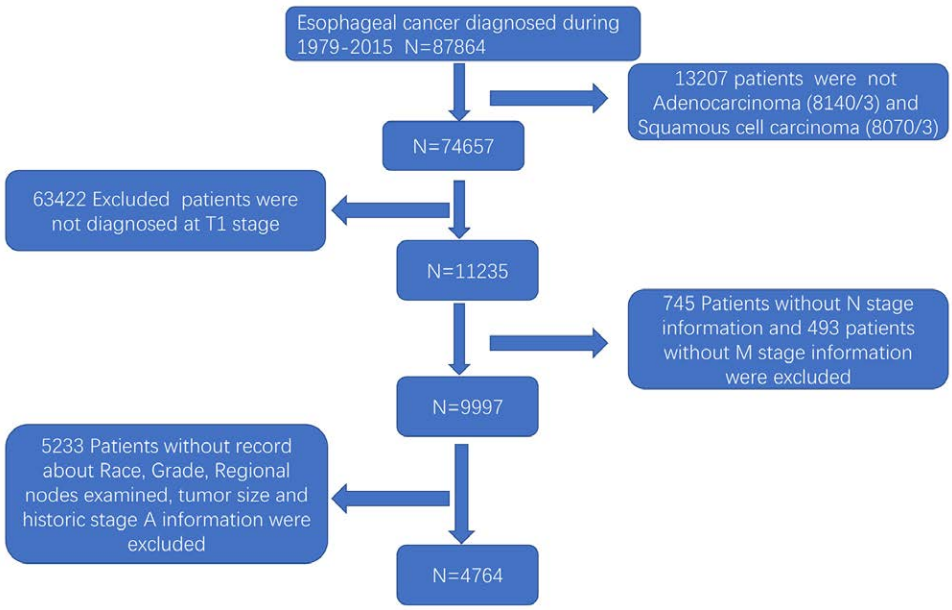

Figure 1. Flowchart of selection of patients with T1 EC of SCC or AC using the SEER database. AC = adenocarcinoma, EC = esophageal cancer, SCC = squamous cell carcinoma, SEER = Surveillance, Epidemiology, and End Results.

LNM was described as N1 (Yes) or N0 (No). M1 (Yes) indicated positive M stage. Tumor size was categorized into 4 groups: ≤2 cm, ≤3 cm, ≤5 cm, and >5 cm. With respect to regional nodes examined, we figured out the cutoff was 13 via receiver operating characteristic (ROC) curve. Therefore, regional nodes examined were divided into 2 groups: ≤13 and >13. In our study, the main observation indicators were LNM status, OS and cancer-specific survival (CSS). CSS was defined as death attributable to this cancer, while OS included CSS and death attributable to other causes.

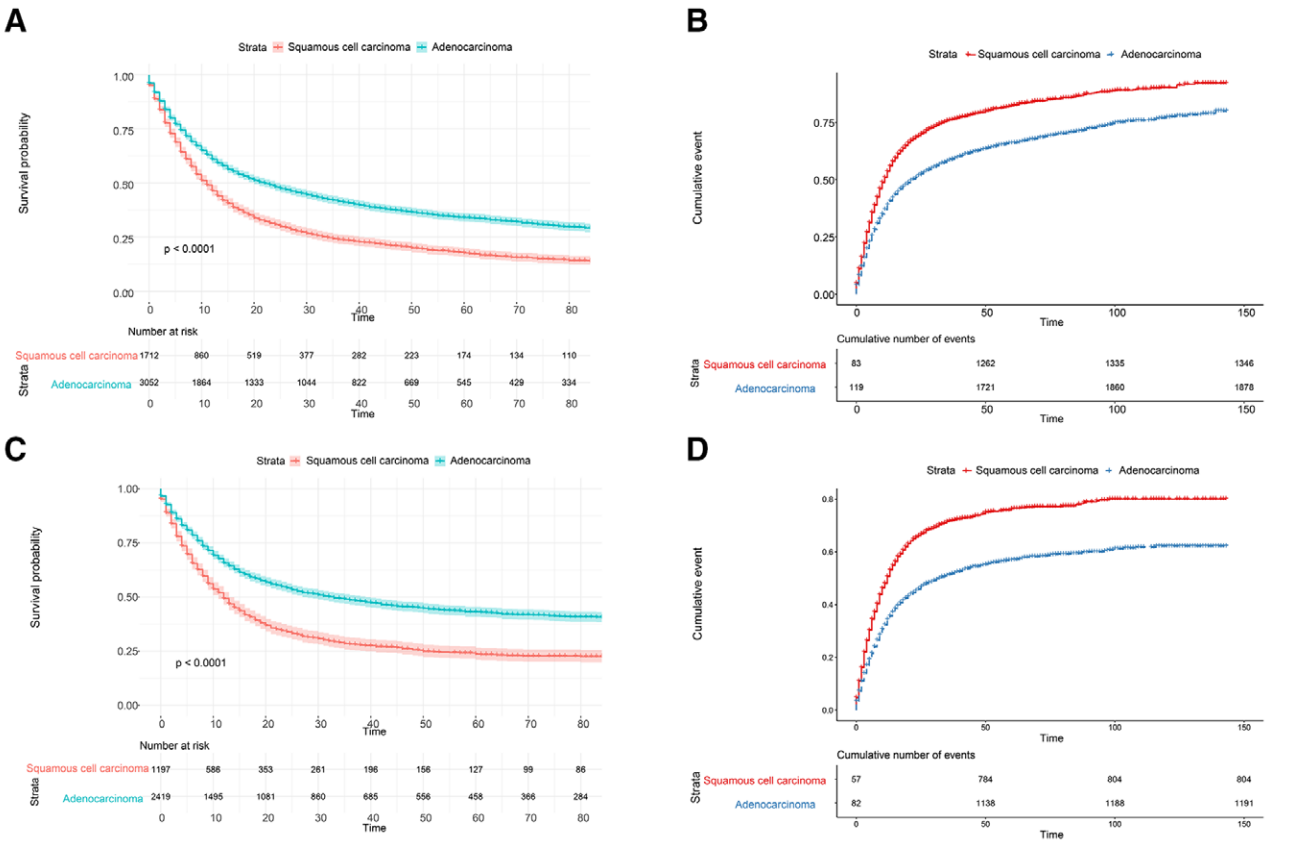

Figure 2. Comparison of survival and cumulative probability for 4764 patients from the SEER database between SCC and AC. (A–B) the plot of OS and cumulative probability of OS. (C–D) the plot of CSS and cumulative probability of CSS. AC = adenocarcinoma, CSS = cancer-specific survival, OS = overall survival, SCC = squamous cell carcinoma, SEER = Surveillance, Epidemiology, and End Results.

Table 3

One-, 3- and 5-year survival of OS and CSS among patients according to different histology analysis.

Variables	Squamous cell carcinoma	Adenocarcinoma	*P*-value
OS			.0001
1-year	46.38% (44.03%–51.5%)	60.9% (59.1%–64.8%)	
3-year	23.95% (21.88%–26.5%)	41.5% (39.7%–44%)	
5-year	17.75% (15.82%–19.9%)	34.1% (32.3%–36.1%)	
CSS			.021
1-year	49.3% (46.5%–55%)	65.7% (63.8%–69.6%)	
3-year	28.3% (25.6%–31.5%)	48.6% (46.4%–51.3%)	
5-year	23.6% (21%–24.5%)	43% (40.7%–45.3%)	

CSS = cancer-specific survival, OS = overall survival.

2.3. Statistical analysis

For the basic statistics, patients were divided into 2 groups, that is, SCC and AC, and Pearson chi-squared test was utilized to investigate the association among the categorical variables. To explore the potential risk factors for LNM, we performed univariate and multivariate logical regression, and we present the results as the odds ratio (OR) with the 95% confidence interval (CI). With respect to the OS and CSS of patients with SCC and AC, we performed survival curves using the survminer package in R software. Furthermore, to analyze the related risk factors for survival, we performed multivariate Cox regression, and we present the result as forest plots. For the competing risk model, we constructed the model as described in a previous study.[21] Briefly, we selected CSS as the outcome of interest, whereas death caused by other reasons was considered a competing risk event, and a patient being alive was regarded as censored event. We performed cumulative risk curves using Fine and Gray competing risk regression analysis. In addition, a multivariate competition risk model was used to explore the potential risk factors for CSS by R software with the cmprsk package.

Regarding the imbalance between SCC and AC groups, we performed PSM to obtain new data for analysis with the MatchIt package in R software. The value of the caliper was set as 0.05, and the effect was evaluated based on *P*-value. The effect was balanced when the *P*-value was >.05.[22] The detailed process was as follows. First, we calculated the propensity scores of each patient according to the histology (SCC and AC) with the multivariate logistic regression model. Then, we matched patients between 2 groups at a ratio of 1:1; we list the detailed information for all clinical factors in Tables 5 and 6. Next, we analyzed the differences in all variables between the SCC and AC groups with the chi-squared test. Finally, we explored the correlation

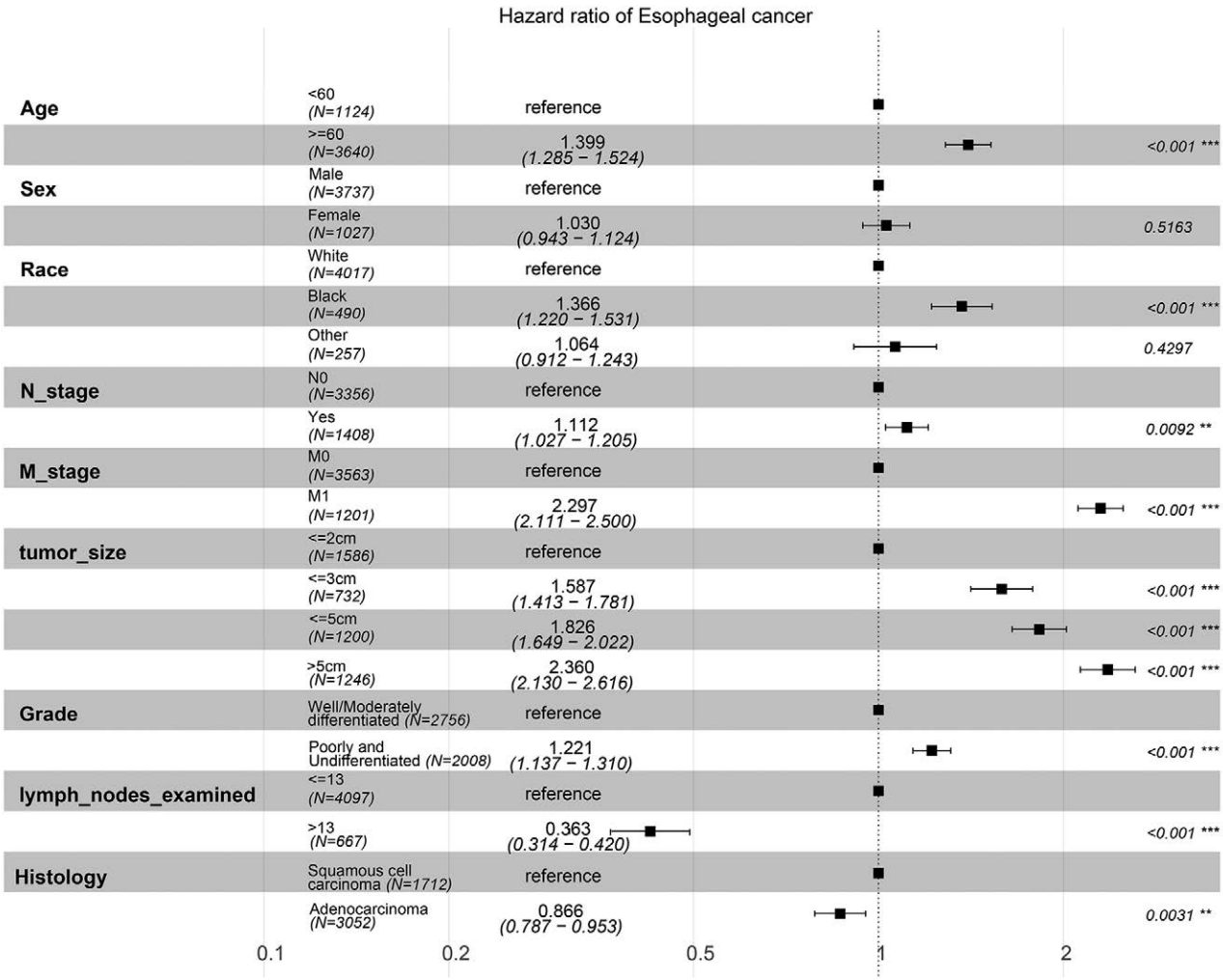

Figure 3. Forest plot shows results of the multivariate Cox regression model for exploring the potential risk factors for CSS in 4764 patients with EC in T1 stage. CSS = cancer-specific survival, EC = esophageal cancer.

between survival and histologic type using the univariate Cox regression model. Additionally, a plot of cumulative events was also constructed. All statistical analysis was performed with R software (version 3.6.1, StataCorp LLC, College Station, TX). The main packages used in our study included ggplot2, MatchIt, survival, rms, cmprsk, kaps, survminer and forest package. The chi-squared test was carried out with SPSS (version 24.0). The results were statistically significant when the *P*-value was <.05.

3. Results

3.1. Basic characteristics of patients with EC in the t1 stage

As the flow chart in Figure 1 shows, a total of 4764 patients from the SEER database were enrolled according to the inclusion criteria. All patients were distributed into the SCC and AC groups according to our predefined aims. Table 1 shows the demographic and clinical characteristics of patients in the 2 groups. Between the SCC and AC groups, there were significant differences in age ($P = .008$), race ($P < .001$), sex ($P < .001$), LNM ($P = .0036$), tumor size ($P < .001$), historic stage ($P = .013$) and regional nodes examined ($P < .001$), while metastasis ($P = .196$) and pathology grade ($P = .084$) were not significantly different. Compared with the patients in the AC group, patients in the SCC group were more likely to be older, defined as >60 years (79.15% vs. 74.87%); to be black (24.71% vs. 2.2%); to have LNM (32.13% vs. 28.11%); to be female (36.27%–13.3%); to have a larger tumor size (31.02% vs. 23.43%); to have an advanced tumor (27.92% vs. 26.9%); and to have a tumor located in the upper third (13.81% vs. 1.21%) or middle third (37.81% vs. 7.24%).

3.2. Risk of LNM in SCC and AC in t1 EC

Since the data in Table 1 suggested that the rate of LNM differed between the SCC and AC groups, we performed univariate and multivariate logistic regression to explore the potential risk factors for LNM in patients. As shown in Table 2, the univariate analysis showed that age, sex, pathology grade, tumor size, regional node examined and histology were associated with LNM. However, after adjusting the potential confounding factors by multivariate logistic regression analysis, we found that only age ($P < .001$), pathology grade ($P = .018$), tumor size ($P < .001$) and histology ($P = .037$) were independent risk factors for LNM.

3.3. Analysis of survival of t1 EC between patients with SCC and AC

To explore the differences in survival between patients with SCC and AC, we first calculated the Kaplan–Meier curves and

Table 4

Results of competing risks regression with inclusion of all possible risk factors in patients with T1 esophageal cancer.

Variables	Subdistribution hazard ratio (SHR)	*P*-value
Age		.0001
<60	Reference	-
≥60	1.203 (1.092–1.425)	.0001
Race		.093
White	Reference	-
Black	0.897 (0.833–1.01)	.32
Other	1.07 (0.814–1.21)	.07
Sex		.23
Male	Reference	-
Female	1.076 (0.954–1.213)	.23
Tumor size		<.001
≤2 cm	Reference	-
≤3 cm	1.25 (1.091–1.612)	<.001
≤5 cm	2.475 (2.021–4.312)	<.001
>5 cm	5.029 (4.781–6.261)	<.001
Regional nodes examined		<.001
≤13	Reference	-
>13	0.361 (0.257–0.523)	<.001
Histology		
Squamous cell carcinoma	Reference	-
Adenocarcinoma	0.704 (0.435–0.853)	.0009
Lymph node metastasis		
No	Reference	-
Yes	1.071 (0.932–1.322)	.31
Metastasis		
No	Reference	-
Yes	2.036 (1.657–2.471)	<.001
Pathology grade		.0054
Well/Moderately	Reference	
Poorly and undifferentiated	1.128 (0.921–1.334)	.0054

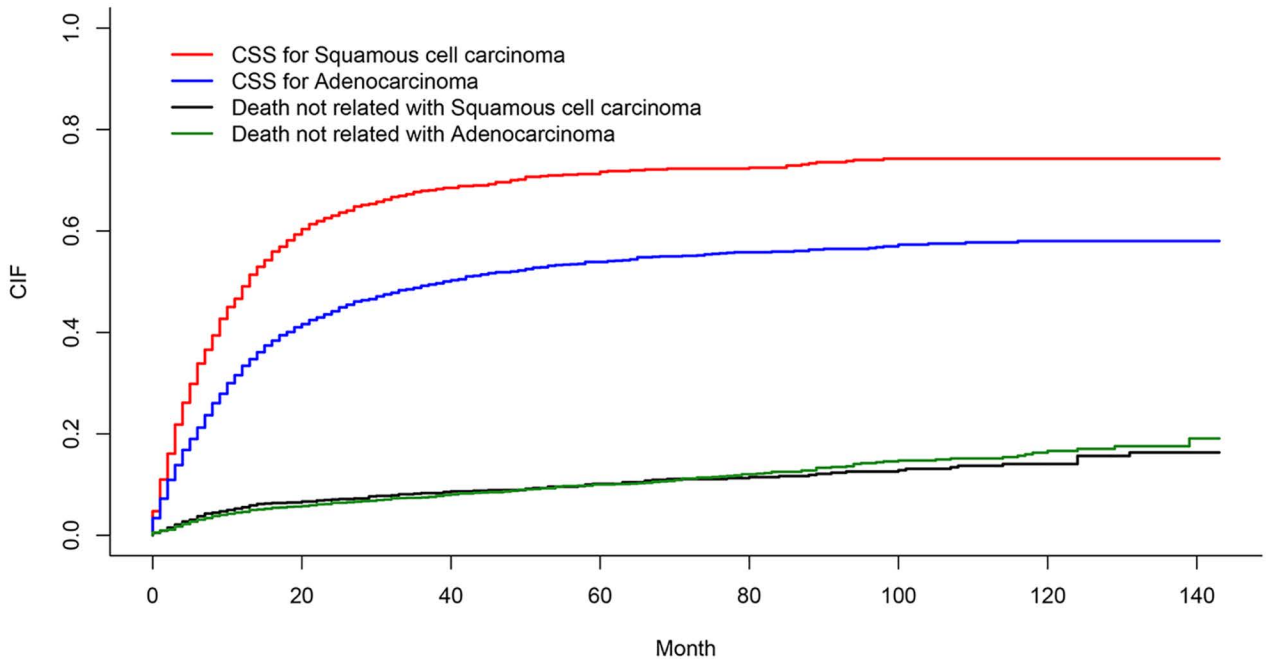

Figure 4. Competing risk model was performed to evaluate the value of histology (SCC and AC) for predicting survival. AC = adenocarcinoma, SCC = squamous cell carcinoma.

cumulative events plots for OS and CSS (Fig. 2). The log-rank test showed that patients with AC had better OS and CSS rates than SCC patients (Fig. 2A and C, $P < .001$). Additionally, the cumulative events plot suggested that patients with SCC had more deaths and EC-related deaths than patients with AC (Fig. 2B and D). As shown in detail in Table 3, the 5-year OS and CSS rates for patients with SCC were 17.75% (95% CI: 15.82%–19.9%) and 23.6% (95% CI: 21%–24.5%),

Table 5

Patients' demographics, clinical characteristics at diagnosis after propensity score matching for analyzing the risk of LNM between SCC and AC.

Variables	Total (%)	LNM negative	LNM positive	*P*-value
n	2732	1366	1366	
Age				.18
<60	727 (26.61%)	348 (25.48%)	379 (%)	
≥60	2005 (73.39%)	1018 (74.52%)	987 (%)	
Race				.593
White	2269 (83.05%)	1132 (82.87%)	1137 (83.24%)	
Black	309 (11.31%)	167 (12.23%)	142 (10.4%)	
Other	154 (5.64%)	67 (4.9%)	87 (6.37%)	
Sex				.309
Male	2203 (80.64%)	1091 (79.87%)	1112 (81.4%)	
Female	529 (19.36%)	275 (20.13%)	254 (18.59%)	
Pathology grade				.759
Well/Moderately differentiated	1320 (48.32%)	656 (48.02%)	664 (48.61%)	
Poorly and undifferentiated	1412 (51.68%)	710 (51.98%)	702 (51.39%)	
Tumor size				.624
≤2 cm	458 (16.76%)	227 (16.62%)	231 (16.91%)	
≤3 cm	374 (13.69%)	178 (13.03%)	196 (14.35%)	
≤5 cm	820 (30.01%)	420 (30.75%)	400 (29.28%)	
>5 cm	1080 (39.53%)	541 (39.6%)	539 (39.46%)	
Regional nodes examined				.251
≤13	2423 (88.69%)	1202 (88%)	1221 (89.39%)	
>13	309 (11.31%)	164 (12%)	145 (10.61%)	

AC = adenocarcinoma, LNM = lymph node metastasis, SCC = squamous cell carcinoma.

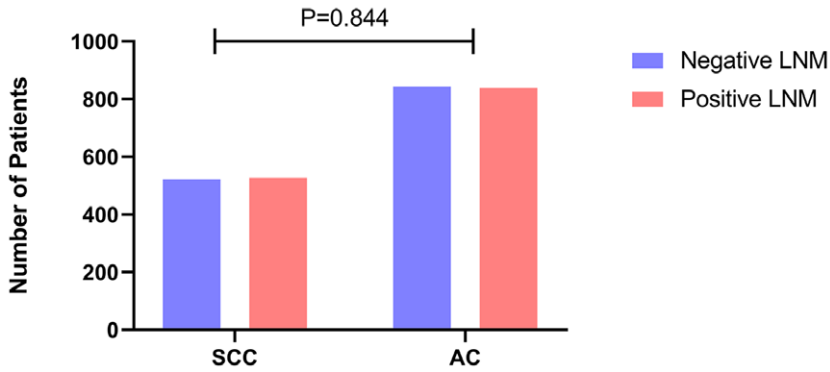

Figure 5. Standardized mean difference across covariates before and after PSM was showed while exploring the association between LNM and histology. LNM = lymph node metastasis, PSM = propensity score matching.

respectively. With respect to patients with AC, the 5-year OS and CSS rates were 34.1% (95% CI: 32.3%–36.1%) and 43% (95% CI: 40.7%–45.3%), respectively. To adjust for potential confounding factors, we performed multivariate Cox regression for CSS. As shown in Figure 3, the model revealed that patients with AC had better survival than patients with SCC (hazard ratio [HR] = 0.866, 95% CI: 0.787–0.953, $P = .031$). Furthermore, age ($P < .001$), race ($P < .001$), LNM ($P = .0092$), M stage ($P < .001$), tumor size ($P < .001$), pathology grade ($P < .001$) and lymph node were independent factors correlated with CSS. For further analysis of risk factors for CSS, we included cases of death not associated with EC and calculated a multivariate Gray competing risk regression model (Table 4) and found that patients with AC had a better survival rate than those with SCC (subdistribution hazard ratio [SHR] = 0.704, 95% CI: 0.435–0.853) and that the histology classification affected CSS but not deaths unrelated to EC (Fig. 4). Age ($P = .0001$), tumor size ($P < .001$), lymph node examined ($P < .001$), pathology grade ($P = .0054$) and metastasis ($P < .001$) were identified as independent factors related to CSS.

3.4. Comparison of LNM and survival between the SCC and AC groups after matching

For the analysis of associations between LNM and histology, we matched 1366 patients with negative LNM and 1366 patients with positive LNM. As shown in Figure 5 and Table 5, the SMD of all matched characteristics was <0.1, and the *P*-value was >.05. Then, we performed univariate logistic regression to explore the relation between LNM and histology type and found a negative correlation between them (OR = 0.985, 95% CI: 0.844–1.149, $P = .844$) (Fig. 6). To compare survival between patients with SCC and AC, we matched 972 SCC patients with 972 AC patients and performed univariate Cox regression. As shown in Figure 7 and Table 6, we found that most of the matched factors were balanced, which

Table 6

Patients' demographics, clinical characteristics at diagnosis after propensity score matching for analyzing the association between CSS and histology.

Variables	Total (%)	Squamous cell carcinoma	Adenocarcinoma	*P*-value
n	1944	972	972	
Age				.2492
<60	425 (21.86%)	202 (20.78%)	223 (22.94%)	
≥60	1519 (78.14%)	770 (79.22%)	749 (77.06%)	
Race				.36
White	1627 (83.69%)	783 (80.56%)	844 (86.84%)	
Black	218 (11.21%)	154 (15.84%)	64 (6.58%)	
Other	99 (5.1%)	35 (3.6%)	64 (6.58%)	
Sex				.027
Male	1339 (68.88%)	692 (71.2%)	647 (66.57%)	
Female	605 (31.12%)	280 (28.8%)	325 (33.43%)	
Pathology grade				.55
Well/Moderately	1047 (53.86%)	530 (54.53%)	517 (53.19%)	
Poorly and undifferentiated	897 (46.14%)	442 (45.47%)	455 (46.81%)	
Lymph node metastasis				.596
No	1295 (66.62%)	653 (67.18%)	642 (66.05%)	
Yes	649 (33.38%)	319 (32.82%)	330 (33.95%)	
Metastasis				.644
No	1425 (73.3%)	717 (73.77%)	708 (72.84%)	
Yes	519 (26.7%)	255 (26.23%)	264 (27.16%)	
Tumor size				.6207
≤2 cm	496 (25.51%)	240 (24.69%)	256 (26.34%)	
≤3 cm	312 (16.05%)	164 (16.87%)	148 (15.23%)	
≤5 cm	572 (29.42%)	286 (29.42%)	286 (29.42%)	
>5 cm	564 (29.02%)	282 (29.02%)	282 (29.02%)	
Regional nodes examined				.565
≤13	1717 (88.32%)	872 (89.71%)	845 (86.93%)	
>13	227 (11.68%)	100 (10.29%)	127 (13.07%)	
Historic stage				.615
Localized	1093 (56.22%)	552 (56.8%)	541 (55.66%)	
Regional	272 (14%)	140 (14.4%)	132 (13.58%)	
Distant	579 (29.78%)	280 (28.82%)	299 (30.76%)	

CSS = cancer-specific survival.

was demonstrated by the SMD value of <0.1 and the *P*-value. The Kaplan–Meier curves and cumulative events plots of OS and CSS showed that SCC was a stronger risk factor for poor prognosis than AC (Fig. 8).

4. Discussion

With the increased awareness of surveillance of EC, an increasing number of cases of EC in the early stage are being found, which has led to a preference for endoscopic therapy such as EMR and ESD.[7,23] EMR or ESD can be safely applied when complete resection is feasible and patients have a low risk for LNM.[24,25] Therefore, as Fariha H. et al concluded, the risk of LNM must be assessed in combination with other clinical factors such as tumor size, histology, pathology grade and lymph vascular invasion.[14] To the best of our knowledge, the present study was the first to comprehensively explore the differences in LNM and survival between SCC and AC patients, and it included many patients (a total of 4764 patients) with EC at the T1 stage. Using the PSM method, we demonstrated that patients with SCC have a similar risk of LNM as patients with AC, and we found that patients with SCC had poorer CSS and OS, which was similar with the results of some retrospective studies, by performing Gray competing risk regression model and PSM.[14]

LNM is generally considered as an important indicator to determine which methods should be selected among endoscopic therapy, surgery and radiotherapy for patients.[9,26] In our study, at the beginning of the analysis, we found that the histology type had an obvious correlation with LNM by multivariate logistic regression analysis; additionally, patients with AC had a lower risk of LNM (OR = 0.654, 95% CI: 0.574–0.747), which was consistent with results from previous studies.[14,26] However, the PSM results suggested there was no association between LNM and histology type among 1366 SCC patients matched with 1366 AC patients (OR = 0.985, 95% CI: 0.844–1.149, *P* = .844), which was consistent with results from other studies.[17,27] Contradictory results have been reported by other studies that focused on the potential risk factors of LNM: 3 studies[26,28,29] found that patients with SCC were more likely to have LNM than patients with AC, but 2 studies[16,30] found that patients with AC had a higher risk of LNM; moreover, some studies[17,31] determined that the histology type was not associated with LNM. The reasons leading to the contradictory results may be due to the clinical heterogeneity, different samples and racial disparities.[17] For our results, a comprehensive analysis was performed using univariate and multivariate logistic regression after PSM, which indicated that the histology type was not associated with LNM.

Many studies have suggested that patients with AC have a better prognosis than those with SCC.[5,32] We performed multivariate Cox regression analysis and found that the histology type of SCC was a risk factor for prognosis, which was confirmed using PSM to adjust for other confounding factors. Additionally, we calculated a multivariate competing risk model that could avoid bias derived from the competing events and found that SCC remained a risk factor for survival of EC in the T1 stage.

Finally, our study has some limitations to be discussed. First, due to the lack of some information, such as the depth of invasion, we could not explore the differences in invasive ability between SCC and AC. Second, we only focused on the

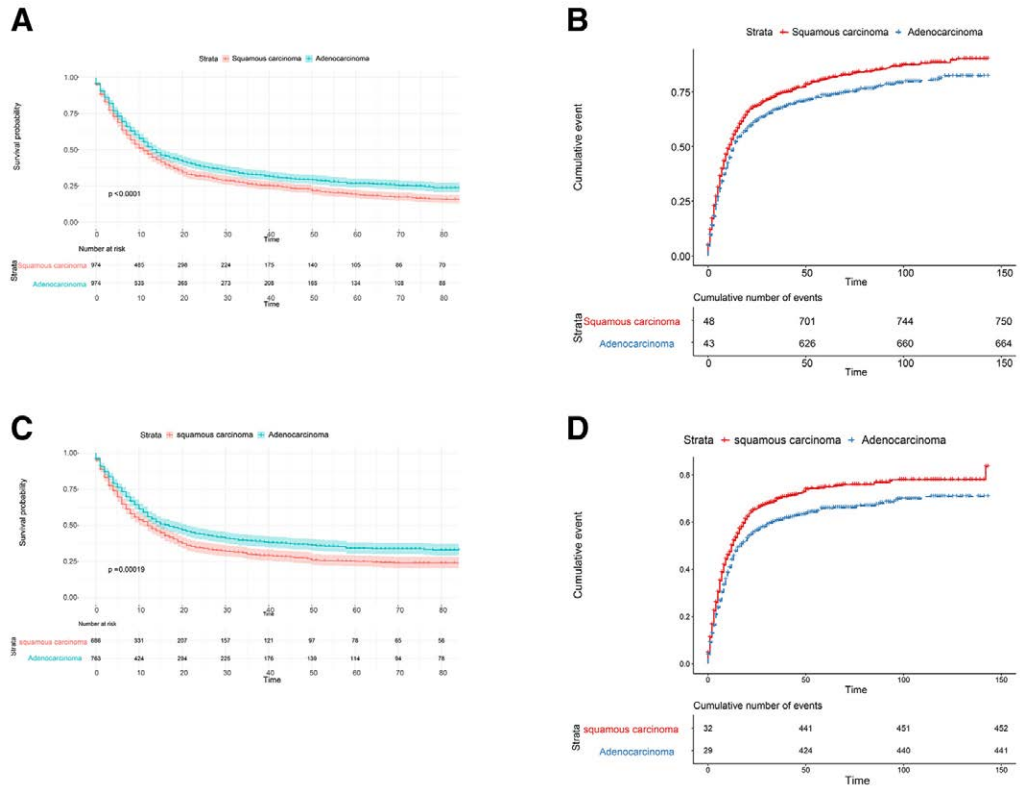

Figure 6. The distribution of patients with different histology in negative LNM and positive LNM groups after PSM. LNM = lymph node metastasis, PSM = propensity score matching.

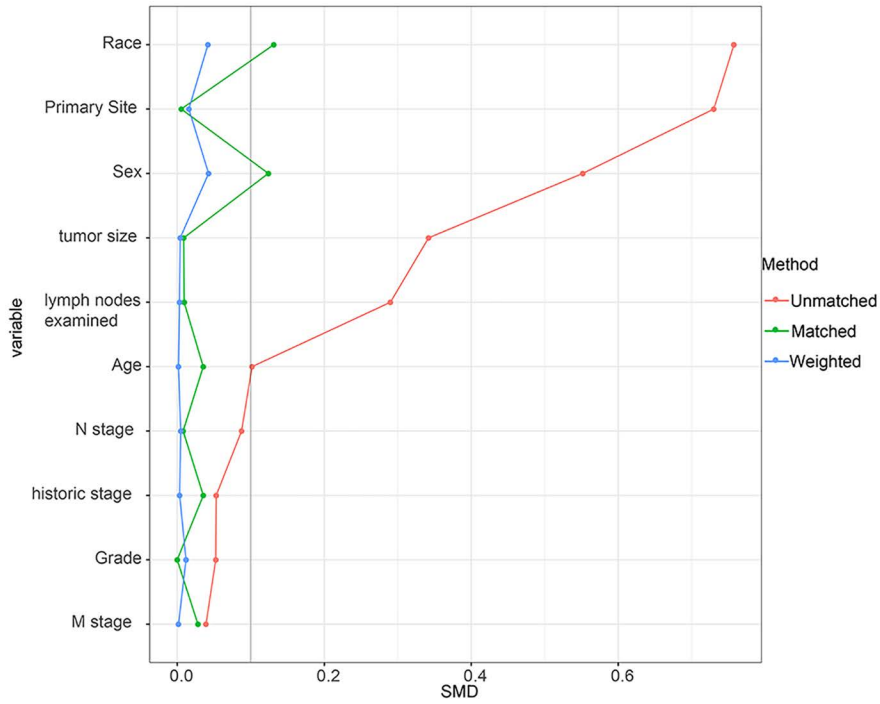

Figure 7. Standardized mean difference across covariates before and after PSM was showed while exploring the association between CSS and histology. CSS = cancer-specific survival, PSM = propensity score matching.

OS and CSS of patients without considering cancer recurrence and disease-free survival, making our results limited for clinical assessment. However, a competing risk model was developed to assess the value of histology for predicting survival by considering death not caused by cancer. Finally, information on lymphatic vessel invasion (LVI), which is a powerful predictor of

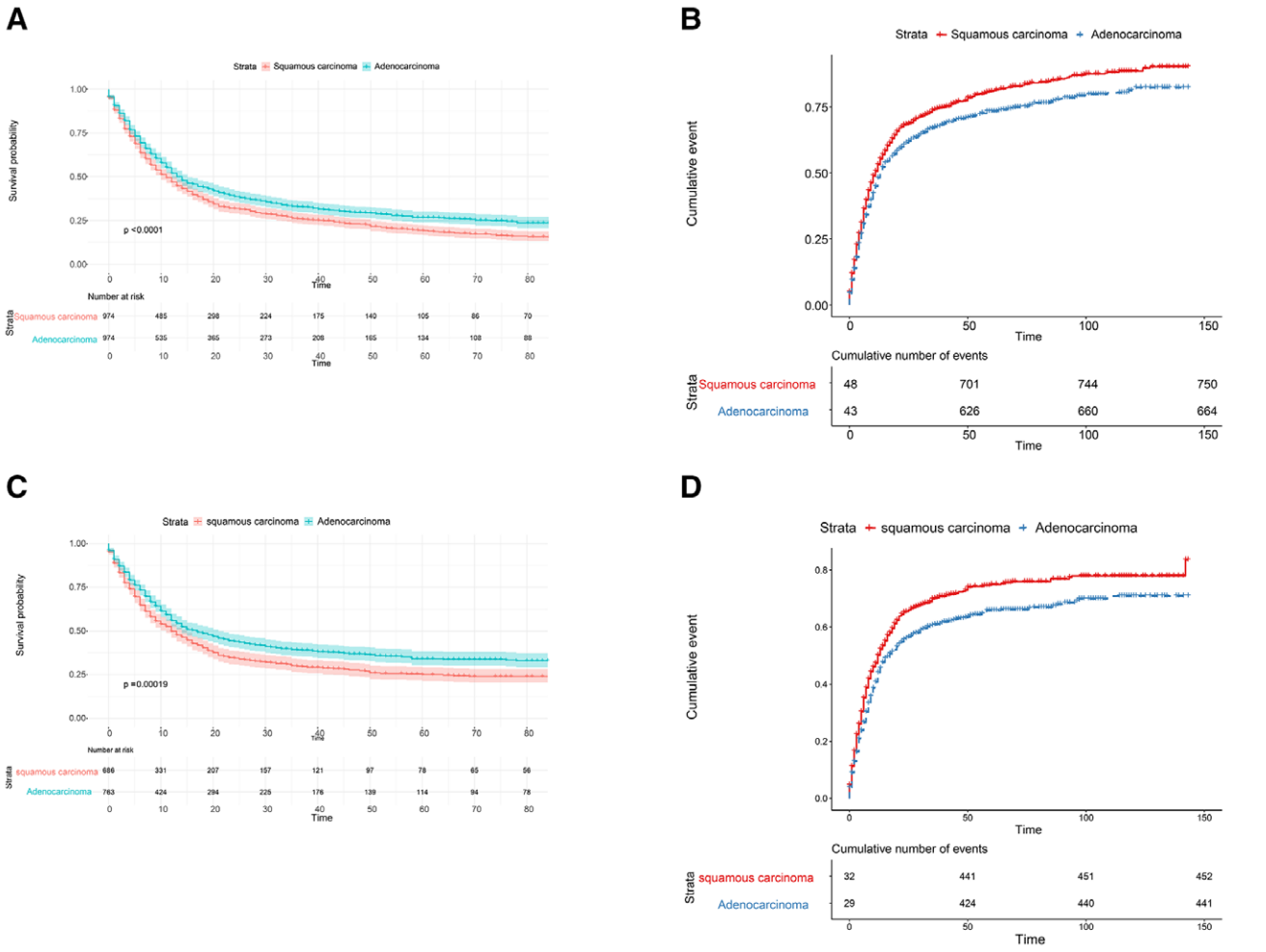

Figure 8. Comparison of survival and cumulative probability for 1944 patients between SCC and AC after PSM. (A–B) the plot of OS and cumulative probability of OS. (C–D) the plot of CSS and cumulative probability of CSS. AC = adenocarcinoma, CSS = cancer-specific survival, OS = overall survival, PSM = propensity score matching, SCC = squamous cell carcinoma.

endoscopic therapy, was not provided by the SEER database, which motivates us to investigate the association between LVI and histology type by comprehensive analysis in the future. Therefore, determination of SCC or AC for patients with EC at the T1 stage requires caution.

In conclusion, our results revealed that compared to AC, SCC was characterized by a similar likelihood of LNM and poorer survival.

Author contributions

Data analysis: Hui Liu.
Data curation: Hui Liu.
Investigation: Hui Liu.
Methodology: Hui Liu.
Project administration: Jun Meng.
Supervision: Jun Meng.
Validation: Jun Meng.
Writing – original draft: Hui Liu.

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