Original Article

Population-based analysis of esophageal large cell neuroendocrine carcinoma between 2004 and 2015

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Background: Esophageal large cell neuroendocrine carcinoma (ELCNC) seems a rarely gastrointestinal malignancy. By far, its clinicopathological characteristics and prognosis have not been deeply studied.

Methods: The data of patients having ELCNC was extracted from the Surveillance, Epidemiology, and End Results (SEER) database, then assessed and compared with information from patients with esophageal small cell neuroendocrine carcinoma (ESCNC) or esophageal squamous cell carcinoma (ESCC). We used univariate and multivariate analyses to accurately detect independent prognostic factors.

Results: The data of 36 patients for ELCNC were obtained between 2004 and 2015. Compared with patients with ESCNC and ESCC, the mean survival time of ECLNC patients was worse than those with ESCC, while similar to ESCNC. Thus, ELCNC had significantly different clinicopathological characteristics compared to ESCNC and ESCC. Univariate and multivariate analyses revealed that age (P=0.001) and M stage (P=0.004) were independent prognostic factors.

Conclusions: ELCNC is a rare subtype of esophageal neuroendocrine carcinoma. The clinicopathological features differ from those of other esophageal carcinomas. Prognosis may be closely related to age and M stage.

Keywords: Esophageal large cell neuroendocrine carcinoma (ELCNC); SEER database; prognosis; overall survival (OS)

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Introduction

Esophageal carcinoma generally has a high mortality rate and poor prognosis, with a dramatic increase in incidence of approximately 572,000 new cases and 509,000 deaths detected per year worldwide for 36 cancer types, in 185 countries. Approximately 70% of the cases occur in males, and a nearly 2- to 3-fold difference in mortality rates is noted among the sexes (1). In addition to small cell carcinoma of esophageal cancers, esophageal large cell neuroendocrine carcinoma (ELCNC) is accepted as a rarely malignant, esophageal neuroendocrine tumor (2,3), which accounts for 3.80% to less than 30% of primary esophageal neuroendocrine carcinomas (4,5).

ELCNC has unique clinicopathological features. According to the currently used classification, the pathological manifestations of esophageal large cell carcinoma are mainly large cancer cells, more mononuclear

or multinucleated giant cells, and thus have higher mitotic cell numbers (6,7). In this study, we utilized the SEER (Surveillance, Epidemiology, and End Results) database to compare the clinicopathological characteristics between ELCNC, esophageal small cell neuroendocrine carcinoma (ESCNC), and esophageal squamous cell carcinoma (ESCC) to better predict the prognoses of patients by analyzing the related risk factors of ELCNC.

Methods

Data extraction

The comprehensive data of ELCNC patients diagnosed from 2004 to 2015 were extracted from the SEER database (http://seer.cancer.gov/) using SEER*Stat software version 8.3.5 (https://seer.cancer.gov/seerstat/). The study recruited patients according to the third edition (ICD-O-3) histology code 8013/3, as determined by the International Classification of Diseases for Oncology. Each selected patient had histopathologically proven malignant ELCNC. Patients with non-primary tumors, less detailed personal features, and incomplete follow-up data were excluded.

Variables

Race, age, sex, insurance type, marital status, tumor size, number of malignant tumors, grade, the American Joint Committee on Cancer (AJCC) stage of the primary cancer, therapeutic methods used, vital status, year of diagnosis, and survival data of selected patients were included in the SEER database. The TNM staging system was confirmed according to the AJCC seventh edition criteria. Survival data [overall survival (OS)] meant the time from the date of diagnosis until the date of death from any reason, or the point of the last follow-up.

Statistical analysis

Multi-class variables such as race, age, or tumor size were contrasted by chi-square tests between ELCNC, ESCNC, and ESCC, while two categorical variables or ordered variables like sex, tumor grade, or stage were compared through rank sum tests. Log-rank tests and Kaplan-Meier analyses were applied for univariate analyses, aiming to construct survival curves. Furthermore, Cox model tests were used for multivariate analyses to further predict the progress of ELCNC. All the analyses were conducted by using SPSS (version 25) software (SPSS, Chicago, IL, USA), and $P<0.05$ was regarded as statistically significant. All were two-sided tests. Survival curves were generated using R language (v3.5.1) software, and the primary packages were Survival and Survminer (8,9).

Results

Comparisons of clinicopathological characteristics between ELCNC, ESCNC, and ESCC

In total, 36 patients with ELCNC, 218 patients with ESCNC, and 7,901 patients with ESCC were enrolled between 2004 and 2015 after careful screening. As shown in *Table 1*, 31 males and 5 females were included among the ELCNC group, with the majority ranging in age 60–80 years and a median age of 66.75 years. Thirty-three (91.7%) of the patients were Caucasian. Most ELCNC patients (58.4%) were AJCC stage IV, 8.3% were stage I, 13.9% were stage II, and 8.3% were stage III. Patients diagnosed as ELCNC were statistically less commonly female patients ($P=0.007$), had larger tumor sizes ($P=0.010$), had more poorly or undifferentiated grades ($P=0.030$), and more N+ disease ($P<0.001$) than those of ESCNC patients. Nevertheless, the risk factors of race ($P=0.004$), sex ($P=0.009$), having insurance ($P<0.001$), marital status ($P=0.026$), tumor size ($P=0.003$), tumor grade ($P<0.001$), AJCC 7th stage ($P<0.001$), surgery ($P<0.001$), and radiotherapy ($P<0.001$) indicated significant differences between ELCNC versus ESCC.

Analyses of ELCNC prognostic factors

Survival data indicated that the 1- and 3-year survival rates of ELCNC were 27.8% and 8.3%, respectively. No patients survived for more than 5 years. There were significant differences in the progresses between ELCNC, ESCNC and ESCC using a calibration curve ($P=0.00042$) especially for ELCNC and ESCC ($P=0.0058$) (*Figure 1* and *Figure S1A*). Nevertheless, as suggested by the data shown in *Figure S1B*, the survival times of ELCNC and ESCNC were similar ($P=0.2$).

Specific prognostic factors in patients with ELCNC were investigated by univariate analyses. As shown in *Figure 2*, age ($P=0.015$), AJCC 7th stage ($P=0.039$), and M stage ($P=0.02$) with prognoses of ELCNC were proven to be significantly different. Older age and higher AJCC 7th stage were correlated with shorter survival time.

Table 1 Comparison of the clinicopathological characteristics between esophageal large cell neuroendocrine carcinoma (ELCNC) esophageal small cell neuroendocrine carcinoma (ESCNC), and esophageal squamous cell carcinoma (ESCC)

Characteristics	ELCNC	ESCNC	P value	ESCC	P value
Race, n (%)			0.216		0.004
White	33 (91.7)	173 (79.4)		5,160 (65.3)	
Black	2 (5.5)	28 (12.8)		1,931 (24.4)	
Other	1 (2.8)	17 (7.8)		810 (10.3)	
Age, n (%)			0.365		0.659
<40 years	0 (0.0)	0 (0.0)		21 (0.3)	
40–60 years	12 (33.3)	49 (22.5)		1,975 (25.0)	
60–80 years	18 (50.0)	129 (59.2)		4,661 (59.0)	
>80 years	62 (16.7)	40 (18.3)		1,244 (15.7)	
Sex, n (%)			0.007		0.009
Male	31 (86.1)	138 (63.3)		5,163 (65.3)	
Female	5 (13.9)	80 (36.7)		2,738 (34.7)	
Insurance, n (%)			0.084		<0.001
No	12 (33.3)	67 (30.7)		355 (4.5)	
Yes	24 (66.7)	151 (69.3)		7,546 (95.5)	
Marital status, n (%)			0.026		0.026
No	30 (83.3)	95 (43.6)		4,102 (51.9)	
Yes	6 (16.7)	123 (56.4)		3,799 (48.1)	
Tumor size, n (%)			0.010		0.003
0–70 mm	10 (27.8)	107 (49.1)		4,019 (50.8)	
70+ mm	10 (27.8)	25 (11.5)		961 (12.2)	
Unknown	16 (44.4)	86 (39.4)		2,921 (37.0)	
No. of malignant tumors, n (%)			0.588		0.835
1	24 (66.7)	159 (72.9)		5,569 (70.5)	
2	8 (22.2)	47 (21.6)		1,765 (22.3)	
3	3 (8.3)	10 (4.6)		437 (5.5)	
4	1 (2.8)	2 (0.9)		130 (1.7)	
Grade, n (%)			0.030		<0.001
Well differentiated	0 (0.0)	2 (0.9)		340 (4.3)	
Moderately differentiated	0 (0.0)	1 (0.5)		3,033 (38.4)	
Poorly differentiated	18 (50.0)	72 (33.0)		2,851 (36.1)	
Undifferentiated	10 (27.8)	47 (21.6)		54 (0.7)	
Unknown	8 (22.2)	96 (44.0)		1,623 (20.5)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	ELCNC	ESCNC	P value	ESCC	P value
AJCC 7th stage, n (%)			0.357		<0.001
I	3 (8.3)	28 (12.8)		1,344 (17.0)	
II	5 (13.9)	20 (9.2)		1,680 (21.3)	
III	3 (8.3)	35 (16.1)		2,288 (29.0)	
IV	21 (58.4)	124 (56.9)		2,261 (28.6)	
Unknown	4 (11.1)	11 (5.0)		328 (4.2)	
T stage, n (%)			0.813		0.136
T1	10 (27.8)	61 (28.0)		2,311 (29.2)	
T2	2 (5.5)	5 (2.3)		795 (10.1)	
T3	8 (22.2)	42 (19.3)		2,372 (30.0)	
T4	6 (16.7)	39 (17.9)		1,365 (17.3)	
Tx	6 (27.8)	71 (32.6)		1,058 (13.4)	
N stage, n (%)			<0.001		<0.001
N0	1 (2.8)	75 (34.4)		3,259 (41.2)	
N1	12 (33.3)	109 (50.0)		3,586 (45.4)	
N2	19 (52.8)	7 (3.2)		517 (6.5)	
N3	3 (8.3)	0 (0.0)		138 (1.7)	
Nx	1 (2.8)	27 (12.4)		401 (5.1)	
M stage, n (%)			0.870		<0.001
M0	15 (41.7)	94 (43.1)		5,640 (71.4)	
M1	21 (58.3)	124 (56.9)		2,261 (28.6)	
Surgery, n (%)			<0.001		<0.001
No	5 (13.9)	202 (92.7)		6,683 (84.6)	
Yes	31 (86.1)	16 (7.3)		1,218 (15.4)	
Radiotherapy, n (%)			<0.001		<0.001
No	23 (63.9)	201 (92.2)		2,688 (34.0)	
Yes	13 (36.1)	17 (7.8)		5,213 (66.0)	
Chemotherapy, n (%)			0.751		0.493
No	11 (30.6)	61 (28.0)		2,849 (36.1)	
Yes	25 (69.4)	157 (72.0)		5,052 (63.9)	

ELCNC, esophageal large cell neuroendocrine carcinoma; ESCNC, esophageal small cell neuroendocrine carcinoma; ESCC, esophageal squamous cell carcinoma.

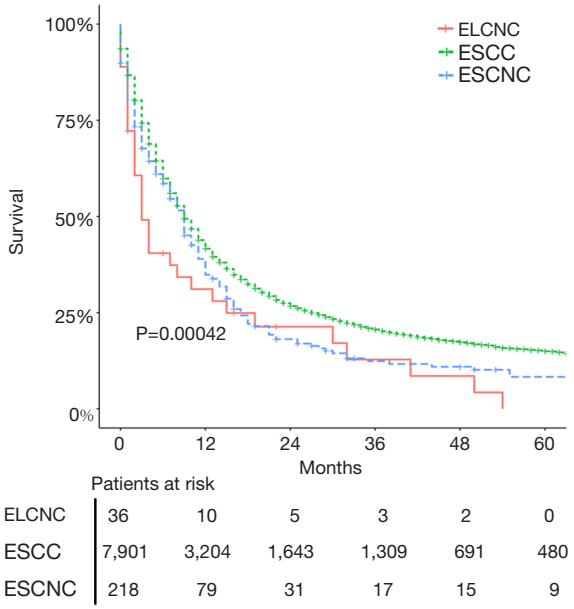

Figure 1 The survival curve between esophageal large cell neuroendocrine carcinoma (ELCNC), esophageal squamous cell carcinoma (ESCC) and esophageal small cell neuroendocrine carcinoma (ESCNC).

Nevertheless, total univariate analyses did not show that patients who accepted any therapy had a better prognosis than patients who did not.

As shown in *Table 2*, a more detailed analysis indicated that the risk factors of age (P=0.001) and M stage (P=0.004) were significantly different as assessed by univariate analyses, which were confirmed to be independent factors in accordance with multivariate analyses. Therefore, older-aged patients and higher M stages may lead to the worse prognoses, according to multivariate analyses data.

Discussion

Few cases of ELCNC have been reported in the literature. This may be a result of the poorly developed neuroendocrine system in the esophagus (10,11). Currently, ELCNC is diagnosed according to the presence of neuroendocrine (NE) morphology, especially when more than 20% of tumor cells express NE markers (7).

Due to the poor prognosis of ELCNC, the general survival time is no more than 5 years. Similar to previous studies (12,13), we indicated that the prognosis of ELCNC was worse than for ESCC (P=0.0058), with no significant difference of ESCNC (P=0.2). It is worth mentioning that ELCNC and ESCNC, forming part of the spectrum of neuroendocrine tumors, show later tumor differentiation and TNM stage relatively. Therefore, the prognosis is worse than squamous cell carcinoma.

We found from the SEER database that there were significant differences between ELCNC, ESCNC, and ESCC in terms of sex, marital status, tumor size, tumor grade, N stage, surgery, and radiotherapy. In addition to this, the risk factors of race, insurance, total TNM stage, and M stage differed between ELCNC and ESCC. Clinically, ELCNC and ESCNC could be distinguished by immunohistochemistry, so it is not difficult to observe similarities and differences in biological characteristics between them (14). However, considering the content of neuroendocrine cells in tumor tissues and the rare number of cases, several clinicopathological features such as tumor size and grade of the two esophageal neuroendocrine tumors could be used in our study. Furthermore, we also detected that age, TNM stage, and M stage were independent influencing factors for the prognosis of patients with ELCNC, using univariate analyses. Thus, only age and M stage remained after multivariate analyses. All the patients from our study were middle-aged and older (>40 years old), and the average age of onset was approximately 65 years of age, which was consistent with previous literature (11,15). Because mucosal glands of the distal esophagus typically contain more neuroendocrine cells, as shown by endoscopic findings, ELCNCs are mainly located in the lower third of the esophagus (11,16). Our research also suggested that most cases were in the advanced stage, in agreement with the four phases of TNM staging. Consequently, the possibility of distant metastasis was greater.

At present, due to the low incidence of ELCNC, prospective and randomized clinical trials of optimal treatments are not easily accomplished. Given the similarities of histological and clinical features between ELCNC and ESCNC, studies have shown that multimodal therapies should be used in ELCNC, which normally is the same regimen used for SCLC (17,18). To some extent, radical surgery is still considered an important part of the comprehensive treatment regimen for the limited period of ELCNC. Medgyesy *et al.* demonstrated that the survival time of the radiotherapy and chemotherapy group was also lower than that of the surgery group (10). However, as a systemic disease, most patients with ELCNC have distant micrometastases and regional lymph node metastasis at the time of surgery. Therefore, surgery alone may not completely eradicate the tumor. Raja *et al.* conducted a large sample

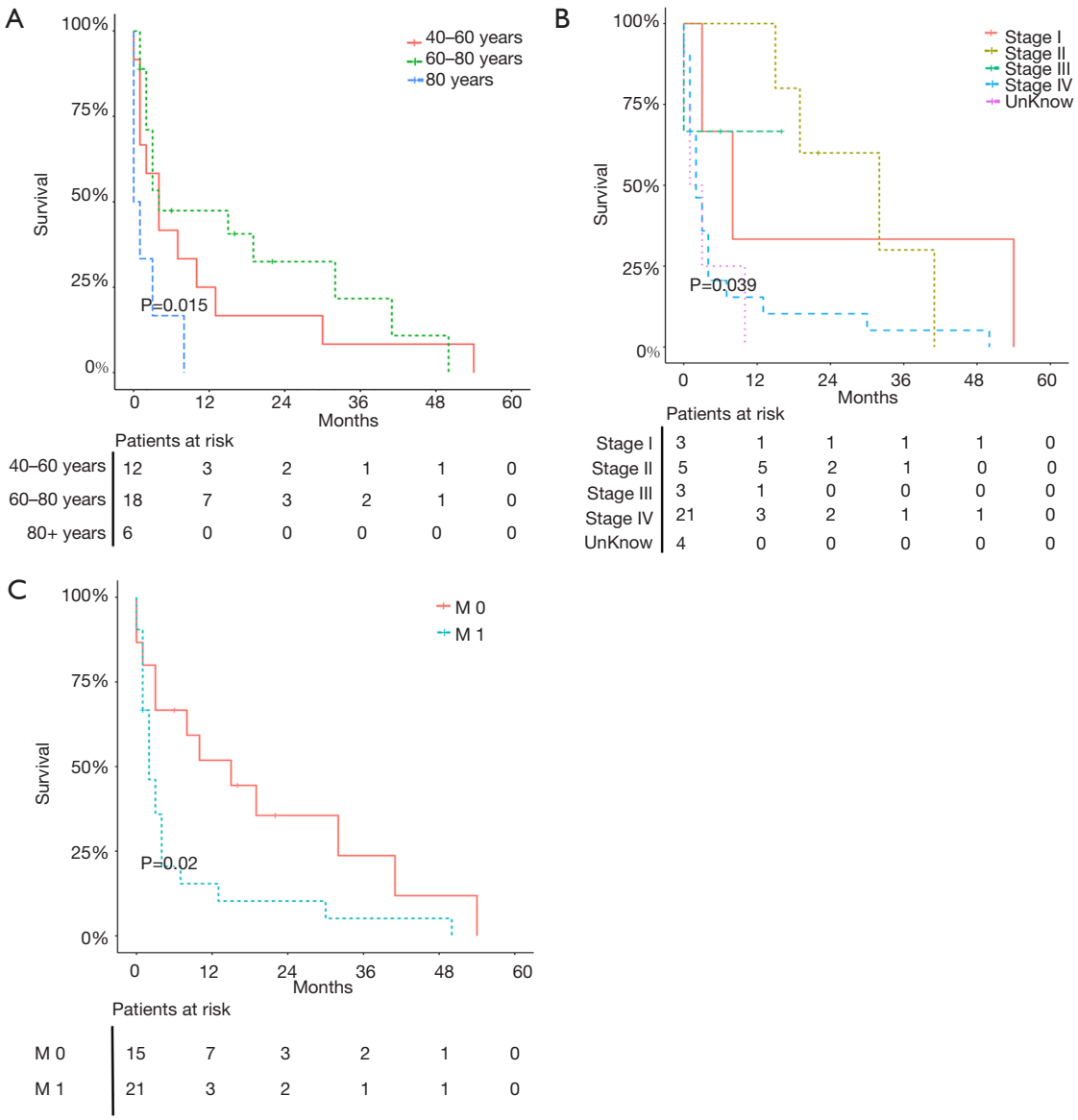

Figure 2 Kaplan-Meier estimate of overall survival in patients treated by (A) age, (B) AJCC TMN stage (C) AJCC M stage.

meta-analysis and concluded that chemotherapy should be the most basic treatment, and chemotherapy combined with surgery or chemotherapy combined with radiotherapy might bring further survival benefits (19). However, resulted from the small sample size, there was no significant difference in the prognosis of all therapeutic treatments in our study.

Some reports on targeted therapies (such as bevacizumab, nimotuzumab, and thalidomide) have been applied in SCLC patients, but they have not brought a clear benefit. The effect of targeted therapy in ELCNC is rarely reported and requires further study; however, this could be a treatment option for ELCNC (20,21).

Conclusions

Our study showed esophageal large cell neuroendocrine carcinoma as having independent clinicopathological features that were different from esophageal small cell carcinoma and esophageal squamous cell carcinoma. We further demonstrated the main related risk factors for the prognosis of ELCNC, and survival curves predicting long-term progress were further analyzed.

Table 2 Univariate and multivariate Cox proportional hazards analysis

Patient characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Race		0.117	–	–
White	Reference		–	–
Black	3.889 (0.825–18.332)	0.086	–	–
Other	0.609 (0.081–4.578)	0.630	–	–
Age		0.015		0.001
40–60 years	Reference		Reference	
60–80 years	0.736 (0.332–1.631)	0.450	0.694 (0.296–1.626)	0.400
80+ years	2.762 (0.980–7.787)	0.055	8.140 (2.344–28.268)	0.001
Sex		0.944	–	–
Male	Reference		–	–
Female	0.967 (0.363–2.573)		–	–
Insurance		0.566	–	–
No	Reference		–	–
Yes	1.311 (0.497–3.464)		–	–
Marital status		0.549	–	–
No	Reference		–	–
Yes	0.806 (0.384–1.692)			
Tumor size		0.719	–	–
0–70 mm	Reference		–	–
70+ mm	1.387 (0.527–3.653)	0.508	–	–
Unknown	1.029 (0.425–2.491)	0.950	–	–
No. of malignant tumors		0.051		
1	Reference	0.958	–	–
2	1.023 (0.430–2.433)	0.035	–	–
3	4.054 (1.105–14.881)	0.983	–	–
4	<0.001	<0.001	–	–
Grade		0.375	–	–
Poorly differentiated	Reference	0.993	–	–
Undifferentiated	1.582 (0.677–3.697)	0.290	–	–
Unknown	1.669 (0.666–4.185)	0.275	–	–
AJCC 7th stage		0.039		0.752
I	Reference		Reference	
II	1.008 (0.180–5.659)	0.993	0.681 (0.033–14.017)	0.803
III	1.048 (0.092–11.946)	0.970	0.492 (0.016–15.318)	0.686
IV	3.402 (0.776–14.920)	0.105	2.279 (0.127–41.042)	0.576
Unknown	4.695 (0.815–27.038)	0.083	0.992 (0.085–11.523)	0.995

Table 2 (*continued*)

Table 2 (*continued*)

Patient characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
T stage		0.133	–	–
T1	Reference		–	–
T2	0.462 (0.058–3.695)	0.467	–	–
T3	0.647 (0.226–1.854)	0.418	–	–
T4	2.522 (0.844–7.539)	0.098	–	–
Tx	1.005 (0.396–2.548)	0.992		
N stage		0.203	–	–
N0	Reference		–	–
N1	0.408 (0.049–3.377)	0.406	–	–
N2	0.801 (0.105–6.127)	0.830	–	–
N3	0.277 (0.017–4.530)	0.368	–	–
Nx	2.280 (0.135–38.379)	0.567		
M stage		0.020		0.004
M0	Reference		Reference	
M1	2.314 (1.083–4.947)	0.020	5.128 (1.668–15.772)	0.004
Surgery		0.221	–	–
No	Reference		–	–
Yes	0.497 (0.150–1.646)	0.221	–	–
Radiotherapy		0.370	–	–
No	Reference		–	–
Yes	0.533 (0.185–1.533)	0.213	–	–
Chemotherapy		0.149	–	–
No	Reference		–	–
Yes	0.587 (0.273–1.263)	0.149	–	–

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All the data files were obtained with permission from the SEER database, which is publicly available, therefore approval was not necessary by the local ethics committee.

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Supplementary

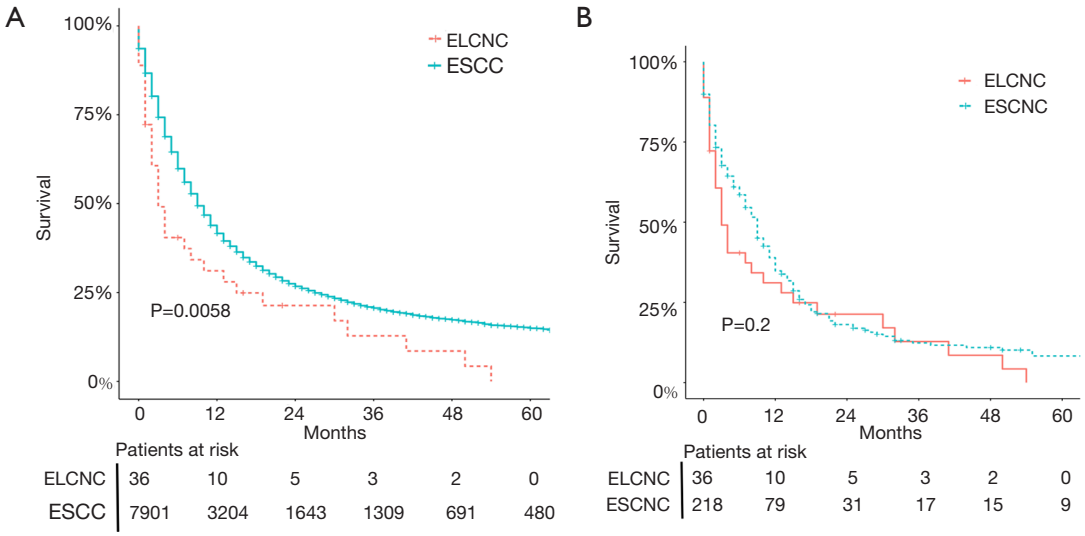

Figure S1 Comparison of the survival curves of different types of esophageal cancer. (A) The survival curve between esophageal large cell neuroendocrine carcinoma (ELCNC) and esophageal squamous cell carcinoma (ESCC); (B) the survival curve of esophageal large cell neuroendocrine carcinoma (ELCNC) and esophageal small cell neuroendocrine carcinoma (ESCNC).