Original Article

Prognostic factors and treatment strategies of limited-stage primary esophageal small-cell carcinoma—a SEER database analysis

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Background: Primary esophageal small-cell carcinoma (PESC) is a rare tumor with poor efficacy, and there is currently no standardized treatment method. Our aim is to explore the prognostic factors and possible optimal treatment modalities for limited-stage PESC.

Methods: We retrospectively searched the Surveillance, Epidemiology, and End Results (SEER) database from 1975 to 2019 for data of patients with limited-stage PESC. Kaplan-Meier method was used to plot survival curves, calculate survival rates, and Log-rank was used to test the differences among survival curves. Prognostic factors were explored through univariate and multivariate Cox regression survival analyses; Cox regression survival analysis was also conducted to analyze the risk of death among treatment groups and compare the survival differences among each treatment group. The non-single treatment (ST) group was defined as the comprehensive treatment (CT) group and it was compared against the ST group.

Results: A total of 186 cases of limited-stage PESC were included in the study, there were differences in survival time among different groups due to differences in age, year, median household income, and N stage (P<0.001, P=0.041, P=0.002, P=0.001). The median overall survival (mOS) of the surgical group (19 months) was longer than that of the nonsurgical group (11 months) (P=0.01). The mOS of the chemotherapy group (16 months) was longer than that of the non-chemotherapy group (4 months) (P<0.001). The mOS of the radiotherapy group (16 months) was longer than that of the non-radiotherapy group (8 months) (P<0.001). Univariate analysis showed that age ≥80 years (P=0.006), year (1997–2007) (P=0.01), year (2008–2019) (P=0.01), N2 (P=0.003), surgery (P=0.02), radiotherapy (P<0.001), and chemotherapy (P<0.001) were prognostic factors affecting overall survival (OS) in limited-stage PESC patients. Multivariate analysis showed that SEER stage (P=0.02), age (P=0.007), radiotherapy (P<0.001), surgery (P=0.006), and chemotherapy (P<0.001) were independent prognostic factors affecting OS in patients of limited-stage PESC. Prognosis was better in the non-monotherapy group than in each monotherapy group. The CT group is superior to the ST group (P<0.001). The surgery combined with chemotherapy (SC) group had the longest mOS and the highest reduced risk of death, but there was no statistical difference.

Conclusions: SEER stage, age, radiotherapy, chemotherapy, and surgery were independent prognostic factors in limited-stage patients; CT outperformed ST; the SC group had the longest median survival, but showed no statistical difference.

Keywords: Primary esophageal small-cell carcinoma (PESC); limited-stage; Surveillance, Epidemiology, and End Results database (SEER database); treatment strategy; prognostic factor

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Introduction

Primary esophageal small-cell carcinoma (PESC) is one of the poorly differentiated esophageal neuroendocrine carcinoma (1), first discovered and reported by McKeown in 1952 (2); the incidence rate of PESC is low, accounting for 0.05–4% of esophageal carcinoma (3,4), so there is still no prospective randomized controlled study. Its malignant degree is high, treatment effect is poor. Of the 515 cases with PESC reported by Li *et al.* (5), the 1-, 2-, and 5-year survival rates were only 31.5%, 14.7%, and 6.0%, respectively, with a median survival of 7.0 months. A single-centre study by Miao *et al.* included 113 patients and showed that the 1-year and 3-year survival rates were 45% and 12%, respectively (4). The 1-, 3-, and 5-year survival rates of 100 PESC patients reported by Xiayimaierdan *et al.* (6) were 57.0%, 18.0%, and 11.0%, respectively, with a median survival of 13.8 months. Most patients metastasize and die within 1 year; even limited-stage patients have a poor prognosis. Verma *et al.* reported 323 cases of non-metastatic PESC, with a median overall survival (mOS) of 21 months in the surgery group, 18 months in the chemoradiotherapy (CR) group, and 10 months in the chemotherapy alone group (7). Its treatment mode has not yet been established. Treatments are mostly based on small cell lung cancer, but that is not necessarily scientific. Recent studies have found that its genetic background is very different (8,9). In recent years, it has been reported that the survival time of the combined treatment group mainly based on surgery is longer than that of the CR group, but it is not known whether it is due to insufficient cases or other reasons, showing no statistical difference (5,7). This is also different from small cell lung cancer. Therefore, there is an urgent need to explore treatment modalities for PESC, particularly for patients with limited-stage PESC, where timely and correct treatment may be more likely to prolong survival. The Surveillance, Epidemiology, and End Results (SEER) database is a public database established by the National Cancer Institute of the United States. Its data represents about 50 percent of the U.S. population. The data are large and reliable. This paper intends to search and analyze the basic characteristics, treatment approaches, and prognosis of patients with limited-stage PESC in the SEER database, explore and summarize prognostic factors and more appropriate treatment approaches for such patients, and provide certain references for clinical use. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-311/rc).

Highlight box

Key findings

- Limited-stage primary esophageal small-cell carcinoma (PESC) also requires a comprehensive treatment (CT) approach.

What is known and what is new?

- The treatment mode of PESC is controversial.
- For limited-stage PESC, any of the currently available combination therapies is preferable to a single treatment modality, and surgery combined with chemotherapy may be the optimal treatment modality.

What is the implication, and what should change now?

- For limited-stage PESC, local treatment alone (surgery or radiotherapy) or systemic treatment alone (chemotherapy) is not enough; we also need CT for limited-stage PESC.

Methods

Data source and participants

This is a retrospective population cohort study performed using data obtained from the SEER database. Case identification and data collection for the SEER program began in 1973 with diagnoses in several geographic areas of the United States and its possessions. Over the past 50 years, the geographic areas and population coverage have expanded and now represent nearly 50% of the United States (https://seer.cancer.gov/). We selected three datasets [Incidence-SEER Research Plus data, 8 Registries (1975–2019), Incidence-SEER Research Plus data, 12 Registries (1992–2019), Incidence-SEER Research Plus data, 17 Registries (2000–2019)] published by the SEER database to cover nearly all tumor patients in this database. SEER*Stat software (SEER*Stat, v8.4.0.1) was used to retrieve our study population by tumor site and pathology type between 1975 and 2019. Selection statement: site recode ICD-0-3 = esophagus, histologic type ICD-0-

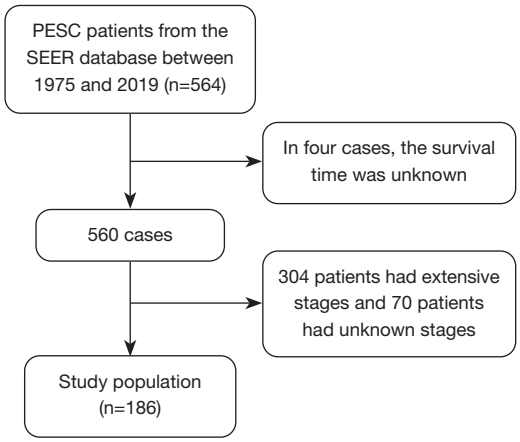

Figure 1 Process of case screen. PESC, primary esophageal small-cell carcinoma; SEER, Surveillance, Epidemiology, and End Results.

3 =8041/8042/8043/8044/8045. The basic information, clinical information, treatment information and prognosis information of these patients were also exported. Specifically as follows: patient ID, age at diagnosis, race, sex, year of diagnosis, median household income, primary site, biopsy pathology, postoperative pathology, TNM stage (AJCC 7th ed), SEER stage, treatment methods (including surgery, chemotherapy, and radiotherapy) and sequence, survival months, vital status and so on. Each of the three databases was retrieved and the data exported, after which duplicates were removed using Excel software based on patient ID. The information was then collated, code interpreted, screened, checked and analysed. After collation, staging was performed using Veterans Administration Lung Study Group (VALSG) staging system. Limited-stage refers to the tumor being confined to the local anatomical range, irrespective of lymph node metastasis (10). Overall survival (OS) was defined as the time from diagnosis to death or last follow-up. Inclusion criteria: (I) PESC is confirmed by pathology. (II) Limited-stage, no distant transfer. (III) There is a clear survival period (OS). (IV) There are definite treatments. *Figure 1* shows the case screening process. This process was carried out independently by two Masters, respectively, after which a PhD was responsible for review and verification. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

The survival curves were plotted using the Kaplan-Meier method to calculate the survival rate, and the Log-rank was used to test the differences between the survival curves. Prognostic factors were explored through univariate and multivariate Cox regression survival analyses. A Cox regression survival analysis was also performed to analyze the risk of death among the treatment groups and to compare the survival differences between each treatment group. The non-single treatment (ST) group was defined as the comprehensive treatment (CT) group and was compared to the ST group. SPSS 21. 0 (IBM, USA) was used for statistical analysis. Follow-up period was 230 months (median: 11.5 months). Test level was set as α =0.05 (two-sided test).

Results

Overall study object

From 1975 to 2019, 94,239 cases of esophageal carcinoma were screened from the SEER database, of which 564 (0.60%) were PESC. A total of 186 limited-stage PESC cases were included in the study, excluding four patients with no survival information, 304 patients with distant metastases, and 70 patients with unknown stage. Among them, 32 patients underwent surgery (1 to 4 regional lymph nodes removed), including six cases of partial esophagectomy, 13 cases of esophagectomy with partial gastrectomy, one case of esophagectomy with laryngectomy, seven cases of esophagectomy and five cases of esophagectomy with gastrectomy. Four patients received neoadjuvant radiotherapy. Seven patients received neoadjuvant radiotherapy and chemotherapy. The method of radiotherapy was beam radiation. The mOS of all the 186 patients was 12.0 months [95% confidence interval (CI): 9.827–14.173]. The 6-, 12- and 24-month OS rates were 72.8%, 47.5% and 27.8%, respectively. Only 12.8 percent of patients survived beyond 5 years.

Analysis of prognostic factors

The demographics and characteristics of the cohort was presented in *Table 1*. And univariate analysis was performed between the different groups. Kaplan-Meier analysis (*Figure 2*) showed that there were statistical differences in survival time among each group with different ages, years, median household income and N stages (P<0.001, P=0.041, P=0.002, P=0.001). The mOS of the operation group (19 months) was longer than that of the non-operation

Table 1 Characteristics and univariate analysis of patients with limited-stage PESC

Factor	Number	mOS (months)	χ^2	P value
Sex			1.550	0.21
Male	110	12		
Female	76	11		
Race			4.871	0.08
White	146	12		
Black	24	10		
Other	16	16		
Age (years)			20.422	<0.001
<50	11	24		
50–69	79	13		
70–79	58	15		
≥80	38	4		
Year			8.234	0.041
1975–1985	18	5		
1986–1996	23	9		
1997–2007	68	12		
2008–2019	77	14		
Income			15.077	0.002
≤$54,999	31	12		
$55,000–$69,999	55	10		
≥$70,000	74	18		
Unknown	26	9		
Primary site			9.956	0.07
Cervical esophagus	5	13		
Upper third	17	10		
Middle third	54	12		
Lower third	80	14		
Overlapping lesion	8	4		
Unknown	22	12		
T staging			3.544	0.47
T1	42	11		
T2	12	14		
T3	31	13		
T4	13	10		
Unknown	88	11		
N staging			19.315	0.001
N0	59	14		
N1	42	14		
N2	2	0		
N3	1	11		
Unknown	82	10		
SEER stage			0.562	0.45
Localized	84	14		
Regional	102	12		
Surgery			5.754	0.01
Yes	32	19		
No/unknown[†]	154	11		
Chemotherapy			41.504	<0.001
Yes	133	16		
No/unknown[†]	53	4		
Radiotherapy			18.562	<0.001
Yes	118	16		
No/unknown[†]	68	8		

[†], statement of SEER database: the overall positive predictive value was high (>85%); because we cannot accurately distinguish between "no treatment" and "unknown if patients received treatment", the variables that are released upon request are classified as "yes" or "no/unknown". PESC, primary esophageal small-cell carcinoma; mOS, median overall survival; SEER, Surveillance, Epidemiology, and End Results.

group (11 months) (P=0.01). The mOS (16 months) in the chemotherapy group was longer than that in the non-chemotherapy group (4 months) (P<0.001). The mOS (16 months) in radiotherapy group was longer than that in the non-radiotherapy group (8 months) (P<0.001).

The results of the univariate and multivariate analyses to identify risk factors for OS are shown in *Figures 3*,*4*. Univariate analysis showed that age ≥80 years (P=0.006), year of diagnosis (1997–2007) (P=0.01), year of diagnosis (2008–2019) (P=0.01), N2 (P=0.003), surgery (P=0.02), radiotherapy (P<0.001), and chemotherapy (P<0.001) were prognostic factors affecting OS in limited-stage PESC patients.

Multivariate analysis showed that SEER stage (P=0.02),

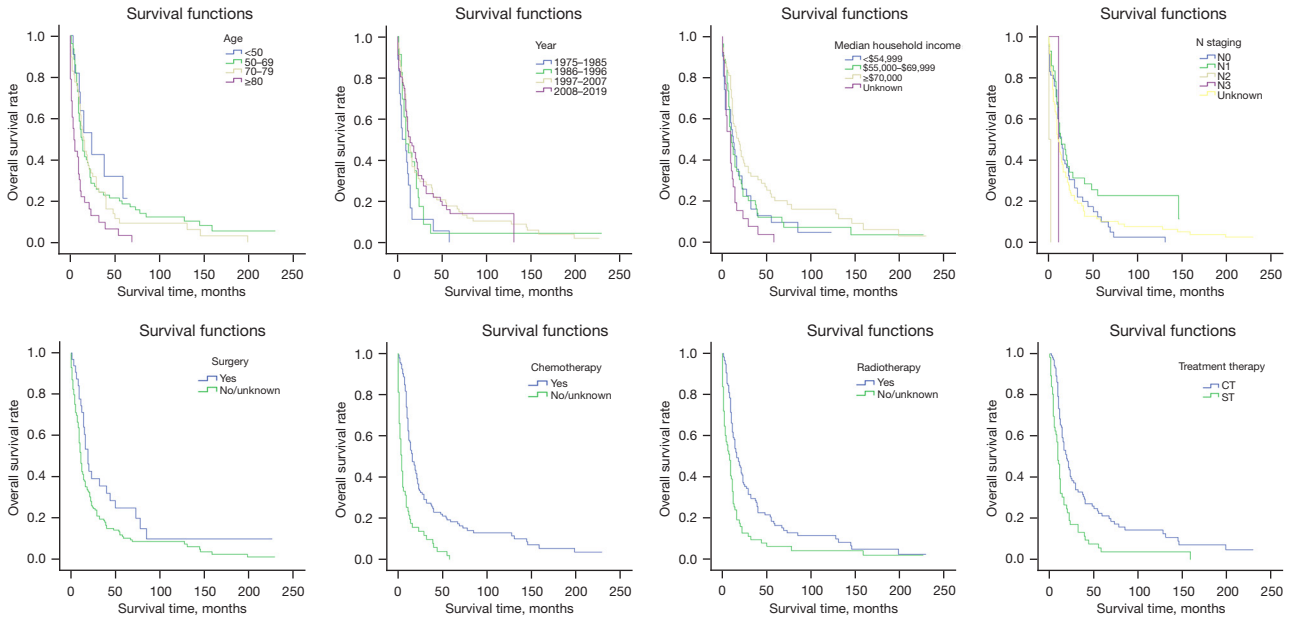

Figure 2 Survival curves. CT, comprehensive treatment; ST, single treatment.

age at diagnosis (P=0.007), radiotherapy (P<0.001), surgery (P=0.006), and chemotherapy (P<0.001) were independent prognostic factors affecting OS in patients of limited-stage PESC.

Treatment strategy

Surgery combined with chemoradiotherapy (SCR), surgery combined with chemotherapy (SC) as well as CR could decrease risk of death for patients with limited-stage PESC by 90.3%, 92.9%, 86.2%, respectively (*Table 2*).

A pairwise comparison between the SCR, SC and CR groups showed no statistical difference.

We defined the SCR, SC and CR groups as CT groups, and the single surgery, single radiotherapy and single chemotherapy groups as ST groups. The difference between the two groups was statistically significant (P<0.001, mOS: 19 *vs.* 9 months, survival curve as shown in the *Figure 2*).

It was also interesting to note that mOS was significantly better in each CT group than in each ST group, as shown in *Table 3*.

Discussion

PESC is a neuroendocrine tumor with a low incidence, high malignancy and poor therapeutic response. Due to its low incidence, there have been no prospective randomized controlled studies and no standardized and validated treatment modalities. Of the 515 patients with PESC reported by Li *et al.* (5), 259 had distant metastases, excluding 95 cases with unknown staging, representing 61.66% of patients with distant metastases at the time of detection. Despite the tireless efforts of physicians and researchers, the currently reported mOS varies from 8 to 12.5 months (11). So, there is an urgent need to explore its effective treatment options, especially for patients without metastases, as they are likely to receive the most benefit.

Currently, the treatment of PESC is mostly taking reference to that of the treatment of small cell lung cancer, but it is still inconclusive whether this is appropriate. The transcriptomic landscape of PESC is very similar to that of small cell lung cancer (12), but the treatment of PESC remains controversial. Some researchers believe that SC may be effective in certain patients. Gu *et al.* studied 69 limited-stage PESC patients treated with curative esophagectomy, and support that surgery alone appears to be adequate for disease control in the surgery response disease group, whereas multimodality therapy was associated with improved survival in the surgery nonresponse disease group (13). Verma *et al.* searched 323 nonmetastatic PESC, and found that despite no OS differences between the surgery-based (median OS: 21 months) and CR arms (18 months), both were superior to chemotherapy alone (10 months) (P<0.001) (7). Jeene *et al.* studied 58

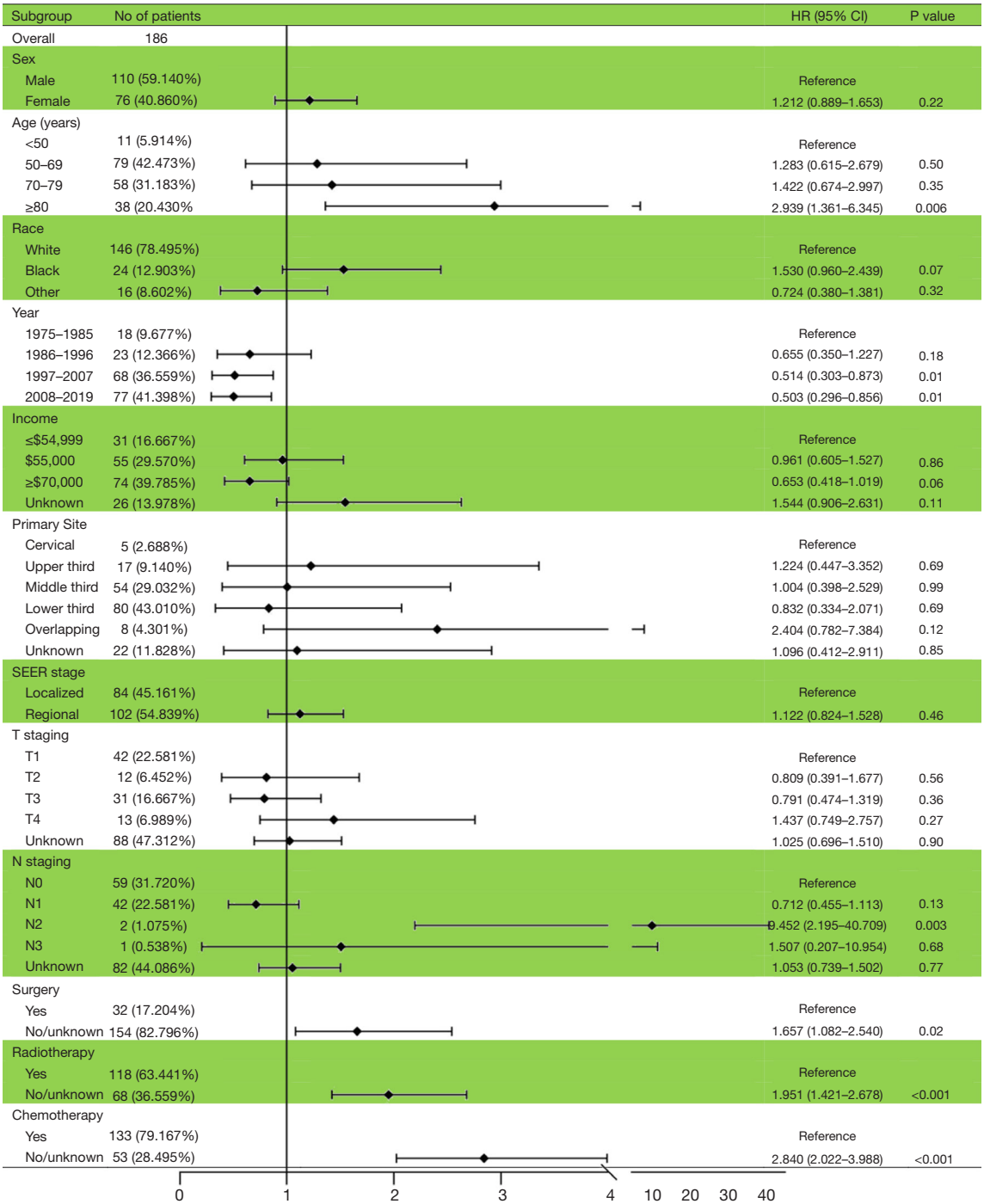

Figure 3 Univariate Cox regression survival analysis. HR, hazard ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

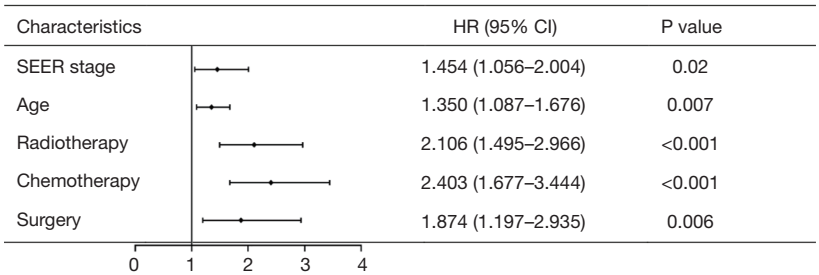

Figure 4 Multivariate Cox regression survival analysis. HR, hazard ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

Table 2 Cox regression survival analysis of treatment mode

Treatment strategy	Number	mOS (months)	HR (95% CI)	P value
Non-treatment	26	1	Reference	
SCR	19	23	0.097 (0.048–0.195)	<0.001
SC	5	50	0.071 (0.024–0.209)	<0.001
CR	80	16	0.138 (0.084–0.226)	<0.001
Surgery alone	8	9	0.293 (0.131–0.656)	0.003
Chemotherapy alone	29	11	0.234 (0.133–0.412)	<0.001
Radiotherapy alone	19	5	0.260 (0.140–0.481)	<0.001

mOS, median overall survival; HR, hazard ratio; CI, confidence interval; SCR, surgery combined with chemoradiotherapy; SC, surgery combined with chemotherapy; CR, chemoradiotherapy.

Table 3 Comparison of survival between groups in comprehensive and single treatment groups

Single treatment group	Comprehensive treatment group	χ^2	P value
Surgery alone	SCR	7.733	0.005
	SC	6.320	0.01
	CR	5.105	0.02
Radiotherapy alone	SCR	8.605	0.003
	SC	5.272	0.02
	CR	7.239	0.007
Chemotherapy alone	SCR	6.800	0.009
	SC	4.311	0.03
	CR	6.259	0.01

SCR, surgery combined with chemoradiotherapy; SC, surgery combined with chemotherapy; CR, chemoradiotherapy.

nonmetastatic PESC, and in multivariable analyses, only the number of chemotherapy cycles was associated with better survival [hazard ratio (HR) =0.78; P=0.006] (14). Zhu *et al.* conducted a multicentre retrospective study that including 458 patients with limited-stage PESC, and the analysis showed that compared with CR treatment, patients with tumor length >5 cm (HR =0.52; 95% CI: 0.3–0.9; P=0.02) or tumor location in the lower 1/3 (HR =0.59; 95%

CI: 0.37–0.93; P=0.03) could achieve significant OS benefit with SC treatment. Patients with tumor length ≤5 cm (HR =1.49; 95% CI: 1.02–2.17; P=0.04) or tumor location in the middle 1/3 (HR =1.55; 95% CI: 1.03–2.36; P=0.04) favored CR treatment (15). Other investigators believe that better outcomes can be achieved with CR. A Japanese study (16) of seven cases of resectable PESC treated with definitive CR showed a median survival of 32 months, and a median survival of 56 months in four patients without recurrence. They therefore concluded that definitive CR is a viable treatment for patients with resectable PESC, and that some patients may have a long survival. Other researchers believe that the sequence of treatments is equally important and emphasise the role of chemotherapy. A multicentre study by Cai *et al.*, which included 280 cases of limited-stage PESC, found that mOS (26.0 *vs.* 19.5 months, respectively; HR =0.69; 95% CI: 0.51 to 0.92; P=0.01) and progression-free survival (16.0 *vs.* 13.0 months, respectively; HR =0.75; 95% CI: 0.57 to 0.99; P=0.03) were longer in the preoperative chemotherapy group than in the direct surgery group (10). Li *et al.* (17) found from 162 patients with PESC who underwent radiotherapy in the SEER database that combination chemotherapy could improve the survival rate of such patients at all stages. Zhao *et al.* (18) reported a single-centre study of 129 cases of limited-stage PESC and found that patients who received concurrent CR had better OS and recurrence-free survival (RFS) than those who received sequential CR (P=0.006).

In this study, in the univariate analysis, age, year, median household income, N stage, whether surgery, radiotherapy, chemotherapy were prognostic factors. Basically, the younger the age, the longer the survival time. As the number of years increases, the survival time of patients also lengthens, which may be related to improved medical technology and living conditions. Supposedly, the higher the income, the better the ability to resist disease, but in this study, median survival increased with household income, but not significantly. The difference in median survival time varies for different N stages, roughly following the rule that higher stages lead to shorter survival times. Compared with surgery, radiation and chemotherapy, the median survival of the treated group was longer than that of the untreated group. In multivariate analysis, only SEER stage, age of diagnosis, surgery, radiotherapy and chemotherapy were independent prognostic factors. And what is the optimal combination of treatments? In terms of reduced risk of death, SCR, SC, and CR decreased by 90.3%, 92.9%, and 86.2%, respectively, with median survival times of 23, 50, and 16 months. It appeared that the SC group had the best survival advantage, but unfortunately no statistical difference was shown when the three groups were compared head-to-head. This may be because the numbers are so small that large randomized controlled studies are urgently needed.

This article has certain limitations. Firstly, due to the rarity of the disease itself, it is difficult for us to conduct prospective randomized controlled studies. Furthermore, we were unable to further reveal the reasons behind these conclusions.

Conclusions

In summary, this study explored limited-stage PESC in the SEER database and found age, year, median household income, stage N, surgery, radiation, chemotherapy to be prognostic factors. SEER stage, age, surgery, radiotherapy and chemotherapy were independent prognostic factors. Among the treatment methods, any type of CT group outperformed the ST, and the CT group even outperformed the ST group. The SC group had the highest reduced risk of death and the longest mOS. Unfortunately, no statistical difference was shown between the three groups.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-311/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-311/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-311/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as

revised in 2013).

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