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A novel risk stratification system for primary small-cell carcinoma of the esophagus: indication for prognostication and staging

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ABSTRACT

Background: Primary small cell carcinoma of the oesophagus (PSCCE) is a gastrointestinal tumour of rare onset. The current study was to investigate the role of a novel risk stratification system (RSS) for PSCCE.

Methods: The study included patients with PSCCE attending any of five medical institutions in China in 2008–2021, four of which served as a training set (n = 422) for construction of the RSS while the other served as a separate cohort (n = 256) for validation of the model. The RSS was established based on covariates associated with overall survival (OS) with a two-sided *P*-value of < 0.05 in multivariable regression. Survival discrimination of RSS was assessed.

Results: In the training cohort, multivariate regression analysis revealed age, Eastern Cooperative Oncology Group score, and initial lymph node metastasis to be independent prognostic factors for OS in non-distant metastatic PESCC; concurrent hepatic metastasis was the only significant predictor of distant metastatic PESCC. Accordingly, the RSS was developed and could classify patients into four subgroups: low-risk localized disease (LLD, defined as non-distant metastasis PESCC without risk factors, n = 58); high-risk localized disease (HLD, defined as non-distant metastasis PESCC with ≥ 1 risk factor, n = 199); low-risk metastatic disease (LMD, defined as metastatic PESCC without concomitant liver metastases, n = 103); and high-risk metastatic disease (HMD, defined as metastatic disease with synchronous liver metastases, n = 63). Three-year OS rates were 52.5%, 29.5%, 14.4%, and 5.7% for LLD, HLD, LMD, and HMD, respectively. When compared with the tumor-node-metastasis (TNM) system, RSS showed a consistently superior ability to predict OS in both the training and validation cohorts.

Conclusion: The RSS is a reliable stratification model that could be used to optimize treatment for PESCC.

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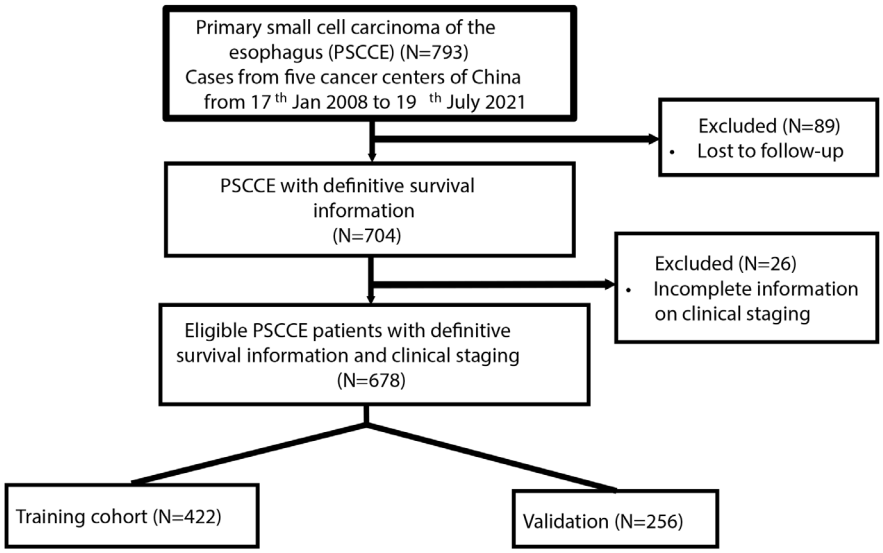

Fig. 1. Flowchart showing the process used to select the patients included in the final analysis. All five medical institutions participating in the study were located in areas of China in which esophageal cancer is endemic. Patients from four institutions (Fujian Medical University Union Hospital, Sun Yat-sen University Cancer Center, Fujian Cancer Hospital, and Chongqing University Cancer Hospital) were enrolled as the training set and those from one (Anyang Cancer Hospital) served as the validation cohort. PSCCE, primary small-cell carcinoma of the esophagus.

1. Introduction

Esophageal cancer is the ninth most common cancer and one of the leading causes of cancer-related mortality worldwide.[1] Primary small-cell carcinoma of the esophagus (PSCCE) is a rare type of esophageal cancer with a poor prognosis and was first reported by McKeown in 1952.[2–6] The rarity of PSCCE had led to a number of treatment options being proposed, including surgery with adjuvant chemotherapy, neoadjuvant chemotherapy followed by surgery, definitive concurrent chemoradiotherapy, and radical radiotherapy combined with consolidated chemotherapy.[7–9] In clinical practice, treatment of PSCCE is based mainly on the recommendations for esophageal cancer, with systemic treatment regimens being derived principally from those for small-cell lung cancer (SCLC). Therefore, a standard paradigm for PSCCE remains elusive.

The biological landscape of PSCCE differs from that of esophageal cancer (squamous cell carcinoma or adenocarcinoma) and SCLC. A whole-exome sequencing study of 55 PSCCE specimens showed that PSCCE was similar to esophageal squamous cell carcinoma and head and neck squamous cell cancers in terms of mutational spectrum and somatic copy number variation profiles.[10] However, inconsistent with this findings, a recent multi-omics analysis of 46 cases found that PSCCE contained a high frequency of Rb1 disruption (95%) and deficiency of generalized T-lymphocyte infiltration, suggesting that PSCCE was closer to SCLC.[11] Moreover, according to the clinical evidence, PSCCE has outcomes that are different from those of both esophageal cancer and SCLC. Therefore, it is necessary to reconceptualize the features of PSCCE, including generating a specific prognostic model to guide treatment strategies.

The tumor-node-metastasis (TNM) system for esophageal cancer is one of the most widely used models for staging PSECC.[12–13] Considering the biological and prognostic differences between PSCCE and esophageal cancer, the applicability of the TNM staging system in such rare malignancies needs further validation. The Veterans Administration (VA) staging system for SCLC is a dichotomous classification that is also commonly used.[14] Despite having a good survival discrimination capacity, the VA system does not allow more detailed stratification of patients with non-distant metastasis, and in particular is unable to provide guidance in terms of the choice between upfront surgery and radical chemoradiotherapy. In this study, we constructed a novel predictive model in a large cohort of 678 patients from five institutions. Our system, which is based on patient characteristics and can classify patients into four subgroups (low-risk localized disease [LLD], high-risk localized disease [HLD], low-risk metastatic disease [LMD], and high-risk metastatic disease [HMD]), allowed improved stratification in comparison with the TNM system.

2. Materials and methods

2.1. Study cohort

Patients with PSECC pathologically confirmed by surgical resection or digestive endoscopic biopsy and complete demographic and follow-up information available were enrolled in the study. Patients who were lost to follow-up (n = 89) and those without staging information available (n = 26) were excluded.

A total of 422 patients from four institutions (Fujian Medical University Union Hospital, Sun Yat-sen University Cancer Center, Fujian Cancer Hospital and Chongqing University Cancer Hospital) were included in the study cohort. Data for these patients were used to develop the training set for generation of the risk stratification system (RSS). A separate cohort of 256 patients from Anyang Cancer Hospital constituted the validation set. A flowchart showing the patient selection process is shown in Fig. 1 and a description of the datasets can be found in Supplementary Table 1.

2.2. Staging evaluation

Assessments before treatment included clinical history-taking and physical examinations, routine blood and biochemistry tests, endoscopy of the aerodigestive tract, computed tomography (CT) scans of the heart, chest, and upper abdomen, CT and/or magnetic resonance imaging of the head and neck, and a bone scan or ^{18}Ffluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) scan. The locations of regional metastatic lymph nodes was identified with reference to the Union for International Cancer Control/American Joint Committee on Cancer 8th edition of the staging system.[15] Regional lymph node involvement was confirmed in accordance with the following criteria: nodules > 1 cm in short diameter, fused nodules or masses, and for suspicious lesions, additional PET-CT scanning or biopsy under endobronchial ultrasound. Diagnosis of distant metastases was essentially based on radiological examinations; for ambiguous metastases, a biopsy was taken for pathological examination.

According to the VA system, patients who had distant metastases at baseline were classified as extensive-stage and otherwise as limited-stage. Cervical metastatic nodes were deemed to be distant metastases,

as were nodes below the level of the celiac artery. Patients with mediastinal lymph node involvement only were characterized as limited-stage. The TNM classification was based on the 8th edition of the clinical staging system for esophageal squamous carcinoma.

2.3. Treatments

The low prevalence of PSCCE arguably leads to significant heterogeneity in treatment options across institutions, including surgery or definitive radiotherapy, sequential adjuvant radiotherapy or chemotherapy, and selected systemic regimens. Of the 257 non-metastatic PSECC, 190 received chemotherapy (73.9%), included neoadjuvant, induced and/or consolidative therapy. Two handred and ninety two (82.7%) underwent radical surgery and the remaining 61 (17.3%) received nonsurgical treatment. Ninety-six of the patients who underwent radical surgery opted for neoadjuvant chemotherapy followed by surgery (32.8%).

In the population with extensive-stage disease, systemic chemotherapy with or without local radiotherapy was the predominant treatment modality, with 25.5% of patients (83/325) receiving radiotherapy to the primary disease at a median dose of 56 Gy (range, 30–60 Gy; dose per fraction, 1.8–2.0 Gy). Etoposide combined with platinum-based doublet chemotherapy was the most common regimen (74.0%), followed by paclitaxel combined with platinum (15.7%).

2.4. Endpoints and statistical analysis

In this study, we constructed and validated a prognostic model based primarily on variables related to overall survival (OS), and assessed its prognostic stratification capability via the secondary study endpoint, progression-free survival (PFS). OS was defined as the interval between diagnosis and the date of death from any cause or the last follow-up. PFS was defined as the time from the date of diagnosis to the date of disease progression, death from any cause, or the last follow-up.

Baseline characteristics were compared between the groups using the Wilcoxon signed-rank test (for continuous variables) or the chi-squared test (for categorical variables). Survival was estimated by the Kaplan–Meier method. Survival curves were compared using the log-rank test. Cox regression analysis was used to identify independent prognostic factors for OS and PFS. The time-dependent receiver-operating characteristic curve and the corresponding area under the curve were used to evaluate the discrimination ability of the risk stratification systems. All statistical analyses were performed using SPSS (version 22.0; IBM Corp., Armonk, NY, USA) and R (version 4.2.2; http://www.r-project.org/). All tests were two-tailed, and a *P*-value of ≤ 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The demographic and clinical characteristics of the patients in the training and validation cohorts are summarized in Table 1. In comparison with the training group, patients in the validation group had more lymph node metastases at diagnosis (N+, 73.0% vs. 66.8%) and a higher proportion of synchronous distant metastases (M1, 62.5% vs. 39.1%). The high percentage of late-stage patients in the validation group could partly explain why fewer of them received surgical treatment. As of March 2023, the median follow-up duration was 49.8 months in the training group and 45.1 months in the validation set. During follow-up, the proportion of fatal events was higher in the training group than in the validation group (67.1% [*n* = 283] vs. 56.6% [*n* = 145]).

3.2. Survival in the training cohort and staging system considerations

In the training cohort, the 3-year OS and PFS rates were 25.5% (95% confidence interval [CI], 21.2–30.9%) and 17.7% (95% CI, 14.1–22.2%), respectively. Patients with limited-stage PESCC had significantly better outcomes than those with extensive-stage disease, with respective 3-year OS rates of 34.4% and 11.3% ($P < 0.001$, Fig. 2B) and respective 3-year PFS rates of 24.9% and 6.8% ($P < 0.001$, Fig. 2C).

Under the TNM staging system, the training cohort was categorized into four stages, of which 34 (8.1%) were stage I, 80 (19.0%) were stage II, 143 (33.9%) were stage III, and 165 (39.1%) were stage IV. The 3-year OS rates for the respective stages were 39.5%, 35.5%, 32.0%, and 11.3%, and the 3-year PFS rates were 34.0%, 29.2%, 19.9%, and 6.8%, respectively (Table 2). Compared with the VA system, TNM staging seemed to improve the prognostic discrimination but did not ade-

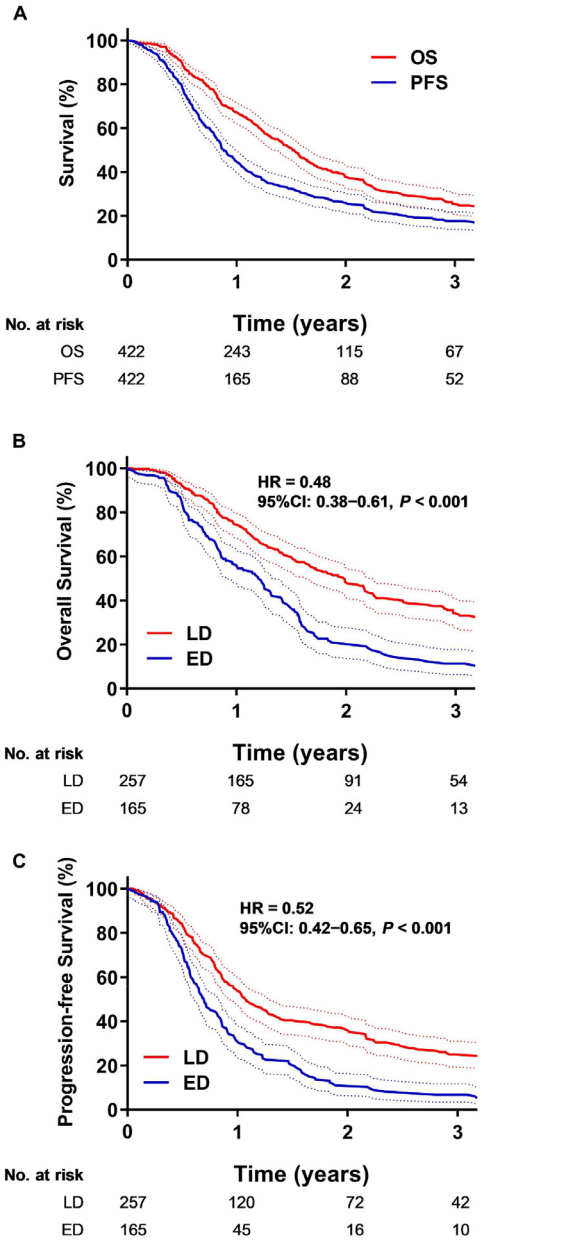

Fig. 2. Progression-free and overall survival curves for the training cohort. (A) PFS and OS in the training cohort. (B) Comparison of OS between limited-stage and extensive-stage PSCCE. (C) Comparison of PFS between limited-stage and extensive-stage PSCCE. CI, confidence interval; ED, extensive-stage; LD, limited-stage; OS, overall survival; PFS, progression-free survival.

Table 1
Characteristics and treatment of PSCCE in the study cohort.

Variable	Overall, No. (%)	Training cohort, No. (%)	Validation cohort, No. (%)	*P* value
No. of patients	678	422	256	
Sex				
Male	469 (69.2)	313 (25.8)	156 (60.9)	0.001*
Female	209 (30.8)	109 (74.2)	100 (39.1)	
Age, years				
≤ 65	433 (63.9)	292 (69.2)	141 (55.1)	0.001*
> 65	245 (36.1)	130 (30.8)	115 (44.9)	
ECOG score				
0-1	595 (87.8)	404 (95.7)	191 (74.6)	< 0.001*
> 1	83 (12.2)	18 (4.3)	65 (25.4)	
Alcohol consumption				
Yes	230 (33.9)	141 (33.4)	89 (34.8)	0.937*
None	448 (66.1)	281 (66.6)	167 (65.2)	
Smoking				
Yes	347 (51.2)	219 (51.9)	128 (50.0)	0.892*
None	331 (48.8)	203 (48.1)	128 (50.0)	
Family history of malignancies				
Yes	159 (23.5)	69 (16.4)	90 (35.2)	< 0.001*
No	519 (76.5)	353 (83.6)	166 (64.8)	
Primary location				
Cervical and Upper thoracic	105 (15.5)	60 (14.2)	45 (17.6)	< 0.001#
Middle thoracic	322 (47.5)	197 (46.7)	125 (48.8)	
Lower thoracic	168 (24.8)	138 (32.7)	30 (11.7)	
Multiple primary	41 (6.0)	23 (5.5)	18 (7.0)	
Unspecified	42 (6.2)	4 (0.9)	38 (14.8)	
Clinical stage (UICC 8th)				
I	55 (8.1)	34 (8.1)	21 (8.2)	< 0.001*
II	109 (16.1)	80 (19.0)	29 (11.3)	
III	189 (27.9)	143 (33.9)	46 (18.0)	
IV	325 (47.9)	165 (39.0)	160 (62.5)	
T stage (UICC 8th)				
Tis	23 (3.4)	23 (5.5)	0 (0.0)	< 0.001#
T1	73 (10.8)	42 (10.0)	31 (12.1)	
T2	182 (26.8)	96 (22.7)	86 (33.6)	
T3	297 (43.8)	171 (40.5)	126 (49.2)	
T4	63 (9.3)	51 (12.1)	12 (4.7)	
Tx	40 (5.9)	39 (9.2)	1 (0.4)	
N stage (UICC 8th)				
N0	209 (30.8)	140 (33.2)	69 (27.0)	< 0.001*
N1	282 (41.9)	194 (46.0)	90 (35.2)	
N2	160 (23.6)	69 (16.4)	91 (35.5)	
N3	25 (3.6)	19 (4.5)	6 (2.3)	
M stage (UICC 8th)				
M0	353 (52.1)	257 (60.9)	96 (37.5)	< 0.001*
M1	325 (47.9)	165 (39.1)	160 (62.5)	
Surgery				
Yes	292 (43.1)	154 (36.5)	138 (53.9)	< 0.001*
No	386 (56.9)	268 (63.5)	118 (46.1)	
Radiotherapy				
Yes	250 (36.9)	170 (40.2)	80 (31.3)	0.061*
No	428 (63.1)	252 (59.8)	176 (68.7)	
Chemotherapy				
Yes	544 (80.2)	323 (76.5)	221 (86.3)	0.008*
No	134 (19.8)	99 (23.5)	35 (13.7)	

* Tested by chi-square test.
# Tested by Fisher's exact test.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSCCE, primary small cell carcinoma of the esophagus; UICC, Union for International Cancer Control.

quately stratify PSECC with non-distant metastases (i.e., there was no significant difference in OS among stages I, II, and III or between any two of these stages; Fig. 3A and C).

Furthermore, multivariate regression analysis of PSECC with non-distant metastases identified age, Eastern Cooperative Oncology Group score, and regional lymph node metastasis at baseline to be independent factors affecting OS. T stage and location of the primary disease were not significantly associated with OS (Table 3). In PSECC with distant metastases, the liver was the most vulnerable organ and the sole contributor to poor OS. Moreover, the outcome was worse in patients with simultaneous liver metastases, irrespective of their combined metastases, than in those without concurrent liver metastases (Fig. 4, Table 4 and Supplementary Tables 2).

3.3. A novel risk stratification system for PSCCE

We subsequently developed a novel RSS based on the VA system. For non-distant metastasis PSECC, a risk score was calculated as per the adjusted hazard ratio (HR) derived from multivariate regression analysis (Supplementary Table 3). We defined patients as having LLD when the risk score was 0 and as having HLD when the score was greater than 0. Patients with PSECC and distant metastases were categorized as

Table 2
The overall survival and progression-free survival of three staging systems in the training cohorts.

Risk group	Patients	3 year-OS		3 year-PFS	
	No. (%)	% (95% CI)	*P*	% (95% CI)	*P*
Dichotomous classification			< 0.001		< 0.001
Limited stage	257 (61.0)	34.4 (28.3-41.8)		24.9 (19.7-31.6)	
Extensive stage	165 (39.0)	11.3 (6.9-18.7)		6.8 (3.8-12.4)	
TNM stage			< 0.001		< 0.001
I	34 (8.1)	39.5 (24.3-64.3)		34.0 (19.8-58.4)	
II	80 (19.0)	35.5 (25.7-49.1)		29.2 (20.3-42.1)	
III	143 (33.9)	32.0 (24.0-42.7)		19.9 (13.6-29.1)	
IV	165 (39.0)	11.3 (6.9-18.7)		6.8 (3.8-12.4)	
RSS			< 0.001		< 0.001
Low-risk localized disease	58 (13.7)	50.2 (37.6-66.9)		45.3 (33.3-61.6)	
High-risk localized disease	199 (47.2)	29.5 (22.9-37.9)		18.8 (13.5-26.1)	
Low-risk metastatic disease	103 (24.4)	14.4 (8.4-24.6)		10.0 (5.4-18.6)	
High-risk metastatic disease	62 (14.7)	5.7 (1.6-20.8)		1.8 (0.3-12.3)	

Abbreviations: CI, confidence interval; OS, overall survival; RSS, risk stratification system.

Table 3
Multivariate analysis of progression-free survival and overall survival for the non-distant metastatic PSCCE in the training cohort.

Variable	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex						
Female	Reference			Reference		
Male	1.024	0.654-1.603	0.919	0.837	0.563-1.245	0.380
Age, years						
≤ 65	Reference			Reference		
> 65	1.257	0.906-1.743	0.171	1.518	1.064-2.164	**0.021**
Smoking						
Yes	Reference			Reference		
No	1.19	0.885-1.600	0.249	0.944	0.591-1.509	0.810
Drinking						
Yes	Reference			Reference		
No	0.971	0.657-1.433	0.880	1.255	0.889-1.773	0.197
ECOG score						
0-1	Reference			Reference		
> 1	2.698	1.187-6.133	**0.018**	2.903	1.246-6.766	**0.014**
T stage						
$T_{1/2}$	Reference			Reference		
$T_{3/4}$	1.079	0.782-1.488	0.643	0.813	0.578-1.143	0.234
T_x	1.346	0.615-2.944	0.457	1.386	0.630-3.050	0.417
N stage						
N_0	Reference			Reference		
N_+	1.489	1.087-2.038	**0.013**	1.383	0.989-1.935	0.058

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PSCCE, primary small-cell carcinoma of the esophagus.

having LMD or HMD on the basis of liver metastases (Supplementary Table 1).

Using the RSS, 58 patients (13.7%) were assigned to the LLD subgroup, 199 (47.2%) to the HLD subgroup, 103 (24.4%) to the LMD subgroup, and 62 (14.7) to the HMD subgroup; the respective 3-year OS rates were 50.2%, 29.5%, 14.4%, and 5.7% ($P < 0.001$, Fig. 3B and D) and the 3-year PFS rates were 45.3%, 18.8%, and 10.0%, and 1.8% ($P < 0.001$, Supplementary Fig. 2).

In comparison with the TNM system, the RSS showed better performance in terms of classifying OS and PFS (Supplementary Table 4). The area under the curve for the RSS for prediction of 5-year OS (0.738 [95% CI, 0.658–0.818]) was higher than that of the TNM staging system (0.711 [95% CI, 0.614–0.808]) and the VA system (0.655 [95% CI, 0.589–0.720]).

3.4. Validating the predictive ability of the RSS

To confirm the predictive accuracy and reproducibility of the RSS, we created a separate cohort of 256 patients for external validation. Using the RSS, 20 patients (7.8%) would enter the LLD group, 76 (29.7%) the HLD subgroup, 136 (53.1%) the LMD subgroup, and 24 (9.4%) the HMD subgroup (Supplementary Fig. 3), with corresponding 3-year OS rates of 58.1%, 30.7%, 19.4%, and 0% and 3-year PFS rates of 31.6%, 19.4%, 16.6% and 0%, respectively ($P < 0.001$, Supplementary Table 5). Relative to the TNM system, RSS was significantly superior in terms of discriminating OS and PFS, especially for non-distant metastatic PSECC, which was consistent with its performance in the training cohort ($P < 0.001$, Fig. 5 and Supplementary Table 6).

4. Discussion

Owing to a low disease aggregation, the clinical trajectory of PSECC draws mostly on experience from esophageal cancer or SCLC. In this study, we found that the TNM staging system for esophageal cancer was unable to efficiently stratify non-distant metastatic PESCC. Based on prognostic characterization, we constructed a new predictive model (the RSS) which was more effective in predicting OS and PFS for PESCC than the TNM system. Finally, we confirmed its discriminating power in an external validation dataset.

An appropriate predictive model could guide not only prognostic assessment but also the optimal treatment choices for PESCC. According to several retrospective studies, surgery has been the main treatment

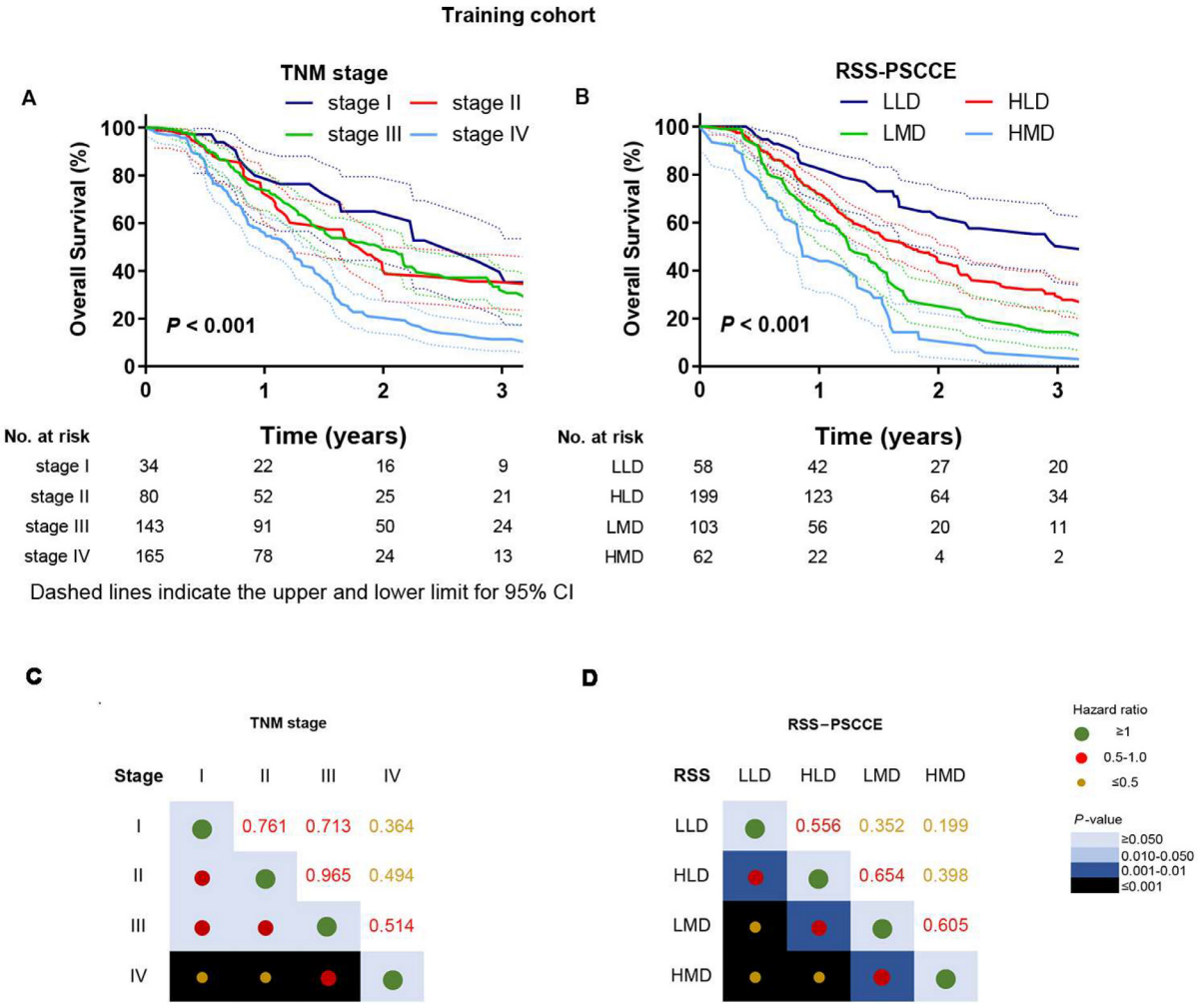

Fig. 3. Survival curves in the training set. (A, B) Stratification of OS by the TNM staging system (A) and the RSS model (B). (C, D) Comparison of OS among patients with stages I, II, III, and IV in the training set under the TNM staging system (C) and the RSS (D). CI, confidence interval; HLD, high-risk localized disease; HMD, high-risk metastatic disease; LLD, non-distant metastasis; LMD, low-risk metastatic disease; OS, overall survival; PFS, progression-free survival; RSS-PSCCE, risk stratification system primary small-cell carcinoma of the esophagus.

Table 4
Multivariate analysis of the progression-free survival and overall survival for the extensive metastatic PSCCE in the training cohort.

Variable	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex						
Female	Reference			Reference		
Male	0.887	0.552-1.425	0.620	0.976	0.56-1.699	0.931
Age, years						
≤ 65	Reference			Reference		
> 65	1.023	0.717-1.459	0.901	1.161	0.807-1.671	0.422
Smoking						
Yes	Reference			Reference		
No	0.955	0.605-1.509	0.845	1.049	0.681-1.616	0.828
Drinking						
Yes	Reference			Reference		
No	1.294	0.927-1.807	0.130	1.126	0.79-1.606	0.511
ECOG score						
0-1	Reference			Reference		
> 1	0.812	0.431-1.531	0.520	1.131	0.577-2.217	0.719

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Table 4 (*continued*)

Variable	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
T stage						
$T_{1/2}$	Reference			Reference		
$T_{3/4}$	0.734	0.493-1.092	0.127	0.817	0.518-1.288	0.384
T_x	0.992	0.619-1.588	0.972	0.892	0.497-1.602	0.702
N stage						
N_0	Reference			Reference		
N_+	1.126	0.717-1.769	0.605	1.085	0.71-1.658	0.707
LM						
NLM	Reference			Reference		
LM	1.827	1.300-2.565	**0.001**	1.652	1.149-2.375	**0.007**

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LM, liver metastases alone; NLM, none liver metastases; OS, overall survival; PFS, progression-free survival; PSCCE, primary small cell carcinoma of the esophagus.

modality for PESCC in clinical practice.[16–18] In another study that included 152 patients with non-distant metastatic disease, based on the TNM staging system, survival was significantly better in patients with stage I or IIA PESCC who underwent upfront surgery alone than in those who were not treated surgically.[19] Even in patients with stage III disease, the prognosis of PESCC treated with neoadjuvant chemotherapy sequential to surgery was still better than in patients without surgical options. According to our findings, the TNM system has deficiencies in classification of non-distant metastatic PESCC, which would inevitably impede the surgical choices for patients. It has been suggested the TNM staging system of esophageal cancer may not be a good prognosis predictor of PESCC.[6] Zhang et al. therefore optimized a prognostic model based on the 7th edition of the TNM system by incorporating age, pathology type, and molecular markers, and exhibited a better classification of

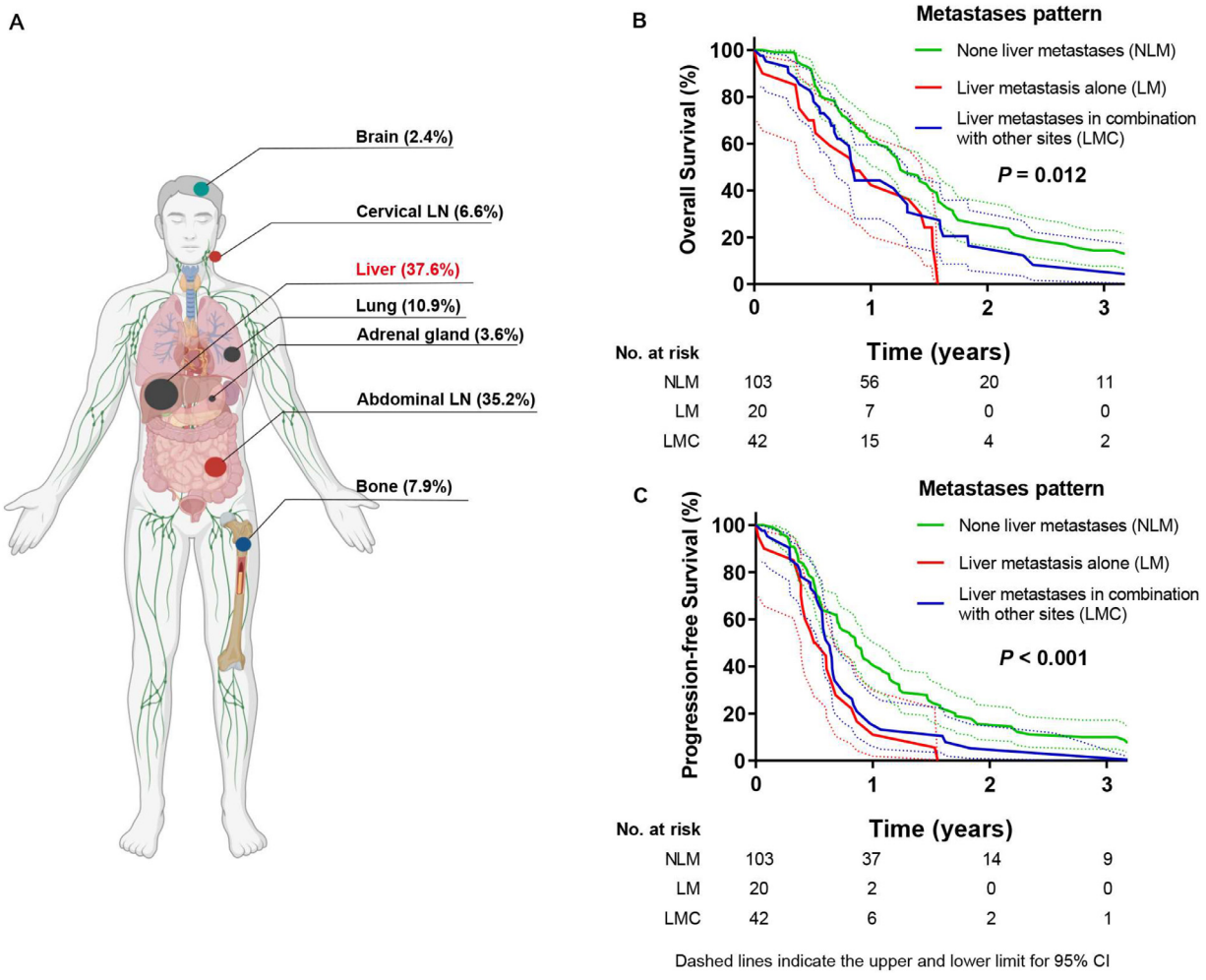

Fig. 4. Initial metastatic pattern and comparison of survival among synchronous liver metastases, liver metastases in combination with other sites, and non-liver metastases in the training cohort. (A) Initial metastatic sites and their percentages. Created with BioRender.com. (B, C) Comparison of OS (B) and PFS (C) among PSCCE with synchronous liver metastases, liver metastases in combination with other sites, and non-liver metastases. CI, confidence interval; OS, overall survival; PFS, progression-free survival; PSCCE, primary small-cell carcinoma of the esophagus.

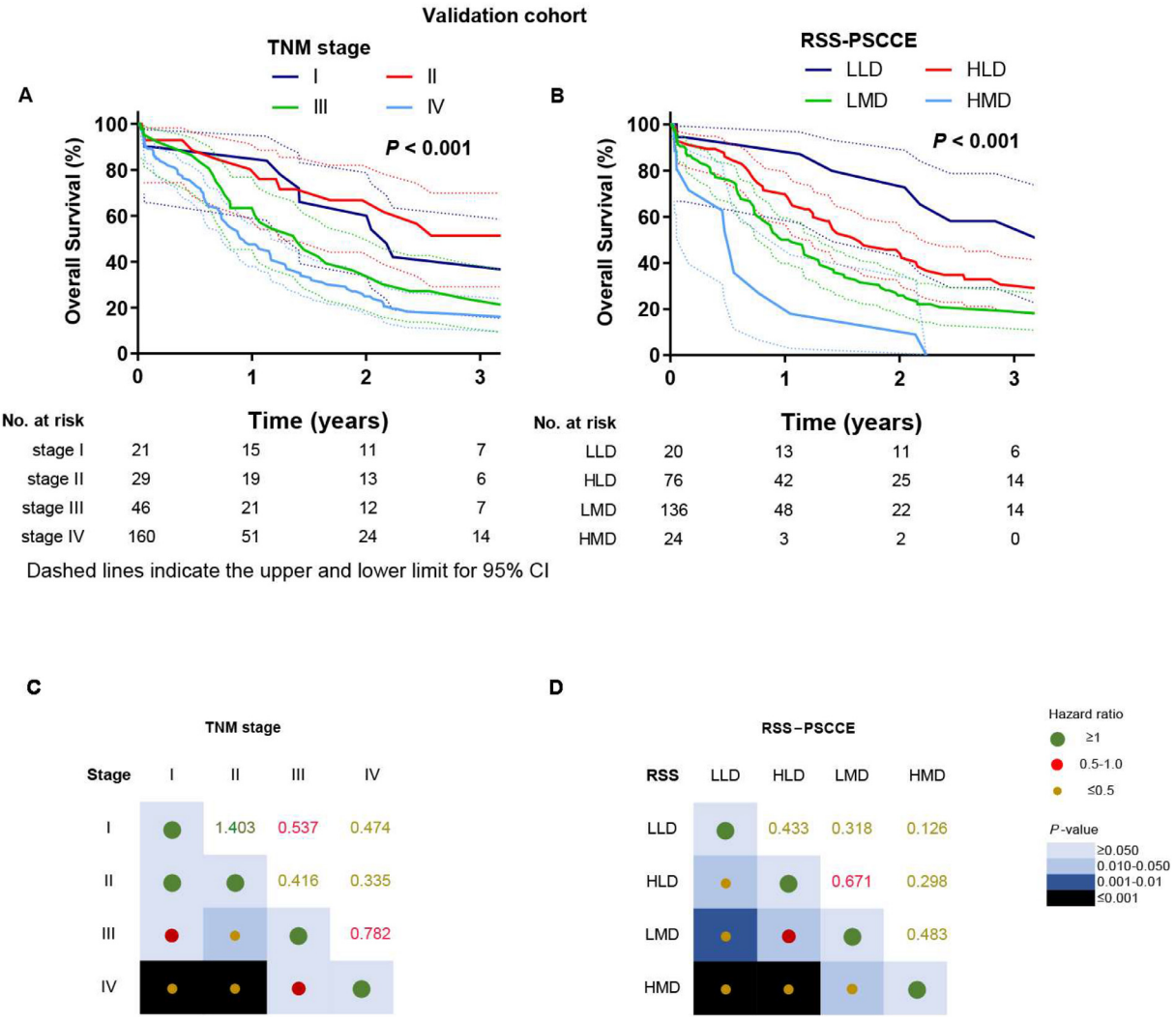

Fig. 5. Survival curves in the validation cohort. (A, B) Stratification of overall survival by the TNM staging system (A) and the RSS model (B). (C, D) Comparison of overall survival among patients with stages I, II, III, and IV in the validation cohort under the TNM staging system (C) and the RSS model (D). CI, confidence interval; HLD, high-risk localized disease; HMD, high-risk metastatic disease; LLD, non-distant metastasis; LMD, low-risk metastatic disease; RSS-PSCCE, risk stratification system primary small-cell carcinoma of the esophagus.

survival.[20] However, we found that regional lymph node metastasis was an independent prognostic factor rather than the number of metastatic nodes or T-stage, which may be due to the highly aggressive nature of PSECC. Several studies have also concluded that N staging, rather than T staging, contributes independently to OS.[19,21,22] Therefore, we proposed a new system based on the features of PESCC instead of optimizing a model from the established TNM system. Compared with Zhang's model, ours is more simplified for application.

Thus far, there have been no reports on the initial metastasis pattern of PSCCE. It is interesting to note that the metastatic behavior of PSCCE differs markedly from that of SCLC, in which the brain is most at risk of metastasis.[23–25] In PSCCE, the liver has the highest risk of metastasis (n = 62, 37.6%) followed by abdominal lymph nodes (n = 58, 35.2%), while synchronous brain metastases are quite rare (n = 4, 2.4%), which is similar to esophageal cancers.[26,27] Moreover, outcomes in patients with initial liver metastases were significantly inferior to those in patients without liver metastases, regardless of the coexistence of metastases at other sites. Therefore, liver metastases is considered as to be a substantial partner for the RSS. We performed an independent external validation experiment to confirm the predictive value of the RSS and found that it outperformed the TNM system, consistent with its performance in the training set.

Although several methods were used to evaluate the accuracy of our novel stratification model, this study has some limitations. First, it was performed in China, so it is unclear whether this model can be applied in other geographic areas. However, it should be noted that our RSS was based on the largest cohort and evolved from the dichotomized system, which could ensure its validity and reproducibility. Furthermore, the simplicity of the RSS should allow it to be validated by other researchers. Second, the majority of patients in our study did not undergo PET-CT at baseline. Given the higher rate of false-negative lymph nodes diagnosis of conventional CT, there may have been a staging bias. However, risks selected in RSS was the presence of regional lymph node involvement rather than the number of metastases, and we therefore hypothesized that PET-CT would have a relatively small impact on our model. Finally, we also did not assess heterogeneity of treatment within or between institutions, and this heterogeneity may reflect the evolving understanding of PSCCE. Continued optimization of the model with addition of other factors or biomarkers, such as ASCL1 and NEUROD[1,28] in subsequent studies may further refine the model.

5. Conclusions

We have developed the first-ever validated clinical model for PSCCE that has a robust ability to predict PFS and OS. In the future, we will strengthen the predictive accuracy of this model by validating it in multiple datasets from various institutions, practice settings, and populations.

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.

Ethics statement

It was conducted in compliance with the principles of the Declaration of Helsinki and approved by the institutional review board of Fujian Medical University Union Hospital (approval number: 2024KY016). The need for informed consent was waived in view of the anonymity of the data.

Data availability

Our research data are stored in an institutional repository and can be shared by the corresponding author (Y.Y., dr_yangyong1983@163.com) upon reasonable request.

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Author contributions

Y.Y., W.W., J.L., Y.W., Y.X., and L.Z. designed the research. Y.Y., J.Y., X.W., F.W., C.H., Y.X., and L.Z collected and analyzed the data; and Y.Y., J.Y., S.C., and X.W. wrote the paper. All authors read and approved the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2025.02.003.

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