Original Article

Establishing a prognostic model for metachronous second squamous cell lung cancer in patients with resected squamous cell lung cancer

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Background: For metachronous second pulmonary squamous cell carcinoma (msPSC) in patients with resected PSC, the method to distinguish tumour clonality has not yet been well established, which makes it difficult to determine accurate staging and predict prognosis.

Methods: Patients who underwent surgery for first PSC and encountered msPSC were recruited from the Surveillance, Epidemiology, and End Results (SEER) database. We extracted overall survival 1 (OS1) for the first PSC, overall survival 2 (OS2) for msPSC, and interval survival for the time interval between the first and second PSC. The nomogram was calibrated for OS2, and recursive partitioning analysis (RPA) was performed for risk stratification.

Results: A total of 617 patients were identified. Several independent prognostic factors were identified and integrated into the nomogram for OS2, including gender, age (2nd), nodal status (1st), node metastasis (2nd), and extrapulmonary metastasis (2nd). The calibration curves showed optimal agreement between the predictions and actual observations, and the c-index was 0.678. Surgery was associated with longer survival for msPSC patients. The prognosis of sublobectomy was comparable and inferior to that of lobectomy in the low- and moderate-risk groups, respectively. Radiotherapy was associated with better outcomes in patients who did not undergo surgery.

Conclusions: The RPA-based clinical nomogram appears to be suitable for the prognostic prediction and risk stratification of OS2 in msPSC. This practical system may help clinicians make decisions and design clinical studies.

Keywords: Metachronous lung cancer; squamous cell carcinoma (SCC); prognostic model

Submitted Jul 13, 2021. Accepted for publication Dec 02, 2021.
doi: 10.21037/jtd-21-1164
View this article at: https://dx.doi.org/10.21037/jtd-21-1164

Introduction

Non-small cell lung cancer (NSCLC) is one of the most common malignancies, causing 1,761,007 deaths worldwide in 2018 (1). Squamous cell carcinoma (SCC) represents approximately 30% of NSCLC cases (2). During the past decades, great advances have been made in surgery, cytotoxic drugs, radiotherapy, targeted therapy, and immunotherapy for NSCLC, the prognosis has been greatly improved, and the number of survivors has increased (3). Because the reported risk of developing metachronous second primary lung cancer varies from 1% to 7% per survivor per year, the number of second lung cancers is expected to rapidly increase (4-6). The physical conditions of patients with second lung cancer are commonly limited, which makes the clinical decision more cautious and complex. In addition, when the pathological type of metachronous second lung cancer is the same as the first, it is hard to determine its origin (primary or metastatic lung cancer). Accurate stage information and appropriate treatment decisions would be difficult to determine in this situation. Assessments of several clinical parameters, including the location of the primary tumour and metastatic node, tumour diameter, histology, and cancer-free survival, have long been used to distinguish multiple primary lung cancer (MPLC) from metastasis (7-10). However, these suggestions remain controversial owing to contradictory results reported by series studies (11-13). Establishing a prognostic model for metachronous second lung cancer presenting the same pathology as first lung cancer would be greatly helpful for prognostic prediction and treatment decision making.

In this study, we used the population-based Surveillance, Epidemiology, and End Results (SEER) registry to include patients with resected pulmonary squamous cell carcinoma (PSC) and further encountered metachronous second pulmonary squamous cell carcinoma (msPSC). The aim of this study was to build a prognostic model and risk stratification system for these msPSCs and explore its effectiveness in assisting treatment decisions.

We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1164/rc).

Methods

Study population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Guangzhou First People's Hospital (K-2020-066-01) and individual consent for this retrospective analysis was waived. The population was selected from the SEER 18 Custom Database using SEER*Stat 8.3.5 software (http://seer.cancer.gov/seerstat/).

Patients from the SEER 18 Regs excluding the AK Custom database (2000 to 2015) with additional treatment fields who had pathologically confirmed lung cancer with squamous cell pathology (International Classification of Diseases for Oncology, Third edition: 8070-8078) as their first malignant tumour and suffered metachronous NSCLC in their patient history were screened. In this cohort, we identified patients according to the following criteria: (I) underwent surgical resection (lobectomy, sublobectomy, or pneumonectomy) for the first PSC; and (II) the pathology for metachronous NSCLC was squamous cell pathology (International Classification of Diseases for Oncology, Third edition: 8070-8078). msPSC was defined as the second lung squamous cell cancer which occurred after diagnosis of the first lung cancer, therefore patients with interval survival ≤1 month were excluded in this study.

The patients' sociodemographic information and clinicopathological parameters for the first PSC and msPSC were collected. For the first PSC, staging was manually performed according to the 8th TNM staging system. Because the tumour characteristics (primary or metastatic cancer) of msPSCs are unclear, the pathological parameters of msPSCs were recorded in an altered way, including tumour diameter (<20 mm, 20–49 mm, ≥50 mm), node metastasis (negative, positive), and extrapulmonary metastasis (no, yes). Two recorded variables, "site-specific surgery codes" and "surgery of primary site codes", were adopted to identify the surgical procedure.

Statistical analysis

The statistical analysis was performed using the SPSS 22.0 software package (SPSS, Inc., Chicago, IL, USA). The survival rate was calculated using the Kaplan-Meier method, and the differences between curves were assessed by the log-rank test. Due to the rules of submitted survival data in the SEER database, overall survival (OS) was adopted as the survival outcome in this study. The survival data of the first PSC were extracted and defined as overall survival 1 (OS1), which means the time duration between surgery date of first PSC and last follow-up or death; and the survival data of msPSC were extracted and defined as

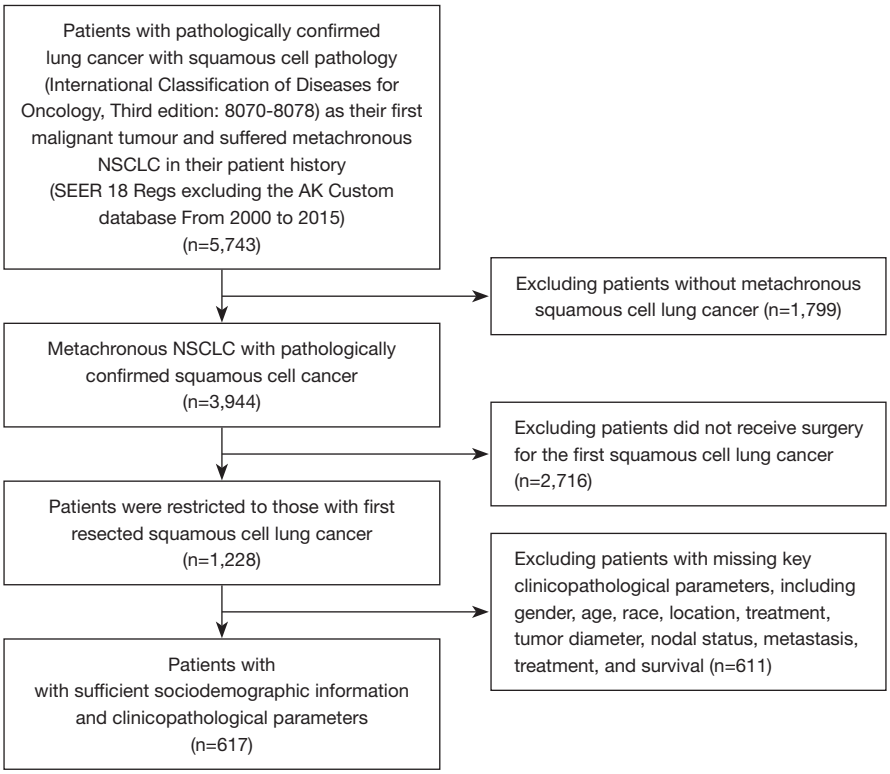

Figure 1 Definition of overall survival 1, overall survival 2, and interval survival for patients with metachronous second squamous cell lung cancer. NSCLC, non-small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results.

overall survival 2 (OS2), which means the time duration between treatment date of msPSC and last follow-up or death. Interval survival is defined as OS1 minus OS2, which indicated as the time duration between surgery date of first PSC and treatment date of msPSC (*Figure 1*). In this study, the main objective is OS2.

Univariate Cox regression models were constructed to identify predictors for interval survival, OS1, and OS2. Categorical clinicopathological parameters were included in the univariate Cox analysis, including gender, race, age (1^{st}), location (1^{st}), grade (1^{st}), surgery (1^{st}), radiotherapy (1^{st}), chemotherapy (1^{st}), tumour diameter (1^{st}), nodal status (1^{st}), distant metastasis (1^{st}), age (2^{nd}), location (2^{nd}), side of second PSC, grade (2^{nd}), tumour diameter (2^{nd}), node metastasis (2^{nd}), and extrapulmonary metastasis (2^{nd}). For the evaluation of OS1 and OS2, the interval survival parameter was also included in the univariate analysis. According to the criteria for the diagnosis of MSPLC proposed by the American College of Chest Physicians (ACCP) in 2013, 24 and 48 months were selected as the cut-off points for interval survival (7). Factors shown with potential significance ($P<0.1$) in univariate analysis were introduced into multivariate Cox regression analysis. Considering the natural impact of tumor diameter (1^{st}), node metastasis (1^{st}), and surgery (1^{st}) on OS1, these parameters would be introduced into multivariate analysis even through the P value is larger than 0.1. Statistical significance was assumed at a two-sided $P<0.05$.

To establish a prognostic prediction system for OS2, a nomogram was formulated with the survival and rms packages on the basis of multivariate analysis (14). The nomogram was subjected to 1,000 bootstrap resamples for internal validation of the primary cohort. Calibration of the nomogram for 3- and 5-year OS was performed by comparing the predicted survival with the observed survival after bias correction. The Akaike information criterion (AIC) as well as the concordance index (c-index) were applied to the Cox proportional hazards regression model to correct for potential bias in comparing prognostic systems with different numbers of stages. A new decision tree group was established for the risk stratification of OS2 through recursive partitioning analysis (RPA). This

method modelled predictors by building decision trees. In every node, each predictor was examined for the best split within that variable and the optimal split corresponding to which has the greatest survival difference between patient groups (15). The efficacy of surgery, chemotherapy, and radiotherapy was evaluated according to the risk stratification system. In this research, the nomogram score was the only predictor, and the PRA was performed using R 3.3.2 (http://www.r-project.org) with the part package. All parameters were set to default values.

Results

Patient characteristics

A total of 617 patients who met the criteria were included in this study (*Table 1*). The median ages for first PSC and msPSC were 69 (range, from 30 to 86) and 73 (range, 31 to 91) years, respectively. The median tumour diameters for the first PSC and msPSC were 30 (range, 4 to 95) and 20 (range, 5 to 96) mm, respectively. The median interval survival was 48 (range, from 2 to 141) months. There were

Table 1 Patient characteristics

Variable	Case number
Gender	
Male	378 (61.3)
Female	239 (38.7)
Race	
White	552 (89.5)
Black	48 (7.8)
Others	17 (2.8)
Age (1st) (years)	
<70	352 (57.1)
≥70	265 (42.9)
Location (1st)	
Left upper	196 (31.8)
Left lower	108 (17.5)
Right upper	172 (27.9)
Right middle	28 (4.5)
Right lower	98 (15.9)
Unknown	15 (2.4)
Tumor diameter (1st) (mm)	
<20	139 (22.5)
20–49	346 (56.1)
≥50	132 (21.4)
Nodal status (1st)	
N0	519 (84.1)
N1	61 (9.9)
N2	37 (6.0)
Grade (1st)	
I	12 (1.9)
II	317 (51.4)
III	261 (42.3)
IV	5 (0.8)
Unknown	22 (3.6)
Distant metastasis (1st)	
M0	599 (97.1)
M1	18 (2.9)
Stage (1st)	
I	470 (76.2)
II	70 (11.4)
III	59 (9.7)
IV	18 (2.8)
Surgery (1st)	
Sublobectomy	87 (14.1)
Lobectomy	506 (82.0)
Pneumonectomy	24 (3.9)
Chemotherapy (1st)	
Yes	126 (20.4)
No/unknown	491 (79.6)
Radiotherapy (1st)	
Yes	59 (9.6)
No/unknown	558 (90.4)
Interval survival (months)	
<24	168 (27.2)
24-47	201 (32.6)
≥48	248 (40.2)

Table 1 *(continued)*

Variable	Case number
Age (2nd) (years)	
<70	214 (34.7)
≥70	403 (65.3)
Location (2nd)	
Left upper	165 (26.7)
Left lower	105 (17.0)
Right upper	160 (25.9)
Right middle	24 (3.9)
Right lower	127 (20.6)
Unknown	36 (5.8)
Tumor diameter (2nd) (mm)	
<20	244 (39.5)
20–49	227 (36.8)
≥50	146 (23.7)
Node metastasis (2nd)	
Negative	469 (76.0)
Positive	148 (24.0)
Extrapulmonary metastasis (2nd)	
No	540 (87.5)
Yes	77 (12.5)
Grade (2nd)	
I	10 (1.6)
II	269 (43.6)
III	172 (27.9)
IV	3 (0.5)
Unknown	163 (26.4)
Surgery (2nd)	
No surgery	363 (58.8)
Sublobectomy	153 (24.8)
Lobectomy	101 (16.4)
Chemotherapy (2nd)	
Yes	140 (22.7)
No/unknown	477 (77.3)
Radiotherapy (2nd)	
Yes	255 (41.3)
No/unknown	362 (58.7)

477 (77.3%) msPSCs located on the contralateral side with respect to the first PSC. Surgery was performed in 254 msPSC patients, including 153 sublobectomies and 101 lobectomies. The median survival times for interval survival, OS1, and OS2 were 41, 86, and 28 months, respectively. Flow chart of patient recruitment is shown in *Figure 2*.

Predictors for interval survival, OS1, and OS2

After univariate analysis, factors with potential significance were further included in multivariate analysis. As shown in *Table 2*, for interval survival, the potential predictors were age (1st), side of second PSC, chemotherapy (1st), and surgery (1st), and the factors that maintained significance after multivariate analysis were age (1st) (adjusted HR =1.210, P=0.020) and side of second PSC (adjusted HR =1.325, P=0.004). For OS1, the potential predictors were gender, age (1st), interval survival, tumor diameter (1st), nodal status (2st), and surgery (1st), and the factors that maintained significance after multivariate analysis were gender (adjusted HR =0.711, P=0.002), age (1st) (adjusted HR =1.301, P=0.013), interval survival (P<0.001). For OS2, the potential predictors were gender, age (2nd), interval survival, tumour diameter (1st), nodal status (1st), tumour diameter (2nd), node metastasis (2nd), and extrapulmonary metastasis (2nd), and the factors that maintained significance after multivariate analysis were gender (adjusted HR =0.750, P=0.012), age (2nd) (adjusted HR =1.364, P=0.006), nodal status (1st) (P=0.047), tumour diameter (2nd) (P<0.001), node metastasis (adjusted HR =1.313, P=0.030), and extrapulmonary metastasis (adjusted HR =2.219, P<0.001).

Nomogram and risk stratification for OS2

A nomogram that incorporated the aforementioned significant prognostic factors was established for OS2 (*Figure 3A*). The nomogram illustrated that tumour diameter (2nd) and extrapulmonary metastasis (2nd) had the largest contributions to prognosis. Each subtype within these variables was assigned a score on the point scale (Table S1). By adding up the scores, we could obtain the nomogram score of each patient (median, 78.6; range, 0–287.3). The calibration plots presented good agreement between the nomogram predictions and actual observations for the 3- and 5-year survival rates (*Figure 3B*). The AIC value was 3208.599, and the c-index was 0.678 (95% CI: 0.642–0.713). These results proved the predictive efficacy of our established nomogram for long-term survival. Then, we

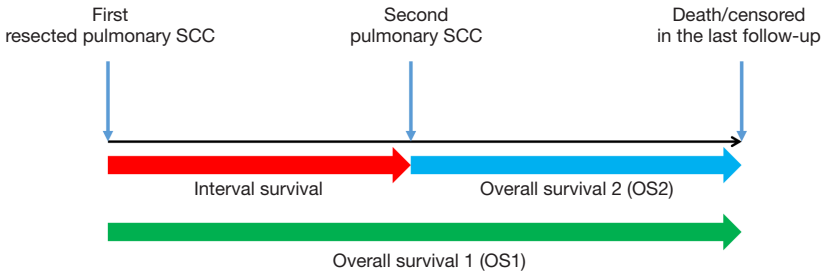

Figure 2 Flow chart of patient recruitment.

Table 2 Univariate and multivariate analysis for overall survival 1, interval survival, and overall survival 2.

Variables	Event	Univariate analysis				Multivariate analysis			
		HR	95% CI	P	P_{trend}	Adjusted HR	95% CI	P	P_{trend}
Interval survival									
Age (1st)		1.209	1.030–1.419	0.020		1.210	1.030–1.420	0.020	
Side (ipsilateral/ contralateral)		1.324	1.096–1.600	0.004		1.325	1.097–1.600	0.004	
Chemotherapy (1st)		1.183	0.971–1.441	0.096		1.145	0.938–1.396	0.183	
Surgery (1st)									
Sublobectomy		1			0.089	1			0.086
Lobectomy		0.876	0.697–1.101	0.257		0.880	0.699–1.107	0.880	
Pneumonectomy		0.602	0.382–0.948	0.029		0.596	0.377–0.943	0.027	
Overall survival 1									
Gender									
Male	241/378	1				1			
Female	121/239	0.763	0.613–0.950	0.016		0.711	0.571–0.886	0.002	
Age (1st)									
<70	195/352	1				1			
≥70	167/265	1.305	1.061–1.605	0.012		1.301	1.057–1.601	0.013	
Interval survival									
<24	99/168	1			<0.001	1			<0.001
24–47	124/201	0.731	0.561–0.953	0.020		0.739	0.567–0.963	0.025	
≥48	139/248	0.278	0.213–0.363	<0.001		0.276	0.211–0.361	<0.001	
Tumor diameter (1st) (mm)									
<20	72/139	1			0.479	1			0.234
20–49	209/346	1.081	0.827–1.413	0.569		1.174	0.887–1.554	0.262	
≥50	81/132	1.213	0.883–1.667	0.233		1.346	0.957–1.894	0.088	
Nodal status (1st)									
N0	299/519	1			0.241	1			0.111
N1	38/61	0.987	0.704–1.384	0.941		1.211	0.848–1.728	0.293	
N2	25/37	1.418	0.942–2.135	0.095		1.526	0.998–2.334	0.051	

Table 2 *(continued)*

Table 2 *(continued)*

Variables	Event	Univariate analysis				Multivariate analysis			
		HR	95% CI	P	P_{trend}	Adjusted HR	95% CI	P	P_{trend}
Surgery (1st)									
Sublobectomy	52/87	1			0.512	1			0.453
Lobectomy	296/506	0.908	0.676–1.220	0.908		0.864	0.632–1.181	0.359	
Pneumonectomy	14/24	0.708	0.392–1.278	0.708		0.690	0.373–1.277	0.238	
Overall survival 2									
Gender									
Male	241/378	1				1			
Female	121/239	0.687	0.551–0.855	0.001		0.750	0.600–0.938	0.012	
Age (2nd)									
<70	120/214	1				1			
≥70	242/403	1.316	1.055–1.642	0.015		1.364	1.092–1.703	0.006	
Interval survival									
<24	99/168	1			<0.001	1			0.140
24–47	124/201	1.409	1.080–1.839	0.012		1.250	0.954–1.637	0.106	
≥48	139/248	1.774	1.360–2.313	<0.001		1.304	0.988–1.721	0.061	
Tumor diameter (1st)									
<20	72/139	1			0.066	1			0.390
20–49	209/346	1.231	0.942–1.609	0.129		1.166	0.887–1.533	0.270	
≥50	81/132	1.460	1.062–2.006	0.020		1.253	0.898–1.748	0.184	
Nodal status (1st)									
N0	299/519	1			0.032	1			0.047
N1	38/61	1.270	0.906–1.782	0.166		1.213	0.862–1.705	0.267	
N2	25/37	1.638	1.087–2.469	0.018		1.633	1.078–2.474	0.021	
Tumor diameter (2nd)									
<20	106/244	1			<0.001	1			<0.001
20–49	143/227	1.781	1.385–2.291	<0.001		1.627	1.262–2.096	<0.001	
≥50	113/146	3.330	2.547–4.354	<0.001		2.735	2.070–3.614	<0.001	
Node metastasis (2nd)									
Negative	259/469	1				1			
Positive	103/148	1.925	1.529–2.424	<0.001		1.313	1.026–1.680	0.030	
Extrapulmonary metastasis (2nd)									
No	300/540	1				1			
Yes	62/77	3.135	2.370–4.147	<0.001		2.219	1.649–2.985	<0.001	

HR, hazard ratio; 95% CI, 95% confidence interval.

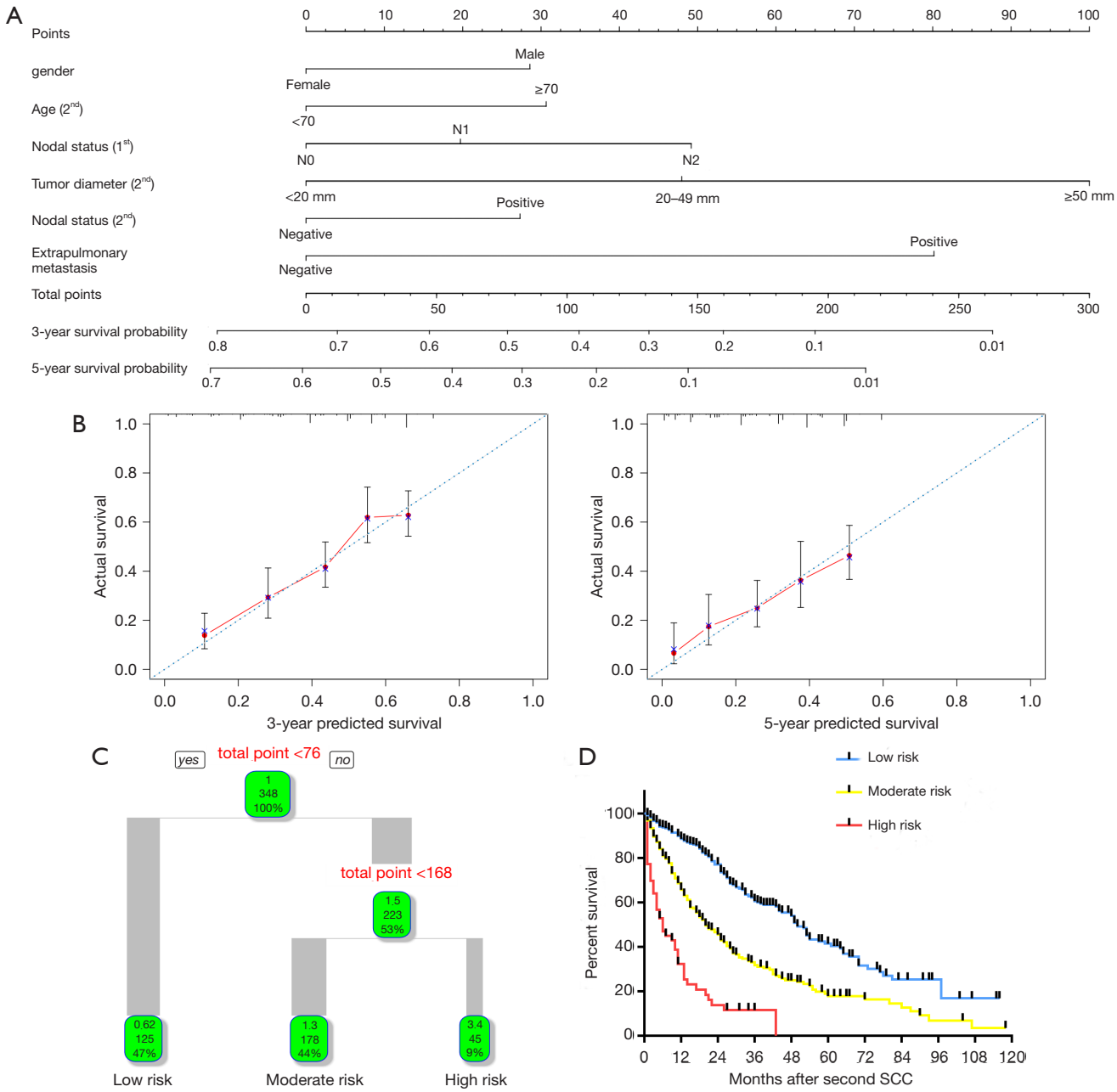

Figure 3 Establishment of a risk stratification system for OS2. (A) Prognostic nomogram for OS2 in patients with metachronous second squamous cell lung cancer; (B) the calibration curves for predicting patient survival at each time point; (C) RPA grouping into three risk categories for OS2; (D) the Kaplan-Meier survival curve for OS2 is well stratified by the RPA risk group. SCC, squamous cell carcinoma; OS, overall survival; RPA, recursive partitioning analysis.

performed RPA for OS2 according to the nomogram score and partitioned the patient population into three risk strata defined as follows: low risk (nomogram score <76) (n=285, 55.8%), moderate risk (nomogram score ≥76 & <168) (n=276, 31.9%), and high risk (nomogram score >168) (n=56, 14.3%) (*Figure 3C*). The risk stratification system presents good operating characteristics for the stratification of OS2. The median survival after msPSC for the low-risk, moderate-risk, and high-risk groups was 50, 20, and 5 months, respectively (P<0.001) (*Figure 3D*).

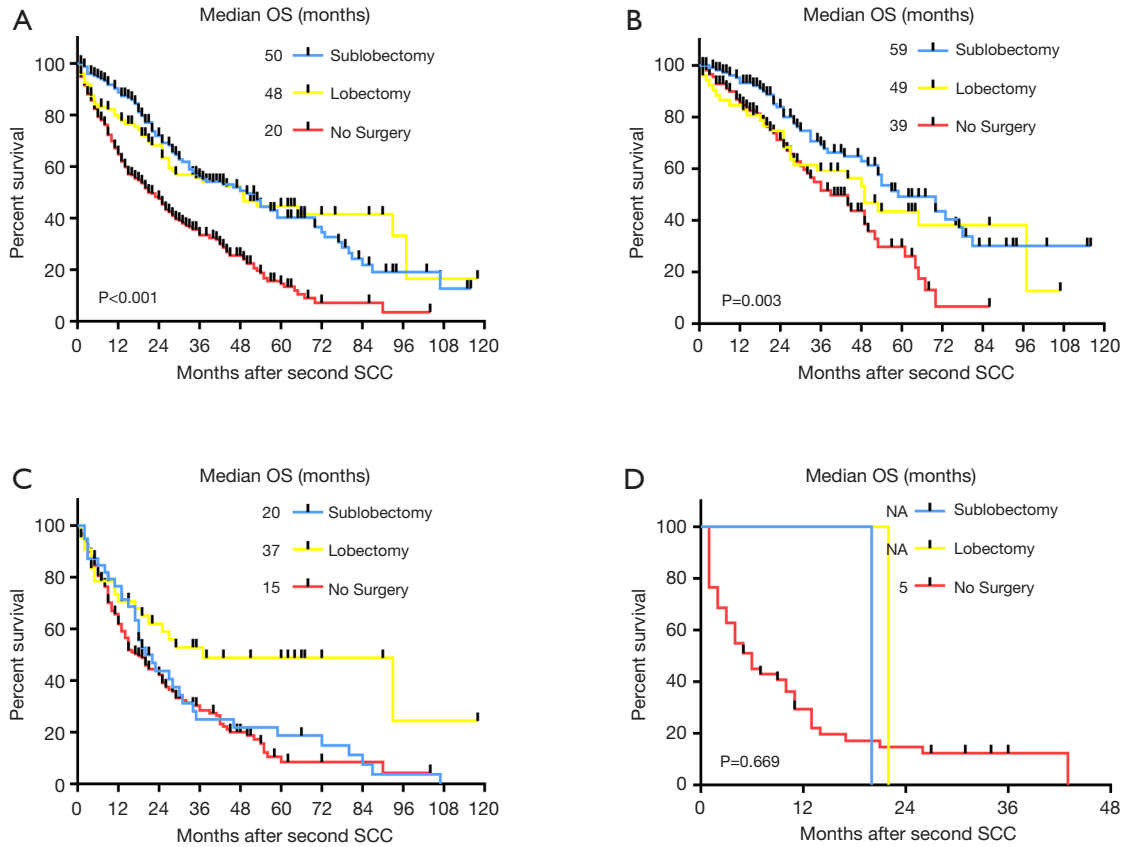

Figure 4 Association between treatment and prognosis in patients with different risk stratification. The impact of surgery type on OS2 for the entire cohort (A), low-risk group (B), moderate-risk group (C), and high-risk group (D). OS, overall survival; SCC, squamous cell carcinoma.

Risk stratification, treatment strategy, and OS2

Patients with msPSC who underwent surgery presented longer OS2 times than those who did not undergo surgery (median, 49 *vs.* 20 months, P<0.001) (*Figure 4A*). Then, we estimated the association between surgery type and OS2 in patients with different stratifications. For the low-risk group, the prognosis of sublobectomy was comparable to that of lobectomy (median survival: 59 *vs.* 49 months, P=0.219) (*Figure 4B*). For the moderate-risk group, the prognosis of sublobectomy was inferior to that of lobectomy (median: 37 *vs.* 20 months, P=0.026) (*Figure 4C*). For the high-risk group, surgery was only performed in two patients (3.6%) (*Figure 4D*). The efficacy of chemotherapy was not observed; radiotherapy was associated with better outcomes in patients who did not undergo surgery for msPSC (median survival, 26 *vs.* 11 months, P<0.001) (Figure S1).

Discussion

Metachronous second lung cancer is a common disease (4-6). However, for metachronous second lung cancer with the same pathology as the first lung cancer, the method to distinguish tumour clonality has not yet been well established, which makes it difficult to determine accurate staging and appropriate therapeutic strategies. In this study, we recruited msPSC patients among survivors of previously resected PSCs from a large, population-based database, constructed a prognostic model, established a risk stratification system, and attempted to identify appropriate treatment strategies for these patients. To the best of our knowledge, this is the first study to address this issue in the literature.

In this study, we defined interval survival as the interval between the first PSC and msPSC and found that it was

significantly influenced by age and side (*Table 2*). It could be expected that older patients would encounter a limited interval survival due to the limited life-time. The shorter interval survival among contralateral msPSCs might be partly explained by the process of functional compensation. Metachronous lung cancer is more likely to be located on the contralateral side, since contralateral pulmonary function would account for a larger proportion after the first resection. This speculation is supported by Yang *et al.*, who observed most (80.2%) metachronous lung cancer in the contralateral lobe after first resection (16).

In the literature, interval survival has long been regarded as an important indicator for the tumour clonality of metachronous multiple lung cancer. In the first edition of the diagnostic criteria proposed by Martini *et al.*, a time interval >2 years is a necessary condition for the diagnosis of metachronous multiple primary lung cancer (mMPLC) (10). This edition was further modified by the ACCP in 2003. According to their suggestions, interval survival >4 years is a necessary condition for mMPLC, and interval survival <2 years is a necessary condition for metastatic lung cancer (9). This suggestion is still used in the following editions (7,8). In our study, the association between interval survival and OS2 was evaluated as well. According to our results, longer interval survival (interval <24 *vs.* 24–47 *vs.* ≥48 months) leads to longer OS2 (23 *vs.* 27 *vs.* 49 months) (P<0.001). However, this association missed significance after adjusting for other confounders (P=0.140) (*Table 2*). A similar result was also reported by Hamaji *et al.* (11). It has been widely accepted that the characteristics of tumour clonality greatly impact staging information and long-term survival. It is plausible that since interval survival is not an independent prognostic factor for OS2, it should not be an essential factor to distinguish tumour clonality. The criterion for MPLC, especially regarding the issues of interval survival, might be biased and merit further modification.

Following an improvement in the prognosis of patients with lung cancer, we also observed an elevated risk of developing second lung cancer (17). However, until now, it is still difficult to distinguish the tumour clonality and determine the accurate stage for metachronous second lung cancer when its pathology is the same as the first. It is worth noting that this is a common problem in clinics. For example, Hamaji *et al.* recruited 161 patients with metachronous second lung cancer, and 123 (76.4%) of them were diagnosed with the same pathology as the first lung cancer (11). Therefore, this study sought to establish a prognostication system for these patients with the aim of resolving the dispute of tumour clonality. To achieve this goal, the characteristics of second lung cancer were recorded, such as tumour diameter, node metastasis (negative *vs.* positive), and extrapulmonary metastasis. Finally, in addition to these parameters, age (2^{nd}), gender, and nodal status (1^{st}) were included in the nomogram. Because nodal status (1^{st}) has an independent impact on OS2, we propose to view metachronous second lung cancer from a continuous perspective.

It has been widely accepted that surgery is an effective treatment for operable metachronous lung cancer (11,16). Similarly, in this study, surgery was associated with a better OS2 than no surgery (median, 49 *vs.* 20 months, P<0.001). After risk stratification, the prognosis of sublobectomy was comparable to that of lobectomy in the low-risk group (median, 59 *vs.* 49 months, P=0.219) but inferior to that of lobectomy in the moderate-risk group (median, 20 *vs.* 37 months, P=0.026). Risk stratification seems to facilitate clinical treatment decisions. In addition, for patients with msPSC who did not undergo surgery, radiotherapy was associated with improved survival (median survival, 26 *vs.* 11 months, P<0.001). Aggressive local therapy is warranted for msPSC.

Our study has several limitations. First, because of the nature of the SEER data, some well-known prognostic factors, such as cigarette smoking and tumour markers, were not included. However, the calibration plots presented good agreement between the nomogram predictions and actual observations, and the c-index was 0.678. These results indicate that the findings are informative regarding patient outcomes. Second, the efficacy of chemotherapy could have been underestimated due to the ambiguous record (yes *vs.* no/unclear) and unaware regimen in the SEER 18 Custom Database. Third, although we carried out 1,000 bootstrap resamples for interval validation, the results still need further external validation with other populations. Fourth, the problem of tumour clonality was not solved by our study. Therefore, we could not quantify the efficacy of the risk stratification by comparison with the current TNM staging system, although prognosis was stratified fairly well according to the survival curves. Fifth, because the biological behaviour of lung adenocarcinoma is significantly different from that of PSC, especially in recurrence/metastatic patterns and multiple nodule models, we did not include patients with metachronous adenocarcinoma lung cancer with previously resected adenocarcinoma in this study (18-20). Therefore, our results, including the

prognostic model, risk stratification system, and treatment recommendations, are not suitable for patients with metachronous adenocarcinoma.

In conclusion, the RPA-based clinical nomogram appears to be suitable for the prognostic prediction and risk stratification of msPSC patients with previously resected PSC. This model validates and refines the classification rules previously used by other authors; it is based on variables that are easy to obtain, it is easy to use and has potential implications for clinical management and study design.

Acknowledgments

Funding: This work was supported by grants from the Guangzhou Health Science and Technology Project (20211A010001).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1164/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1164/prf

Conflicts of Interests: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1164/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). The study was approved by institutional ethics board of Guangzhou First People's Hospital (K-2020-066-01) and individual consent for this retrospective analysis was waived.

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Cite this article as: Fu SS, Zheng YZ, Qin XY, Yang XP, Shen P, Cai WJ, Li XQ, Liao HY. Establishing a prognostic model for metachronous second squamous cell lung cancer in patients with resected squamous cell lung cancer. J Thorac Dis 2022;14(1):90-101. doi: 10.21037/jtd-21-1164

Supplementary

Table S1 Computational formula of nomogram score for each prognostic factor

	Computational formula of nomogram score
Gender	Male =28.6; Female =0
Age (2nd)	<70 =0; ≥70 =30.7
Nodal status (1st)	N0 =0; N1 =19.7; N2 =49.2
Tumor diameter (2nd)	<20 mm =0; 20–49 mm =48.0; ≥50 mm =100.0
Nodal status (2nd)	Negative =0; Positive =27.3
Extrapulmonary metastasis (2nd)	Negative =0; Positive =80.2

https://dx.doi.org/10.21037/jtd-21-1164

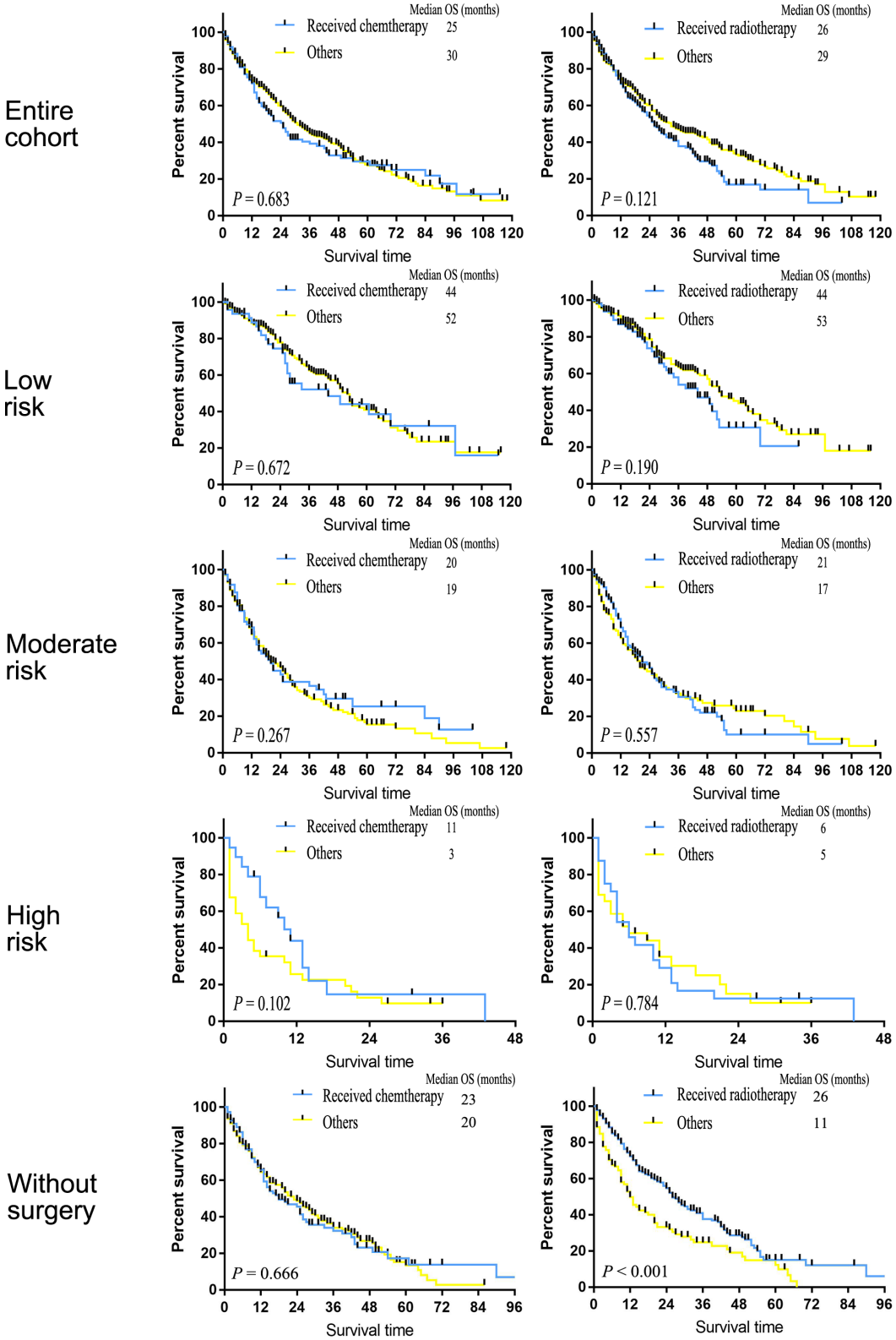

Figure S1 The impact of radiotherapy and chemotherapy on OS2 for the entire cohort, low-risk group, moderate-risk group, high-risk group, and no-surgery group.

https://dx.doi.org/10.21037/jtd-21-1164