Original Article

Establishing a TNM-like risk classification for metachronous second pulmonary adenocarcinoma in patients with previously resected pulmonary adenocarcinoma

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Background: For metachronous second pulmonary adenocarcinoma (msPAD) in patients with resected PAD, 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 received surgery for the primary and encountered msPAD were recruited into the Surveillance, Epidemiology, and End Results database. We extracted overall survival 1 (OS1) for the primary, overall survival 2 (OS2) for the msPAD, and defined interval survival as the interval time between the first and second PAD. Based on the nomogram and recursive partitioning analysis, a tumor, node, metastasis staging system (TNM)-like risk stratification system was established for OS2 on the premise of suspending the dispute of tumor clonality.

Results: A total of 1,045 patients were identified. There is no significant association between interval survival and OS2. A TNM-like risk stratification system was established based on the independent pathological factors for prognosis, including tumor diameter (2^{nd}), node metastasis (2^{nd}), grade (2^{nd}), and extrapulmonary metastasis (2^{nd}). The proposed risk stratification system present well capacity in predicting and stratifying prognosis. Compared with the TNM stage system, the proposed risk stratification system presents a smaller Akaike information criterion (AIC) but larger c-index, and generates higher accuracy to predict prognosis at 160 months of follow-up according to the time-dependent receiver operating curve (ROC) curve.

Conclusions: In conclusion, the TNM-like risk stratification appears to be suitable for prognostic prediction and risk stratification for msPAD patients with former PAD resection. This model validates and refines the known classification rules based on the easily collected variables, and highlights potentially clinical implications.

Keywords: Metachronous lung cancer; adenocarcinoma; prognostic model; risk stratification system

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Introduction

Non-small cell lung cancer (NSCLC) is one of the most tedious malignancies. Adenocarcinoma (ADC) represents approximately 40% of cases of NSCLC (1). In past decades, with great advances in screening techniques and treatment modalities involving surgery, cytotoxic drugs, radiotherapy, targeted therapy, and immunotherapy, the number of survivors from lung cancer is greatly increased (2). Because the reported risk to develop a metachronous second lung cancer varied from 1% to 7% per survivor per year, the number of second lung cancer is expected to rapidly increase (3-5). For patients with second lung cancer, the physical condition is commonly limited, which makes the clinical decision more cautious and complex. Particularly, when the pathological type of metachronous second lung cancer is the same as the first one, it is hard to determine its origin (primary or metastatic lung cancer). Although assessment on several clinical parameters, including the location of the primary tumor and metastatic node, tumor diameter, histology, and cancer-free survival, have long been used to distinguish metachronous primary lung cancer (MPLC) from metastasis (6-8). However, these suggestions remain controversial owing to contradictory results reported by series of studies (9-11). This makes it difficult to obtain an accurate stage on a current staging system, and restrict the development of effective prognostication and appropriate treatment decision. Therefore, establishing a TNM-like risk stratification system in the premise of suspending the dispute of tumor clonality for metachronous second pulmonary adenocarcinoma (msPAD) patients with previously resected PAD is still merit.

In this study, we used the population-based Surveillance, Epidemiology, and End Results (SEER) registry to include msPAD patients with previously resected PAD. This study aims to establish a TNM-like risk stratification system on the premise of laying aside the dispute of tumor clonality for these patients. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1982/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-2021-186-01). A statement that the participants gave informed consent before taking part is not required because this study is performed on an established retrospective database. 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 AK Custom database (2000 to 2015) with additional treatment fields who had pathologically confirmed lung cancer with adenocarcinoma (International Classification of Disease for Oncology, Third edition: 8140, 8144, 8230, 8250, 8253, 8254, 8255, 8260, 8333, and 8480) as their first malignant tumor and suffered metachronous NSCLC in their patient history were screened. In this cohort, we identified patients according to the following criteria: (I) received surgical resection (lobectomy, sublobectomy, or pneumonectomy) for the primary; (II) the pathology for metachronous NSCLC was ADC pathology (International Classification of Disease for Oncology, Third edition: 8140, 8144, 8230, 8250, 8253, 8254, 8255, 8260, 8333, and 8480). msPAD was defined as the second PAD which occurred after diagnosis of the first PAD, therefore patients with interval survival ≤1 month were excluded in this study. According to the 2015 World Health Organization Classification of Lung Tumors, patients with grade IV (undifferentiated) were excluded (12).

Information on the sociodemographic and clinicopathological features of patients of the primary PAD and msPAD were collected. For the primary tumors, the stage was manually performed according to the 8th TNM staging system (13). Because the tumor characteristic (primary or metastatic cancer) of msPAD is ambiguous, the pathological parameters of msPAD were recorded in the premise of laying aside the dispute of tumor clonality, including tumor diameter, node metastasis (negative, intrapulmonary metastasis, mediastinal metastasis), and extrapulmonary metastasis (no, yes). To verify the efficacy of the risk stratification system, we also extracted the stage record of the msPAD from the SEER database as well. 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) and R 3.3.2 (http://www.r-project.org). Survival data of patients

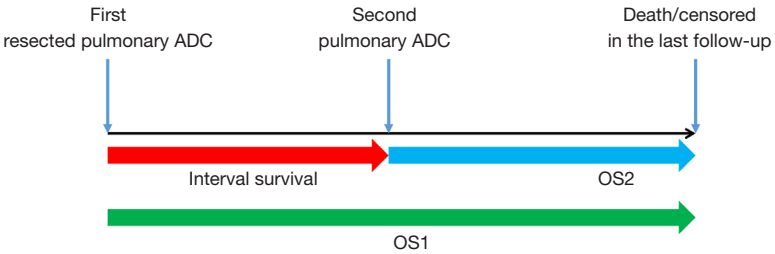

Figure 1 Definition of OS1, OS2, and interval survival for patients with metachronous second adenocarcinoma cell lung cancer. OS1, overall survival 1; OS2, overall survival 2.

with the primary tumors were extracted and defined as overall survival 1 (OS1), and the survival data of the msPAD were extracted and defined as the overall survival 2 (OS2). The interval between the diagnosis of the two PADs was recorded as the interval survival (*Figure 1*). The survival rate was calculated using the Kaplan-Meier method. Univariate and multivariate Cox regressions were constructed to identify independent predictors for interval survival, OS1, and OS2. In this study, the main objective is OS2. According to the criteria for the diagnosis of metachronous second primary lung cancer (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 (8). Statistical significance was assumed at a two-sided P<0.05.

Then, we built a nomogram system involving independent pathological parameters through the survival and rms package. A new decision tree group through recursive partitioning analysis (RPA) was established for risk stratification for OS2. To validate the effectiveness of the proposed TNM-like risk stratification system, we calculated the Akaike information criterion (AIC) and the concordance index (c-index) and carried out a time-dependent receiver operating curve (ROC) analysis (14). In this research, the nomogram score is the only predictor, and the PRA and time-dependent ROC curves were performed using R 3.3.2 (http://www.r-project.org) with the rpart package and survival ROC package, all parameters were set as default values.

Results

Patients' characteristics

A total of 1,045 patients were met the mentioned criteria and included in this study. The median age of the primary and msPAD was 64 (range, 37 to 88) and 69 (range, 39 to 93) years, respectively. The median tumor diameters of the primary and msPAD were 23 (range, 4 to 95) and 17 (range, 2 to 95) mm, respectively. There were 751 (71.9%) msPAD located in the contralateral side to the primary. Third metachronous PAD was observed in 63 patients. Time distribution of the diagnosis of the primary PAD and msPAD was shown in Figure S1. The median survival time for the interval survival, OS1 and OS2 were 42, 112, and 51 months, respectively. The patients' characteristics were listed in *Table 1*. Flow chart of patient recruitment is shown in *Figure 2*.

Predictors for interval survival, OS1, and OS2

After univariate and multivariate analysis, several independent prognostic factors were identified (*Table 2*). For interval survival, these parameters included gender, age (1st), side of second ADC, chemotherapy (1st), surgery (1st), tumor diameter (2nd), and node metastasis (2nd). For OS1, these parameters included gender, age (1st), surgery (1st), T status (1st), tumor diameter (2nd), node metastasis (2nd), grade (2nd), extrapulmonary metastasis, and interval survival. For OS2, these parameters included gender, race, age (1st), tumor diameter (2nd), node metastasis (2nd), grade (2nd), and extrapulmonary metastasis.

Nomogram and RPA stratification for OS2

A nomogram that incorporated aforementioned independently pathological factors was established for OS2 (*Figure 3A*). The calibration plots presented well agreement between the nomogram prediction and actual observation for 1-, 3-, and 5-year survival rate (*Figure 3B*). Then, we perform RPA for the dichotomous OS according to the nomogram score, partitioned the patient population into three risk strata defined as the followings: low

Table 1 Patient characteristics

Variable	Case number (%)
Gender	
Male	425 (40.7)
Female	620 (59.3)
Race	
White	874 (83.6)
Black	104 (10.0)
Others	67 (6.4)
Age (1st) (years)	
<70	749 (71.7)
≥70	296 (28.3)
Location (1st)	
Left upper	305 (29.2)
Left lower	132 (12.6)
Right upper	361 (34.5)
Right middle	57 (5.5)
Right lower	156 (96.7)
Unknown	34 (3.3)
Tumor diameter (1st) (mm), mean ± SD	26.7±14.6
T status (1st)	
T1	525 (50.2)
T2	384 (36.7)
T3	103 (9.9)
T4	33 (3.2)
Nodal status (1st)	
N0	790 (75.6)
N1	100 (9.6)
N2	132 (12.6)
N3	23 (2.2)
Grade (1st)	
I	160 (15.3)
II	483 (46.2)
III	359 (34.4)
Unknown	43 (4.1)
Distant metastasis (1st)	
M0	892 (85.4)
M1	153 (14.6)
Stage (1st)	
I	562 (53.8)
II	196 (18.8)
III	134 (12.8)
IV	153 (14.6)
Surgery (1st)	
Sublobectomy	165 (15.8)
Lobectomy	860 (82.3)
Pneumonectomy	20 (1.9)
Chemotherapy (1st)	
Yes	227 (21.7)
No/unknown	818 (78.3)
Radiotherapy (1st)	
Yes	92 (8.8)
No/unknown	953 (91.2)
Interval survival (months)	
<24	317 (30.3)
24–47	284 (27.2)
≥48	444 (42.5)
Age (2nd) (years)	
<70	565 (54.1)
≥70	480 (45.9)
Location (2nd)	
Left upper	278 (26.6)
Left lower	210 (20.1)
Right upper	257 (24.6)
Right middle	74 (7.1)
Right lower	189 (18.1)
Unknown	37 (3.5)
Tumor diameter (2nd) (mm), mean ± SD	20.3±12.9
Node metastasis (2nd)	
Negative	852 (81.5)
Intrapulmonary metastasis	72 (6.9)
Mediastinal metastasis	121 (11.6)

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Case number (%)
Extrapulmonary metastasis (2nd)	
No	991 (94.8)
Yes	54 (5.2)
Grade (2nd)	
I	269 (25.7)
II	461 (44.1)
III	315 (30.1)
Stage (2nd)	
I	444 (42.5)
II	82 (7.8)
III	84 (8.0)
IV	376 (36.0)
Unknown	59 (5.6)
Surgery (2nd)	
No surgery	325 (31.1)
Sublobectomy	442 (42.3)
Lobectomy	278 (26.6)
Chemotherapy (2nd)	
Yes	248 (23.7)
No/unknown	797 (76.3)
Radiotherapy (2nd)	
Yes	251 (24.0)
No/unknown	794 (76.0)
Followed ADC	
No	982 (94.0)
Yes	63 (6.0)

ADC, adenocarcinoma.

risk (nomogram score <35), moderate risk (nomogram score ≥35 & <76), and high risk (nomogram score >76) (Figure S2A). The RPA stratification system present well-operating characteristics for stratification of OS2 (P<0.001) (Figure S2B).

Proposed a TNM-like risk stratification for OS2

A TNM-like risk stratification system for OS2 was established on tumor diameter (2nd), node metastasis (2nd), grade (2nd), and extrapulmonary metastasis (2nd), based on the nomogram and PRA analysis (*Table 3*). The median survival after msPAD for category I, II, III, and IV was 88, 58, 32, and 12 months, respectively (P<0.001) (*Figure 3C*). However, according to the extracted stage information, survival curves were overlapped as the long-term survival of cases with stage IV was similar to that of cases with stage II (P=0.308) but better than that of cases with stage III (P<0.001) (*Figure 3D*). The AIC value for the proposed risk classification was smaller than that for the applied staging system (5,890.612 *vs.* 6,015.516). The c-index value was larger for the proposed version than for the applied staging system (0.656 *vs.* 0.572, P<0.001). Meanwhile, according to the time-dependent ROC curve, the predict accuracy of the proposed risk stratification system is better than the TNM stage system at 160 months of follow-up (*Figure 3E*).

Then, the entire cohort is stratified into three group according to the diagnosis year (2000–2005, 2006–2010, and 2011–2015), the sample size for each group is 117, 394, and 534, respectively. As shown in Figure S3, the calibration plots presented well agreement between the nomogram prediction which is established on the entire cohort and actual observation for 1-, 3-, and 5-year survival in all three subgroups. The proposed risk stratification system presented a higher prediction accuracy on prognosis than the TNM stage system in all three groups according to the time-dependent ROC curve (Figure S3). Furthermore, the proposed risk stratification system could distinguish the OS2 well in all stages (I, P<0.001; II, P=0.004; III, P<0.001; IV, P<0.001) (*Figure 4*).

Then we estimated the association between treatment decision and OS2 in patients with different risk categories (*Figure 5*). Chemotherapy would improve prognosis in patients in IV category (P=0.028) and those without surgery (P=0.015). Radiotherapy would improve prognosis in patients without surgery (P=0.034). While surgery could benefit prognosis in patients with II (P<0.001) and III (P=0.049) category. In addition, the effectiveness of sublobectomy is comparable to lobectomy in all categories.

Discussion

In this study, we observed longer interval survival in the younger female patients. This might be correlated to the fact that the risk for lung cancer development is relatively low in this cohort (15). More aggressive resection in the first time is associated with less residual pulmonary tissue, which

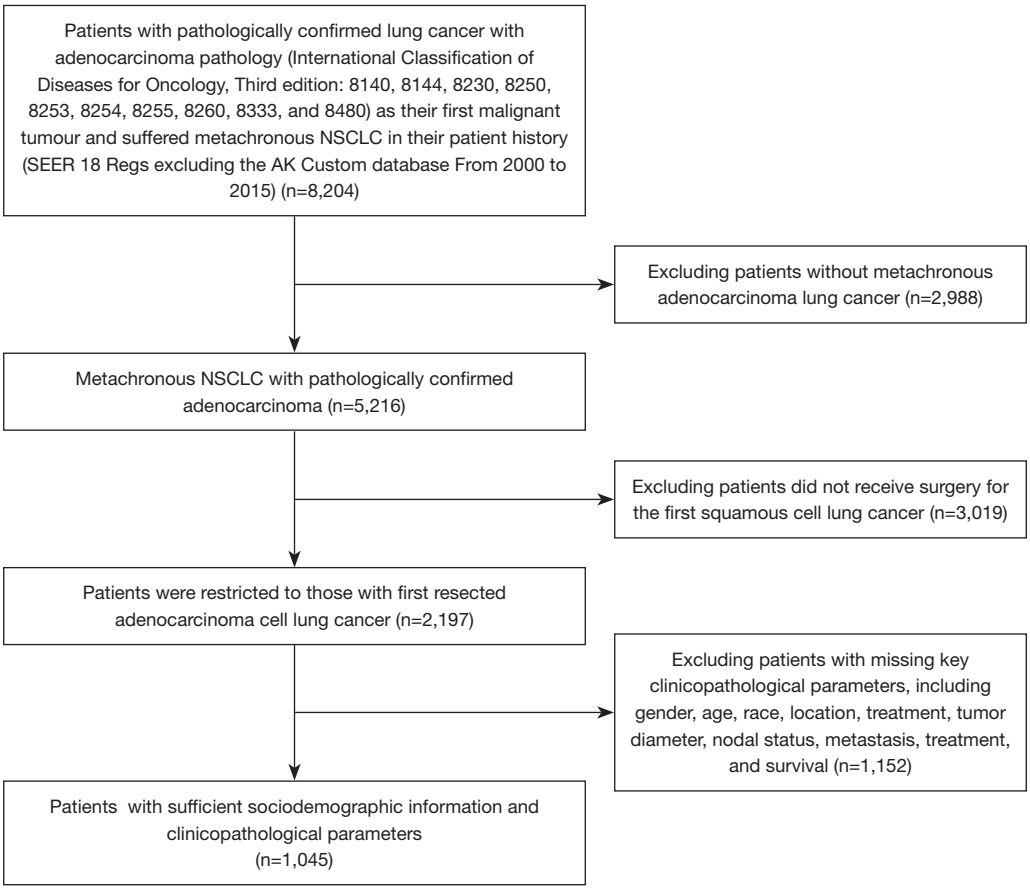

Figure 2 Flow chart of patient recruitment. NSCLC, non-small cell lung cancer.

reduces the rate to develop metachronous lung cancer and thus is associated with shorter interval survival. Besides, shorter interval survival was observed in contralateral msPAD. This might be partially explained by the process of unction compensation. Because the contralateral pulmonary function is accounted for a larger proportion after the first resection, metachronous lung cancer is more likely to be located in the contralateral side. This speculation is in line with the observation that there are most metachronous (80.2%) lung cancers in the contralateral lobe after first resection (16).

The interval survival has long been regarded as an important indicator for the tumor clonality of metachronous multiple lung cancer. In the first edition of diagnostic criteria proposed by Martini *et al.*, time interval >2 years is a necessary condition for the diagnosis of metachronous multiple primary lung cancer (mMPLC) (17). 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 the interval survival <2 years is a necessary condition for metastatic lung cancer (7). This suggestion is still used in the following editions (6,8). However, in this study, there is no significant association between interval survival between OS2, even in the univariate analysis (P=0.105). A similar result is also reported by Hamaji *et al.* (9). It has been widely accepted that the characteristic of tumor clonality would greatly impact long-term survival. It is plausible that, because interval survival is not a predictor for OS2, it should not be an essential factor to distinguish tumor clonality. The criterion for mMPLC, especially in the issue of interval survival, might be biased and merit further modification.

According to the extracted stage information, overlaps among OS2 are commonly observed. Because the methodology to distinguish tumor clonality is still biased, some patients with truly primary PAD might be overestimated, and some patients with truly metastatic PAD might be underestimated. To establish a TNM-like

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

Variables	Univariate analysis				Multivariate analysis			
	HR	95% CI	P	P_{trend}	Adjusted HR	95% CI	P	P_{trend}
Interval survival								
Gender	0.827	0.731–0.936	0.003		0.807	0.710–0.918	0.001	
Age (1st)	1.293	1.129–1.480	<0.001		1.304	1.132–1.502	<0.001	
Side of second ADC (ipsilateral/contralateral)	1.321	1.154–1.513	<0.001		1.365	1.185–1.573	<0.001	
Grade difference (same/different)	0.880	0.777–0.997	0.045		0.889	0.784–1.007	0.064	
Chemotherapy (1st)	0.852	0.735–0.987	0.033		0.858	0.736–1.000	0.050	
Surgery (1st)								
Sublobectomy	1			<0.001	1			0.002
Lobectomy	0.700	0.592–0.827	<0.001		0.727	0.611–0.866	<0.001	
Pneumonectomy	0.676	0.906–1.441	0.676		0.765	0.467–1.253	0.287	
Tumor diameter (2nd)	0.983	0.978–0.988	<0.001		0.984	0.979–0.990	<0.001	
Node metastasis (2nd)								
Negative	1			<0.001	1			0.024
Intrapulmonary metastasis	0.987	0.776–1.256	0.917		1.094	0.850–1.407	0.485	
Mediastinal metastasis	0.629	0.519–0.763	<0.001		0.767	0.624–0.943	0.012	
Extrapulmonary metastasis	0.619	0.469–0.817	0.001		0.814	0.604–1.099	0.179	
Overall survival 1								
Gender	0.741	0.624–0.881	0.001		0.792	0.664–0.945	0.009	
Age (1st)	1.595	1.323–1.924	<0.001		1.509	1.246–1.827	<0.001	
Side of second ADC (ipsilateral/contralateral)	1.278	1.051–1.554	0.014		1.208	0.839–1.258	0.793	
Surgery (1st)								
Sublobectomy	1			0.013	1			0.039
Lobectomy	0.708	0.561–0.894	0.004		0.743	0.584–0.934	0.016	
Pneumonectomy	0.866	0.473–1.585	0.641		0.611	0.330–1.132	0.117	
T status (1st)								
T1	1			0.019	1			0.001
T2	1.020	0.847–1.230	0.832		1.110	0.917–1.344	0.285	
T3	0.928	0.690–1.249	0.623		0.911	0.673–1.232	0.543	
T4	1.994	1.278–3.114	0.002		2.542	1.606–4.024	<0.001	
Tumor diameter (2nd)	1.010	1.004–1.016	<0.001		1.013	1.007–1.020	<0.001	
Node metastasis (2nd)								
Negative	1			<0.001	1			<0.001
Intrapulmonary metastasis	1.739	1.276–2.370	<0.001		1.642	1.196–2.254	0.002	
Mediastinal metastasis	1.529	1.210–1.932	<0.001		2.013	1.544–2.623	<0.001	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate analysis				Multivariate analysis			
	HR	95% CI	P	P_{trend}	Adjusted HR	95% CI	P	P_{trend}
Grade (2nd)								
I	1			0.005	1			0.009
II	1.262	1.003–1.587	0.047		1.332	1.056–1.681	0.015	
III	1.488	1.170–1.892	0.001		1.465	1.143–1.877	0.003	
Extrapulmonary metastasis	1.552	1.132–2.128	0.006		1.458	1.041–2.044	0.028	
Interval survival, months								
<24	1			<0.001	1			<0.001
24–47	0.536	0.429–0.670	<0.001		0.483	0.385–0.607	<0.001	
≥48	0.254	0.206–0.312	<0.001		0.183	0.146–0.231	<0.001	
Overall survival 2								
Gender	0.834	0.702–0.991	0.039		0.791	0.664–0.942	0.009	
Race								
White	1			0.049	1			0.034
Black	0.950	0.711–1.269	0.727		0.887	0.660–1.191	0.425	
Others	0.585	0.381–0.898	0.014		0.573	0.371–0.884	0.012	
Age (1st)	1.369	1.137–1.648	0.001		1.446	1.197–1.747	<0.001	
Age (2nd)	1.335	1.123–1.587	0.001		1.120	0.873–1.437	0.372	
Tumor diameter (2nd)	1.028	1.023–1.033	<0.001		1.022	1.016–1.028	<0.001	
Node metastasis (2nd)								
Negative	1			<0.001	1			<0.001
Intrapulmonary metastasis	1.985	1.457–2.704	<0.001		1.673	1.219–2.296	0.001	
Mediastinal metastasis	3.066	2.418–3.886	<0.001		2.489	1.937–3.199	<0.001	
Grade (2nd)								
I	1			<0.001	1			0.001
II	1.313	1.044–1.651	0.020		1.260	1.000–1.588	0.050	
III	1.825	1.435–2.321	<0.001		1.566	1.227–1.999	<0.001	
Extrapulmonary metastasis	2.944	2.144–4.044	<0.001		2.342	1.677–3.271	<0.001	
Followed ADC	0.644	0.456–0.908	0.012		0.723	0.510–1.024	0.068	

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

stratification system in the context of suspending dispute for the tumor clonality, including pathologic parameters were designed in a compromise way. For example, we applied tumor diameter to describe primary tumor status. Node status was reclassified into three groups, including negative, intrapulmonary metastasis, and mediastinal metastasis. Definition of distant metastasis in the current TNM stage was replaced into expulmonary metastasis. We found that the proposed risk stratification system well stratify the prognosis.

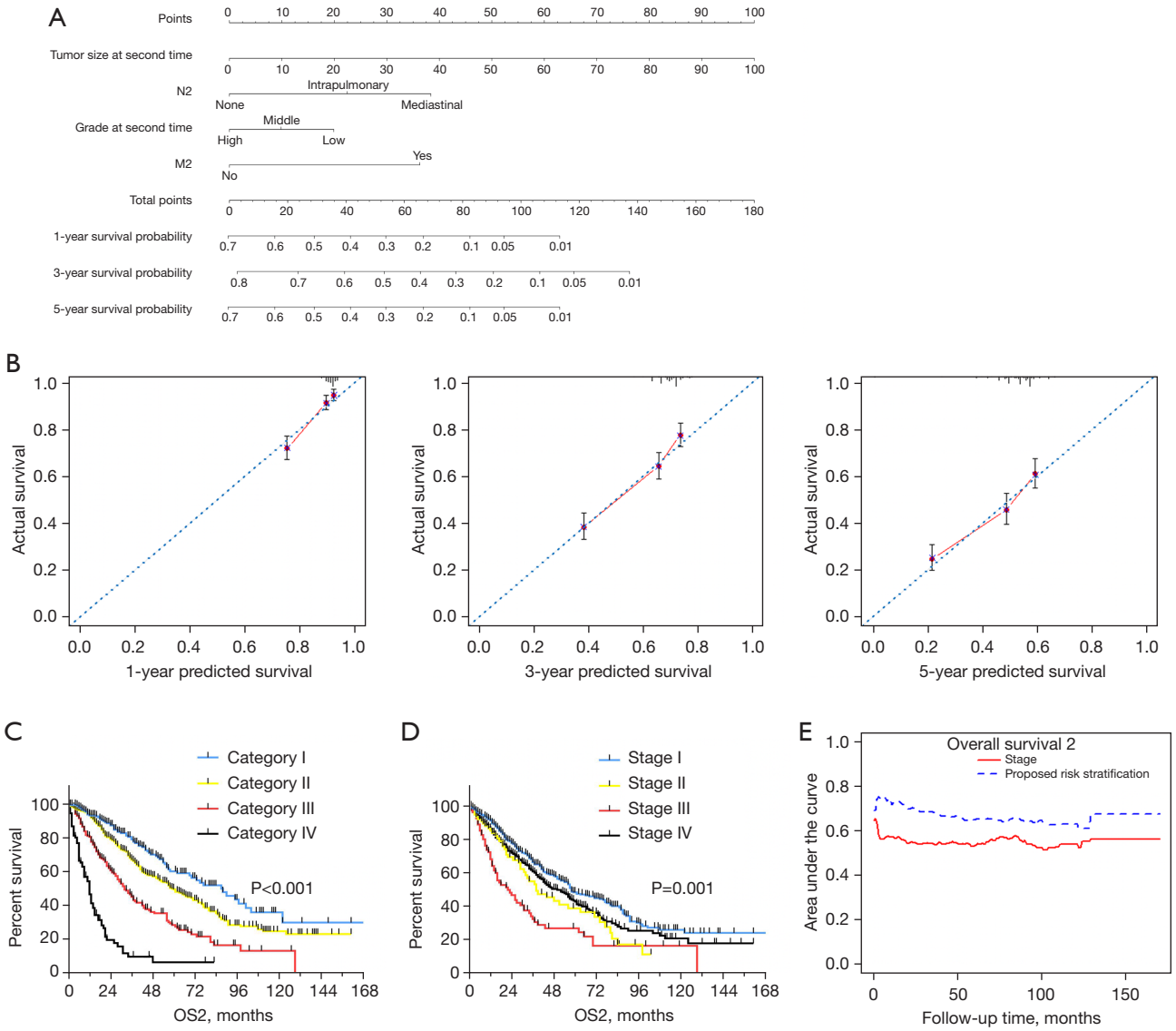

Figure 3 Establishment of a risk stratification based on nomogram. (A) Prognostic nomogram for overall survival 2 (OS2) in patients with metachronous second adenocarcinoma cell lung cancer; (B) the calibration curves for predicting patient survival at each time point; (C) the Kaplan-Meier survival curve for OS2 is well stratified by the recursive partitioning analysis (RPA) risk group; (D) overlap among different survival curves is observed according to the current staging system; (E) the predict accuracy of the proposed risk stratification system is better than the TNM stage system at 160 months of follow up according to the time-dependent receiver operating curve (ROC) curve. TNM, tumor, node, metastasis.

In addition, the proposed risk system yields a smaller AIC, but higher c-index than the TNM staging system. Besides, the AUC value from the proposed risk stratification is usually higher than that from the staging system with 160 months of follow-up. The risk system seems to be reliable for prognostication.

In this study, characteristics of the msPAD were included in the analysis of interval survival. In our opinion, when the msPAD is found and treated in early stage, the interval survival is short; when the msPAD is found and treated in advanced stage, the interval survival is long. In addition, it is plausible that, the characteristics of first PAD should impact OS2 as well. Therefore, in the survival analysis of OS2, characteristics of the first primary lung cancer were involved. We found that, although the T status (1st) present significant association with OS2 in the univariate

Table 3 Tentative risk stratification on pathological parameters for overall survival 2

Tumor diameter (2nd)	Node metastasis (2nd)			Grade (2nd)	Extrapulmonary metastasis (2nd)
	Negative	Intrapulmonary	Mediastinal		
≤30 mm	Category I	Category III	Category III	I	No
	Category II	Category III	Category III	II-III	No
>30 & ≤70 mm	Category III	Category IV	Category IV	Any	No
>70 mm	Category IV	Category IV	Category IV	Any	No
≤30 mm	Category III	Category IV	Category IV	I	Yes
	Category III	Category IV	Category IV	I	Yes
>30 mm	Category IV	Category IV	Category IV	Any	Yes

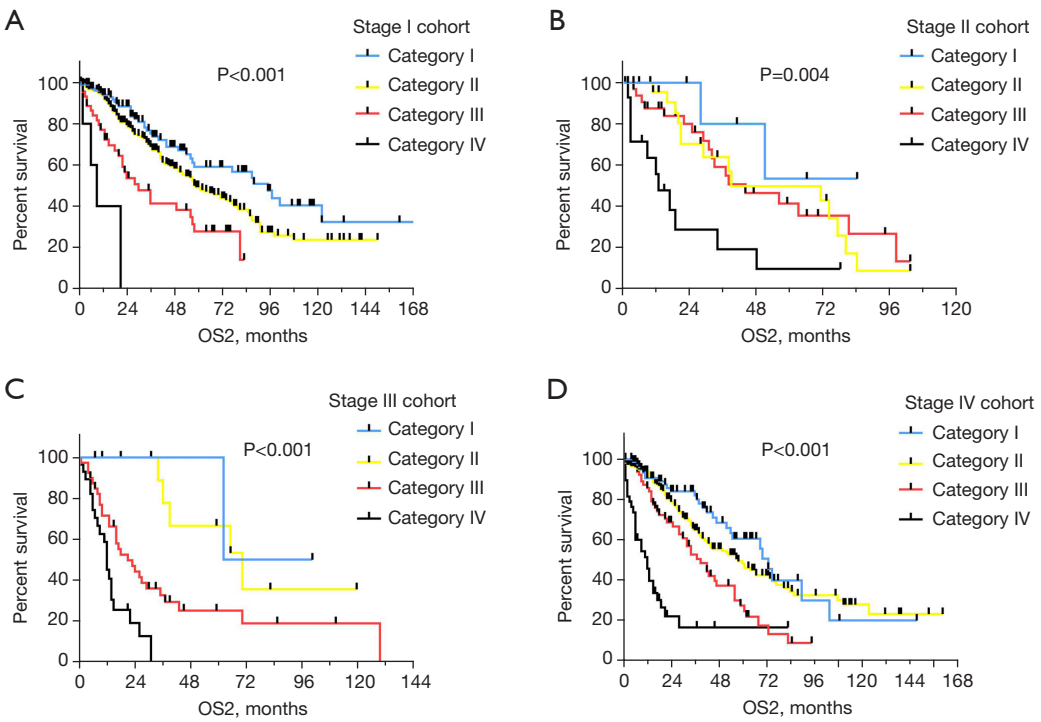

Figure 4 The proposed risk stratification system well stratified the prognosis among patients with stage I (A), stage II (B), stage III (C), and stage IV (D) according to the TNM staging system. OS2, overall survival 2; TNM, tumor, node, metastasis.

analysis (P=0.045), however, it missed significance after adjusting other confounders in the multivariate analysis. Thus, the tentative risk stratification system was established on the characteristics of first primary lung cancer. For this phenomenon, there is two potential explanations. The first is that, the characteristics of the msPAD play an more important impact on OS2 than PAD. The second is that, the tumor clonality of the msPAD is still unclear, therefore its association with the first primary lung cancer is still unknown, which would greatly limit the impact of first primary lung cancer on OS2.

It has been widely accepted that surgery is an effective treatment for operable metachronous lung cancer (9,16). Similarly, in this study, surgery is associated with longer survival in patients with category II (P<0.001) and III (P=0.049) category. For patients with category I risk,

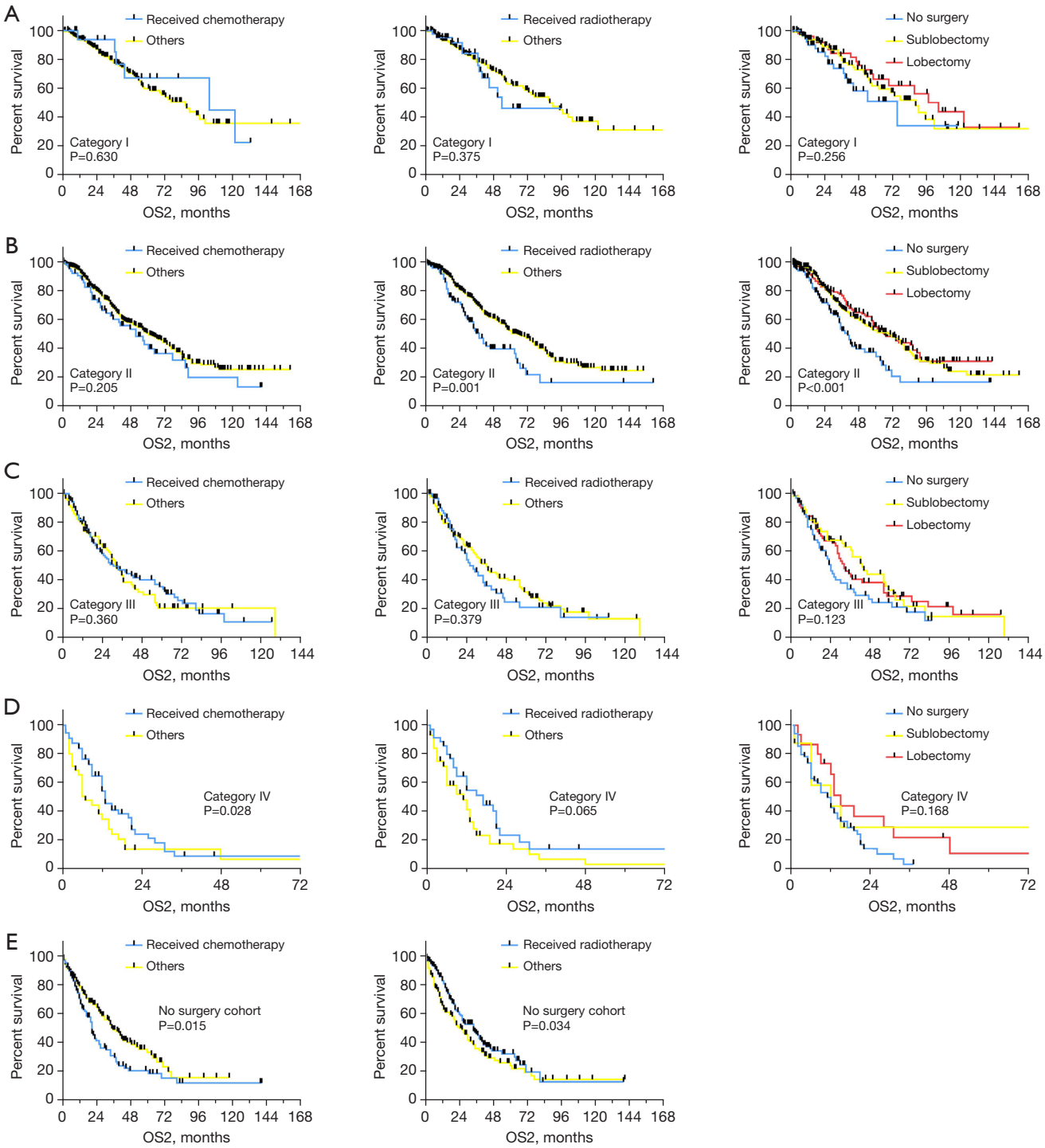

Figure 5 The impact of radiotherapy, chemotherapy, and surgery on overall survival 2 for category I risk (A), category II risk (B), category III risk (C), category IV group (D), and no surgery group (E). OS2, overall survival 2.

surgery is associated with longer survival than those without (median OS2, 90 *vs.* 75 months), although the difference is not statistically significant (P=0.132). Therefore, we recommended performing surgery for patients with categories I, II, and III. Sublobectomy is a preferred plan on the premise of ensuring sufficient margin distance.

The findings of the present study should be considered in the context of certain weaknesses. First, because of the nature of SEER data, some well-known prognostic factors such as ground-glass opacity (GGO) ratio, cigarette smoking, and tumor markers were not included. Second, because the source problem of tumor clonality is not solved by our study, the proposed system could only be considered as a risk stratification rather than a staging system, although it is proved with well capacity in predicting and stratifying prognosis. Because the risk stratification is established in the premise of suspending dispute of tumor clonality, it is not suitable for msPAD when the tumor clonality is identified, such as pathologically confirmed ADC *in situ* and radiographically observed pure GGO (18). moreover, because the biological behavior of lung squamous cell carcinoma (SCC) is significantly different from PAD, especially in recurrence/metastatic pattern and multiple nodule model, our results could not be applied for metachronous second SCC patients after previously resected pulmonary SCC (19,20). Finally, although we carried out 1000 bootstrap resamples for interval validation, further external validation with other populations is still needed.

In conclusion, the TNM-like risk stratification appears to be suitable for prognostic prediction and risk stratification for msPAD patients with former PAD resection. This model validates and refines the known classification rules based on the easily collected variables, and highlights potential implications for clinical management and study design.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1982/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1982/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1982/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-2021-186-01). A statement that the participants gave informed consent before taking part is not required because this study is performed on an established retrospective database.

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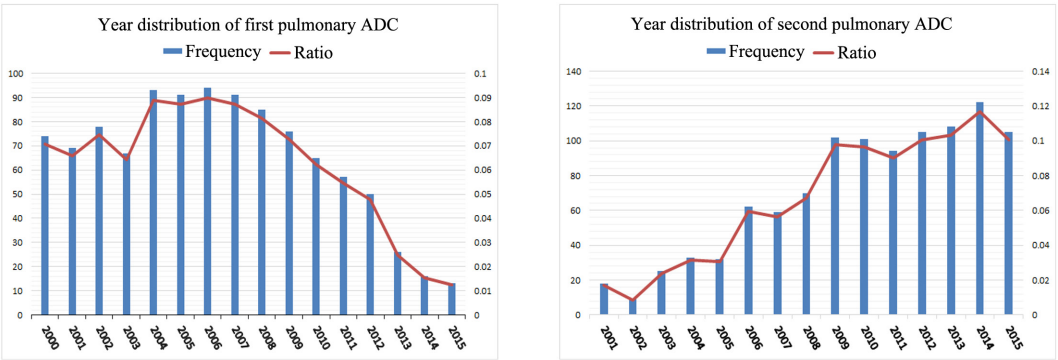

Figure S1 Year distribution of the first pulmonary adenocarcinoma cell carcinoma and second pulmonary adenocarcinoma cell carcinoma.

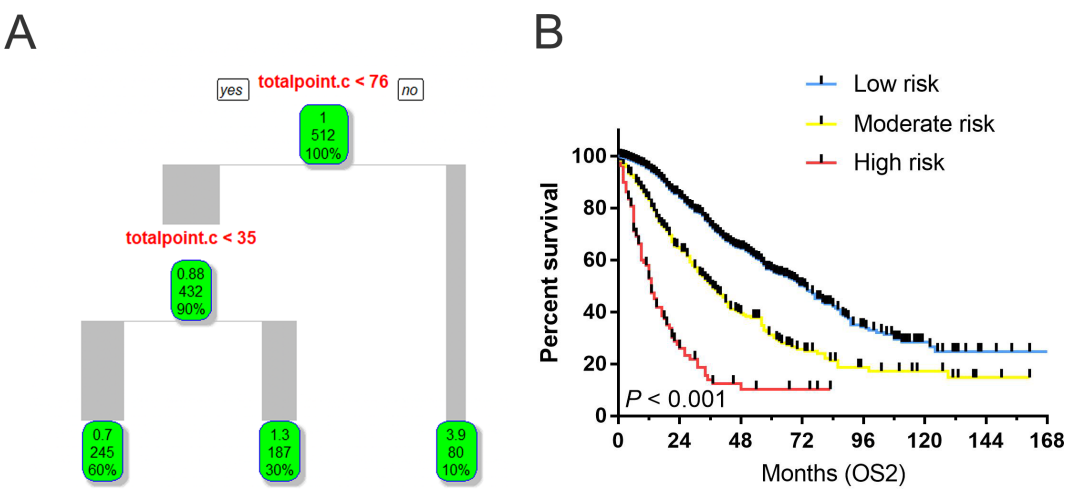

Figure S2 The recursive partitioning analysis (RPA) grouping into three risk categories for OS2 (A); the Kaplan-Meier survival curve for OS2 is well stratified by the RPA risk stratification system (B).

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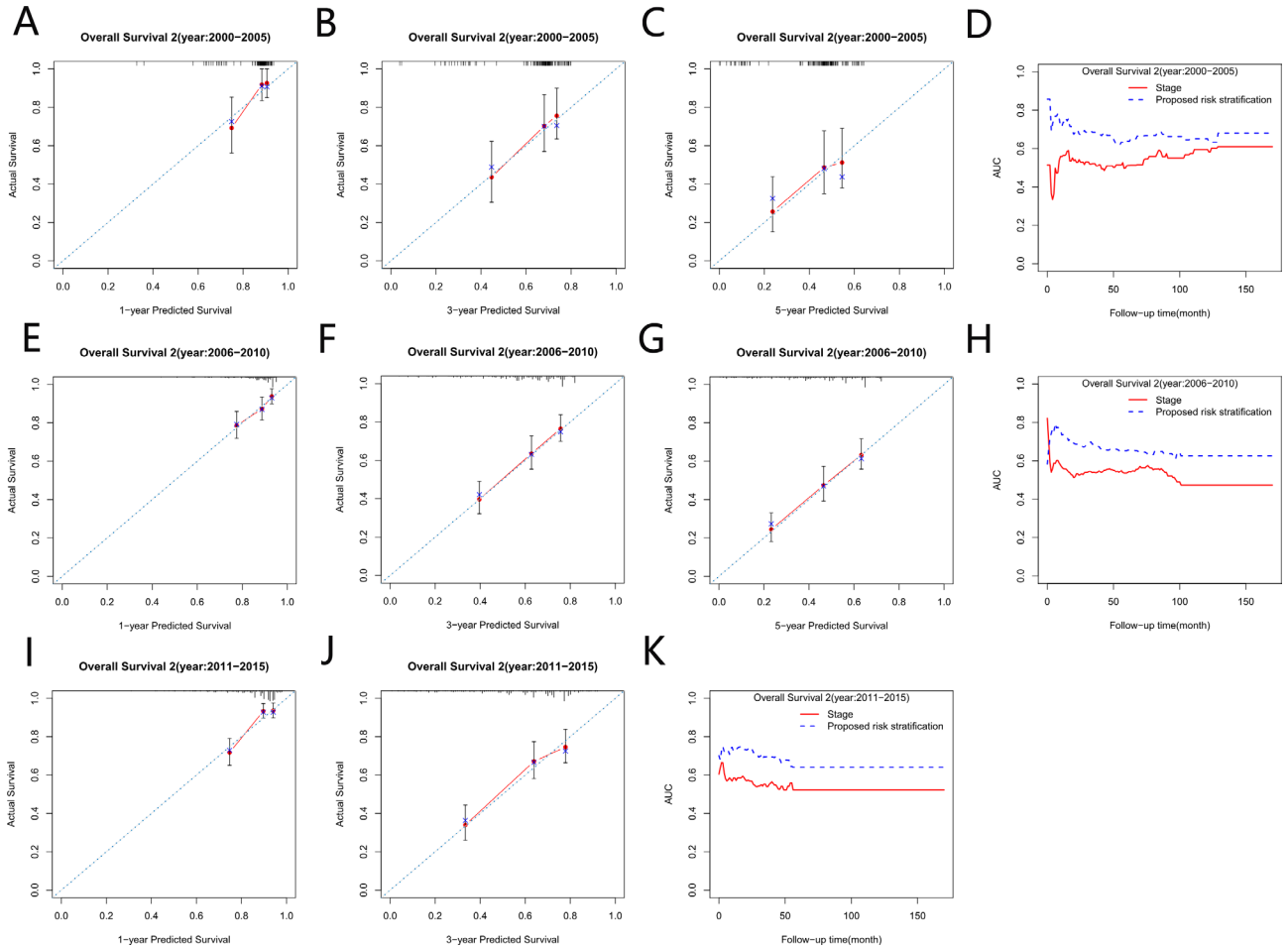

Figure S3 The proposed risk stratification system present a higher predict accuracy on prognosis than the TNM stage system in patients with 2000-2005 group (A/B/C/D), and 2006-2010 group (E/F/G/H), and 2011-2015 group (I/J/K).

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