Improvement of pathological staging system for neuroendocrine tumors of the lung

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Background: Currently, the tumor, node, and metastasis (TNM) staging system has a limited value in prognostic stratification for neuroendocrine tumors of the lung (NETL). A specific pathological staging system was therefore explored.

Methods: Two cohorts were assessed: the training cohort was composed of surgically treated patients from the Surveillance, Epidemiologic, and End Results (SEER) database [2004–2015]; the Shanghai cohort included Shanghai resident patients treated at Shanghai Pulmonary Hospital [2009–2018]. Multivariable Cox regression analysis was performed to identify factors associated with overall survival. A new staging system was proposed based on survival tree, and was further compared with the 8th edition of the TNM staging system.

Results: In the training set (n=3,204), multivariate Cox analysis showed that tumor histotype and nodal status were independently associated with survival, but not T stage. Therefore, by incorporating NETL histotype (G1, low-grade typical pulmonary carcinoids; G2, intermediate-grade atypical pulmonary carcinoids; G3, high-grade large-cell neuroendocrine carcinomas) and N stage, a new staging system was developed: IA, G1N0; IB, G1N1 or G2N0; II, G1N2, G2N1-2, or G3N0; III, G3N1-2. Five-year survival rates were 91.2%, 81.3%, 50.2% and 27.6% for the new stages IA to III in the validation set (n=3,204), respectively (P<0.001). Additionally, the new staging system had significantly better predictive ability than the TNM staging system, in both the SEER [C-index, 0.75 *vs.* 0.62; net reclassification improvement (NRI), 0.62; integrated discrimination improvement (IDI), 20%] and Shanghai (IDI, 8%) cohorts. Based on the new staging system, adjuvant chemotherapy conferred a significantly better survival in stage-III NETL cases (HR =0.34, 95% CI, 0.25–0.45).

Conclusions: The new pathological staging system can better predict NETL prognosis than the 8th edition of the TNM staging system, with the potential to guide postoperative treatment.

Keywords: Neuroendocrine tumor; TNM stage; lung cancer; survival; adjuvant chemotherapy

Introduction

Neuroendocrine tumors of the lung (NETL) constitute a unique clinical subgroup of primary pulmonary cancers, with particular morphological, ultrastructural, immunohistochemical and molecular characteristics. Tumor histotype and differentiation are crucial determinants of the clinical behavior of NETL. Well-differentiated NETL consist of low-grade typical pulmonary carcinoids and intermediate-grade atypical pulmonary carcinoids, while poorly differentiated tumors include high-grade large cell neuroendocrine carcinomas and small-cell lung cancer (SCLC) (1). The incidence of neuroendocrine tumors approximates 5.25 cases per 100,000 persons in the United States (2). Owing to the increased lung cancer screening, NETL prevalence currently has the fastest growth (3).

The International Association for the Study of Lung Cancer launched a worldwide tumor, node, and metastasis (TNM) staging project (4,5), and the TNM staging system is used for NETL. However, a recent study pointed out that staging systems for NETL should include histotype (6). Further, the use of tumor size for staging the T-category in lung carcinoids has been questioned (7). Therefore, staging of these tumors needs to be optimized. This study aimed to develop a new pathological staging system that could refine prognostic stratification and guide subsequent treatment in NETL. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-5910).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study population

Patient data were obtained from the Surveillance, Epidemiologic, and End Results (SEER) database. Inclusion criteria were: site recode "ICD-O-3/WHO 2008" (International Classification of Diseases for Oncology, Third Edition) restricted to "Lung and Bronchus"; histotype pathologically confirmed as typical pulmonary carcinoids {ICD-O-3 [8240/3]}, atypical pulmonary carcinoids {ICD-O-3 [8249/3]} or large cell neuroendocrine carcinomas {ICD-O-3 [8013/3]} between 2004 and 2015; known patient age, TNM stage, and survival data; surgical treatment. Considering its strong invasion ability and unique pathological characteristics, SCLC was not included

in this study (6). Besides, patients whose tumors could not be confirmed for diaphragm invasion status were excluded. TNM staging was converted to the 8th edition of the TNM staging system (5). Low-grade (typical pulmonary carcinoids), intermediate-grade (atypical pulmonary carcinoids) and high-grade (large-cell neuroendocrine carcinomas) neuroendocrine histotypes were designated as G1, G2 and G3, respectively. Overall survival was used as an endpoint of survival. Patients not diagnosed with NETL for the first time were excluded. Finally, 6,408 patients were included.

In the Shanghai cohort, Shanghai resident patients administered lung resection and pathologically confirmed with G1, G2 and G3 histotypes, respectively, at Shanghai Pulmonary Hospital between January 2009 and September 2018 were included. The pathologic diagnosis was confirmed after bronchoscopic examination, percutaneous lung puncture and/or surgical resection according to the 2015 World Health Organization (WHO) classification (1). Patients with no TNM stage assessment or survival data were excluded (Figure S1). According to the National Comprehensive Cancer Network (NCCN) guidelines (8), surgical resection was administered in TNM stage-I to II and select stage-III patients. Adjuvant treatment was routinely recommended for TNM stage-IIB to IIIB patients and individuals with stage IB-IIA large-cell neuroendocrine carcinoma, and comprised 4–6 cycles of a platinum-based doublet therapy.

Study design

In the SEER cohort, patients were randomly assigned at a 1:1 ratio to the training (n=3,204) and validation (n=3,204) sets. In the SEER training set, significant variables were selected to generate a survival tree by hazards ratio (HR) for survival. A new staging system was proposed by incorporating groups with similar HRs and validated in the SEER validation set. Moreover, the new and TNM staging systems were compared in the SEER and Shanghai cohorts. Furthermore, for patients in whom adjuvant chemotherapy is recommended based on the NCCN guidelines (TNM stages IIB to IIIB; IB and IIA large-cell neuroendocrine carcinomas), the value of adjuvant chemotherapy based on the TNM and new staging systems was assessed.

Statistical analysis

Continuous variables with normal distribution were

presented as mean ± standard deviation (SD), and categorical data as number (percentage, %). Two-tailed *t*-test and the chi-square test were performed to examine the differences in clinical variables between the two sets. Overall survival curves were generated by the Kaplan-Meier method, and differences were examined by the log-rank test. Variables with P<0.1 in univariate analysis and treatment relevant parameters were included in multivariate Cox regression analysis and the random forest (RF) model, respectively. The proportional hazard assumption in the Cox model was tested based on the Schoenfeld residuals, and 1,000 bootstrapping replications were performed. C-index, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were further used to assess the survival prediction abilities of different staging systems. NRI was calculated from the survival probabilities of the ordered staging systems among those moving up and down the stage classifications (9), and IDI was calculated as the difference in the proportion of explained variation at time *t* between staging systems (10). A P value of less than 0.05 was considered statistically significant. Interaction assessments were performed by the likelihood ratio test. Kaplan-Meier curve generation and the log-rank test were performed with GraphPad Prism version 7.00 for Windows (GraphPad Software, Inc., www.graphpad.com). Statistical analysis was performed with the R version 3.5.3 software (http://www.r-project.org/).

Results

Establishment of a new staging system in the SEER cohort

In the SEER training group, 2,361 (73.7%) patients were identified as G1, 260 (8.1%) as G2 and 583 (18.2%) as G3; based on N stage, the majority (86.5%; n=2,772) of patients had N0 tumors. Lobectomy was performed in 2,207 (68.9) patients, and 1,917 (59.8%) underwent more than 3 regional lymph node samplings. In addition, adjuvant chemotherapy and radiotherapy (RT) were performed in 270 (8.4%) and 108 (3.4%) patients, respectively (*Table 1*).

Univariate Cox regression analysis showed that age, race, gender, histology, adjuvant chemotherapy, and TNM stage were all significant variables; however, hazards ratios for survival in TNM stages IA2 to IIA were similar, ranging from 0.96 to 1.33 (IA1 as reference, *Table 2*). Multivariate Cox analysis revealed that N stage was independently associated with survival, while T stage was not. The histotypes G2 (HR =2.42, 95% CI: 1.81–3.23) and G3 (HR

=5.89, 95% CI: 4.83–7.19) were significantly associated with reduced survival compared with G1. Consistently, histotype and N-stage were significantly associated with survival in the RF model (importance: 0.102, 0.005, *Table 2*). In subgroup analysis, tumor histotype could better discriminate patient survival in each subgroup of the N stage compared with the T stage (*Table 3*). Subgroup analysis based on histotype showed that the TNM stage was not suitable for discriminating patient survival in different histotypes (Table S1).

A survival tree was then built by regrouping tumor histotypes and nodal stages (*Figure 1*). A new pathological staging system was developed by incorporating groups with similar hazards ratios for survival, and included stages IA (G1N0), IB (G1N1 or G2N0), II (G1N2, G2N1-2, or G3N0) and III (G3N1-2).

In the SEER validation group, patient demographics followed a similar pattern: 2,358 (73.6%), 259 (8.1%) and 587 (18.3%) were diagnosed as G1, G2 and G3, respectively; the majority of patients had N0 tumors (85.3%; n=2,732; *Table 1*). Kaplan-Meier curves showed a good stratification of survival with 5-year survival rates of 91.2%, 81.3%, 50.2% and 27.6% for new stages IA, IB, II and III, respectively (P<0.001, Figure S2).

Comparison between the new and TNM staging systems in the SEER and Shanghai cohorts

In the SEER cohort, the new staging system showed better discrimination for survival than the TNM system (*Figure 2A,B*). The respective 5-year survival rates were 91.4%, 81.5%, 52.8% and 29.1% for stages IA, IB, II, and III according to the new system, respectively (P<0.001), and 83.7%, 86.1%, 85.4%, 83.5%, 82.3%, 69.1%, 58.5% and 55.5% in the TNM staging system, respectively (P<0.001). In the Cox proportional hazards model (*Table 4*), the new staging system had significantly better predictive ability compared with the 8th edition of the TNM staging system [C-index: 0.75 (95% CI: 0.74–0.76) *vs.* 0.62 (95% CI: 0.60–0.63)]. In addition, it enhanced the identification of high-risk patients with an NRI of 0.62 (95% CI: 0.55–0.68) and improved survival prediction with an IDI of 20% (95% CI: 18–23%).

In the Shanghai cohort, patient characteristics were different from those of the SEER cohort [more patients were male (46.5% *vs.* 34.6%, P<0.001) and G3 was the main group (49.2% *vs.* 18.3%, P<0.001), *Table 1*]. Kaplan-Meier curves showed 5-year survival rates of 98.1%, 85.7%,

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Table 1 Characteristics of the patients

Variables	Training group (n=3,204)	Validation group (n=3,204)	P value	SEER cohort (n=6,408)	Shanghai cohort (n=132)	P value
Age (mean ± SD)	60.3±14.1	60.6±14.0	0.48	60.5±14.1	59.8±9.7	0.58
Race, n (%)			0.59			–
White	2,886 (90.1)	2,869 (89.5)		5,755 (89.8)	–	
Black	198 (6.2)	218 (6.8)		416 (6.5)	–	
Others	120 (3.7)	117 (3.7)		237 (3.7)	–	
Male, n (%)	1,070 (33.4)	1,146 (35.8)	0.05	2,216 (34.6)	82 (46.5)	<0.001
Histotype, n (%)			0.99			<0.001
G1	2,361 (73.7)	2,358 (73.6)		4,719 (73.6)	61 (46.2)	
G2	260 (8.1)	259 (8.1)		519 (8.1)	6 (4.5)	
G3	583 (18.2)	587 (18.3)		1,170 (18.3)	65 (49.2)	
8th edition stage, n (%)			0.77			<0.001
IA1	351 (11.0)	355 (11.1)		706 (11.0)	20 (15.2)	
IA2	1,085 (33.9)	1,119 (34.9)		2,204 (34.4)	16 (12.1)	
IA3	584 (18.2)	583 (18.2)		1,167 (18.2)	12 (9.1)	
IB	473 (14.8)	427 (13.3)		900 (14.0)	35 (26.5)	
IIA	107 (3.3)	120 (3.7)		227 (3.5)	5 (3.8)	
IIB	322 (10.0)	324 (10.1)		646 (10.1)	16 (12.1)	
IIIA	254 (7.9)	244 (7.6)		498 (7.8)	26 (19.7)	
IIIB	28 (0.9)	32 (1.0)		60 (0.9)	2 (1.5)	
8th edition T stage, n (%)			0.28			<0.001
T1a	376 (11.7)	383 (12.0)		759 (11.8)	21 (15.9)	
T1b	1,184 (37.0)	1,223 (38.2)		2,407 (37.6)	20 (15.2)	
T1c	663 (20.7)	689 (21.5)		1,352 (21.1)	16 (12.1)	
T2a	597 (18.6)	549 (17.1)		1,146 (17.9)	45 (34.1)	
T2b	148 (4.6)	162 (5.1)		310 (4.8)	13 (9.8)	
T3	135 (4.2)	118 (3.7)		253 (3.9)	9 (6.8)	
T4	101 (3.2)	80 (2.5)		181 (2.8)	8 (6.1)	
8th edition N stage, n (%)			0.36			<0.001
N0	2,772 (86.5)	2,732 (85.3)		5,504 (85.9)	103 (78.0)	
N1	262 (8.2)	285 (8.9)		547 (8.5)	9 (6.8)	
N2	170 (5.3)	187 (5.8)		357 (5.6)	20 (15.2)	
Surgery, n (%)			0.59			0.104
Sub-lobectomy	871 (27.2)	857 (26.7)		1,728 (27.0)	25 (18.9)	
Lobectomy	2,207 (68.9)	2,201 (68.7)		4,408 (68.8)	99 (75.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Training group (n=3,204)	Validation group (n=3,204)	P value	SEER cohort (n=6,408)	Shanghai cohort (n=132)	P value
Pneumonectomy	114 (3.6)	129 (4.0)		243 (3.8)	8 (6.1)	
Unknow	12 (0.4)	17 (0.5)		29 (0.5)	0 (0.0)	
Number of regional lymph nodes removed, n (%)			0.73			–
None	547 (17.1)	578 (18.0)		1,125 (17.6)	–	
1–3	616 (19.2)	603 (18.8)		1,219 (19.0)	–	
>3	1,917 (59.8)	1,893 (59.1)		3,810 (59.5)	–	
Unknow	124 (3.9)	130 (4.1)		254 (4.0)	–	
Radiotherapy, n (%)			0.81			0.797
No	3,075 (96.0)	3,077 (96.0)		6,152 (96.7)	124 (93.9)	
Neoadjuvant	16 (0.5)	19 (0.6)		35 (0.5)	0 (0.0)	
Adjuvant	108 (3.4)	106 (3.3)		214 (3.3)	8 (6.1)	
Neo- and adjuvant	2 (0.1)	1 (0.0)		3 (0.0)	0 (0.0)	
Unknow	3 (0.1)	1 (0.0)		4 (0.1)	0 (0.0)	
Adjuvant chemotherapy, n (%)			0.20			<0.001
No	2,943 (91.9)	2,914 (90.9)		5,857 (91.4)	86 (65.2)	
Yes	261 (8.1)	290 (9.1)		551 (8.6)	46 (34.8)	

G1, low-grade typical pulmonary carcinoids; G2 intermediate-grade atypical pulmonary carcinoids; G3, high-grade large cell neuroendocrine carcinomas; SD, standard deviation.

86.7% and 40.3% for stages IA, IB, II and III in the new system, respectively (P<0.001), and 94.4%, 100.0%, 90.0%, 100.0%, 75.0%, 73.8%, 50.7% and 0.0% in the TNM staging system, respectively (P<0.001, *Figure 2C,D*). The new staging system improved survival prediction with an IDI of 8% (95% CI: –7% to 23%, *Table 4*) relative to the TNM staging system.

Value of the new staging system in the use of adjuvant chemotherapy

There were 46 patients (n=132, 34.8%) administered adjuvant chemotherapy [platinum combined with paclitaxel (10.9%), gemcitabine (13.0%), pemetrexed (23.9%), etoposide (23.9%), or other (28.3%)] in the Shanghai cohort, versus 551 (n=6,408, 8.6%) in the SEER cohort. Kaplan-Meier curves showed that adjuvant chemotherapy was associated with improved survival in new stage III cases, and worse survival in new stage IA–II cases (*Figure 3*). In the Shanghai cohort, median survival was prolonged

in the adjuvant chemotherapy group with new stage III tumors (26 *vs.* 22 months, P=0.69, *Figure 4*), but no survival benefit of chemotherapy was found for various TNM stages (Figures S3,S4). In subgroup analysis, adjuvant chemotherapy provided a significant survival benefit in G3 (HR =0.61, 95% CI: 0.46–0.75), but decreased survival in G1 (HR =1.37, 95% CI: 0.69–2.71) and G2 (HR =0.68, 95% CI: 0.34–1.35; *Figure 5A*). The P value for interaction was 0.11. However, a role for adjuvant chemotherapy was not observed in any T stage (P for interaction =0.52). Besides, by subgroup analysis of both staging systems, chemotherapy provided significant survival benefit in new stage III cases (HR =0.34, 95% CI: 0.25–0.45), and survival benefit differed among various new stage-based subgroups significantly (P for interaction <0.001, *Figure 5B*).

Discussion

In this large-sample retrospective study of NETL, we explored factors associated with prognosis in patients with

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Table 2 Univariate, multivariate Cox regression analysis and random forest model on factors influencing survival in the training group

Variables	Univariate analysis		Multivariate analysis		Random forest model	
	HR (95% CI)	P value	HR (95% CI)	P value	Importance	Relative importance
Age	1.06 (1.05, 1.07)	<0.001	1.05 (1.05, 1.06)	<0.001	0.044	0.430
Race (White as reference)					−0.0001	−0.011
Black	1.49 (1.12, 1.98)	<0.01	1.33 (1.00, 1.79)	0.05		
Others	0.77 (0.49, 1.29)	0.30	0.57 (0.34, 0.95)	0.03		
Gender (female as reference)					−0.005	−0.047
Male	1.77 (1.51, 2.07)	<0.001	1.32 (1.12, 1.56)	<0.01		
T (T1a as reference)					−0.006	−0.056
T1b	0.95 (0.71, 1.27)	0.74	0.89 (0.67, 1.20)	0.45		
T1c	1.02 (0.75, 1.39)	0.90	0.86 (0.63, 1.19)	0.36		
T2a	1.21 (0.89, 1.65)	0.21	1.12 (0.81, 1.54)	0.51		
T2b	1.74 (1.17, 2.59)	<0.01	1.03 (0.68, 1.57)	0.88		
T3	2.07 (1.39, 3.08)	<0.001	1.10 (0.71, 1.70)	0.68		
T4	2.81 (1.86, 4.25)	<0.001	1.47 (0.95, 2.28)	0.09		
N (N0 as reference)					0.005	0.046
N1	2.12 (1.67, 2.69)	<0.001	2.10 (1.62, 2.73)	<0.001		
N2	3.11 (2.43, 3.99)	<0.001	2.75 (2.05, 3.69)	<0.001		
Histotype (G1 as reference)					0.102	1.000
G2	2.96 (2.24, 3.92)	<0.001	2.42 (1.81, 3.23)	<0.001		
G3	7.61 (6.42, 9.02)	<0.001	5.89 (4.83, 7.19)	<0.001		
8th edition stage (IA1 as reference)					−0.008	−0.082
IA2	1.10 (0.81, 1.50)	0.53	–	–		
IA3	0.96 (0.74, 1.25)	0.78	–	–		
IB	1.20 (0.93, 1.56)	0.17	–	–		
IIA	1.33 (0.84, 2.09)	0.22	–	–		
IIB	2.14 (1.65, 2.78)	<0.001	–	–		
IIIA	3.18 (2.48, 4.09)	<0.001	–	–		
IIIB	4.26 (2.42, 7.50)	<0.001	–	–		
Surgery (sub-lobectomy as reference)					–	–
Lobectomy	0.85 (0.71, 1.02)	0.07	0.87 (0.69, 1.10)	0.24		
Pneumonectomy	1.63 (1.14 ,2.33)	<0.01	1.53 (1.00, 2.34)	0.05		
Unknow	0.25 (0.04, 1.80)	0.17	0.60 (0.08, 4.33)	0.61		
Number of regional lymph nodes removed (none as reference)					–	–
1–3	1.00 (0.77, 1.28)	0.97	0.94 (0.71, 1.25)	0.66		
>3	0.91 (0.74, 1.13)	0.39	0.69 (0.52, 0.91)	0.01		

Table 2 (*continued*)

Table 2 (*continued*)

| Variables	Univariate analysis		Multivariate analysis		Random forest model	
	HR (95% CI)	P value	HR (95% CI)	P value	Importance	Relative importance
Unknow	0.99 (0.66, 1.49)	0.95	0.59 (0.38, 0.91)	0.02		
Radiotherapy (no as reference)						
Neoadjuvant	0.00 (0.00, 1.532E+052)	0.89				
Adjuvant	0.92 (0.56, 1.52)	0.75				
Neo- and adjuvant	8.62 (1.21, 61.37)	0.03				
Unknow	0.00 (0.00, 1.644E+185)	0.97				
Adjuvant chemotherapy (no as reference)					−0.0001	−0.001
Yes	3.14 (2.55, 3.85)	<0.001	0.62 (0.47, 0.81)	<0.001		

G1, low-grade typical pulmonary carcinoids; G2 intermediate-grade atypical pulmonary carcinoids; G3, high-grade large cell neuroendocrine carcinomas.

NETL. NETL histotype had a better survival predictive ability than the T stage. Therefore, we developed a new pathological staging system based on histotype and nodal status for NETL, which showed a better discriminative ability in the SEER and Shanghai cohorts. In addition, the new system had the potential to identify patients suitable for adjuvant chemotherapy, while the benefit conferred by adjuvant chemotherapy was not associated with the TNM stage.

The importance of specific staging systems for NETL has been realized recently. Several reports have shown an overlapping survival of patients with NETL in stages I and II (11,12). Tumor histotype and differentiation are crucial determinants of the clinical behavior of NETL. Corroborating a study by Skuladottir *et al.* (13), we found that NETL histotype was a significant prognostic factor of NETL. As for the N stage, many studies have pointed out that nodal invasion obviously influences NETL prognosis and is related to poor outcome (12,14,15). In line with these previous findings, the present study showed that nodal stage still had the potential to predict prognosis and constituted an independent factor for patient survival.

Conversely, the 8th edition of the T staging system had a weak discriminative ability in the prognosis of patients with NETL in this study. A single-center trial also pointed out that the T stage is not independently associated with survival in NETL (16). Aly *et al.* (17) found that tumor

size (per 1 centimeter increase) is not associated with recurrence (HR =1.09, 95% CI: 0.97–1.22; P=0.20) or lung cancer-specific death (HR =1.11, 95% CI: 0.98–1.26; P=0.10).

Although Jackson *et al.* (6) explored a staging system for NETL including histotype, N- and T-stage, there was no significant improvement in its ability of prognostic discrimination compared to the new staging system developed in this work (NRI =0.03, 95% CI: <–0.01 to 0.38; IDI =–0.6%, 95% CI: –1.7% to 0.7%; Table S2). This supported our results that the T stage had no good prognostic discrimination in NETL. Moreover, histotype showed a good survival discrimination in non-surgical patients, while T-stage did not (Figure S5). Given the practicality of the staging system, it is reasonable to replace the T stage with NETL histotype.

The pathological stage is important not only for predicting prognosis but also for advising postoperative treatment. However, there is no consensus regarding adjuvant therapy in NETL. For large-cell neuroendocrine carcinomas, adjuvant chemotherapy after surgery appears promising for the improvement of prognosis (18). In this study, adjuvant chemotherapy showed no survival benefit in various TNM stages, but the new system could select appropriate patients (new stage III) who might achieve survival benefit after adjuvant chemotherapy. Moreover, by subgroup analysis, we observed no association of

Table 3 Multivariate Cox regression analysis to compare histotype and T stage by subgroup analysis of N stage, adjusted by race, gender, age, surgery, number of regional lymph nodes removed and adjuvant chemotherapy

Variables	HR (95% CI)	P value
N0		
G1 as reference		
G2	2.45 (1.71, 3.51)	<0.001
G3	6.14 (4.95, 7.62)	<0.001
T1 as reference		
T2	1.30 (1.03, 1.64)	0.03
T3	1.67 (1.08, 2.58)	0.02
T4	1.36 (0.85, 2.18)	0.20
N1		
G1 as reference		
G2	3.01 (1.40, 6.46)	<0.01
G3	10.66 (5.21, 21.79)	<0.001
T1 as reference		
T2	1.24 (0.72, 2.15)	0.43
T3	0.54 (0.20, 1.44)	0.22
T4	1.38 (0.58, 3.29)	0.47
N2		
G1 as reference		
G2	1.54 (0.75, 3.18)	0.24
G3	6.10 (2.42, 15.35)	<0.01
T1 as reference		
T2	0.87 (0.49, 1.53)	0.62
T3	0.96 (0.40, 2.31)	0.93
T4	2.57 (0.96, 6.83)	0.06

G1, low-grade typical pulmonary carcinoids; G2 intermediate-grade atypical pulmonary carcinoids; G3, high-grade large cell neuroendocrine carcinomas.

chemotherapy effect with T stage; however, survival advantage was noted in G3 patients administered adjuvant chemotherapy. Taken together, replacing the T stage with histotype may help redefine prognostication and would have great potential for advising postoperative treatment in patients with these tumors.

The limitations of the current study include its retrospective nature, with the inherent trend of selection bias. Secondly, detailed data about diaphragm invasion, positive margins, mitotic rate and Ki-67 were not recorded in the SEER database, all of which are reportedly associated with survival. Furthermore, this study only included M0 postoperative patients. Therefore, the proposed staging system needs to be explored for stage N3 or M1 patients with NETL. Finally, even though the new staging system has been verified in the Shanghai cohort, the lack of data (especially for G2 patients, adjuvant chemotherapy and hormonal or targeted therapy) and the effect of different eras (2004–2015 and 2009–2018 for the SEER and Shanghai cohorts, respectively), which has implications on the variation of diagnostic and therapeutic options available, could cause bias. Therefore, the new staging system for NETL still needs more external validation and detailed data in an independent cohort before its clinical application.

In conclusion, NETL constitute a unique clinical subgroup of primary lung tumors. However, there is no specific pathological staging system for these tumors. This study found that tumor histotype and nodal status were independently associated with survival in NETL patients, rather than the T stage. Therefore, we established a new pathological staging system for postoperative patients by combining NETL histotype and nodal stage, which was validated in the Shanghai cohort. The new pathological staging system could predict the prognosis of NETL patients better than the 8th TNM staging system, and also has the potential to guide postoperative chemotherapy.
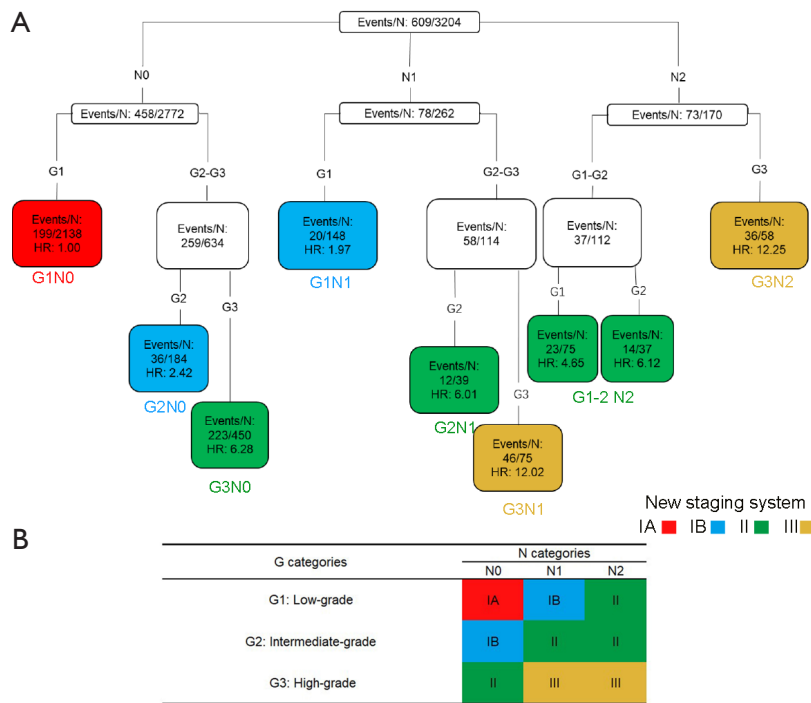
Figure 1 New staging system proposed by the survival tree. (A) Survival tree based on the best stage for 3,224 M0 resected cases in the training group. Histotype and N categories were modeled as ordered variables. (B) The new staging system proposed by regrouping G and N stages based on hazards ratios (HRs).
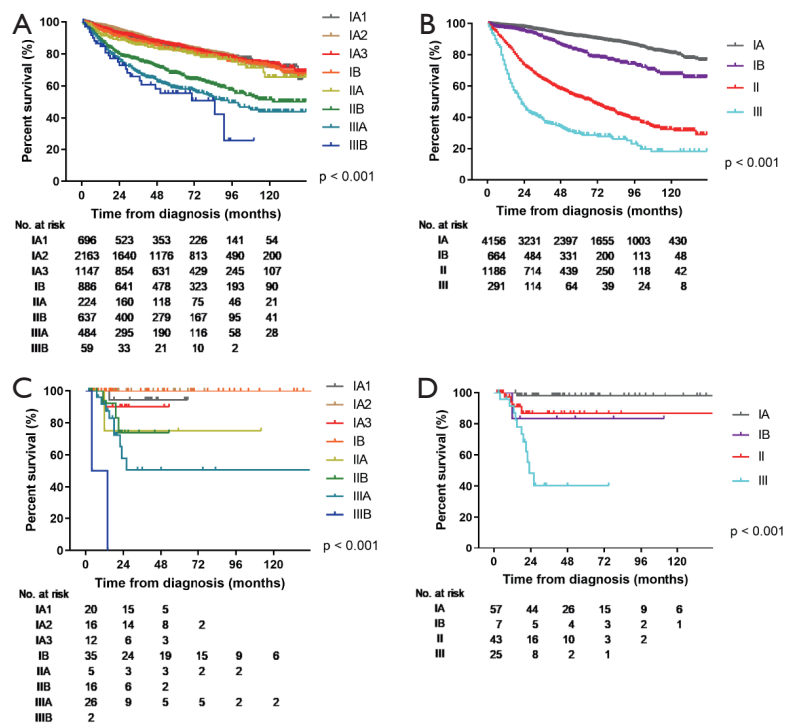

Figure 2 Overall survival by pathologic stage. (A) TNM stage in the SEER cohort; (B) new stage in the SEER cohort; (C) TNM stage in the Shanghai cohort; (D) new stage in the Shanghai cohort.

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Table 4 Comparison of univariate Cox regression analysis and survival prediction ability for the 8th edition TNM stage and new stage

| Stage | 8th Ed. | | Stage | New-Ed. | | New-Ed. vs. 8th Ed. | |
	HR (95% CI)	C-index (95% CI)		HR (95% CI)	C-index (95% CI)	NRI (95% CI)	IDI (%, 95% CI)
SEER cohort							
IA1 as reference		0.62 (0.60, 0.63)	IA as reference		0.75 (0.74, 0.76)	0.62 (0.55, 0.68)	20 (18, 23)***
IA2	1.10 (0.81, 1.50)		IB***	2.01 (1.64, 2.47)			
IA3	0.96 (0.74, 1.25)		II***	6.45 (5.67, 7.34)			
IB	1.20 (0.93, 1.56)		III***	12.63 (10.63, 15.00)			
IIA	1.33 (0.84, 2.09)						
IIB***	2.14 (1.65, 2.78)						
IIIA***	3.18 (2.48, 4.09)						
IIIB***	4.26 (2.42, 7.50)						
Shanghai cohort							
IA1 as reference		–[†]	IA as reference		0.80 (0.71, 0.88)	0.0048[‡]	8 (–7, 23)
IA2	0.00 (0.00, 3.038E+219)		IB	10.73 (0.67, 171.52)			
IA3	2.11 (0.13, 33.80)		II	8.36 (0.93, 75.03)			
IB	0.00 (0.00, 3.826E+156)		III***	35.18 (4.51, 274.20)			
IIA	5.30 (0.33, 84.94)						
IIB	5.06 (0.52, 48.89)						
IIIA*	9.27 (1.17, 73.53)						
IIIB***	99.67 (8.15, 1,219.39)						

IDI, integrated discrimination improvement; NRI, net reclassification index. *, P<0.05; ***, P<0.001. [†], coefficient may be infinite in the cox model due to little outcome events which may cause data bias; [‡], cox model can't be established due to little outcome events for which 95% CI can't be analyzed by bootstrapping.
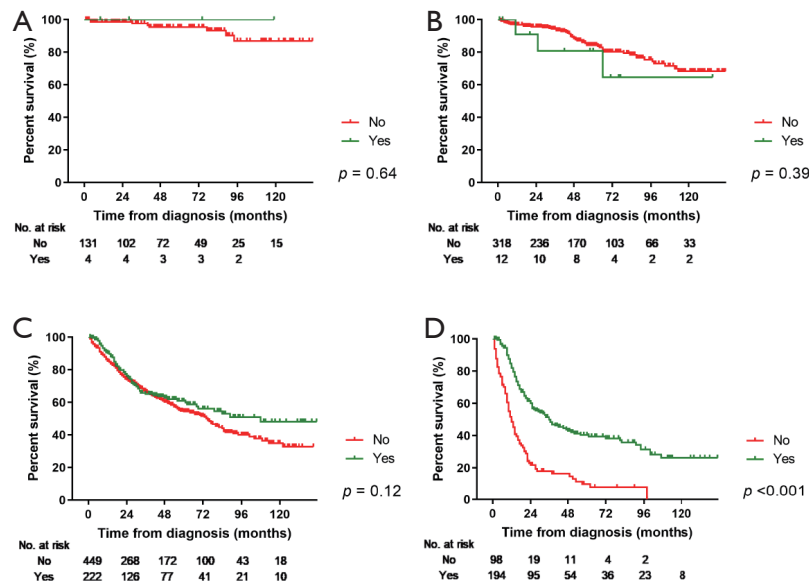
Figure 3 Overall survival by adjuvant chemotherapy according to the new staging system. (A) Stage IA, (B) stage IB, (C) stage II, and (D) stage III in the SEER cohort.
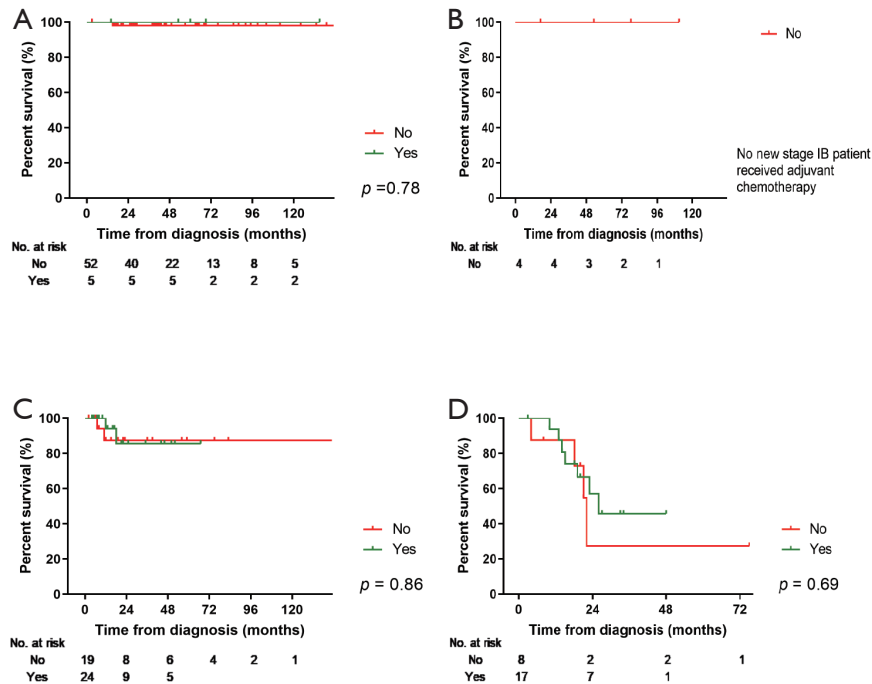
Figure 4 Overall survival by adjuvant chemotherapy according to the new staging system. (A) Stage IA, (B) stage IB, (C) stage II, and (D) stage III in the Shanghai cohort.

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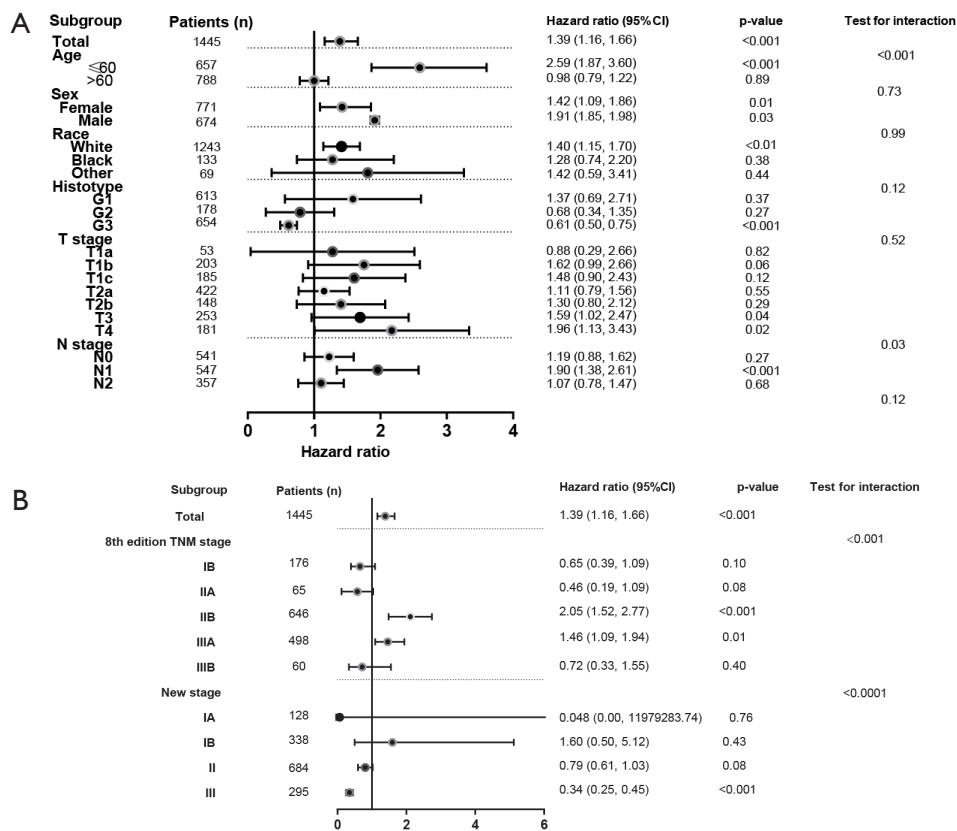
Figure 5 Subgroup analysis for adjuvant chemotherapy (adjuvant chemotherapy as reference). (A) Subgroups based on baseline characteristics; (B) subgroups based on staging systems.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/atm-20-5910). 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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Table S1 Univariate and multivariate Cox regression analysis for 8th edition TNM stage by stratified analysis of histotype, adjusted by race, gender, age, surgery, number of regional lymph nodes removed, radiotherapy and adjuvant chemotherapy

| Variables	Univariate analysis		Variables	Multivariate analysis	
	HR (95% CI)	P value		HR (95% CI)	P value
G1					
IA1 as reference			IA1 as reference		
IA2	0.66(0.45, 0.98)	0.04	IA2	0.74(0.50, 1.11)	0.14
IA3	0.44(0.27, 0.72)	<0.01	IA3	0.53(0.32, 0.89)	0.01
IB	0.78(0.50, 1.22)	0.27	IB	1.25(0.78, 2.01)	0.36
IIA	1.01(0.50, 2.04)	0.97	IIA	1.60(0.78, 3.28)	0.20
IIB	0.95(0.56, 1.60)	0.83	IIB	1.51(0.86, 2.64)	0.15
IIIA	1.70(1.00, 2.88)	0.05	IIIA	2.23(1.27, 3.91)	0.01
IIIB	2.71(0.96, 7.61)	0.06	IIIB	2.36(0.72, 7.72)	0.16
G2					
G1 as reference			T1 as reference		
IA2	1.57(0.46, 5.33)	0.47	IA2	0.99(0.26, 3.80)	0.98
IA3	0.75(0.19, 2.92)	0.68	IA3	0.51(0.12, 2.22)	0.37
IB	0.80(0.20, 3.20)	0.75	IB	0.72(0.16, 3.18)	0.67
IIA	0.00(0.00, 1.471E+262)	0.97	IIA	0.00(0.00, 2.042E+278)	0.97
IIB	1.70(0.47, 6.10)	0.42	IIB	2.07(0.55, 7.88)	0.28
IIIA	1.87(0.54, 6.52)	0.33	IIIA	2.16(0.53, 8.74)	0.28
IIIB	3.30(0.55, 19.85)	0.19	IIIB	3.76 (0.49, 28.77)	0.20
G3					
IA1 as reference			T1 as reference		
IA2	0.97(0.56, 1.71)	0.93	IA2	1.08(0.62, 1.91)	0.78
IA3	1.20(0.68, 2.14)	0.53	IA3	1.30(0.72, 2.33)	0.39
IB	1.03(0.57, 1.86)	0.91	IB	1.32(0.72, 2.40)	0.37
IIA	0.78(0.36, 1.69)	0.53	IIA	1.03(0.46, 2.31)	0.94
IIB	1.62(0.92, 2.85)	0.10	IIB	2.65(1.45, 4.85)	<0.01
IIIA	1.52(0.87, 2.66)	0.14	IIIA	2.35(1.28, 4.31)	<0.01
IIIB	2.11(0.86, 5.18)	0.10	IIIB	4.06(1.55, 10.66)	<0.01

G1, low-grade typical pulmonary carcinoids; G2 intermediate-grade atypical pulmonary carcinoids; G3, high-grade large cell neuroendocrine carcinomas.

Table S2 Comparison of univariate Cox regression analysis and survival prediction ability for the already published classification and new stage

Stage	Already published classification		Stage	New-Ed.		New-Ed. vs already published classification	
	HR(95%CI)	C-index (95%CI)		HR (95% CI)	C-index(95%CI)	NRI(95%CI)	IDI(%,95%CI)
SEER cohort							
IA as reference		0.75 (0.73,0.76)	IA as reference		0.75(0.74, 0.76)	0.03(<-0.01, 0.38)	-0.6(-1.7, 0.7)
IB***	2.09(1.56,2.81)		IB***	1.99(1.62, 2.45)			
IIA***	2.05(1.58,2.67)		II***	6.53(5.74, 7.42)			
IIB***	4.29(3.17,5.79)		III***	12.74(10.72, 15.15)			
IIIA***	7.06(6.18,8.06)						
IIIB***	8.99(6.13,13.17)						
IIIC***	12.04(10.16, 14.28)						
Shanghai cohort							
IA as reference		- [a]	IA as reference		0.80(0.71, 0.88)	-0.1[3]b	-1.7(-14.2, 1.4)
IB	0.00(0.00, -7.98E+307)		IB	10.73(0.67, 171.52)			
IIA	13.20(0.83,211.22)		II	8.36(0.93, 75.03			
IIB[c]			III***	35.18(4.51, 274.20)			
IIIA	5.76(0.52, 63.64)						
IIIB**	36.97(3.30, 414.47)						
IIIC**	36.15(4.64, 281.86)						

IDI, integrated discrimination improvement; NRI, net reclassification index. *, p< 0.05; **, p<0.01; ***, p< 0.001. [a], coefficient may be infinite in the cox model due to little outcome events which may cause data bias; [b], cox model can't be established due to little outcome events for which 95% CI can't be analyzed by bootstrapping; [c], no patients in the already published classification stage IIB in the Shanghai cohort.
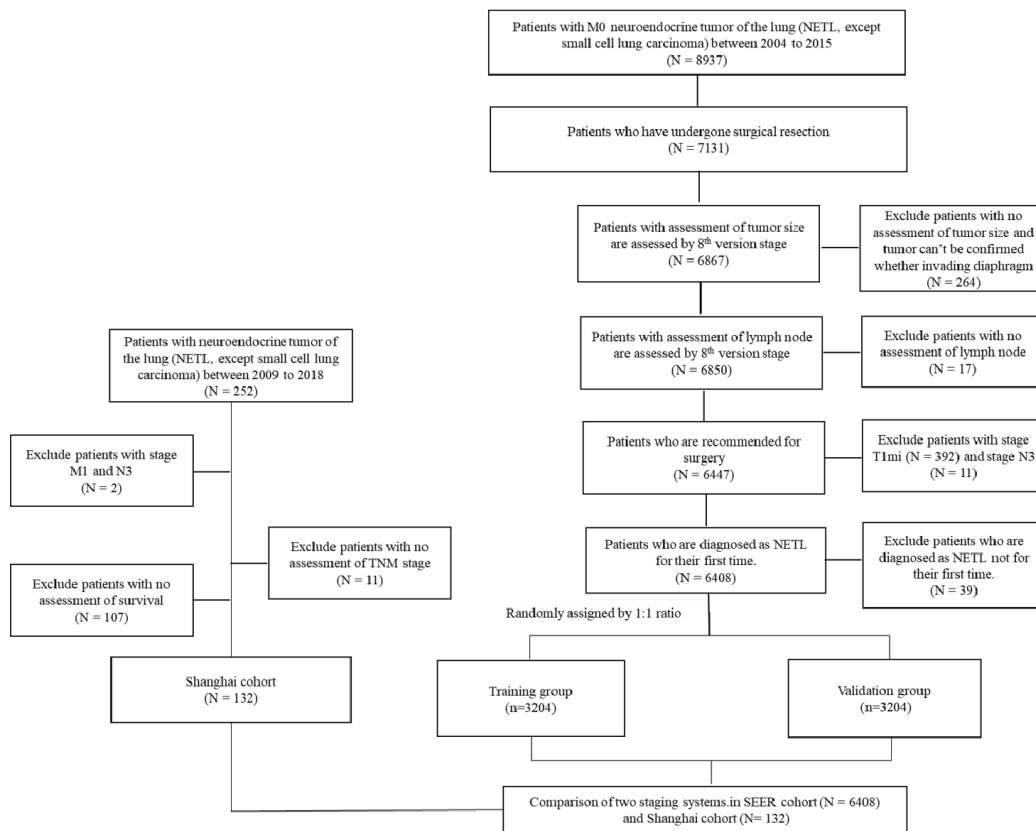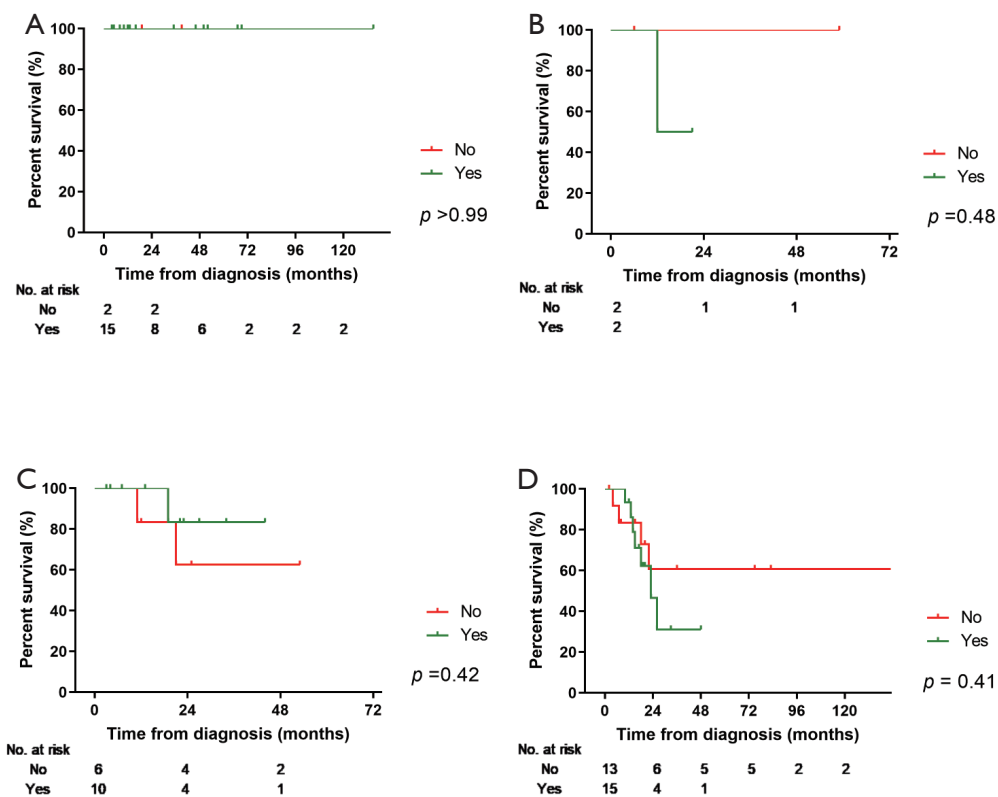
**Figure S1** Flow chart depicting selection criteria and grouping steps.
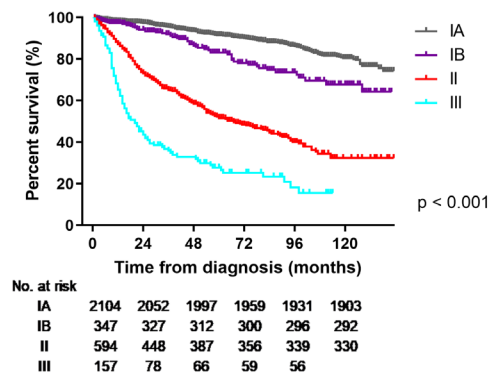
Figure S2 Overall survival by pathologic stage according to the new pathological staging system in the SEER validation group.
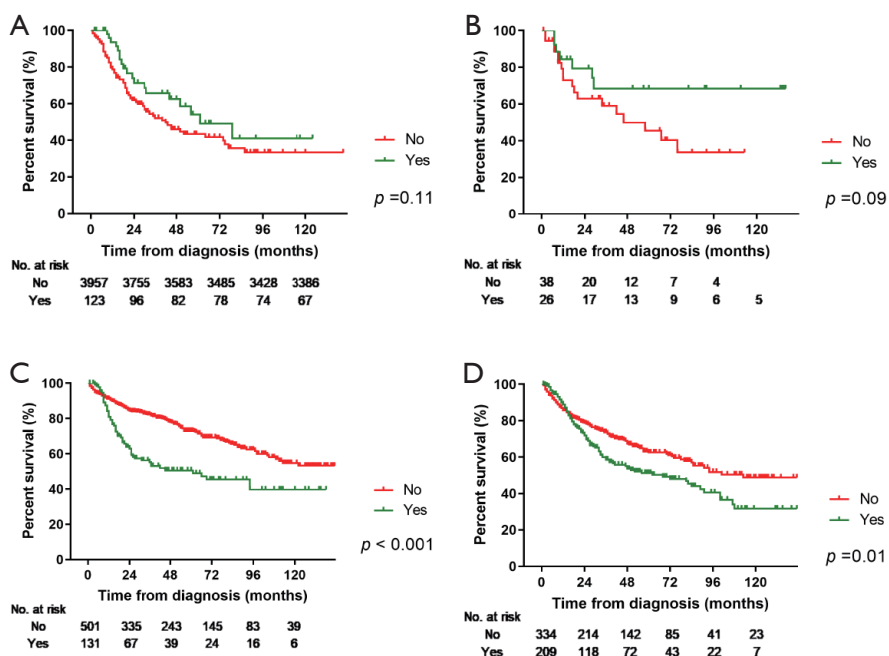
Figure S3 Overall survival by adjuvant chemotherapy according to the TNM staging system. (A) Stage IA, (B) stage IB, (C) stage II, and (D) stage III in the SEER cohort.

Figure S4 Overall survival by adjuvant chemotherapy according to the TNM staging system. (A) Stage IA, (B) stage IB, (C) stage II, and (D) stage III in the Shanghai cohort.
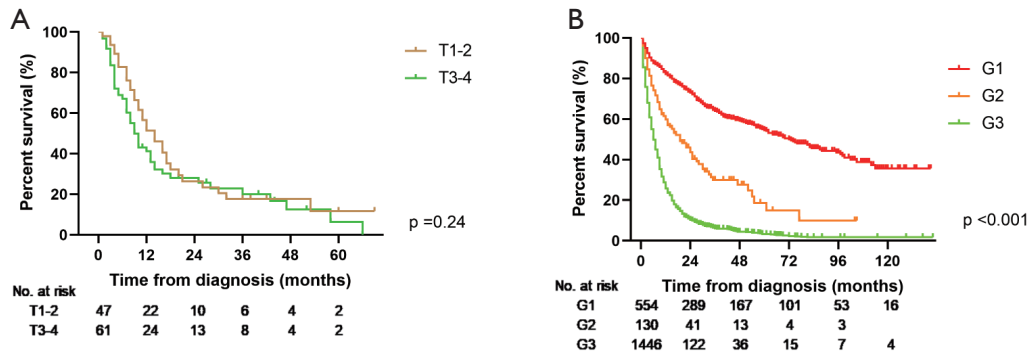
Figure S5 (A) Overall survival by histotype in patients with stage IIIC or IV tumors; (B) Overall survival by the T stage in patients with stage IIIC tumors.