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A Proposal to Modify the 8th IASLC System
Is it Suitable for T4N2M0 Lung Adenocarcinoma to Be Placed in Stage IIIB?

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Purpose: The International Association for the Study of Lung Cancer (IASLC) of TNM staging system has been well accepted as a precise model. However, the latest American Joint Committee on Cancer (AJCC) staging system to solve the different survival and prognosis of lung adenocarcinoma in the same period is still controversial. Therefore, it is necessary to thoroughly explore the applicability between the new system and survival prediction in terms of lung adenocarcinoma.

Methods: We recruited 52,517 patients with lung adenocarcinoma from the Surveillence, Epidemiology, and End Results database. Cox regression analysis was performed to determine survival related factors. The mortality rate per 1000 persons per year of the T4N2M0 lung adenocarcinoma stage and other stages were compared. Survival curves were obtained using the Kaplan-Meier analysis and log-rank test.

Results: The results of Cox proportional hazards regression analysis showed that age at diagnosis, race, T stage, distant metastasis, extrathoracic extension, radiotherapy, chemotherapy, and surgery are independent factors related to cancer-specific survival (CSS) and all-cause survival. Furthermore, patients with stage IIIA disease ($P < 0.001$) and IIIB disease ($P < 0.001$) excluding stage at T4N2M0 had a significantly lower risk of CSS and all-cause survival than those staged with T4N2M0 disease. The mortality rates per 1000 person-years with patients staged at T4N2M0 lung adenocarcinoma had higher mortality than patients in the same period. The CSS curves of patients with stage T4N2M0 reflected an obvious decline compared with those of stages IIIA disease and IIIB excluding T4N2M0, and there is no significant difference between this curve and stage IIIC patients ($P > 0.05$).

Conclusion: The survival rate of patients with T4N2M0 stage was significantly lower than that of patients with IIIA and IIIB stages excluding T4N2M0, there was no significant difference between T4N2M0 and IIIC. It was suggested that this group of patients with stage T4N2M0 were upgraded in the 8th IASLC system.

Key Words: lung adenocarcinoma, TNM staging, IASLC system, survival prognosis, SEER

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Primary lung cancer is the leading cause of cancer-related mortality worldwide, and non–small cell lung cancer accounts for about 85% of all lung cancers, of which ~70% are adenocarcinoma.[1] Lung adenocarcinoma is the most common primary lung cancer, accounting for almost half of these tumors.[2] Although the community's awareness of the risk of lung cancer related to major causal factors such as smoking behavior has gradually increased, the devastating impact of lung cancer remains a main global health burden.

The recent revisions of lung cancer staging have been supervised by a prospective database research conducted by the International Association for the Study of Lung Cancer (IASLC). Significantly, the seventh edition of the TNM staging system (issued in January 2010) was based on the recommendations of the IASLC international staging project, which had collected and analyzed > 100,000 lung cancer cases provided by 46 centers in more than 19 countries in the world.[3–8] Lung tumors were classified in the 8th edition of TNM staging system in terms of primary tumor features (T), the presence or absence of regional lymph node involvement (N) and the presence or absence of distant metastases (M).[9] Compared with the 7th edition of TNM staging system, the newest (8th) edition of TNM classification existed some major changes. The changes in the T component included the subclassification of T1 and T2 in increments of 1 cm, tumors > 5 cm were reclassified as T3, and tumors > 7 cm were reclassified as T4. Diaphragm intrusion became a T4 descriptor. Lung atelectasis whether partial or complete and all cases of main bronchial invasion regardless of the distance from the carina were classified as T2. Tumors with extrathoracic metastases were subdivided into M1b with a single distant metastasis and M1c with multiple distant metastases. There was no change in N component for newest (8th) edition.[10] As demonstrated above, the several key changes are incorporated in the 8th edition that have been shown to improve the accuracy of the survival prediction of staging classification and demarcation points as well as the correlation between survival rates and stages.[9,11] Recently, several studies have suggested that same stage of adenocarcinoma in patients may exist different prognoses.[12–15] Importantly, many studies have been evaluated on the difference of adenocarcinoma in prognosis and survival. However, we should not ignore in a staging system when developing a more accurate discriminatory ability and prognostic performance in clinical practice.[16–18] In particular, the prognoses of some patients in the same substages are different, while the prognoses of some patients in different substages are similar. In our study, we aim to optimize the accuracy of lung cancer staging in the 8th edition of IASLC to offer timely treatment decisions for thoracic surgeon.

METHODS

Patients and Date Collection

In this study, we obtained the data of patients with lung adenocarcinoma included in the openly accessible Surveillance,

Epidemiology, and End Results (SEER) database (National Cancer Institute, Bethesda, MD) between 2010 and 2015. Since SEER is a publicly available database with anonymized data, there is no need for ethical review. In addition, a data use agreement was signed for this project.

In order to explore the prognosis of lung adenocarcinoma, we obtained the patient's overall survival (OS) data and cancer-specific survival (CSS) data. According to the histopathology codes of the International Classification of Disease for Oncology, third edition (ICD-O-3). A total of 197,910 patients with lung adenocarcinoma were identified in the SEER database, and their diagnosis was from 2010 to 2015. We subsequently excluded 145,394 patients (those with T0, TX, T2NOS, NA, NX, M1NOS disease; missing data for survival months; and unknown information including patients id, histology, lung extension). Therefore, 52,516 patients with lung adenocarcinoma were enrolled in this study. Furthermore, these patients were divided into stage IA1, stage IA2, stage IA3, stage IB, stage IIA, stage IIB, stage IIIA, stage IIIB, stage IIIC, stage IVA, stage IVB based on the TNM-8th system. According to the 8th edition of IASLC, patients with lung adenocarcinoma were selected based on the following date information: age of diagnosis, year of diagnosis, sex, race, T/N/M staging, TNM staging, tumor size, extrathoracic extension, surgery, radiation and chemotherapy. Missing or unclear data were treated as user missing values.

TABLE 1. Demographic and Clinical Characteristics of 52,516 Patients With Lung Adenocarcinoma Collected in the Surveillance, Epidemiology, and End Results Database Between 2010 and 2015

Characteristics	N (%)
Sex	
Male	24940 (47.5)
Female	27576 (52.5)
Race	
Black	6609 (12.6)
White	40564 (77.2)
Other	5343 (10.2)
Age at diagnosis (y)	
Mean (interquartile range)	68 (59-75)
Year of diagnosis	
2010-2012	23953 (45.6)
2013-2015	28563 (54.4)
Differentiation grade	
Well-differentiated; grade I	4974 (9.5)
Moderately differentiated; grade II	12024 (22.9)
Poorly differentiated; grade III	13568 (25.8)
Undifferentiated; anaplastic; grade IV	294 (0.6)
Unknown	21656 (41.2)
Tumor size, mean (SD), mm	42.39 (54.39)*
Extension	
No	38433 (73.2)
Yes	14083 (26.8)
T category	
T1a	1509 (2.9)
T1b	8613 (16.4)
T1c	8620 (16.4)
T2a	5733 (10.9)
T2b	3550 (6.8)
T3	3754 (7.1)
T4	20737 (39.5)
Lymph node metastasis	29095 (55.4)
Distant metastasis	25559 (48.7)
Radiation therapy	
None/refused	31522 (60.0)
Yes	20994 (40.0)
Chemotherapy	
None/refused	28005 (53.3)
Yes	24511 (46.7)
Surgery	
None/refused	35369 (67.3)
Yes	17147 (32.7)

*Standard deviation.

Statistical Analysis

The demographic and clinical characteristics are summarized as frequencies, proportion and mean values ± SD. Factors related to CSS rate and OS rate were determined by Cox regression analyses. Moreover, the hazard ratio (HR) and 95% confidence interval (CI) were figured out. Nevertheless, we also calculated and compared the cancer-specific mortality (CSM) and all-cause mortality (ACM) per 1000 person-years for each subgroup. After adjusting for demographics, pathology, and treatment characteristics, Cox proportional hazards regression analyses were performed to quantify the risk of CSS and OS. Finally, survival curves were generated by Kaplan-Meier analyses using log-rank tests. In brief, K-M curves, Cox proportional hazards models, and mortality per 1000-person-year were evaluated in the survival analyses. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 22.0 (IBM Corp., Armonk, NY), Stata/SE version 15 (Stata Corp, College Station, TX), GraphPad Prism version 8 (GraphPad Software Inc., La Jolla, CA).

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the lung adenocarcinoma patients are shown in Table 1. The 52,516 patients

TABLE 2. Demographic Characteristics of Each Subgroup Patients With Lung Adenocarcinoma Identified in the Surveillance, Epidemiology, and End Results Database Between 2010 and 2015

AJCC Staging Grouping (8th Edition)	N (%)
Stage at diagnosis IA1	
T1aN0M0	1028 (1.96)
Stage at diagnosis IA2	
T1bN0M0	5499 (10.47)
Stage at diagnosis IA3	
T1cN0M0	4280 (8.15)
Stage at diagnosis IB	
T2aN0M0	2014 (3.84)
Stage at diagnosis IIA	
T2bN0M0	953 (1.81)
Stage at diagnosis IIB	
T1a-cN1M0	953 (1.81)
T2a-bN1M0	631 (1.20)
T3N0M0	720 (1.37)
Stage at diagnosis IIIA	
T1a-cN2M0	1732 (3.30)
T2a-bN2M0	1259 (2.40)
T3N1M0	236 (0.45)
T4N0M0	2640 (5.03)
T4N1M0	742 (1.41)
Stage at diagnosis IIIB	
T1a-cN3M0	424 (0.81)
T2a-bN3M0	302 (0.58)
T3N2M0	593 (1.13)
T4N2M0	2196 (4.18)
Stage at diagnosis IIIC	
T3-4N3M0	755 (1.44)
Stage at diagnosis IVA	
Any T, any N, M1a-M1b	18625 (35.47)
Stage at diagnosis IVB	
Any T, any N, M1c	6934 (13.20)

included 24,940 (47.5%) men and 27,576 (52.5%) women. The median age was 68 (interquartile range, 59 to 75) years. The number of patients in each subgroup is shown in Table 2. According to the TNM-8th system, 1028 patients (1.96%) were listed in stage IA1; 5499 (10.47%) in stage IA2; 4280 (8.15%) in stage IA3; 2014 (3.83%) in stage IB; 953 (1.81%) in stage IIA; 2304 (4.38%) in stage IIB including 953 (1.81%) in stage T1a-cN1M0, 631 (1.2%) in stage T2a-cN1M0, and 720 (1.37%) in stage T3N0M0; 6609 (12.59%) in stage IIIA including 1732 (3.3%) in stage T1a-cN2M0, 1259 (2.40%) in stage T2a-cN2M0, 236 (0.45%) in stage T3N1M0, 2640 (5.03%) in stage T4N0M0, and 742 (1.41%) in stage T4N1M0; 3515 (6.70%) in stage IIIB including 424 (0.81%) in stage T1a-cN3M0, 302 (0.58%) in stage T2a-cN3M0, 593 (1.13%) in stage T3N2M0, and 2196 (4.18%) in stage T4N2M0; 755 (1.44%) in stage IIIC; 18,625 (35.47%) in stage IVA including any T, any N, M1a-M1bl; 6934 (13.20%) in stage IVB including any T, any N, M1c.

Clinicopathologic Factors Associated With CSS and OS

According to the results of univariate Cox regression analysis, age at diagnosis, sex, race, T-category, lymph node metastasis (LNM), distant metastasis, extrathoracic extension, radiation therapy, chemotherapy, and surgery were significant prognostic factors of CSS (all, $P < 0.05$, Table 3). In addition, in the multivariate analyses, age at diagnosis, race, and sex showed no significant difference for CSS (all, $P > 0.05$, Table 4), and yet CSS was also associated with T-stage, distant metastasis, radiation therapy, and surgery (all, $P < 0.05$, Table 4). The above results indicated that age at diagnosis, race, and sex may be associated with other factors to influence CSS. Meanwhile, similar results were displayed in the Cox regression analyses of the factors related to OS.

TABLE 3. Univariate Analysis of Clinicopathologic Variable Associate With Lung Cancer-specific Survival and All-cause Survival

	Lung Cancer-specific Survival			Lung Cancer All-cause Survival		
Characteristic	**Hazard Ratio**	**95% CI**	***P***	**Hazard Ratio**	**95% CI**	***P***
Age at diagnosis (y)	0.997	0.996-0.998	<0.001*	0.998	0.997-0.999	<0.001*
Year at diagnosis						
2010-2012	Ref			Ref		
2013-2015	1.014	0.991-1.038	0.225	1.015	0.994-1.037	0.158
Sex						
Male	Ref			Ref		
Female	0.874	0.854-0.894	<0.001*	0.882	0.863-0.901	<0.001*
Race						
Black	Ref			Ref		
White	0.894	0.864-0.925	<0.001*	0.894	0.866-0.922	<0.001*
Other	0.946	0.902-0.991	0.021	0.939	0.899-0.981	0.005
Differentiation grade						
Unknown	Ref			Ref		
Grade I	0.394	0.375-0.415	<0.001*	0.436	0.417-0.456	<0.001*
Grade II	0.591	0.573-0.610	<0.001*	0.615	0.597-0.632	<0.001*
Grade III	0.942	0.917-0.968	<0.001*	0.940	0.9160.964	<0.001*
Grade IV	0.884	0.764-1.023	0.098	0.848	0.738-0.975	0.020
T category						
T1a	Ref			Ref		
T1b	1.350	1.178-1.547	<0.001*	1.303	1.169-1.453	<0.001*
T1c	2.289	2.003-2.616	<0.001*	1.941	1.744-2.160	<0.001*
T2a	4.692	4.108-5.359	<0.001*	3.523	3.165-3.920	<0.001*
T2b	4.938	4.312-5.655	<0.001*	3.614	3.2384.034	<0.001*
T3	9.783	8.560-11.181	<0.001*	7.033	6.314-7.834	<0.001*
T4	13.014	11.436-14.811	<0.001*	9.220	8.316-10.222	<0.001*
Lymph node metastasis						
No	Ref			Ref		
Yes	2.030	1.981-2.080	<0.001*	1.909	1.867-1.952	<0.001*
Distant metastasis						
No	Ref			Ref		
Yes	2.391	2.335-2.448	<0.001*	2.212	2.164-2.260	<0.001*
Extrathoracic extension						
No	Ref			Ref		
Yes	1.285	1.254-1.318	<0.001*	1.230	1.202-1.259	<0.001*
Radiation therapy						
No	Ref			Ref		
Yes	1.592	1.556-1.630	<0.001*	1.522	1.490-1.555	<0.001*
Chemotherapy						
No	Ref			Ref		
Yes	1.323	1.293-1.354	<0.001*	1.179	1.155-1.205	<0.001*
Surgery						
No	Ref		Ref			
Yes	0.158	0.152-0.163	<0.001*	0.183	0.177-0.188	<0.001*

*$P < 0.05$.
CI indicates confidence interval; Ref, reference.

Lung CSM and Lung ACM Rates Per 1000 Person-Years

As is shown in Table 5, CSM rates are different from ACM rates. The CSM of staging T4N2M0 group (776.007, 95% CI: 738.752-815.141) was obviously higher than those in the same group T1a-cN3M0, T2a-bN3M0, T3N2M0 (273.429, 95% CI: 253.271-295.192) and subgroup T1a-cN2M0, T2a-bN2M0, T3N1M0, T4N0M0, T4N1M0 (334.794, 95% CI: 324.149-345.790) belonged to stage IIIA. Nevertheless, The CSM in the group T4N2M0 was no difference than those in the group T3-4N3M0 belonged to stage IIIC. However, the ACM rates demonstrated similar results.

HR of Different Substage for CSS

We compared the T4N2M0 group with other substages in terms of HRs for CSS. As shown in Table 6, the unadjusted HR of the group T1a-cN2M0, T2a-bN2M0, T3N1M0, T4N0M0, T4N1M0 was 0.500 (95% CI: 0.472-0.530, $P < 0.001$). The HR adjusted for demographic data was 0.501 (95% CI: 0.473-0.530, $P < 0.001$). The HR adjusted for demographic and pathologic data was 0.503 (95% CI: 0.475-0.532, $P < 0.001$). The HR adjusted for demographic, pathologic, and clinical data was 0.661 (95% CI: 0.624-0.701, $P < 0.001$). In comparison with the group T4N2M0, the Cox regression HRs of the same stage group T1a-cN3M0, T2a-bN3M0, T3N2M0 for unadjusted, adjusted 1, adjusted 2, and adjusted 3 models were 0.418 (95% CI: 0.383-0.456, $P < 0.001$), 0.418 (95% CI: 0.383-0.456, $P < 0.001$), 0.421 (95% CI: 0.385-0.460, $P < 0.001$), and 0.572 (95% CI: 0.524-0.626, $P < 0.001$), respectively. Furthermore, the adjusted *P*-values of IIIC subgroup were all > 0.05. These data indicated that the T4N2M0 group was significantly different from the stage IIIA and stage IIIB subgroups, but there was no distinct difference between T4N2M0 and stage IIIC. The HRs for OS were displayed similar results in Table 7.

TABLE 4. Multivariate Analysis of Clinicopathologic Variable Associated With Lung Cancer-specific Survival and All-cause Survival

	Lung Cancer-specific Survival			Lung Cancer All-cause Survival		
Characteristic	**Hazard Ratio**	**95% CI**	***P***	**Hazard Ratio**	**95% CI**	***P***
Age at diagnosis	1.000	0.999-1.001	0.760	1.001	1.000-1.001	0.278
Year at diagnosis						
2010-2012	Ref			Ref		
2013-2015	0.987	0.964-1.009	0.247	0.987	0.966-1.008	0.235
Sex						
Male	Ref			Ref		
Female	0.988	0.966-1.011	0.307	0.987	0.967-1.009	0.241
Race						
Black	Ref			Ref		
White	1.012	0.977-1.047	0.510	0.999	0.968-1.032	0.975
Other	0.965	0.920-1.012	0.143	0.956	0.915-0.999	0.044
Differentiation grade						
Unknown	Ref			Ref		
Grade I	0.836	0.793-0.881	< 0.001*	0.865	0.825-0.907	< 0.001*
Grade II	0.980	0.948-1.013	0.224	0.985	0.956-1.015	0.323
Grade III	1.014	0.986-1.043	0.321	1.014	0.988-1.041	0.289
Grade IV	0.968	0.836-1.121	0.664	0.937	0.815-1.076	0.356
T category						
T1a	Ref			Ref		
T1b	1.240	1.082-1.422	< 0.001*	1.204	1.080-1.342	< 0.001*
T1c	2.160	1.889-2.469	< 0.001*	1.865	1.675-2.076	< 0.001*
T2a	4.164	3.639-4.764	< 0.001*	3.272	2.935-3.648	< 0.001*
T2b	4.160	3.625-4.774	< 0.001*	3.203	2.863-3.583	< 0.001*
T3	6.148	5.362-7.049	< 0.001*	4.621	4.135-5.164	< 0.001*
T4	8.162	7.149-9.319	< 0.001*	6.122	5.503-6.811	< 0.001*
Lymph node metastasis						
No	Ref			Ref		
Yes	1.067	1.039-1.096	< 0.001*	1.069	1.043-1.096	< 0.001*
Distant metastasis						
No	Ref			Ref		
Yes	1.222	1.189-1.256	< 0.001*	1.204	1.174-1.235	< 0.001*
Extrathoracic extension						
No	Ref			Ref		
Yes	1.259	1.227-1.292	< 0.001*	1.235	1.205-1.265	< 0.001*
Radiation therapy						
No	Ref			Ref		
Yes	0.945	0.922-0.969	< 0.001*	0.925	0.904-0.946	< 0.001*
Chemotherapy						
No	Ref			Ref		
Yes	0.465	0.453-0.477	< 0.001*	0.443	0.432-0.453	< 0.001*
Surgery						
No	Ref			Ref		
Yes	0.290	0.278-0.303	< 0.001*	0.293	0.283-0.305	< 0.001*

*$P < 0.05$.
CI indicates confidence interval; Ref, reference.

TABLE 5. Calculate the Cancer-specific Mortality and All-cause Mortality Rates Per 1000 Person-years of Lung Adenocarcinoma

			Cancer-specific Mortality	Cancer-specific Mortality		All-cause Mortality	All-cause Mortality	
		Total Number	N (%)	1000 Person-Years	95% CI	N (%)	1,000 Person-Years	95% CI
Stage IIIA	T1a-cN2M0 T2a-bN2M0 T3N1M0 T4N0M0 T4N1M0	6609	3679 (0.557)	334.794	324.149-345.790	4235 (0.641)	385.391	373.957-397.175
Stage IIIB	T1a-cN3M0 T2a-bN3M0 T3N2M0	1319	655 (0.497)	273.429	253.271-295.192	722 (0.547)	322.271	300.321-345.825
Stage IIIB	T4N2M0	2196	1587 (0.723)	776.0075	738.752-815.141	1771 (0.806)	865.979	826.573-907.265
Stage IIIC	T3-4N3M0	755	537 (0.711)	782.989	719.488-852.095	590 (0.781)	860.267	793.579-932.560

CI indicates confidence interval.

Kaplan-Meier Analyses Reflect the Survival Prognosis of Lung Adenocarcinomar

Kaplan-Meier analyses reflected that CSS and OS were significant difference between the groups T4N2M0 and stage IIIB excluding T4N2M0 ($P < 0.001$, Fig. 1). Furthermore, compared with the groups stage IIIA and stage IIIB excluding T4N2M0, the group T4N2M0 showed a sharply decline in the CSS and OS curve ($P < 0.001$, Fig. 2). Notably, the CSS and OS was not obviously different between the group T4N2M0 and the group stage IIIC ($P > 0.05$, Fig. 3).

DISCUSSION

The IASLC staging system of NSCLC has been considered as the accurate model for the prognostic classification of lung cancer patients, which has been widely used in clinical practice to evaluate the risk hierarchy of pulmonary cancer. This system is mainly based on the anatomic extent of cancer and is constantly developed to maintain relevant to current clinical practice and advances in lung cancer prognosis.[19] Although the eighth edition of IASLC staging system has been demonstrated to provide better precise survival prognosis for NSCLC in despite of the malignant tumor as the most common NSCLC subtype, few studies have shown specific effects on the survival and prognosis of lung adenocarcinoma in the TNM-8th system. As a consequence, we intend to enhance the survival prognostic ability of patients with lung adenocarcinoma by exploring the applicability of this new staging system on patients with lung adenocarcinoma.

As is obviously shown in our analysis, the differentiation of prognoses of substages, especially in the substage IIIB and IIIC, was dissatisfied in the current TNM-8th system. Specifically, we perceived that patients with stage T4N2M0 should be upgraded in

TABLE 6. Hazard Ratios for Cancer-specific Survival of Lung Adenocarcinoma

		Unadjusted Cox Regression		Adjusted 1 Cox Regression		Adjusted 2 Cox Regression		Adjusted 3 Cox Regression	
Stage at Diagnosis	Stage Based on TNM-8th System	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95%CI)	*P*	HR (95% CI)	*P*
T4N2M0 T1a-cN2M0 T2a-bN2M0	IIIB	Ref		Ref		Ref		Ref	Ref
T3N1M0 T4N0M0 T4N1M0 T1a-cN3M0	IIIA	0.500 (0.472-0.530)	< 0.001*	0.501 (0.473-0.530)	< 0.001*	0.503 (0.475-0.532)	< 0.001*	0.661 (0.624-0.701)	< 0.001*
T2a-bN3M0 T3N2M0	IIIB	0.418 (0.383-0.456)	< 0.001*	0.418 (0.383-0.456)	< 0.001*	0.421 (0.385-0.460)	< 0.001*	0.572 (0.524-0.626)	< 0.001*
T3-4N3M0	IIIC	1.009 (0.920-1.108)	0.844	1.010 (0.920-1.108)	0.835	1.009 (0.919-1.107)	0.855	0.997 (0.909-1.095)	0.958

*$P < 0.05$.

Adjusted 1 Cox regression: cox regression for year at diagnosis, sex, and race matched substage.

Adjusted 2 Cox regression: cox regression for year at diagnosis, sex, race, and extrathoracic extension, differentiation grade matched substage.

Adjusted 3 Cox regression: cox regression for age at diagnosis, year at diagnosis, sex, race, extrathoracic extension, differentiation grade, radiation therapy and surgery matched substage.

CI indicates confidence interval; HR, hazard ratio; Ref, reference.

TABLE 7. Hazard Ratios for Overall Survival of Lung Adenocarcinoma

Stage at Diagnosis	Stage Based on TNM-8th System	Unadjusted Cox Regression HR (95% CI)	*P*	Adjusted 1 Cox Regression HR (95% CI)	*P*	Adjusted 2 Cox Regression HR (95% CI)	*P*	Adjusted 3 Cox Regression HR (95% CI)	*P*
T4N2M0 T1a-cN2M0 T2a-bN2M0	IIIB	Ref		Ref		Ref		Ref	Ref
T3N1M0	IIIA	0.514 (0.487-0.542)	< 0.001*	0.515 (0.488-0.543)	< 0.001*	0.512 (0.485-0.540)	< 0.001*	0.664 (0.628-0.701)	< 0.001*
T4N0M0 T4N1M0 T1a-cN3M0 T2a-bN3M0	IIIB	0.439 (0.405-0.477)	< 0.001*	0.439 (0.405-0.476)	< 0.001*	0.452 (0.416-0.490)	< 0.001*	0.595 (0.548-0.647)	< 0.001*
T3N2M0 T3-4N3M0	IIIC	0.997 (0.913-1.089)	0.949	0.977 (0.913-1.089)	0.942	1.007 (0.922-1.100)	0.871	0.991 (0.907-1.082)	0.836

*$P < 0.05$.

Adjusted 1 Cox regression: cox regression for year at diagnosis, sex and race matched substage.

Adjusted 2 Cox regression: cox regression for year at diagnosis, sex, race and extrathoracic extension, differentiation grade matched substage.

Adjusted 3 Cox regression: cox regression for age at diagnosis, year at diagnosis, sex, race, extrathoracic extension, differentiation grade, radiation therapy and surgery matched substage.

CI indicates confidence interval; HR, hazard ratio; Ref, reference.

the 8th edition of IASLC/TNM staging system of lung adenocarcinoma. In all patients with lung adenocarcinoma, the proportion of each stage was, respectively, shown that stage IA1, stage IA2, stage IA3, stage IB, stage IIA, stage IIB, stage IIIA, stage IIIB, stage IIIC, stage IVA, and stage IVB accounted for 1.96%, 10.47%, 8.15%, 3.84%, 1.81%, 4.38%, 12.59%, 6.70%, 1.44%, 35.46%, and 13.20% of patients according to the 8th edition of IASLC/TNM staging system. And then what we want to do was to divide each substage into specific groups, and it was confirmed whether these groups were fit for the IASLC/TNM-8th system. Furthermore, Cox proportional hazard regression analysis demonstrated by unadjusted analysis or adjusted analysis that the risk of CSM and ACM were higher in the substage T4N2M0 than in the other substages belonged to stage IIIB. The CSM and ACM rates per 1000 person-years for stage T4N2M0 extended far beyond the corresponding period with stage IIIB not including T4N2M0 and paralleled to the period with stage IIIC. We performed univariate and multivariate Cox proportional hazards regression analysis to determine prognostic factors related to CSS and OS. It could be predicted that patients with differentiation grade, T stage, LNM, distant metastasis, and pulmonary extension had a worse survival and prognosis and needed to accept more positive treatments such as chemotherapy, radiation therapy and surgery. Kaplan-Meier curves illustrated similar results that

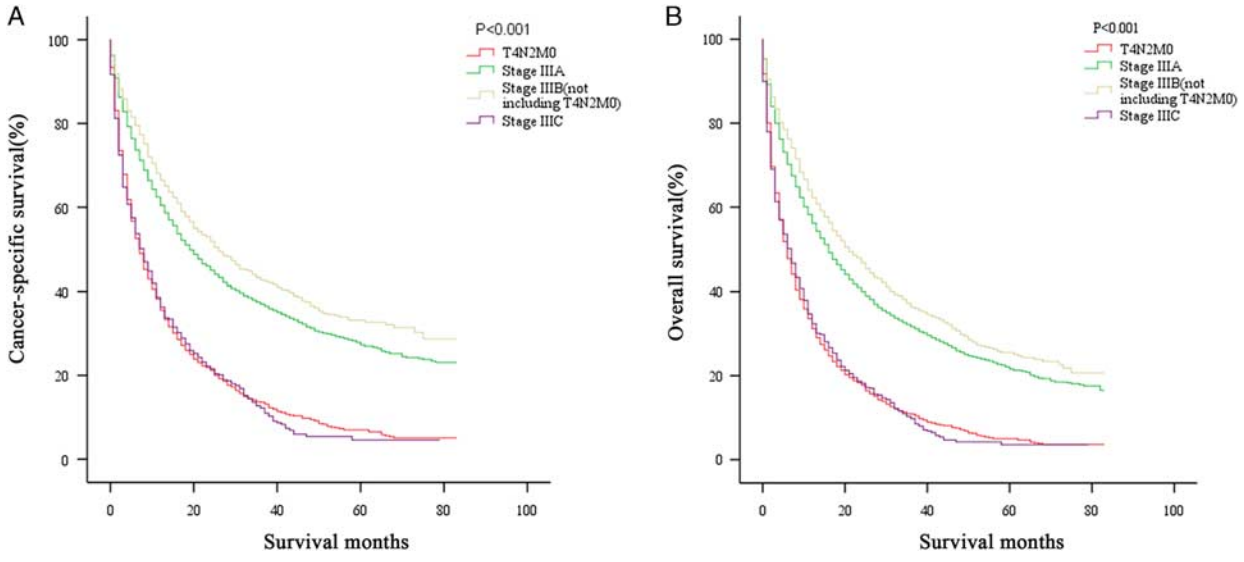

FIGURE 1. Kaplan-Meier curves for cancer-specific survival (A) and overall survival (B) between lung adenocarcinoma patients in group T4N2M0 and those with groups stage IIIA, IIIB (not including T4N2M0), IIIC. full color online

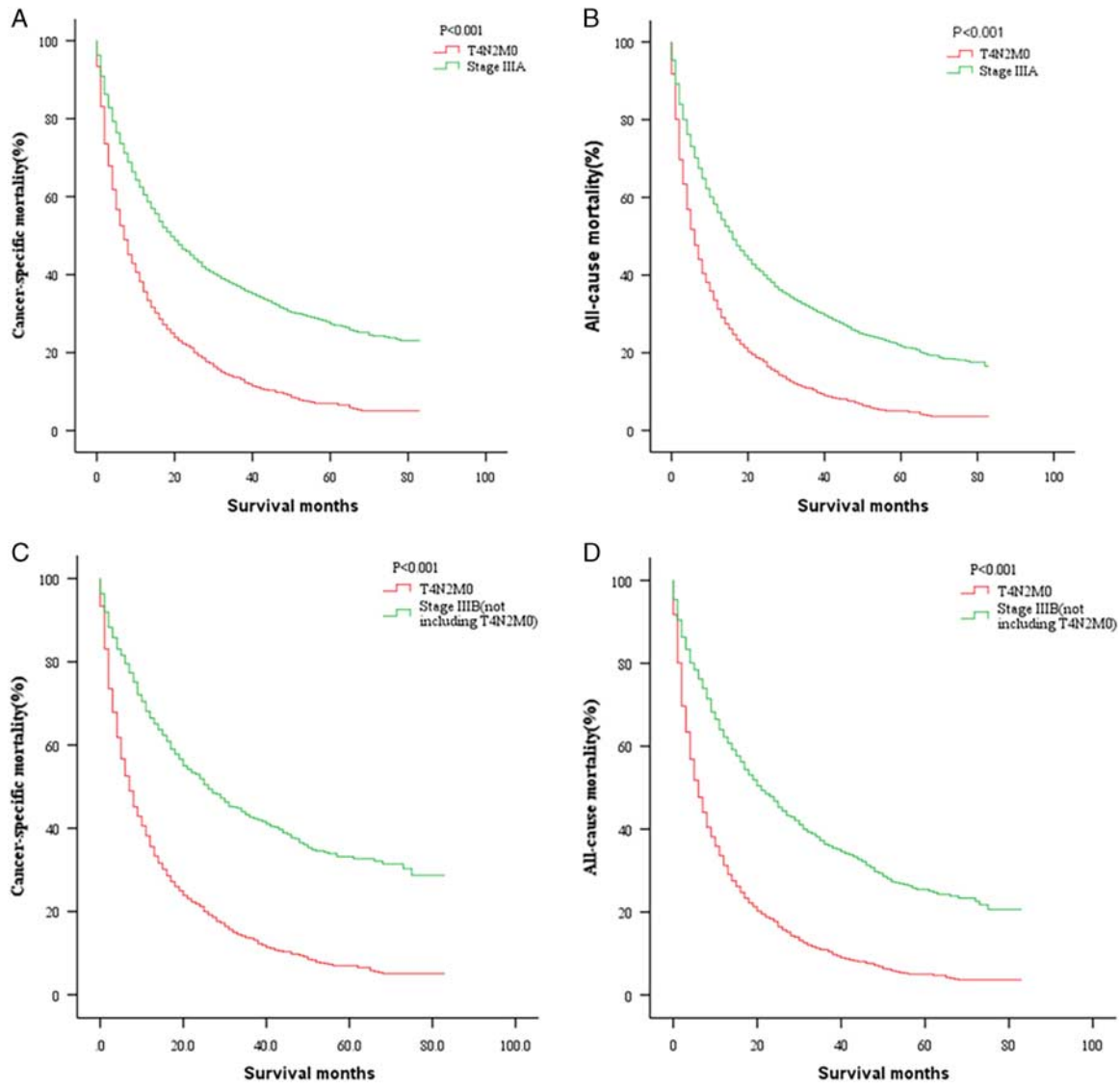

FIGURE 2. Kaplan-Meier curves for cancer-specific survival (A) and overall survival (B) between lung adenocarcinoma patients in group T4N2M0 and group stage IIIA. Kaplan-Meier curves for cancer-specific survival (C) and overall survival (D) between lung adenocarcinoma patients in group T4N2M0 and group stage IIIB (excluding T4N2M0). full color online

indicated patients with stage T4N2M0 revealed remarkable worse survival than patients in the same groups belonging to stage IIIB and revealed no difference in mortality compared to patients with stage IIIC. As described above, these analyses demonstrated by and large why patients diagnosed with stage T4N2M0 had an awful prognosis and required to be upstaged. All in all, we recommended that the substage T4N2M0 was not confirmed to the stage IIIB and should be upgraded. However, in Table 3, regardless of ACM and CSM, the univariate and multivariate cox analyses indicated that stage T4 was relevant to higher mortality than stage T1a-1c, T2a-2b,T3. Thus, tumor size was deemed as an important prognostic factor of lung adenocarcinoma.[20] In 2011, new entities of adenocarcinoma in situ, minimally invasive adenocarcinoma and adenocarcinoma subtype were defined and were later brought into the 2015 World Health Organization classification of lung cancer.[21] However, the change of concept inspired potential about the best way to measure tumor size in lung adenocarcinoma <3 cm. A document on this topic has been issued by the IASLC.[22] It was of great significance to measure tumor size of lung adenocarcinoma to accurate staging for thoracic surgeon. LNNM, pulmonary extension, chemoradiotherapy and surgery were also associated with survival prognosis of lung adenocarcinoma. Our study had some limitations. Based on SEER database, it contained limited information on chemotherapy, radiation therapy, and surgery. And it was impossible to acquire information on methods used for lymph node staging which included mediastinoscopy, computed tomography, positron emission tomography. Furthermore, genetic, environment, biological factors, smoke history, previous lung disease should be incorporated in staging model. Nevertheless, there were some controversies about the importance of these factors. Consequently, we aim to add more relevant factors to IASLC staging system in the future to improve the survival prognosis, risk stratification, management, and treatment decision.

In conclusion, pulmonary adenocarcinoma patients with stage T4N2M0 have a worse survival prognosis than stage IIIB

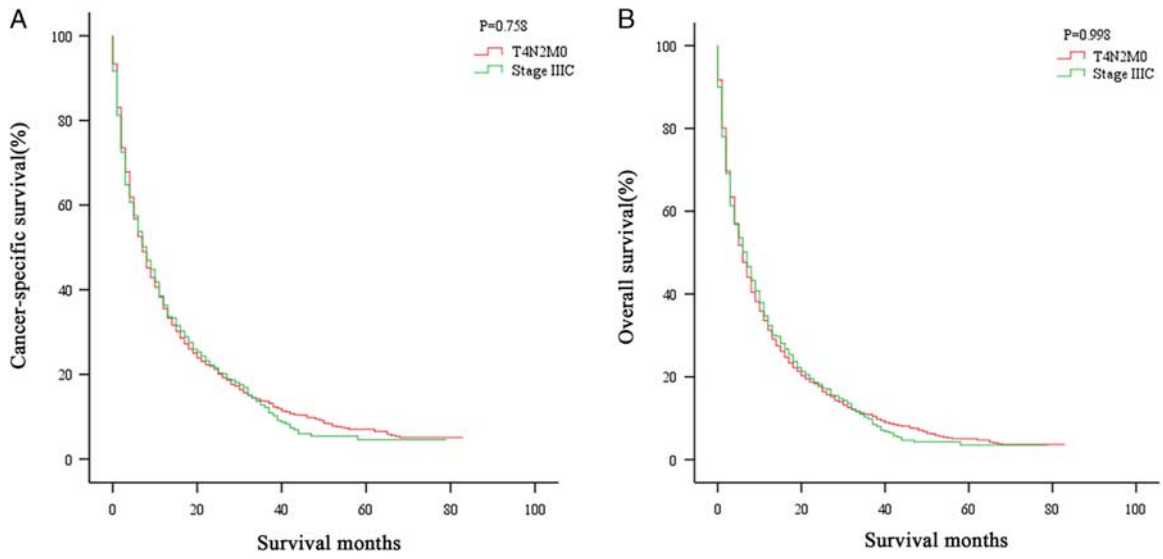

FIGURE 3. Kaplan-Meier curves for cancer-specific survival (A) and overall survival (B) between lung adenocarcinoma patients in group T4N2M0 and group stage IIIC. full color online

patients. In contrast, it has a similar survival prognosis compared with stage IIIC patients. Finally, we suggest that lung adenocarcinoma patients with stage T4N2M0 should be upstaged and accept more aggressive treatments.

REFERENCES

1. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer*. 1995;75:2844–2852.
2. Devesa S, Bray F, Vizcaino A, et al. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer*. 2005;117:294–299.
3. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007;2:706–714.
4. Groome P, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol*. 2007;2:694–705.
5. Postmus P, Brambilla E, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2007;2:686–693.
6. Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2007;2:593–602.
7. Rusch V, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4:568–577.
8. Travis W, Giroux D, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the inclusion of broncho-pulmonary carcinoid tumors in the forthcoming (seventh) edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2008;3:1213–1223.
9. Detterbeck F, Boffa D, Kim A, et al. The eighth edition lung cancer stage classification. *Chest*. 2017;151:193–203.
10. Rami-Porta R, Bolejack V, Giroux D, et al. The IASLC lung cancer staging project: the new database to inform the eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2014;9:1618–1624.
11. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:39–51.
12. Tian S. Classification and survival prediction for early-stage lung adenocarcinoma and squamous cell carcinoma patients. *Oncol Lett*. 2017;14:5464–5470.
13. Fukui T, Taniguchi T, Kawaguchi K, et al. Comparisons of the clinicopathological features and survival outcomes between lung cancer patients with adenocarcinoma and squamous cell carcinoma. *Gen Thorac Cardiovasc Surg*. 2015;63:507–513.
14. Usui S, Minami Y, Shiozawa T, et al. Differences in the prognostic implications of vascular invasion between lung adenocarcinoma and squamous cell carcinoma. *Lung Cancer (Amsterdam, Netherlands)*. 2013;82:407–412.
15. Ogawa H, Uchino K, Tanaka Y, et al. Outcomes of segmentectomy for cT1bN0M0 lung adenocarcinoma and squamous cell carcinoma: a possible association with pathological invasion. *Eur J Cardiothorac Surg*. 2015;48:77–82.
16. Herbst R, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383:1328–1339.
17. Fan H, Shao Z, Xiao Y, et al. Incidence and survival of non-small cell lung cancer in Shanghai: a population-based cohort study. *BMJ Open*. 2015;5:e009419.
18. Rosen J, Hancock J, Kim A, et al. Predictors of mortality after surgical management of lung cancer in the National Cancer Database. *Ann Thorac Surg*. 2014;98:1953–1960.
19. Vesikari T, Isolauri E, Mäki M, et al. Clostridium difficile in young children. Association with antibiotic usage. *Acta Paediatr Scand*. 1984;73:86–91.
20. Zhang J, Gold K, Lin H, et al. Relationship between tumor size and survival in non-small-cell lung cancer (NSCLC): an analysis of the surveillance, epidemiology, and end results (SEER) registry. *J Thorac Oncol*. 2015;10:682–690.
21. Travis W, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol*. 2011;6:244–285.
22. Travis W, Asamura H, Bankier A, et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2016;11:1204–1223.