ORIGINAL ARTICLE

Prognostic Impact of Single and Multiple Descriptors in Pathologically Staged T3N0M0 NSCLC

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ABSTRACT

Introduction: T components of the current eighth edition of lung cancer American Joint Commission on Cancer (AJCC) staging assignment include size of primary tumor and others such as chest wall invasion. The role of the presence of multiple T3 descriptors in prognosis remains unknown.

Methods: Using the National Cancer Database and the AJCC seventh edition, pathologically staged (R0) N0M0 NSCLC cases diagnosed in 2010 to 2016 were analyzed. The selected cases had primary size larger than 5 cm or staged as T3 by the AJCC seventh edition despite the size of less than 5 cm. T3 descriptor status according to the eighth edition was defined as single descriptor ("T3-single") with primary size of 5 to 7 cm or size less than 5 cm and T3 based on the seventh edition ("T3-other") or multiple descriptor ("T3-multi") with presence of both descriptors. Survival analysis was performed with validation of multivariate analyses.

Results: Of the 108,632 surgically resected pathologically staged N0M0R0 NSCLC cases, 9931 met the following criteria: 8955 as T3-single (4381 as T3-size, 4574 as T3-other) and 884 as T3-multi. Univariate and multivariate analyses revealed that T3-multi had significantly worse overall survival than T3-single with a median survival of 37.3 versus 69.3 months, respectively. Propensity score matching analysis validated the statistical significance. Exploratory analysis also revealed that the survival of the T3-multi group is similar to that of the T4 groups.

Conclusions: Our retrospective analysis using the National Cancer Database suggests that prognosis of patients with multiple T3 descriptors is substantially worse than those with single descriptors. Further research may be required to accurately define the prognosis of NSCLC for future staging update.

Keywords: Non–small cell lung cancer; T3; NCDB; Staging

Introduction

Despite concerted effort and technological advances in early detection, diagnosis, and treatment, lung cancer remains the deadliest disease among adult malignancies. According to the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results program, more than 135,000 people are expected to succumb to the disease in 2020, accounting for 22% of all cancer deaths in the United States.[1] Patient survival is largely dependent on assigned TNM stage. Lung cancer staging manuals have been published and updated every several

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years by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC).[2-4]

AJCC/UICC staging manuals have been routinely used as tools by clinicians to estimate survival. The most recent edition of lung cancer staging manual (version 8) was published in 2017 and implemented in January 2018 after thorough investigation on cases submitted by international researchers, yielding much larger sample size than previous versions.[5,6] The accuracy and distinction among stages in prognosis have been validated in a number of external retrospective studies.[7-10] As more diagnostic and therapeutic technology develops over the next decades, the staging manuals must be updated regularly to reflect the change in management.

Regarding updates in the AJCC/UICC eighth edition of lung cancer staging, emphasis was made on modification of the T component.[11,12] After intense investigation in survival estimation, tumors with a size larger than 5 cm but not larger than 7 cm were assigned to T3 and those larger than 7 cm were assigned to T4. Although other nonsize descriptors defining T3 were reevaluated, only minor changes were made to reclassify T3 to T2 or T4. Prognosis of cases with multiple T3 descriptors (e.g., size between 5 and 7 cm and chest wall invasion) has never been incorporated into even the AJCC/UICC eighth edition because no solid conclusion had been made from their analysis at the time.[11,12] The objective of the present study is to analyze the prognostic impact of single and multiple T3 descriptors in pathologically staged, completely resected NSCLC.

Materials and Methods

National Cancer Database

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the sources of the deidentified data used herein; however, they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. The data are considered as hospital-based rather than population-based.[13]

After obtaining approval from the CoC, access to information of deidentified cases with NSCLC was granted in October 2019. A total of 590,891 adult cases diagnosed between 2010 and 2016 at the CoC-participating institution in the United States were screened for this study.

Eligible cases must have been pathologically staged as pN0M0 according to the AJCC/UICC seventh edition and must have undergone R0 resection of the primary tumor. Obtained data with the AJCC/UICC seventh edition were converted to the eighth edition as follows. Cases with pT2 based on the AJCC/UICC seventh edition[14] and a size between 5 and 7 cm would have been assigned to pathologic T3 (pT3) on the basis of the AJCC eighth edition[11,12] and grouped as "T3-size." Those with pT3 and a size equal or less than 5 cm were considered as having T3 descriptor other than size by the AJCC/UICC seventh and eighth editions and were therefore assigned to "T3-other." T3 descriptors other than size, which were not reported by NCDB, have presumably included the following: chest wall invasion, parietal pleura, phrenic nerve, intrapulmonary nodule in the same lobe, parietal pericardium, main bronchus within 2 cm from carina, atelectasis, mediastinal pleura, and diaphragm. Although invasion of the diaphragm was reclassified to T4 based on the AJCC/UICC ninth version, it seems infrequent according to the study by Rami-Porta et al.[5] There were only 40 of 1882 cases (3%) with T3 cases (Supplementary Table 2). T3 size and T3 other were then grouped together as "T3-single." Those with pT3 and a size between 5 and 7 cm were considered as having T3 descriptor other than size by the AJCC/UICC seventh edition and size itself defines T3 by the AJCC/UICC eighth edition; therefore, they are grouped as "T3-multi" (Supplementary Table 1). Definition of "T3" in all the groups are based on the AJCC/UICC eighth edition. Of note, a size between 5 and 7 cm is T2 by the AJCC/UICC seventh edition and T3 by the AJCC/UICC eighth edition. Cases with survival time less than one month were removed from the final analysis (Fig. 1).

Key clinical characteristics were obtained and examined for association with T3-multi group. They included age (<70 versus ≥ 70), sex (male versus female), race (White versus others), insurance status (uninsured versus insured), institution (academic versus others), Charlson-Deyo comorbidity score, year of diagnosis (2010–2013 versus 2014–2016), cell type (adenocarcinoma not otherwise specified versus others), radiation (yes versus no), multiagent chemotherapy (yes versus no), and immunotherapy (yes versus no). Of note, information on cancer treatment was available only for first-course of therapy before recurrence. Treatment details in cases of recurrent disease were not obtained.

In an exploratory analysis, the subclassification of T4 as in T3 was performed. Cases with AJCC/UICC eighth edition T4 were divided into T4-size, T4-other, and T4-multi (Supplementary Table 1). Definition of "T3 and T4" in all the groups are based on the AJCC/UICC eighth edition.

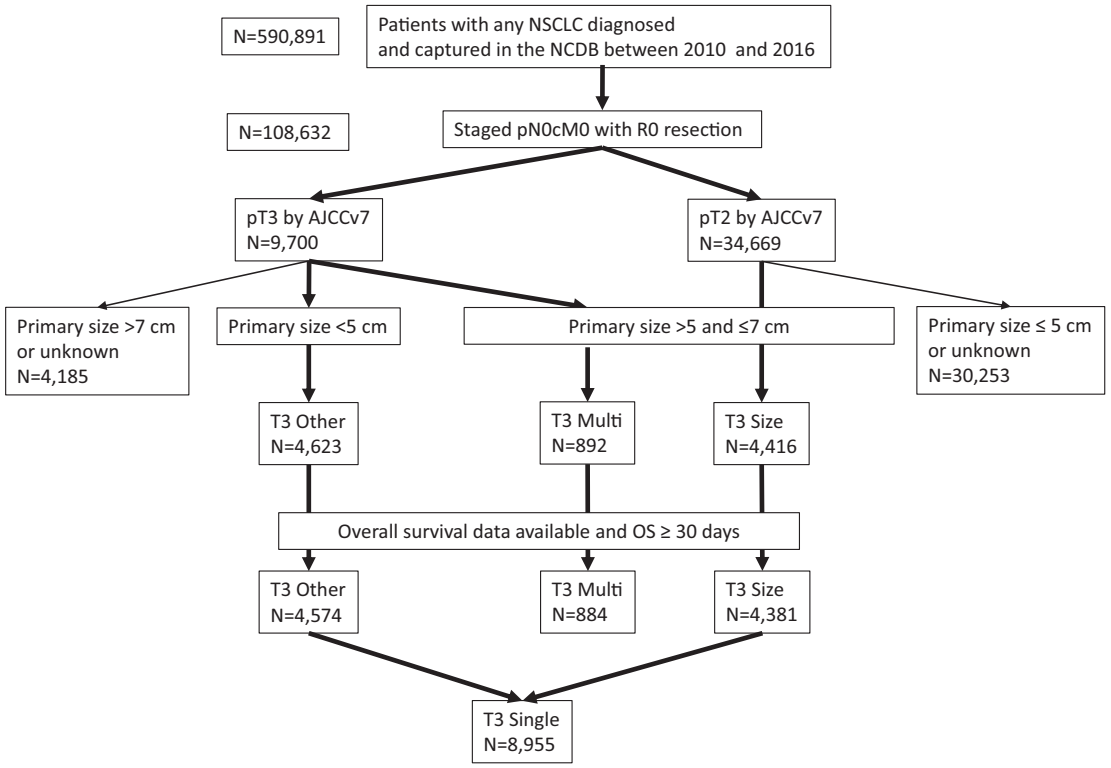

Figure 1. Study flow diagram of case eligibility. AJCCv7, American Joint Commission on Cancer seventh edition; NCDB, National Cancer Database; OS, overall survival; pT2, pathologic T2; pT3, pathologic T3.

Statistics

Correlation between the clinical characteristics listed previously and the T3 groups was determined by chi-square tests. Survival analysis was conducted using Kaplan-Meier and log-rank methods. A p value of less than 0.05 on a two-tailed statistical analysis was considered significant. Univariate and multivariate Cox proportional hazard analyses were performed using JMP version 14 (SAS Institute, Cary, NC). Hazard ratios with 95% confidence intervals were provided. Propensity score matching (PSM) analysis included all the variables listed in Table 1 except insurance, race, and year of diagnosis and was performed according to the XLSTAT software guideline.[15]

This is not a population-based but a hospital-based study that involves no identifiable information for individuals throughout the analyses. This study was reviewed by the institutional review board at Parkview Health and was designated exempt from human subject research before beginning data analysis.

Results

Although detailed information about all the descriptors to define T3 by the seventh edition was not available, we were able to presume that one of the nonsize T3 descriptors was present if the case was pathologically staged as T3 and its primary size was 5 cm or smaller. The screening process of the candidate cases is illustrated in Figure 1. Of the 590,891 NSCLC cases diagnosed between 2010 and 2016, a total of 108,632 cases have undergone R0 resection with pathologic stage of N0M0 based on the AJCC/UICC seventh edition. A total of 9700 and 34,669 cases had pT3 and pT2, respectively. Subsequently, 4623 pT3 cases with a primary size less than 5 cm, 892 pT3 cases with a primary size greater than 5 and less than or equal to 7 cm, and 4416 pT2 cases with a primary size greater than 5 and less than or equal to 7 cm were defined as T3-other, T3-multi, and T3-size, respectively, according to the AJCC/UICC eighth edition. Of note, a primary size greater than 5 and less than or equal to 7 cm is defined as T2 and T3 according to the seventh and the eighth edition, respectively. A size greater than 7 cm is defined as T3 based on the seventh edition. T3 assignment by the seventh edition despite a primary size greater than 5 and less than or equal to 7 cm indicates presence of nonsize T3 descriptors. Therefore, those in T3-multi group have a size to define T3 by the eighth edition (i.e., a primary size >5 and ≤ 7 cm) and

Table 1. Characteristics of AJCCv8 Pathologic T3-Single Versus T3-Multi Descriptors According to AJCCv7 Data

	Before PSM			After PSM		
Factors	Single	Multiple	*p* Value	Single	Multiple	*p* Value
Total	N = 8955 (100%)	N = 884 (100%)		N = 884	N = 884	
Age, y			0.0288			1.0000
<70	4741 (53)	502 (57)		502 (57)	502 (57)	
≥70	4214 (47)	382 (43)		382 (43)	382 (43)	
Sex			0.0089			1.0000
Male	4632 (52)	498 (56)		498 (56)	498 (56)	
Female	4323 (48)	386 (44)		386 (44)	386 (44)	
Race			0.2913			0.6495
White	7885 (88)	789 (89)		783 (89)	789 (89)	
Others	1070 (12)	95 (11)		101 (11)	95 (11)	
Insurance status			<0.0001			0.0002
Uninsured	146 (2)	35 (4)		10 (1)	35 (4)	
Insured	8809 (98)	849 (96)		874 (99)	849 (96)	
Institution			0.7285			0.9615
Academic	3782 (42)	368 (42)		367 (42)	368 (42)	
Others	5173 (55)	516 (58)		517 (58)	516 (58)	
CD score			0.5482			0.8448
0-1	7456 (83)	743 (84)		746 (84)	743 (84)	
≥2	1499 (17)	141 (16)		138 (16)	141 (16)	
Year of diagnosis			0.9205			0.4840
2010-2013	5941 (66)	585 (66)		571 (65)	585 (66)	
2014-2016	3014 (34)	299 (34)		313 (35)	299 (34)	
Cell type			<0.0001			0.9561
A-NOS	2862 (32)	220 (25)		219 (25)	220 (25)	
Others	6093 (68)	664 (75)		665 (75)	664 (75)	
Radiation			<0.0001			1.0000
Yes	771 (9)	233 (26)		233 (26)	233 (26)	
No	8184 (91)	651 (74)		651 (74)	651 (74)	
Multiagent chemotherapy			<0.0001			1.0000
Yes	3146 (35)	459 (52)		459 (52)	459 (52)	
No	5809 (65)	425 (48)		425 (48)	425 (48)	
Immunotherapy			0.9311			0.5634
Yes and No	8955 (100%)	884 (100%)		884 (100%)	884 (100%)	

AJCCv7, American Joint Commission on Cancer seventh edition; AJCCv8, American Joint Commission on Cancer eighth edition; A-NOS, adenocarcinoma not otherwise specified; CD, Charlson-Deyo; PSM, propensity score matching.
Due to agreement with National Cancer Database, reporting cells <10 cases is prohibited. They were combined with the opposing cells.

a nonsize T3 descriptor. After removing cases with overall survival less than 1 month, 4574, 884, and 4381 patients were analyzed further, respectively.

The characteristics of the T3 groups according to the AJCC/UICC eighth edition are illustrated in Table 1. Before PSM, presence of multiple descriptors (T3-multi group) was significantly associated with younger age ($p = 0.0288$), male sex ($p = 0.0089$), uninsured status ($p < 0.0001$), history other than adenocarcinoma not otherwise specified ($p < 0.0001$), radiation therapy ($p < 0.0001$), and multiagent chemotherapy ($p < 0.0001$). After adjustment with PSM, all factors except uninsured status ($p = 0.0002$) had no significant association with the T3-multi group.

Analysis on overall survival revealed that the T3-multi group had a significantly worse survival than T3-size and T3-other, with hazard ratios of 0.65 and 0.58, respectively (Fig. 2*A*). The magnitude of difference in survival between T3-size and T3-other was comparatively smaller with a hazard ratio of 0.89. When T3-size and T3-other were grouped together as T3-single, a significantly better survival than T3-multi was also found with median overall survivals of 69.3 versus 37.3 months, respectively (Fig. 2*B*). This difference was statistically significant, as univariate and multivariate analyses revealed that T3-single status had a significantly longer overall survival than the T3-multi group with a hazard ratio of 0.61 and 0.62, respectively (Table 2). Other clinical groups with significantly longer survival in multivariate analysis included younger age, female, academic institution, low Charlson-Deyo comorbidity score, lack of radiation, and multiagent chemotherapy.

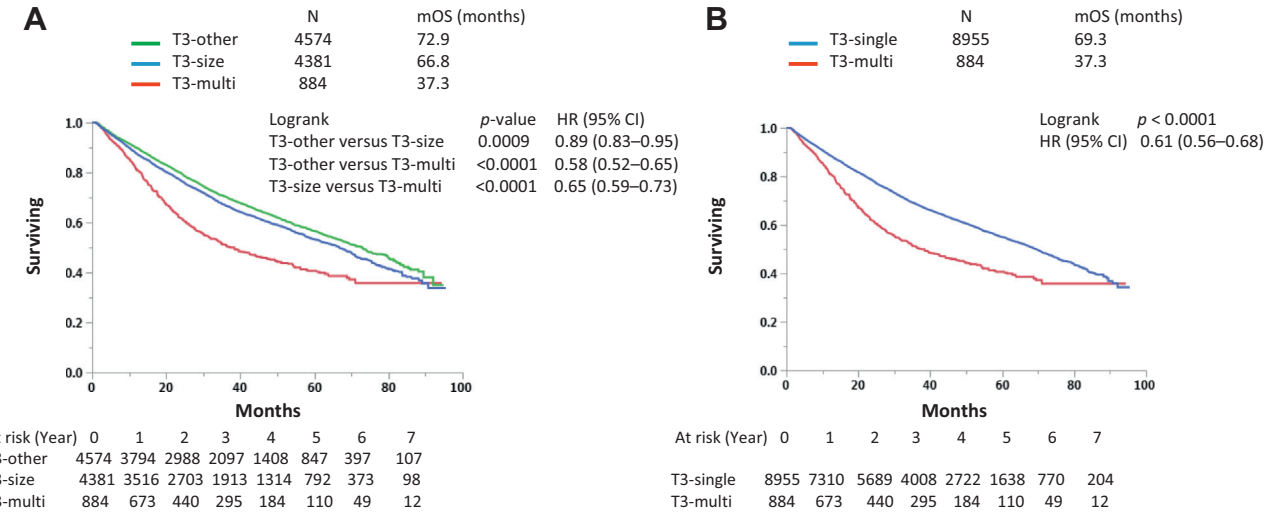

Figure 2. Overall survival according to AJCCv8 T3 descriptor status. Survival curves were plotted according to T3 status. Numbers of cases at risk are revealed for each calendar year. (*A*) Survival curves for T3-other, T3-size, and T3-multi. (*B*) Survival curves for T3-single and T3-multi. AJCCv8, American Joint Commission on Cancer eighth edition; CI, confidence interval; HR, hazard ratio; mOS, median overall survival.

PSM analysis also supported the above-mentioned finding that the T3-multi group has reduced overall survival. With a hazard ratio of 0.66, median survivals were 66.3 and 37.3 months in T3-single versus T3-multi, respectively (Fig. 3). Multivariate analysis on the cases selected for PSM revealed that groups with younger age, female, low Charlson-Deyo comorbidity score, lack of radiation, multiagent chemotherapy, and T3-single status had significantly longer survival time (Table 2, Supplementary Fig. 1).

As an exploratory analysis, survival curves of the T3 subgroups were compared with those of the T4 subgroups (Supplementary Fig. 1). Survival of the T3-multi group was similar to the T4 subgroups, and even worse than the T4-size/other.

Discussion

To estimate the prognosis of patients diagnosed with cancer, cancer staging systems have been developed over the past several decades.[2,3] They are useful tools for providing clinicians and patients with information necessary to determine therapeutic intervention. As novel technology develops, these staging systems need to be adjusted to reflect the current diagnosis and therapeutic interventions. For lung cancer, new diagnostic and therapeutic modalities over the past few decades include positron emission tomography scan, endobronchial ultrasound, intensity-modulated radiation therapy/stereotactic body radiation therapy, robotic-assisted surgery, and others. Staging systems were built and updated periodically with recent cases registered for this purpose.

The AJCC/UICC eighth edition lung cancer staging was revolutionary in several aspects. The committee recruited 94,708 cases that were diagnosed to have lung cancer between 1999 and 2010 from 35 sources in 16 countries. This was a remarkable increase in sample size from the sixth edition in 1997 with 5319 cases.[16]

The AJCC/UICC eighth edition committee proposed to divide T1–2 into small subsets on the basis of primary tumor size, revealing notable separation in survival between the T subgroups.[11] It allowed estimation of each patient's survival more precisely. The definition of T3 and T4 was also revisited. A tumor size larger than 7 cm was reclassified from T3 to T4, and those between 5 and 7 cm were assigned from T2 to T3. Nonsize T descriptors were reconsidered; invasion to the diaphragm was upstaged to T4, whereas main bronchus lesion within 2 cm and total atelectasis were downstaged to T2 (Supplementary Table 2).[11]

The nonsize T descriptors are uncommonly reported. According to Rami-Porta et al.,[11] less than 10% overall were defined as T3 with the AJCC/UICC seventh edition. Jeon et al.[17] in Korea conducted a single institutional retrospective analysis to review cases diagnosed to have pT3 according to the AJCC/UICC seventh edition between 2001 and 2013. They reported that the T3-multi group with 63 patients had an inferior survival as compared with other T3 groups. Their small sample size limited its significance as a poor prognostic indicator. The role of coexisting size and nonsize T3 descriptors in comparison with a single descriptor remained unclear.

To address the significance of multiple T3 descriptors, we conducted a retrospective analysis with cases obtained from NCDB. Patients with pathologically staged T2

Table 2. AJCCv8 Pathologic T3-Single Versus T3-Multi Descriptors According to AJCCv7 Data. Overall Survival Analysis

	Before PSM		After PSM	
	N = 8599 vs. 884		N = 884 vs. 884	
	Univariate	Multivariable	Univariate	Multivariable
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Factors	*p* Value	*p* Value	*p* Value	*p* Value
Age, y				
<70	0.63 (0.59-0.67)	0.68 (0.63-0.72)	0.69 (0.59-0.80)	0.64 (0.55-0.73)
≥70	<0.0001	<0.0001	<0.0001	<0.0001
Sex				
Female	0.69 (0.65-0.74)	0.73 (0.68-0.78)	0.70 (0.60-0.81)	0.76 (0.65-0.88)
Male	<0.0001	<0.0001	<0.0001	0.0002
Race				
Others	0.88 (0.79-0.97)	0.97 (0.87-1.07)	1.01 (0.79-1.26)	1.07 (0.84-1.34)
Whites	0.0114	0.5296	0.9546	0.5676
Insurance status				
Uninsured	0.89 (0.69-1.12)	1.03 (0.81-1.32)	1.28 (0.84-1.87)	1.42 (0.95-2.14)
Insured	0.3254	0.7838	0.2400	0.0876
Institution				
Academic	0.79 (0.74-0.84)	0.80 (0.75-0.86)	0.87 (0.75-1.00)	0.90 (0.78-1.04)
Others	<0.0001	<0.0001	0.0536	0.1712
CD score				
0-1	0.75 (0.69-0.81)	0.81 (0.74-0.88)	0.67 (0.56-0.80)	0.72 (0. 60-0.86)
≥2	<0.0001	<0.0001	<0.0001	0.0004
Year of diagnosis				
2014-2016	0.95 (0.87-1.03)	0.96 (0.89-1.05)	1.03 (0.87-1.22)	1.06 (0.89-1.25)
2010-2013	0.1855	0.3736	0.6995	0.5298
Cell type				
A-NOS	0.87 (0.81-0.93)	0.93 (0.87-1.00)	0.84 (0.71-0.99)	0.92 (0.78-1.09)
Others	0.0001	0.0518	0.0390	0.3509
Radiation				
No	0.72 (0.66-0.80)	0.64 (0.58-0.71)	0.77 (0.66-0.90)	0.60 (0.51-0.71)
Yes	<0.0001	<0.0001	0.0009	<0.0001
Multiagent chemotherapy				
Yes	0.68 (0.63-0.73)	0.67 (0.62-0.72)	0.68 (0.59-0.78)	0.66 (0.56-0.77)
No	<0.0001	<0.0001	<0.0001	<0.0001
Immunotherapy				
Yes	0.90 (0.39-1.75)	1.02 (0.49-2.15)	0.60 (0.03-2.66)	1.00 (0.14-7.13)
No	0.7870	0.9507	0.5800	0.9980
T3 status				
Single	0.61 (0.56-0.68)	0.62 (0.56-0.69)	0.66 (0.57-0.76)	0.66 (0.58-0.77)
Multiple	<0.0001	<0.0001	<0.0001	<0.0001

AJCCv7, American Joint Commission on Cancer seventh edition; AJCCv8, American Joint Commission on Cancer eighth edition; A-NOS, adenocarcinoma not otherwise specified; CD, Charlson-Deyo; CI, confidence interval; HR, hazard ratio; PSM, propensity score matching.

to T3N0M0 according to the AJCC seventh edition were selected and reassigned to T3 based on the AJCC/UICC eighth edition. They were further classified into T3-single (T3-size + T3-other) and T3-multi based on the above-mentioned criteria (Supplementary Table 1). Survival of the T3-multi group was significantly shorter than that of the T3-single, and this statistical significance held true after PSM analyses. The T3-multi group was similar to the T4-multi group, and both groups had worse overall survival than other T4 subgroups. Our findings suggest that the T3-multi group may be reassigned to or grouped together with T4 subgroups.

Although our data suggest a novel approach and finding for staging amendment expected in coming years, we acknowledge several limitations. First, our analyses rely on the database that collected information in CoC-participating institutions. It is possible that there might be reporting errors and misclassification in staging assignment. Owing to deidentified data, it is impossible to collect information that was not recorded previously.

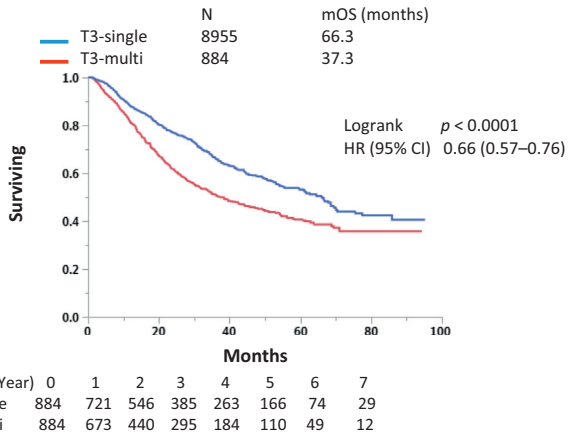

Figure 3. Overall survival according to AJCCv8 T3 descriptor status. Propensity score matching analysis for single versus multiple T3 descriptors. AJCCv8, American Joint Commission on Cancer eighth edition; CI, confidence interval; HR, hazard ratio; mOS, median overall survival.

Second, staging methods used in the cases are not available. Although all the cases underwent surgical and pathologic staging, surveys for metastasis may not be consistent. Cases in recent years might have undergone more advanced techniques such as positron emission tomography and endobronchial ultrasound. Difference in surgical technique has not been addressed in this study.

Third, we focused on surgically resected, pathologically staged T3N0M0 cases. The roles of the multiple descriptors in node-positive cases or clinically staged T3N0 cases were not investigated. This is to minimize influence by nodal status and presence/absence of surgery, respectively.

Finally and perhaps more importantly, there are several modifications in T3 when updated to the AJCC/UICC eighth edition. Beside size criteria, several factors to define T3 by the AJCC/UICC seventh edition were reassigned to T2 or T4 (Supplementary Table 2). NCDB does not provide all the descriptions regarding T3 assignment. However, according to a comprehensive study conducted by the eighth edition staging working group, only 6% and 3% of single T3 descriptor cases were downstaged and upstaged because of any reason other than size criteria, respectively (Supplementary Table 2),[11] suggesting the vast majority of cases assigned to T3 by the AJCC/UICC seventh edition can still be assigned to T3 by the AJCC/UICC eighth edition.

In conclusion, our retrospective study of a large sample size indicates that pathologically staged T3N0M0 NSCLCs defined by single and multiple descriptors have different prognoses. This finding is relevant in clinical practice to refine postoperative prognosis, and it should be taken into consideration, pending clinical and external validations, in the preparation of the forthcoming AJCC/UICC ninth edition for lung cancer.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2020.100111.

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