ORIGINAL ARTICLE

Reconsidering the American Joint Committee on Cancer Eighth Edition TNM Staging Manual Classifications for T2b and T3 NSCLC

Arvind Kumar, BS,[a] Sanjeevani Kumar,[b] Shivee Gilja, BS,[a] Alexandra L. Potter,[b] Vignesh Raman, MD,[c] Ashok Muniappan, MD,[b] Douglas Z. Liou, MD,[d] Chi-Fu Jeffrey Yang, MD[b,e,*]

[a]*Department of Thoracic Surgery, Icahn School of Medicine at Mount Sinai, New York, New York*
[b]*Division of Thoracic Surgery, Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts*
[c]*Division of Thoracic Surgery, Department of Surgery, Duke University Medical Center, Durham, North Carolina*
[d]*Department of Cardiothoracic Surgery, Stanford University Medical Center, Stanford, California*
[e]*Department of Surgery, Wentworth-Douglass Hospital, Dover, New Hampshire*

Received 21 April 2021; revised 7 June 2021; accepted 14 June 2021
Available online - 6 July 2021

ABSTRACT

Introduction: The American Joint Committee on Cancer (AJCC) eighth edition TNM staging manual for NSCLC, derived from the International Association for the Study of Lung Cancer (IASLC) Staging Project, designates tumors with additional nodule(s) in the same lobe as T3. This study sought to externally validate the results of the IASLC, which showed a trend in improved survival for such tumors, but excluded treatment-based adjustment, by assessing whether these tumors have worse survival than T2b NSCLC.

Methods: Overall survival of patients with T2b-T3, N0-3, M0 NSCLC (satisfying a single T descriptor of tumors >4 cm but ≤5 cm in greatest dimension ["T2b"], tumors >5 cm but ≤7 cm in greatest dimension ["T3-Size"], or tumors with additional nodule(s) in the same lobe ["T3-Add"]), according to the AJCC eighth edition, in the National Cancer Database (2010–2015), was evaluated using multivariable Cox proportional hazards modeling and propensity score matching.

Results: 31,563 patients with T2b-T3, N0-3, M0 NSCLC met the study inclusion criteria. In multivariable-adjusted analysis, T3-Add tumors had improved overall survival compared with T3-Size tumors (Hazard Ratio = 0.86, 95% Confidence Interval: 0.82–0.89, $p < 0.001$) and similar survival compared with T2b tumors (Hazard Ratio = 1.04, 95% Confidence Interval: 0.97–1.12, $p = 0.28$). A propensity score-matched analysis of 2260 T3-Add and 2,260 T2b patients, well-balanced on 16 common prognostic covariates, including treatment type (surgery, chemotherapy, or radiation), revealed similar 5-year survival (53.4% versus 52.3%, $p = 0.30$).

Conclusions: In this national analysis, T3-Add tumors had better survival than other T3 tumors and similar survival to T2b tumors. These findings may be taken into consideration for the AJCC ninth edition staging classifications.

Keywords: Additional nodules; T3 non–small-cell lung cancer; Restaging; TNM staging guidelines

Introduction

Staging for primary NSCLC that presents as a tumor with additional intrapulmonary nodule(s) has been challenging to develop and continues to evolve.[1] In 2016, the American Joint Committee on Cancer (AJCC) published the eighth edition TNM staging manual and assigned tumors with additional nodule(s) to specific T categories on the basis of the location of the separate

*Corresponding author.

Disclosure: *The authors declare no conflict of interest.*

Presented at the American Association of Thoracic Surgery, a virtual conference, April 30th, 2021.

Address for Correspondence: Chi-Fu Jeffrey Yang, MD, Division of Thoracic Surgery, Department of Surgery, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114. E-mail: cjyang@mgh.harvard.edu

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2021.06.016

nodule(s) (T3 for same lobe, T4 for different ipsilateral lobe, M1a for contralateral lobe).[2] These tumors are defined as a solid lung cancer with at least one separate tumor nodule of similar solid appearance and presumed matching histologic appearance; these definitions specifically exclude synchronous primary lung cancers and multifocal lung cancer with ground-glass or lepidic features or pneumonic type.[2,3]

The new eighth edition staging guidelines are derived from analysis conducted by the International Association for the Study of Lung Cancer (IASLC) Staging Project, which uses an international database of 70,967 patients with NSCLC diagnosed between 1999 and 2010, representing 35 different databases from 16 countries on five continents.[4-6] In their reported results, patients with tumors with additional nodules in the same lobe had similar survival as patients with other T3 tumors satisfying either a single or multiple T descriptors. These other T3 descriptors in the eighth edition guidelines include tumors greater than 5 cm but less than or equal to 7 cm in greatest dimension (previously staged as T2b in the seventh edition staging manual) and tumors that invade the parietal pleura, chest wall, pericardium, or phrenic nerve.[2] Additional relevant updates to the eighth edition include redefining stage T2b to only consist of tumors greater than 4 cm but less than or equal to 5 cm in greatest dimension.

In the analysis by the IASLC, results revealed a trend in improved survival among patients with tumors with additional nodules in the same lobe when compared with other types of T3 tumors, though the results were not statistically significant.[6] This finding builds on results from previous single-institution and national studies, which have presented conflicting results on the survival of patients with such tumors. Two single-center studies previously found similar overall survival between tumors with additional nodules in the same lobe and tumors with malignant pleural or pericardial effusion, pleural dissemination, or invasion to adjacent major organ,[7] and tumors greater than 7 cm in size.[8] Of note, however, various studies have found that such tumors with additional nodules in the same lobe, mostly when surgically resected and node negative, can have long-term survival comparable with stage I or stage II NSCLC.[9-14] Since the AJCC eighth edition guidelines were published, the results of one national analysis from the Netherlands by Blaauwgeers et al.[15] suggested improved survival among patients with additional nodules in the same lobe treated surgically and noted that the subgroup of patients with node-negative adenocarcinoma had survival similar to patients with T2, N0, M0 tumors within the IASLC database.

The objective of this study is to externally validate the results of the IASLC Staging Project for patients with T3 NSCLC presenting with a primary tumor with additional nodule(s) in the same lobe by comparing the long-term survival of these patients with that of patients with T2b NSCLC. The IASLC encourages external validation of their results against outside databases to account for various potential biases in their analysis, including incomplete global geographic distribution of their data and insufficient diversity in treatment type, the latter of which prevents analysis that accounts for varying treatment modalities.[4,5,16,17] One such data source suggested by the IASLC is the National Cancer Database (NCDB), which includes long-term survival data for patients with lung cancer across the United States, with broad representation from all treatment modalities and range of institution types.[4] Thus far, however, external validation with the NCDB has not evaluated specific T descriptors and has not previously included multivariable modeling adjusting for treatment modality.[16] To that end, this study used the NCDB to test the hypothesis that tumors presenting with additional nodules in the same lobe, currently staged as T3, would be associated with better survival, after adjusting for treatment modality, when compared with other T3 tumors and would be associated with similar survival when compared with T2b NSCLC.

Materials and Methods

Data Source

The data used in this study were from the NCDB. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB is estimated to capture 80% of all newly diagnosed cases of lung cancer in the United States and Puerto Rico.[18]

Study Design

This study was approved by the Institutional Review Board of Massachusetts General Hospital, and data were analyzed from a deidentified NCDB participant user file.

All patients with stage T2b, N0-3, M0 (tumors >4 cm but ≤ 5 cm in greatest dimension ["T2b"]) or T3, N0-3, M0 (exclusively satisfying a single T descriptor of tumors >5 cm but ≤ 7 cm in greatest dimension ["T3-Size"] or tumors with additional nodule(s) in the same lobe ["T3-Add"]) NSCLC, according to the AJCC eighth edition TNM staging manual, were identified using the International Classification of Diseases for Oncology, third edition histology and topography codes.[2] Staging in the NCDB was reclassified using best available data according to the most recent AJCC eighth edition staging criteria.[2,19] Other types of T3 tumors were not included because of unavailable data.

Exclusion criteria consisted of nonmalignant disease and history of previous unrelated malignancy. The study was limited to patients diagnosed beginning in 2010 to most accurately reflect current outcomes for patients with T3-Add tumors given the evolution of diagnostic and treatment guidelines for such patients.[1,20] Patients diagnosed after 2015 were excluded owing to cessation of data collection for specific T3 descriptors. Patients with missing tumor descriptor or survival data were also excluded.

Overall survival from time of diagnosis to time of death or last follow-up was the primary outcome measured.

Statistical Analysis

Baseline characteristics were evaluated using Wilcoxon Rank Sum test for continuous variables and Pearson's chi-square or Fisher's exact test for discrete variables. Overall survival of T3-Add versus T3-Size tumors and T3-Add versus T2b tumors was compared for patients diagnosed with clinical N0-3, M0 NSCLC using the Kaplan-Meier method and multivariable Cox proportional hazards modeling (adjusting for age, sex, race, Charlson-Deyo comorbidity score, median census-tract household income and education level, facility type, insurance type, TNM clinical N status, tumor location, treatment type [i.e., surgery, chemotherapy, or radiation], histologic subtype, grade, and distance from patient's residence to hospital). Additional Cox proportional hazards modeling comparing survival of T3-Add versus T2b tumors was performed using the exact same covariates as mentioned previously, with the exception of treatment type (treatment type was excluded as one of the covariates). Survival was measured from time of diagnosis to time of death or last follow-up. The selected covariates for the Cox proportional hazards model were chosen on the basis of previously described variables that have a known impact on survival in patients with lung cancer.[21-24]

A matched analysis based on propensity scores using methodology similar to as previously described[25] was also used to compare overall survival between T3-Add versus T3-Size and T3-Add versus T2b tumors. Propensity scores were assigned using a logistic regression model that calculated the scores on the basis of patient- and disease-related variables determined *a priori* to most likely act as confounders, including age, sex, race, Charlson-Deyo comorbidity score, median census-tract household income and education level, facility type, insurance type, TNM clinical N status, tumor location, treatment type (i.e., surgery, chemotherapy, or radiation), histologic subtype, grade, and distance from patient's residence to hospital. Using a greedy nearest neighbor-matching algorithm without replacement, with a caliper of 0.01, we identified the most appropriately matched pairs. Standardized differences were used to evaluate the balance of the match. After propensity score matching, Kaplan-Meier analysis was used to compare overall survival of the groups. A case complete analysis was used to address any potential missing data.

Additional propensity score-matched analyses, using the same covariates and matching algorithm described previously, comparing overall survival between patients with T3-Add versus T2b tumors who underwent surgical resection and diagnosed with pathologic N0 or N1 disease were conducted as sensitivity analyses to better compare outcomes between patients receiving surgery as primary treatment.

Model balance and diagnostics were evaluated with no violation of major assumptions observed. All statistical analyses were performed using Stata Statistical Software: Release 13.0 (StataCorp LP, College Station, TX). A two-sided p value of 0.05 was used to define significance.

Results

Study Cohort

Between 2010 and 2015, of the 31,563 patients diagnosed with having T2b-T3, N0-3, M0 NSCLC who met the study inclusion criteria, 19,569 (62.0%) satisfied the criteria exclusively for a single T3 descriptor of T3-Size, whereas 8,546 (27.1%) satisfied the criteria for a single T3 descriptor of T3-Add, and 3,448 (10.9%) satisfied the criteria for T2b (Supplementary Fig. 1, which details schema of study subject selection). Median follow-up was 28.6 months (interquartile range: 10.6–52.5 mo) for the entire cohort.

Comparison of T3-Add Versus T3-Size Tumors

Baseline and tumor characteristics for patients with tumors that satisfied criteria for T3-Size and T3-Add are found in Table 1. When compared with patients with T3-Size tumors, patients with T3-Add tumors were more likely to be of female sex, white, have more comorbidities, have higher census-tract education and income levels, be treated at academic or research programs, and have Medicare insurance. Patients with T3-Add tumors were also more likely to have tumors located in the right upper lobe, adenocarcinoma histology, tumors of lower grade, clinical N0 disease, and be treated surgically.

In Kaplan-Meier analysis, T3-Add tumors were associated with better 5-year overall survival than T3-Size tumors ($p < 0.001$) (Fig. 1*A*). T3-Add tumors continued to have better overall survival in multivariable-adjusted analysis (hazard ratio [HR] =

Table 1. Baseline Characteristics of Patients With T3, N0-3, M0 NSCLC Satisfying the Criteria for T3-Add Versus T3-Size

	Total Cohort			Propensity Score-Matched Analysis		
Patient Characteristics	T3-Size (N = 19,569)	T3-Add (N = 8546)	*P*	T3-Size (N = 5670)	T3-Add (N = 5670)	Standardized Differences (%)
Age (y, IQR)	69 (61-76)	69 (62-76)	0.96	69 (62-77)	69 (62-76)	−0.2
Female, n (%)	8175 (41.8)	4827 (56.5)	<0.001	2927 (51.6)	2942 (51.9)	0.5
Race, n (%)			0.038			
White	16,639 (85.6)	7362 (86.7)		4882 (86.7)	4886 (86.7)	0.2
Black	2226 (11.5)	887 (10.5)		586 (10.4)	586 (10.4)	0.0
Other	575 (3.0)	240 (2.8)		164 (2.9)	164 (2.9)	0.0
Charlson-Deyo comorbidity score, n (%)			0.019			
0	10,424 (53.3)	4393 (51.4)		2918 (51.5)	2933 (51.7)	0.5
1	5895 (30.1)	2711 (31.7)		1782 (31.4)	1777 (31.3)	−0.2
2	2324 (11.9)	1013 (11.9)		697 (12.3)	695 (12.3)	−0.1
3+	926 (4.7)	429 (5.0)		273 (4.8)	265 (4.7)	−0.7
Education: % without HS diploma, n (%)			<0.001			
>17.5%	4178 (23.0)	1608 (20.6)		1190 (21.0)	1201 (21.2)	0.5
10.9%-17.5%	5318 (29.3)	2211(28.3)		1629 (28.7)	1613 (28.5)	−0.6
6.3%-10.8%	5118 (28.2)	2283 (29.2)		1623 (28.6)	1630 (28.8)	0.3
<6.3%	3559 (19.6)	1722 (22.0)		1228 (21.7)	1226 (21.6)	−0.1
Median household income, n (%)			<0.001			
<$40,227	4083 (22.5)	1548 (19.8)		1157 (20.4)	1180 (20.8)	1.0
$40,227-$50,353	4596 (25.3)	1850 (23.7)		1374 (24.2)	1363 (24.0)	−0.5
$50,354-$63,332	4287 (23.6)	1846 (23.7)		1385 (24.4)	1367 (24.1)	−0.7
≥$63,333	5183 (28.6)	2557 (32.8)		1754 (30.9)	1760 (31.0)	0.2
Facility type, n (%)			<0.001			
Community cancer program	1962 (10.1)	712 (8.4)		492 (8.7%)	492 (8.7%)	0.0
Comprehensive community cancer program	8775 (45.1)	3580 (42.1)		2483 (43.8%)	2479 (43.7%)	−0.1
Academic or research program	6112 (31.4)	3031 (35.6)		1950 (34.4%)	1944 (34.3%)	−0.2
Integrated network cancer program	2611 (13.4)	1191 (14.0)		745 (13.1%)	755 (13.3%)	0.5
Insurance, n (%)			<0.001			
Private	5169 (26.7)	2175 (25.8)		1418 (25.3)	1445 (25.8)	1.1
Medicaid	1249 (6.5)	499 (5.9)		333 (6.0)	335 (6.0)	0.1
Medicare	12,023 (62.2)	5456 (64.6)		3630 (64.9)	3619 (64.6)	−0.4
Other government	335 (1.7)	156 (1.9)		96 (1.7)	92 (1.6)	−0.6
Uninsured	569 (2.9)	155 (1.8)		120 (2.1)	110 (2.0)	−1.1
Received surgery, n (%)	8257 (42.4%)	4747 (55.8%)	<0.001	2933 (51.7%)	2973 (52.4%)	1.5
Received chemotherapy, n (%)	11,489 (60.8)	4015 (48.7)	<0.001	2978 (52.5)	2993 (52.8)	0.5
Received radiation therapy, n (%)	9082 (47.8)	2997 (36.1)	<0.001	2220 (39.2)	2195 (38.7)	−1.0
Tumor location, n (%)			<0.001			
Right upper lobe	5836 (32.6)	3244 (39.5)		2243 (39.6)	2180 (38.5)	−2.3
Right middle lobe	779 (4.4)	372 (4.5)		230 (4.1)	220 (3.9)	−0.9
Right lower lobe	3777 (21.1)	1391 (16.9)		990 (17.5)	1007 (17.8)	0.8
Left upper lobe	4556 (25.5)	2169 (26.4)		1460 (25.8)	1505 (26.5)	1.8
Left lower lobe	2993 (16.4)	1038 (12.6)		747 (13.2)	757 (13.4)	0.5
Histologic subtype, n (%)			<0.001			
Adenocarcinoma	6374 (35.9)	4264 (53.7)		3028 (53.4)	3155 (55.6)	4.5
Squamous	9671 (54.5)	2149 (27.1)		1785 (31.5)	1745 (30.8)	−1.5
Large cell	387 (2.2)	152 (1.9)		115 (2.0)	129 (2.3)	1.7
Adenosquamous	365 (2.1)	131 (1.7)		105 (1.9)	110 (1.9)	0.6
Neuroendocrine tumors	378 (2.1)	520 (6.5)		229 (4.0)	173 (3.1)	−5.2
Bronchioloalveolar	585 (3.3)	730 (9.2)		408 (7.2)	358 (6.3)	−4.2
Grade, n (%)			<0.001			
Well differentiated	999 (5.1)	967 (11.3)		533 (9.4)	477 (8.4)	−4.1
Moderately differentiated	5007 (25.6)	2541 (29.7)		1678 (29.6)	1741 (30.7)	2.7
Poorly differentiated	7368 (37.7)	2465 (28.8)		1808 (31.9)	1794 (31.6)	−0.5
Undifferentiated or anaplastic	301 (1.5)	86 (1.0)		48 (0.9)	54 (1.0)	1.0
Cell type not determined	5894 (30.1)	2487 (29.1)		1603 (28.3)	1604 (28.3)	0.0

(continued)

Table 1. Continued

Patient Characteristics	Total Cohort			Propensity Score-Matched Analysis		
	T3-Size (N = 19,569)	T3-Add (N = 8546)	*P*	T3-Size (N = 5670)	T3-Add (N = 5670)	Standardized Differences (%)
Clinical N status, n (%)			<0.001			
cN0	9468 (48.4)	5322 (62.3)		3372 (59.5)	3345 (59.0)	−1.0
cN1	2374 (12.1)	838 (9.8)		538 (9.5)	587 (10.4)	2.8
cN2	6098 (31.2)	1814 (21.2)		1336 (23.6)	1323 (23.3)	−0.5
cN3	1629 (8.3)	572 (6.7)		424 (7.5)	415 (7.4)	−0.5
Distance to facility (miles, IQR)	10.1 (4.3-24.3)	10.1 (4.4-24.1)	0.45	10.4 (4.4-25)	10 (4.3-23.7)	1.0

HS, high school; IQR, interquartile range; T3-Add, tumors with additional nodule(s) in the same lobe; T3-Size, tumors greater than 5 cm but less than or equal to 7 cm in greatest dimension.

0.86, 95% confidence interval [CI]: 0.82–0.89, $p < 0.001$) (Table 2).

A propensity score-matched analysis of these patient cohorts yielded two groups of 5670 patients with T3-Size tumors and 5670 patients with T3-Add tumors (Table 1). Both groups were well-balanced on all baseline characteristics, with standardized differences less than or equal to 5.2%. In this matched analysis, T3-Add tumors were associated with better overall survival when compared with T3-Size tumors ($p < 0.001$) (Fig. 1*B*).

Comparison of T3-Add Versus T2b Tumors

Table 3 details the baseline and tumor characteristics for the 3448 patients satisfying the criteria for T2b tumors and 8546 patients satisfying the criteria for T3-Add tumors. Compared with patients with T2b tumors, those with T3-Add tumors were more likely to be older, of female sex, black, have fewer comorbidities, have Medicare insurance, and be closer to their treatment facility. T3-Add tumors were also more likely to be located in the right upper lobe, have adenocarcinoma histology, and higher clinical N status.

Comparing treatment modalities in these two groups of patients reveals that those with T3-Add tumors were less likely to undergo surgery in both the entire cohort (55.8% versus 90.0%, $p < 0.001$) and when stratified by clinical N status (N0: 72.8% versus 94.0%, $p < 0.001$; N1: 54.9% versus 91.3%, $p < 0.001$; N2: 22.3% versus 66.6%, $p < 0.001$) (Supplementary Fig. 2, which compares rates of surgical resection for T3-Add versus T2b tumors). Among the 44.2% of patients with T3-Add tumors who did not receive surgery, 81.4% did not receive surgery because the patients' treating physicians did not include surgery as part of the planned first course of treatment. In addition, 14.7% of patients did not receive surgery because it was contraindicated owing to patient risk factors, including severely comorbid conditions,

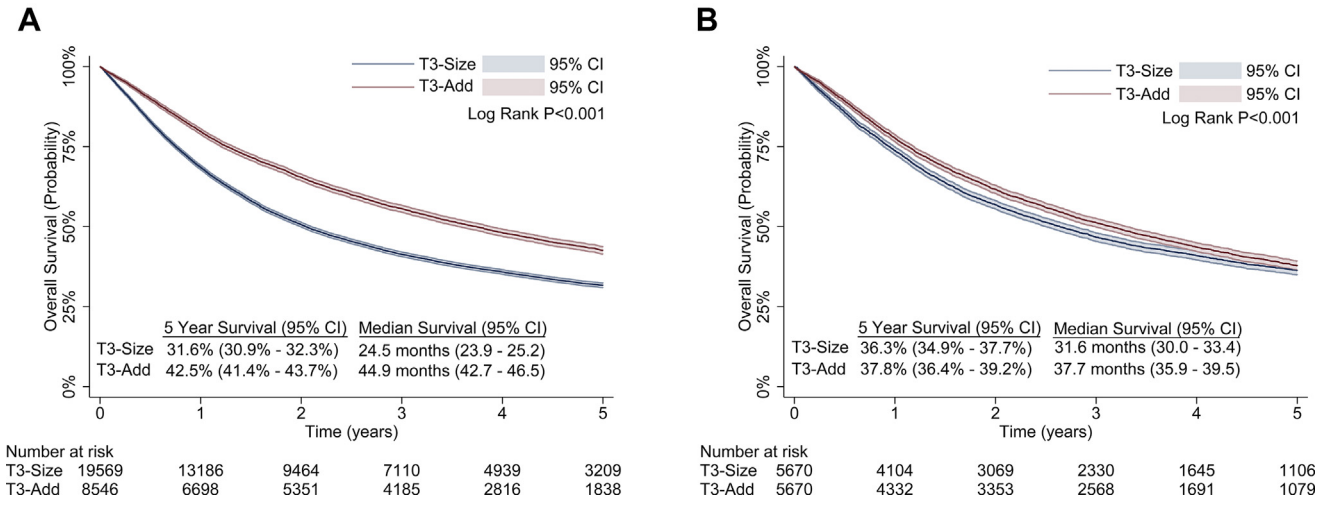

Figure 1. Overall survival of patients with T3, N0-3, M0 NSCLC satisfying the criteria for T3-Add versus T3-Size (*A*) in the entire cohort (*B*) after propensity score matching. CI, confidence interval; T3-Add, tumors with additional nodule(s) in the same lobe; T3-Size, tumors greater than 5 cm but less than or equal to 7 cm in greatest dimension.

Table 2. Independent Predictors of Overall Survival After Cox Proportional Hazards Adjustment for Patients With T3, N0-3, M0 NSCLC Satisfying the Criteria for T3-Add Versus T3-Size

Variable	HR	95% CI	*p*
T3-Add vs. T3-Size	0.86	0.82-0.89	<0.001
Age (per y)	1.02	1.02-1.02	<0.001
Female vs. male	0.82	0.79-0.85	<0.001
Race (ref = white)			
Black	0.88	0.83-0.93	<0.001
Other	0.76	0.68-0.85	<0.001
Charlson-Deyo comorbidity score (ref = 0)			
1	1.16	1.12-1.21	<0.001
2	1.27	1.20-1.34	<0.001
3+	1.33	1.23-1.43	<0.001
Education: % without HS diploma (ref >17.5%)			
10.9%-17.5%	1.06	1.01-1.12	0.023
6.3%-10.8%	1.08	1.02-1.15	0.009
<6.3%	1.06	0.98-1.13	0.13
Median household income (ref < $40,227)			
$40,227-$50,353	0.92	0.87-0.97	0.002
$50,354-$63,332	0.91	0.85-0.96	0.001
≥$63,333	0.82	0.76-0.87	<0.001
Facility type (ref = community)			
Comprehensive	0.95	0.89-1.00	0.066
Academic or research	0.83	0.78-0.88	<0.001
Integrated network	0.89	0.83-0.96	0.002
Insurance type (ref = uninsured)			
Private	0.88	0.78-1.00	0.043
Medicaid	1.00	0.87-1.14	0.97
Medicare	0.93	0.83-1.06	0.27
Other government	0.87	0.72-1.03	0.11
Tumor location (ref = right upper lobe)			
Right middle lobe	0.95	0.86-1.04	0.26
Right lower lobe	1.16	1.10-1.21	<0.001
Left upper lobe	1.01	0.97-1.06	0.55
Left lower lobe	1.14	1.08-1.21	<0.001
Surgery vs. no surgery	0.32	0.30-0.34	<0.001
Chemotherapy vs. no chemotherapy	0.68	0.65-0.71	<0.001
Radiation therapy vs. no radiation therapy	0.75	0.72-0.78	<0.001
Histologic subtype (ref = adenocarcinoma)			
Squamous	1.12	1.08-1.16	<0.001
Large cell	1.32	1.16-1.49	<0.001
Adenosquamous	1.30	1.15-1.46	<0.001
Neuroendocrine	0.60	0.52-0.69	<0.001
Bronchioloalveolar	0.92	0.84-1.02	0.12
Grade (ref = well differentiated)			
Moderately differentiated	1.37	1.25-1.49	<0.001
Poorly differentiated	1.47	1.35-1.60	<0.001
Undifferentiated or anaplastic	1.63	1.34-1.98	<0.001
Cell type not determined	1.39	1.28-1.52	<0.001
Clinical N status (ref = cN0)			
cN1	1.39	1.31-1.47	<0.001
cN2	1.62	1.55-1.70	<0.001
cN3	1.72	1.60-1.83	<0.001
Distance from facility (per mile)	1.00	1.00-1.00	0.42

CI, confidence interval; HR, hazard ratio; ref, referent; HS, high school; T3-Add, tumors with additional nodule(s) in the same lobe; T3-Size, tumors greater than 5 cm but less than or equal to 7 cm in greatest dimension.

advanced age, or progression of the tumor before surgery, and 3.0% of patients refused surgery after it was recommended to them.

Kaplan-Meier analysis revealed that patients with T3-Add tumors had worse 5-year overall survival than those with T2b tumors ($p < 0.001$) (Fig. 2*A*). T3-Add tumors

Table 3. Baseline Characteristics of Patients With T2-3, N0-3, M0 NSCLC Satisfying the Criteria for T3-Add Versus T2b

	Total Cohort			Propensity Score-Matched Analysis		
Patient Characteristics	T2b (N = 3448)	T3-Add (N = 8546)	*P*	T2b (N = 2260)	T3-Add (N = 2260)	Standardized Differences (%)
Age (y, IQR)	68 (61-75)	69 (62-76)	<0.001	69 (61-75)	68 (62-75)	0.5
Female, n (%)	1572 (45.6)	4827 (56.5)	<0.001	1092 (48.3)	1042 (46.1)	−4.4
Race, n (%)			<0.001			
White	3038 (88.7)	7362 (86.7)		1988 (88.5)	1980 (88.1)	−1.0
Black	278 (8.1)	887 (10.5)		182 (8.1)	190 (8.4)	1.2
Other	110 (3.2)	240 (2.8)		77 (3.4)	77 (3.4)	0.0
Charlson-Deyo comorbidity score, n (%)			0.003			
0	1715 (49.7)	4393 (51.4)		1130 (50.0)	1108 (49.0)	−2.0
1	1155 (33.5)	2711 (31.7)		749 (33.1)	746 (33.0)	−0.3
2	447 (13.0)	1013 (11.9)		285 (12.6)	318 (14.1)	4.6
3+	131 (3.8)	429 (5.0)		96 (4.3)	88 (3.9)	−1.8
Education: % without HS diploma, n (%)			0.51			
>17.5%	672 (21.6)	1608 (20.6)		474 (21.0)	481 (21.3)	0.8
10.9%-17.5%	890 (28.6)	2211 (28.3)		639 (28.3)	634 (28.1)	−0.5
6.3%-10.8%	877 (28.2)	2283 (29.2)		646 (28.6)	628 (27.8)	−1.8
<6.3%	668 (21.5)	1722 (22.0)		501 (22.2)	517 (22.9)	1.7
Median household income, n (%)			0.58			
<$40,227	627 (20.2)	1548 (19.8)		437 (19.3)	444 (19.7)	0.8
$40,227-$50,353	743 (24.0)	1850 (23.7)		544 (24.1)	534 (23.6)	−1.0
$50,354-$63,332	757 (24.4)	1846 (23.7)		559 (24.7)	562 (24.9)	0.3
≥$63,333	975 (31.4)	2557 (32.8)		720 (31.9)	720 (31.9)	0.0
Facility type, n (%)			<0.001			
Community cancer program	204 (6.0)	712 (8.4)		141 (6.2)	136 (6.0)	−0.8
Comprehensive community cancer program	1446 (42.4)	3580 (42.1)		984 (43.5)	986 (43.6)	0.2
Academic or research program	1253 (36.7)	3031 (35.6)		814 (36.0)	817 (36.2)	0.3
Integrated network cancer program	510 (14.9)	1191 (14.0)		321 (14.2)	321 (14.2)	0.0
Insurance, n (%)			<0.001			
Private	1018 (29.8)	2175 (25.8)		663 (29.7)	655 (29.3)	−0.8
Medicaid	182 (5.3)	499 (5.9)		115 (5.2)	121 (5.4)	1.2
Medicare	2099 (61.5)	5456 (64.6)		1394 (62.4)	1391 (62.3)	−0.3
Other government	40 (1.2)	156 (1.9)		28 (1.3)	28 (1.3)	0.0
Uninsured	75 (2.2)	155 (1.8)		35 (1.6)	38 (1.7)	0.9
Received surgery, n (%)	3101 (90.0)	4747 (55.8)	<0.001	1995 (88.3)	2006 (88.8)	1.1
Received chemotherapy, n (%)	1275 (38.5)	4015 (48.7)	<0.001	913 (40.4)	910 (40.3)	−0.3
Received radiation therapy, n (%)	462 (13.9)	2997 (36.1)	<0.001	356 (15.8)	356 (15.8)	0.0
Tumor location, n (%)			<0.001			
Right upper lobe	1006 (30.3)	3244 (39.5)		741 (32.8)	728 (32.2)	−1.2
Right middle lobe	157 (4.7)	372 (4.5)		107 (4.7)	108 (4.8)	0.2
Right lower lobe	725 (21.8)	1391 (16.9)		469 (20.8)	459 (20.3)	−1.1
Left upper lobe	863 (26.0)	2169 (26.4)		578 (25.6)	598 (26.5)	2.0
Left lower lobe	568 (17.1)	1038 (12.6)		365 (16.2)	367 (16.2)	0.2
Histologic subtype, n (%)			<0.001			
Adenocarcinoma	1414 (43.1)	4264 (53.7)		1131 (50.0)	1119 (49.5)	−1.1
Squamous	1324 (40.4)	2149 (27.1)		726 (32.1)	764 (33.8)	3.7
Large cell	79 (2.4)	152 (1.9)		50 (2.2)	53 (2.4)	0.9
Adenosquamous	82 (2.5)	131 (1.7)		55 (2.4)	59 (2.6)	1.3
Neuroendocrine tumors	157 (4.8)	520 (6.5)		113 (5.0)	99 (4.4)	−2.9
Bronchioloalveolar	225 (6.9)	730 (9.2)		185 (8.2)	166 (7.4)	−3.3
Grade, n (%)			<0.001			
Well differentiated	404 (11.7)	967 (11.3)		293 (13.0)	284 (12.6)	−1.3
Moderately differentiated	1311 (38.0)	2541 (29.7)		883 (39.1)	870 (38.5)	−1.3
Poorly differentiated	1314 (38.1)	2465 (28.8)		797 (35.3)	825 (36.5)	2.7
Undifferentiated or anaplastic	68 (2.0)	86 (1.0)		27 (1.2)	30 (1.3)	1.1

(continued)

Table 3. Continued

Patient Characteristics	Total Cohort T2b (N = 3448)	Total Cohort T3-Add (N = 8546)	P	Propensity Score-Matched Analysis T2b (N = 2260)	Propensity Score-Matched Analysis T3-Add (N = 2260)	Standardized Differences (%)
Cell type not determined	351 (10.2)	2487 (29.1)		260 (11.5)	251 (11.1)	−0.9
Clinical N status, n (%)			<0.001			
cN0	2698 (78.3)	5322 (62.3)		1756 (77.7)	1747 (77.3)	−0.8
cN1	358 (10.4)	838 (9.8)		224 (9.9)	235 (10.4)	1.6
cN2	347 (10.1)	1814 (21.2)		248 (11.0)	242 (10.7)	−0.7
cN3	45 (1.3)	572 (6.7)		32 (1.4)	36 (1.6)	0.7
Distance to facility (miles, IQR)	12.25 (5.1-29.6)	10.1 (4.4-24.1)	<0.001	12 (5.1-28.3)	11.1 (4.8-26.8)	0.0

HS, high school; IQR, interquartile range; T2b, tumors greater than 4 cm but less than or equal to 5 cm in greatest dimension; T3-Add, tumors with additional nodule(s) in the same lobe.

were also associated with worse survival than T2b tumors after multivariable-adjusted Cox proportional hazards modeling without treatment modality (i.e., surgery, chemotherapy, or radiation) as a covariate (HR = 1.30, 95% CI: 1.21–1.39, $p < 0.001$) (Supplementary Table 1, which compares overall survival for patients with T3-Add versus T2b tumors). Nevertheless, after multivariable-adjusted Cox proportional hazards modeling including treatment modality as a covariate, no significant differences were found between the overall survival of the two groups (HR = 1.04, 95% CI: 0.97–1.12, $p = 0.28$) (Table 4).

Furthermore, a propensity score-matched analysis was conducted of 2260 patients with T2b tumors and 2260 patients with T3-Add tumors, well-balanced on all baseline characteristics (Table 3). Standardized differences were less than or equal to 4.6%. Kaplan-Meier analysis of 5-year overall survival yielded no significant differences between patients with T3-Add tumors and those with T2b tumors ($p = 0.30$) (Fig. 2*B*).

Sensitivity Analysis: Stratification by Pathologic N Status

Two additional propensity score-matched analyses were conducted, specifically comparing survival of patients with T3-Add versus T2b tumors who underwent surgical resection and diagnosed with pN0 or pN1 disease.

3134 patients (36.7%) with T3-Add tumors and 2229 patients (64.6%) with T2b tumors underwent surgical resection and were diagnosed with pN0 disease, respectively. A propensity score-matched analysis yielded two groups of 1419 patients in each arm. Kaplan-Meier analysis revealed no significant difference in 5-year overall survival between T3-Add and T2b tumors in patients with pN0 disease ($p = 0.76$) (Supplementary Fig. 3*A*, which demonstrates overall survival for patients with T3-Add versus T2b tumors and pN0 disease in a propensity score-matched analysis).

Similarly, when evaluating the frequency of pN1 disease, 668 patients (7.8%) with T3-Add tumors and

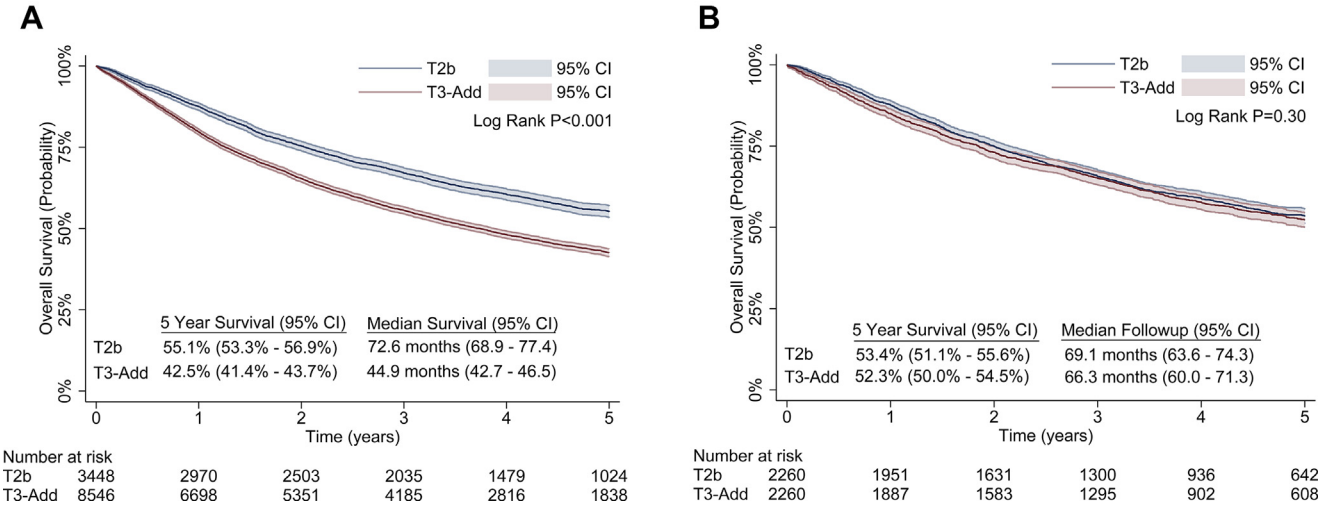

Figure 2. Overall survival of patients with T2-3, N0-3, M0 NSCLC satisfying the criteria for T3-Add versus T2b (*A*) in the entire cohort (*B*) after propensity score matching. CI, confidence interval; T2b, tumors greater than 4 cm but less than or equal to 5 cm in greatest dimension; T3-Add, tumors with additional nodule(s) in the same lobe.

Table 4. Independent Predictors of Overall Survival After Cox Proportional Hazards Adjustment for Patients With T2-3, N0-3, M0 NSCLC Satisfying the Criteria for T3-Add Versus T2b

Variable	HR	95% CI	*p*
T3-Add vs. T3-Size	1.04	0.97-1.12	0.28
Age (per y)	1.02	1.01-1.02	<0.001
Female vs. male	0.73	0.69-0.77	<0.001
Race (ref = white)			
Black	0.96	0.87-1.06	0.45
Other	0.72	0.60-0.87	0.001
Charlson-Deyo comorbidity score (ref = 0)			
1	1.14	1.07-1.22	<0.001
2	1.24	1.14-1.36	<0.001
3+	1.29	1.14-1.47	<0.001
Education: % without HS diploma (ref >17.5%)			
10.9%-17.5%	1.02	0.93-1.11	0.72
6.3%-10.8%	0.99	0.90-1.09	0.83
<6.3%	0.91	0.81-1.02	0.10
Median household income (ref < $40,227)			
$40,227-$50,353	0.97	0.89-1.06	0.47
$50,354-$63,332	0.99	0.90-1.09	0.89
≥$63,333	0.92	0.82-1.02	0.11
Facility type (ref = community)			
Comprehensive	0.88	0.79-0.97	0.013
Academic or research	0.76	0.68-0.85	<0.001
Integrated network	0.83	0.73-0.94	0.003
Insurance type (ref = uninsured)			
Private	0.87	0.69-1.09	0.23
Medicaid	0.92	0.72-1.19	0.54
Medicare	1.00	0.79-1.25	0.99
Other government	0.91	0.66-1.24	0.55
Tumor location (ref = right upper lobe)			
Right middle lobe	0.85	0.72-1.00	0.052
Right lower lobe	1.16	1.07-1.26	<0.001
Left upper lobe	1.05	0.98-1.13	0.19
Left lower lobe	1.02	0.93-1.12	0.61
Surgery v no surgery	0.35	0.32-0.39	<0.001
Chemotherapy vs. no chemotherapy	0.78	0.73-0.84	<0.001
Radiation therapy vs. no radiation therapy	0.86	0.80-0.93	<0.001
Histologic subtype (ref = adenocarcinoma)			
Squamous	1.14	1.07-1.21	<0.001
Large cell	1.61	1.34-1.94	<0.001
Adenosquamous	1.31	1.08-1.60	0.007
Neuroendocrine	0.61	0.51-0.73	<0.001
Bronchioloalveolar	0.99	0.88-1.12	0.86
Grade (ref = well differentiated)			
Moderately differentiated	1.39	1.23-1.56	<0.001
Poorly differentiated	1.49	1.32-1.68	<0.001
Undifferentiated or anaplastic	1.57	1.16-2.14	0.004
Cell type not determined	1.34	1.18-1.52	<0.001
Clinical N status (ref = cN0)			
cN1	1.54	1.40-1.69	<0.001
cN2	1.73	1.59-1.88	<0.001
cN3	1.98	1.75-2.24	<0.001
Distance from facility (per mile)	1.00	1.00-1.00	0.46

CI, confidence interval; HR, hazard ratio; ref, referent; HS, high school; T2b, tumors greater than 4 cm but less than or equal to 5 cm in greatest dimension; T3-Add, tumors with additional nodule(s) in the same lobe.

534 patients (15.5%) with T2b tumors received surgery and were diagnosed with having pN1 disease. Propensity score matching of these patients generated a cohort of 580 patients (290 in each arm). Comparison of 5-year overall survival between each arm revealed that there were no significant differences in survival for T3-Add tumors and T2b tumors ($p = 0.18$) (Supplementary Fig. 3*B*, which demonstrates overall survival for patients T3-Add versus T2b tumors and pN1 disease in a propensity score-matched analysis).

Discussion

In this national analysis, patients with T3 NSCLC presenting with a primary tumor with additional nodule(s) in the same lobe ("T3-Add") were found to have better long-term survival than those with T3 tumors greater than 5 cm and less than or equal to 7 cm ("T3-Size") and were found to have similar long-term survival to those with T2b tumors in both multivariable Cox proportional hazards modeling and propensity score-matched analysis. We also found that in the United States, T3-Add tumors were much less likely to be surgically resected when compared with T2b tumors, even though the National Comprehensive Cancer Network (NCCN) guidelines recommend similar treatment for both types of tumors.

This study is the first national analysis to externally validate the T2b and T3 results drawn by the IASLC Staging Project,[6] which suggested that tumors with additional nodules in the same lobe be classified as T3 in the AJCC eighth edition TNM staging manual.[2] A primary finding of this study—that T3-Add tumors are associated with better survival than other types of T3 tumors—builds on results from the IASLC analysis, which revealed a trend in improved survival among T3-Add tumors compared with tumors satisfying other T3 descriptors, but found no significant differences.[6] The 5-year overall survival for T3-Add tumors, in this study, of 42.5% was similar to the survival rates observed in the IASLC database, with such tumors having 47% 5-year overall survival when clinically staged and 42% 5-year survival when pathologically staged. Older population-based studies have reported survival between 23% and 35%,[1,6] though most of these studies primarily used data collected before 2003. A more recent national study of 683 patients diagnosed with having pT3, N0, M0 NSCLC between 2010 and 2013 from the Netherlands reported 5-year survival of 62.8% for patients with T3-Add, N0, M0 who underwent surgery. Smaller, single-institution studies have reported 5-year survival for all T3-Add tumors in the range of 20% to 57%.[1,6]

This study has the following strengths. The NCDB serves as a valuable database to use for external validation of the IASLC results owing to its size and scope of inclusion. The IASLC previously used the NCDB for external validation of the eighth edition revision for the TNM stage groupings, citing the original database's underrepresentation of both North American patients and nonsurgical patients.[4,5,16,17] In the IASLC database, 15.5% of patients were treated without surgery. The NCDB not only accounts for both of these potential limitations but also offers detailed information on patients' treatment sequence and breakdown of treatment type by stage.

In this study, unlike previous related studies, we were also able to adjust for treatment modality (surgery, chemoradiation, or radiation) in our multivariable analysis. According to the NCCN treatment guidelines, primary treatment for T3-Add tumors is as follows: (1) surgery followed by adjuvant chemotherapy for clinical N0 or N1 disease (stages IIB–IIIA); (2) concurrent chemoradiation or induction chemotherapy followed by surgery or radiation depending on progression for N2 disease (stage IIIB); and (3) concurrent chemoradiation only for N3 disease (stage IIIC).[26] These differences in treatment recommendations highlight not only the association between treatment type and long-term survival but also the importance of adjusting for treatment in multivariable Cox proportional hazards analyses. For example, in the IASLC database, patients with T3-Add, N0, M0 NSCLC who received surgery had much better estimated 5-year survival than those treated nonsurgically (68% surgical versus 0% nonsurgical).[6] The difference between the findings in this study, that T3-Add tumors were associated with better survival than T3-Size tumors, and the results in the IASLC analysis, which found no significant differences between the survival of these two groups, could be due to the fact that the IASLC analysis did not account for treatment type.

Current NCCN treatment guidelines for T2b tumors are similar to T3-Add tumors.[26] In practice, however, T3-Add tumors are far less likely to be treated surgically than T2b tumors, as reflected by our results, which revealed that only 55.8% of patients with T3-Add tumors received surgery as compared with 90.0% of patients with T2b tumors—a finding consistent regardless of clinical N status. In addition, of the patients with T3-Add tumors who did not receive surgery, 81.4% did not receive surgery because their primary treating physician did not include it as part of the planned first course of treatment. This is in contrast to only 14.7% of patients whose physicians considered surgical resection but eventually decided the patients would not be candidates owing to severely comorbid conditions, advanced age, or tumor progression before surgery.

The difference between the incorporation of surgery during treatment for T3-Add and T2b tumors is

especially important given our finding that T3-Add and T2b tumors have similar long-term overall survival after both multivariable adjustment accounting for treatment type and propensity score matching on treatment type. At present, patients with T3-Add tumors are far less likely to receive surgery as compared with patients with T2b tumors, primarily owing to a lack of their consideration as surgical candidates. In light of these findings, we believe that reevaluating whether T3-Add tumors should be grouped together with T2b tumors in the same category for the upcoming AJCC ninth edition guidelines would be valuable in the long-term care of these patients. This reevaluation of staging may simplify treatment guidelines and promote a multidisciplinary treatment approach for patients with such tumors, thereby leading to more guideline-concordant surgical treatment of T3-Add tumors.

This study has several limitations. First, due to its retrospective nature, unobserved confounding and selection bias may persist despite our use of multivariable modeling and propensity score matching to account for confounding factors. Second, due to the method of coding for specific T descriptors in the NCDB, this study was unable to accurately identify patients exclusively satisfying the final T3 descriptor of tumors invading the parietal pleura, chest wall, pericardium, or phrenic nerve. Third, this study only analyzed patients satisfying a single T3 descriptor. Patients who satisfy multiple T descriptors may potentially have worse survival than those who satisfy a single T descriptor,[6,15] and future studies should incorporate such patients as well. Fourth, information on recurrence, disease-free survival, and disease-specific survival is unavailable in the NCDB. Finally, the NCDB only captures data from Commission on Cancer-accredited hospitals in the United States and Puerto Rico, which may not accurately reflect cancer incidence, treatment rates, or outcomes in the various other countries represented in the IASLC database.

In conclusion, in this national, population-based analysis, patients with T3 NSCLC owing to the presence of additional nodules in the same lobe, according to the AJCC eighth edition TNM staging classifications, were found to have better long-term survival than those with T3 tumors that are greater than 5 cm and less than or equal to 7 cm in greatest dimension and found to have similar long-term survival as patients with T2b tumors that are greater than 4 cm and less than or equal to 5 cm in greatest dimension, in both multivariable Cox proportional hazards modeling and propensity score-matched analysis. In addition, we found that, nationally, T3 tumors consisting of a primary tumor with additional nodules were much less likely to be surgically resected when compared with T2b tumors. The results of this study suggest that tumors with additional nodules in the same lobe, which are currently classified as T3, should be considered for restaging as T2b when determining criteria for the upcoming ninth edition of the AJCC staging manual for lung cancer that is due to be developed and published by 2024.

CRediT Authorship Contribution Statement

Arvind Kumar: Conceptualization, Methodology, Formal Analysis, Investigation, Writing—original draft preparation, Visualization.

Sanjeevani Kumar: Formal Analysis, Investigation, Writing—original draft preparation, Visualization.

Shivee Gilja: Investigation, Writing—original draft preparation.

Alexandra Potter: Investigation, Visualization.

Vignesh Raman: Formal Analysis.

Ashok Muniappan, Douglas Liou: Writing—review and editing, Supervision.

Chi-Fu Jeffrey Yang: Conceptualization, Methodology, Data Curation, Writing—review and editing, Supervision.

Acknowledgments

The data used in the study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.06.016.

References

1. Kim AW, Cooke DT. Additional pulmonary nodules in the patient with lung cancer: controversies and challenges. *Clin Chest Med*. 2011;32:811–825.
2. Amin MB, Edge S, Greene F, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
3. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67:138–155.
4. Detterbeck FC, Chansky K, Groome P, et al. The IASLC lung cancer staging project: methodology and validation used in the development of proposals for revision of the stage classification of NSCLC in the forthcoming (eighth) edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2016;11:1433–1446.

5. Rami-Porta R, Bolejack V, Giroux DJ, 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.
6. Detterbeck FC, Bolejack V, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: background data and proposals for the classification of lung cancer with separate tumor nodules in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:681–692.
7. Okumura T, Asamura H, Suzuki K, Kondo H, Tsuchiya R. Intrapulmonary metastasis of non-small cell lung cancer: a prognostic assessment. *J Thorac Cardiovasc Surg*. 2001;122:24–28.
8. Ruffini E, Filosso PL, Bruna MC, et al. Recommended changes for T and N descriptors proposed by the International Association for the Study of Lung Cancer - Lung Cancer Staging Project: a validation study from a single-centre experience. *Eur J Cardiothorac Surg*. 2009;36:1037–1044.
9. Bryant AS, Pereira SJ, Miller DL, Cerfolio RJ. Satellite pulmonary nodule in the same lobe (T4N0) should not be staged as IIIB non-small cell lung cancer. *Ann Thorac Surg*. 2006;82:1808–1814.
10. Pennathur A, Lindeman B, Ferson P, et al. Surgical resection is justified in non-small cell lung cancer patients with node negative T4 satellite lesions. *Ann Thorac Surg*. 2009;87:893–899.
11. Port JL, Korst RJ, Lee PC, Kansler AL, Kerem Y, Altorki NK. Surgical resection for multifocal (T4) non-small cell lung cancer: is the T4 designation valid? *Ann Thorac Surg*. 2007;83:397–400.
12. Terzi A, Falezza G, Benato C, et al. Survival following complete resection of multifocal T4 node-negative NSCLC: a retrospective study. *Thorac Cardiovasc Surg*. 2007;55:44–47.
13. William WN Jr, Lin HY, Lee JJ, Lippman SM, Roth JA, Kim ES. Revisiting stage IIIB and IV non-small cell lung cancer: analysis of the surveillance, epidemiology, and end results data. *Chest*. 2009;136:701–709.
14. Battafarano RJ, Meyers BF, Guthrie TJ, Cooper JD, Patterson GA. Surgical resection of multifocal non-small cell lung cancer is associated with prolonged survival. *Ann Thorac Surg*. 2002;74:988–994.
15. Blaauwgeers H, Damhuis R, Lissenberg-Witte BI, de Langen AJ, Senan S, Thunnissen E. A population-based study of outcomes in surgically resected T3N0 non-small cell lung cancer in the Netherlands, defined using TNM-7 and TNM-8; justification of changes and an argument to incorporate histology in the staging algorithm. *J Thorac Oncol*. 2019;14:459–467.
16. Chansky K, Detterbeck FC, Nicholson AG, et al. The IASLC lung cancer staging project: external validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2017;12:1109–1121.
17. 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.
18. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15:683–690.
19. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest*. 2017;151:193–203.
20. Fonseca A, Detterbeck FC. How many names for a rose: inconsistent classification of multiple foci of lung cancer due to ambiguous rules. *Lung Cancer*. 2014;85:7–11.
21. Ambroggi M, Biasini C, Del Giovane C, Fornari F, Cavanna L. Distance as a barrier to cancer diagnosis and treatment: review of the literature. *Oncologist*. 2015;20:1378–1385.
22. Bryant AS, Cerfolio RJ. Impact of race on outcomes of patients with non-small cell lung cancer. *J Thorac Oncol*. 2008;3:711–715.
23. Shi R, Diaz R, Shi Z, Duvall E, Mills G. The effect of payer status on survival of patients with Stage I/II non-small cell lung cancer: NCDB 1998–2011. *Anticancer Res*. 2016;36:319–326.
24. Tannenbaum SL, Koru-Sengul T, Zhao W, Miao F, Byrne MM. Survival disparities in non-small cell lung cancer by race, ethnicity, and socioeconomic status. *Cancer J*. 2014;20:237–245.
25. Yang CF, Kumar A, Gulack BC, et al. Long-term outcomes after lobectomy for non-small cell lung cancer when unsuspected pN2 disease is found: a National Cancer Data Base analysis. *J Thorac Cardiovasc Surg*. 2016;151:1380–1388.
26. Ettinger DS, Wood DE, Aggarwal C, et al. NCCN guidelines insights: non-small cell lung cancer, version 1.2020. *J Natl Compr Canc Netw*. 2019;17:1464–1472.