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Treatment implications of the new lung cancer staging system

ABSTRACT

The American Joint Commission on Cancer along with the International Association for the Study of Lung Cancer (IASLC) has published new guidelines for lung cancer staging based on observations from 100,869 lung cancer patients. Revised tumor, node, metastasis (TNM) criteria were derived from IASLC patient survival curves, and were validated using data from the Surveillance, Epidemiology, and End Report program. The seventh edition TNM classification revised the T1, T2, T3, and M1 descriptors.

It is estimated that 10% to 15% of newly diagnosed lung cancer patients will be assigned a different disease stage as a result of these changes.

The tumor, node, metastasis (TNM) staging system for lung cancer was first developed in 1973 using a sample of 2,155 patients who were treated at the MD Anderson Cancer Center in Houston, Texas.[1] Important limitations of this first staging system included the relatively small number of patients studied, the geographic restriction of all patients to a single medical center, the limited generalizability to patients from other parts of the world, and the lack of external validation of TNM staging as a predictor of clinical outcome. This system was revised in 1997 using data from 5,319 patients at the MD Anderson Cancer Center, and it remained unchanged until the American Joint Committee on Cancer (AJCC) seventh edition was published in 2009.

The AJCC seventh edition TNM staging guidelines are the result of a multinational undertaking led by the International Association for the Study of Lung Cancer (IASLC), in which data from 100,869 patients were collected from study centers in North America, Asia, Australia, and Europe from 1990 to 2000.[2] Staging recommendations for non–small cell lung cancer were developed using data from 67,725 patients. Of these, 53,640 were clinically staged, and 33,933 underwent pathologic staging. In 20,006 patients, both clinical and pathologic staging information were available.[2] Approximately 95% of patients underwent follow-up for at least 2 years or until death.

The revised AJCC lung cancer staging system provided a much larger and more diverse patient database than the earlier TNM staging system, with robust long-term follow-up and rigorous validation of the prognostic significance of TNM groupings. The revised TNM descriptors were validated internally by confirming the consistency of Kaplan-Meier survival curves across different study centers. External validation of the staging system was performed by using patient survival data from the Surveillance, Epidemiology, and End Report (SEER) program of the National Cancer Institute.[2] Data analysis was conducted by Cancer Research and Biostatistics, an independent statistical center in Seattle, Washington.

Potential limitations of the revised staging system included the lack of standardization of diagnostic technology across different regions and time periods, as well as the exclusion of patients from Africa, South America, and India.[3] In addition, the AJCC seventh edition continues to classify patients entirely on the basis of anatomic characteristics. Certain tumor molecular markers are now recognized as both prognostic and predictive of the responses to certain treatments, but these have yet to be taken into consideration in lung cancer staging.

UNDERSTANDING REVISED SEVENTH EDITION TNM DESCRIPTORS

A summary of TNM descriptors in the sixth and seventh editions of the AJCC staging criteria, the use of the most recent criteria in lung cancer staging, and

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TABLE 1
Revisions to the AJCC lung cancer staging system TNM classification[3,7]

T and M descriptors		Stage			
6th Edition	**7th Edition**	**N0**	**N1**	**N2**	**N3**
T1(≤ 2 cm)	T1a (≤ 2 cm)	IA	IIA	IIIA	IIIB
T1 (> 2–3 cm)	T1b (> 2 cm but ≤ 3 cm)	IA	IIA	IIIA	IIIB
T2 (≤ 5 cm)	T2a (> 3 cm but ≤ 5 cm)	IB	IIA (IIB)	IIIA	IIIB
T2 (>5–7 cm)	T2b (> 5 cm but ≤ 7 cm)	IIA (IB)	IIB	IIIA	IIIB
T2 (>7 cm)	T3 (> 7 cm)	IIB (IB)	IIIA (IIB)	IIIA	IIIB
T3 invasion	T3	IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T3	IIB (IIIB)	IIIA (IIIB)	IIIA (IIIB)	IIIB
T4 (extension)	T4	IIIA (IIIB)	IIIA (IIIB)	IIIB	IIIB
M1 (ipsilateral lung)	T4	IIIA (IV)	IIIA (IV)	IIIB (IV)	IIIB (IV)
T4 (pleural effusion)	M1a	IV (IIIB)	IV (IIIB)	IV (IIIB)	IV (IIIB)
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

( ) = change in classification; M = metastasis; T = tumor

changes in staging from one edition to the next are summarized in **Table 1**.

T1 comprises two subcategories

In the previous AJCC staging system published in 2002 (sixth edition), the T1 tumor size classification was defined as a tumor measuring greater than 3 cm in size without invasion more proximal than the lobar bronchus.[4] In the seventh edition TNM classification, the T1 category is separated into T1a, which is defined as tumor measuring greater than 2 cm, and T1b, ie, tumor measuring 2 to 3 cm.[5] This new classification is based on data from both pathologic and clinical staging datasets, which demonstrate significant differences in median survival for tumors measuring smaller than 2 cm versus tumors that were 2 to 3 cm in size within the T1 category. These survival differences were subsequently validated using the SEER patient database.[5]

T2 also subdivided

A similar subdivision was performed for the T2 category. In the sixth edition TNM classification, a T2 tumor was defined either as a tumor greater than 3 cm in size, or with at least one of the following criteria: involvement of a mainstem bronchus 2 cm or more distal to the carina; invasion of the visceral pleura; or atelectasis extending to the hilar region, but not involving the entire lung.[4] In the seventh edition, the T2 category is divided into T2a (tumor size, 3 to 5 cm) and T2b (tumor size, 5 to 7 cm).[5] The median survival difference between these two subsets varied from approximately 10% to 27% across different study sites.[2] Validation of the T2a and T2b classification using the SEER database demonstrated that the proportion of patients who survived 5 years was 14% higher for patients in the T2a than the T2b group (hazard ratio, 1.45; $P < .0001$), confirming the prognostic importance of these two subcategories.

T3 redefined

The investigators also made changes to the T3 classification in the AJCC seventh edition staging system. Tumors measuring greater than 7 cm (classified as T2 using the sixth edition) were reclassified as T3. Additionally, the subset of sixth edition T4 tumors that were defined by the presence of additional nodules in the same lobe were reclassified as T3. The revised AJCC seventh edition TNM classification, therefore, defines T3 tumors as those greater than 7 cm in size, or tumors of any size with the following characteristics: invasion of the chest wall, diaphragm, mediastinal pleura, or parietal pericardium; more than 2 cm from carina; atelectasis of entire lung; or satellite nodules in the same lobe.

T4 redefined based on survival outcomes

Finally, tumors that were previously classified as M1 because of additional nodules in different lobes of the ipsilateral lung are classified as T4 in the seventh

edition. This change reflected the observation that 5-year survival outcomes for these patients differed markedly from other M1 tumors, but were similar to outcomes for patients with T4 tumors.[2] The revised AJCC seventh edition criteria for T4 lesions includes tumors of any size with invasion of the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina, or a satellite tumor nodule in the same lung.

N criteria unchanged

The N criteria subcommittee recommended that the existing N staging criteria should be retained without revision from the sixth edition.

M1 reclassified and subdivided

In the sixth edition, M1 disease was defined as any distant metastasis, including separate tumor nodules in a different lung lobe. In the seventh edition, pleural dissemination is reclassified from category T4 to M1 owing to significantly poorer survival among these subgroup of T4 patients.[2] In addition, M1 disease is divided into two subcategories. M1a disease is defined as one or more tumor nodule(s) in a contralateral lobe, tumor with pleural nodules, or malignant pleural or pericardial effusion, whereas M1b disease is defined as any distant metastasis.

TABLE 2
The non–small cell lung cancer "stage shifters" in the IASLC population

	AJCC 6th edition characteristics	6th edition stage	7th edition stage	IASLC patients (%)
Upstaged	$T2_{(> 5 \text{ but} \leq 7 \text{ cm})}$ N0 M0	1B	2A	3.8
	$T2_{(> 7 \text{ cm})}$ N0 M0	1B	2B	1.7
	$T2_{(> 7 \text{ cm})}$ N1 M0	2B	3A	0.8
	Malignant pleural involvement	3B	4	2.5
Downstaged	$T2_{(\leq 5 \text{ cm})}$ N1	2B	2A	4.4
	Separate tumor nodules in same lobe, N0	3B	2B	0.6
	Separate tumor nodules in same lobe, N1, N2	3B	3A	0.7
	Separate tumor nodules in different ipsilateral lobe, N0, N1	4	3A	0.4
	Separate tumor nodules in different ipsilateral lobe, N2, N3	4	3B	0.3
	$T4_{(\text{extension})}$ N0, N1	3B	3A	1.6

AJCC = American Joint Commission on Cancer; IASLC = International Association for the Study of Lung Cancer

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WHAT ARE THE IMPLICATIONS OF A NEW STAGING SYSTEM?

It is estimated that approximately 10% to 15% of newly diagnosed patients with lung cancer will be assigned to a different disease stage on the basis of this new classification system.[6] **Table 2** compares cancer staging using the sixth and seventh edition TNM classification criteria and includes the proportion of patients in the IASLC database who would be upstaged or downstaged.[6] For example, 3.8% of patients in the IASLC database would be upstaged from the former stage 1B to the new stage 2A, and approximately 4.4% of patients would be downstaged from 2B to 2A.

These changes to lung cancer staging may have significant implications for clinical decision-making. In a recent survey, clinicians who treat lung cancer were presented with three patient scenarios in which the lung cancer stage differed between the sixth and seventh AJCC editions.[6] The clinicians were first presented with the clinical vignettes accompanied by their sixth edition designations, and then with their seventh edition designations. At each presentation, clinicians were asked to choose from several possible management options. Approximately 77% of clinicians surveyed changed their management strategy based on the change in staging classification.

SUMMARY AND CONCLUSIONS

The AJCC seventh edition TNM classification is based on internally and externally validated survival curves derived from tens of thousands of patients with different disease characteristics enrolled at study sites around the world. Because the treatments received by the patients are not included in this analysis, it is essential to exercise caution when using staging information to make treatment decisions. Prospective patient data will be required to determine whether this

classification system significantly improves long-term treatment outcomes. In addition, it will be important to consider the potential effects of different staging systems when comparing the results of clinical trials.

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