The revised tumor-node-metastasis staging system for lung cancer: changes and perspectives*, **

Revisão do sistema de estadiamento tumor-nódulo-metástase para câncer de pulmão: mudanças e perspectivas

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Abstract

The tumor-node-metastasis (TNM) staging system for lung cancer has been modified since its first edition in the late 1960s. Its seventh edition has been recently published and, for the first time, a truly worldwide database was analyzed in order to propose modifications in the staging. Significant changes have been made in the tumor and metastasis descriptors. Although the recommendations for the node descriptor have remained unchanged, the analysis of the factors related to this descriptor suggests that modifications will be made in the future. The forthcoming revisions of the TNM staging system might take the molecular aspects of lung cancer into consideration, aiming at a more refined staging system.

Keywords: Lung neoplasms; Neoplasm staging; Epidemiologic methods.

Resumo

O sistema de estadiamento tumor-nódulo-metastase (TNM) para câncer de pulmão tem sido modificado desde sua primeira edição no final da década de 1960. Recentemente foi publicada sua sétima edição e, pela primeira vez, um banco de dados verdadeiramente mundial foi analisado para se propor modificações no estadiamento. Alterações significativas foram feitas nos descritores tumor e metástase. Embora as recomendações para o descritor nódulo permaneceram inalteradas, as análises dos fatores relacionados a esse descritor sugerem que modificações serão realizadas no futuro. As próximas revisões do sistema de estadiamento TNM podem levar em consideração aspectos moleculares do câncer de pulmão, objetivando um sistema de estadiamento mais refinado.

Descritores: Neoplasias pulmonares; Estadiamento de neoplasias; Métodos epidemiológicos.

The tumor-node-metastasis (TNM) staging system is a well-known classification system based on the characteristics of the tumor itself, regional lymph nodes, and potentially metastatic sites. It has been adopted for the staging of lung cancer since the late 1960s. According to this system, each of the descriptors (tumor, node, and metastasis) are subdivided into categories that are combined in order to provide a final classification, which aims to group patients with similar prognosis into the same staging category. This also helps in the selection of the best treatment for each case of lung cancer.[1,2]

In January of 2010, thoracic surgeons and pulmonologists were introduced to the seventh edition of the American Joint Commission on Cancer (AJCC)[3] and *Union Internationale Contre le Cancer* (UICC, International Union Against Cancer) staging manual. This document revised the TNM staging system for lung cancer. Unlike the previous editions, the AJCC manual was based on an extensive database of findings from Europe, Asia, North America, and Oceania. It is important that all thoracic surgeons and pulmonologists be aware of these revisions because they directly affect daily clinical practice.

The previous revision of the lung cancer staging system occurred in 1997. It was based on the analysis of 5,319 cases of non-small cell

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Financial support: None.
Submitted: 3 April 2010. Accepted, after review: 4 May 2010.
** A versão completa em português deste artigo está disponível em www.jornaldepneumologia.com.br

lung cancer in the United States, and nearly all of those patients had undergone surgical treatment between 1975 and 1988.[4] However, there were evident limitations, since the revision was based on a geographically specific population of patients who therefore did not represent the entire population of patients with lung cancer. These deficiencies were highlighted at an International Association for the Study of Lung Cancer (IASLC) workshop held in London in 1996,[5] prompting the establishment of the International Staging project and Committee (ISC), under the leadership of Professor Peter Goldstraw of the Royal Brompton Hospital in London. The objective of that committee was to collect and analyze data from lung cancer patients worldwide. With the agreement of the UICC and AJCC, the results of the analysis would be released for their inclusion in the seventh edition of the TNM staging system, scheduled for publication in 2009.[6]

For the purposes of biostatistical analysis, the Cancer Research and Biostatistics (CRAB), located in Seattle, WA, USA, a group with extensive experience in the management of large clinical trials and databases, agreed to support this work. In conjunction with the IASLC, the CRAB developed a data dictionary for the submission of data from institutions worldwide.[6] The database included data related to 100,869 lung tumor cases diagnosed between 1990 and 2000, a relatively short interval during which the staging methods were constant and which also allowed five years of follow-up prior to the analysis. Cases submitted to any treatment modality were included. After the exclusion of cases that did not meet the established criteria, there were 81,495 cases from 45 sources from more than 20 countries that were included in the database, of which 68,643 were cases of non-small cell lung cancer and 13,032 cases of small cell lung cancer.[7] During the analysis, all findings that could result in changes in any component of the TNM classification system had to be internally validated by geographic region and type of database. These findings also had to be externally validated by being tested against the Surveillance, Epidemiology, and End Results registries for the relevant period,[7] a project supported by the CRAB.

Analyses led to changes in the tumor and metastasis descriptors. We report them briefly: T1 and T2 were divided into "a" and "b" subcategories according to the tumor size, reflecting a similar prognosis to the same subcategories. In addition, T2 tumors larger than 7 cm were reclassified as T3. Separate tumor nodules in the same lobe of the primary cancer were reclassified from T4 to T3, whereas those in a different, but ipsilateral lobe, were reclassified from M1 to T4 (Table 1).[7] These changes reflected a "feeling" that most experienced thoracic surgeons had—the size of the tumor has special implications on the prognosis, and its importance was underestimated in the previous edition of the TNM manual.

Table 1 - Suggested changes in the seventh edition of the tumor-node-metastasis staging system for lung cancer.[7]

Descriptor	Suggested change
Tumor	Subclassify T1 according to tumor size
	T1a: ≤ 2 cm
	T1b: > 2 cm but ≤ 3 cm
	Subclassify T2 according to tumor size
	T2a: > 3 cm but ≤ 5 cm (or another T2 descriptor but ≤ 5 cm)
	T2b: > 5 cm but ≤ 7 cm
	Reclassify T2 tumors > 7 cm as T3
	Reclassify T4 tumors by additional nodule(s) in the same lobe as the primary tumor as T3
	Reclassify M1 tumors by additional nodule(s) in another ipsilateral lobe as T4
	Reclassify T4 tumors by malignant pleural effusion as M1a
Node	No changes
Metastasis	Subclassify M1
	M1a: separate tumor nodule(s) in the contralateral lung; tumor with pleural nodules or malignant pleural (or pericardial) effusion
	M1b: distant metastasis

The M1 category was subdivided into "a" and "b" subcategories, with M1a including contralateral lung nodules and malignant pleural or pericardial effusions, whereas M1b designated distant metastasis (Table 1).[7] These changes are in accordance with many reports of successful total pneumonectomy or contralateral lung resection after an initial resection for lung cancer, after which the patients had better survival in comparison with those in whom the cancer had spread to other sites.

The analysis of the node descriptor validated its division into N0, N1, N2, and N3 as prognostic factors, analyzed in a clinical and pathological basis. In addition, no single N1 or N2 nodal station had a significantly better or worse prognosis than did the others. This analysis prompted the ISC to suggest classifying the node descriptor in nodal zones, instead of nodal stations.[8,9] A relevant finding was that the five-year survival according to the involvement of nodal zones was as follows: single N1 zone, 48%; multiple N1 zone or single N2 zone, 35% and 34%, respectively; and multiple N2 zone, 20%.[10] These findings showed three different prognostic patterns, since multiple N1 or single N2 had practically the same five-year survival. Although these differences in survival were statistically significant, the findings could not be validated by geographic area because most of the data related to patients with specific details regarding nodal status came from Asia. Nor could the findings be validated by tumor category, due to the small number of patients in each category. Therefore, the node descriptor remained unchanged in the seventh edition of the TNM staging system for lung cancer. However, the analysis suggested that, in future revisions, it might be appropriate to subdivide the N1 and N2 categories into "a" and "b" subcategories on the basis of the number of lymph node zones involved.[10]

A dichotomous system has been classically adopted for small-cell lung cancer, classifying the disease as limited or extensive. In this edition of the TNM staging system, 13,032 patients with small-cell lung cancer were studied, and information about the TNM classification was available for 8,088 of those. When analyzing the tumor descriptor with any node category, the five-year survival for T1, T2, T3, and T4 showed a progressively worse prognosis. When the node component (with any tumor category) was analyzed in respect to the five-year survival, there were three different groups: N0 and N1, for which the prognoses were similar; N2; and N3. Although future studies are needed in order to achieve a better delineation of the TNM staging system regarding small-cell lung cancer, it seems quite reasonable to use the TNM system rather than the classic dichotomous classification, because it has better prognostic implications.[11]

In conclusion, the seventh edition of the TNM classification system for lung cancer emphasizes the prognostic relevance of the tumor size much more than did the previous editions. Although there were no changes in the node descriptor, the proposed modification to adopt nodal zones instead of nodal stations might reflect the similarity of multiple-N1 or single-N2 affected nodal zones in terms of prognosis. The changes in the classification of additional nodules are in accordance with various studies conducted in the past decade that reported a better survival with reoperation, an issue that is in better agreement with their prognosis. The separation of metastatic disease into two groups (M1a and M1b) aimed at better subclassifying tumors that are ineligible for surgical treatment, but that presented differences in terms of patient survival.

The new TNM staging system initiates the era of worldwide databases, in which the findings of different groups of specialists around the world are validated internally and externally, allowing the refinement of the previous classification system. In addition, rapid advances in molecular medicine in the field of lung cancer over the last six years have shown the importance of classifying lung tumors on the basis of molecular features,[12] which might represent the next frontier for the TNM classification system.

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