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Editorial

New TNM Classification for Lung Cancer

Nueva clasificación TNM del cáncer de pulmón

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The seventh, 2009, edition of the TNM classification for malignant tumors by the International Union Against Cancer and the American Joint Committee on Cancer is to be implemented 1 year after publication. This updated lung cancer classification takes into consideration work carried out by the International Staging Committee of the International Association for the Study of Lung Cancer (IASLC). This committee, created in 1998 to correct the limitations of the sixth edition of the TNM classification, developed a data collection sheet for retrospective recording of information on patients diagnosed with bronchogenic carcinoma between 1990 and 2000 in order to validate and refine the system. At the same time, databases in various countries were identified and their compilers invited to contribute their data to the IASLC database. During the data collection period, from the beginning of 2002 to the middle of 2005, the international database received information on 100 869 patients from 20 countries and 45 different sources, including, for example, those pertaining to clinical trials, hospital records, multicenter registers, and surgical case series. After removing the records of patients whose tumors had been diagnosed outside the established reporting period and those of patients whose tumors were other than bronchogenic carcinoma, 81 495 valid cases remained: 68 463 were non-small cell lung carcinomas and 13 032 small cell lung carcinomas. Slightly more than half of the patients had undergone surgery, whether combined with other treatments or not.[1] Data processing and analysis were carried out by the Cancer Research and Biostatistics group.[2]

Regarding the T component of the classification system, since most of the databases were not established to provide information for validation purposes, the International Staging Committee was only able to study tumor size in detail, along with accompanying nodule(s) either in the same lobe as the primary tumor or in other lobes in the same lung, and pleural involvement (malignant effusion or nodules). Tumor size was studied in patients with completely resected pT1 and pT2N0M0 tumors who had received no induction therapy. Data were randomly shuffled to create multiple permutations and a log-rank test was used to determine cutpoints by tumor size. In the population of patients with pT1N0M0 tumors, the statistical cutpoint was approximately 2 cm. In those with pT2N0M0 tumors, the cutpoints identified a range from 5 cm to 7 cm. These 3 cutpoints, together with the 3-cm limit differentiating T1 from T2 tumors, generated 5 groups with significantly worse survival according to increasing tumor size: *a)* ≤2 cm, *b)* >2 cm and ≤3 cm, *c)* >3 cm and ≤5 cm, *d)* >5 cm and ≤7 cm, and *e)* >7 cm. When these tumor sizes were analyzed with a population of *c*T1 and *c*T2N0M0 tumors, significantly different prognoses were once again observed. These findings led to the subclassification of T1 and T2 tumors and reclassification of the larger T2 tumors, for which survival was similar to that of T3 tumors[3] (Table 1). Regarding the other descriptors, on comparing the survival of patients with tumors classified as T4 (because of additional nodule[s] identified in the same lobe as the primary tumor) to the survival of patients with tumors classified as T3 and T4 for other reasons, it was evident that survival for the first group of T4 patients was more similar to that of T3 patients; accordingly, reclassification was recommended. Likewise, reclassification of M1 tumors was recommended after the survival of patients with tumors thus classified because of additional nodule(s) in another lobe in the same lung was compared to the survival of all patients with T4 tumors and those with distant M1; survival associated with local M1 was more similar to the survival of patients with T4 tumors. However, the survival of patients with malignant pleural effusion or pleural nodules was similar to that of patients with metastasis and, therefore, such cases were reclassified as M1 (Table 1).

Study of the N component did not lead to changes. The present classification was validated since the N component confirmed the worsening prognosis in both the overall population and in patients surgically treated, for whom both clinical and pathologic N classifications were available. Comparison of survival in relation to affected lymph node stations revealed no significant differences although a trend toward a worse prognosis was observed if subcarinal lymphadenopathy was diagnosed. Since no prognostic differences were found in relation to stations, the International Staging Committee proposed grouping the stations into a zone system to facilitate their description and prospective study (Table 2). A more detailed study in a group of patients, mostly from Asia and Australia,

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Table 1
Re-Staging in the Seventh Edition of the Lung Cancer TNM Classification

Classification Component	Restaging
T	T1 has been subdivided into T1a: tumor ≤2 cm T1b: tumor >2 cm and ≤3 cm T2 has been subdivided into T2a: tumor >3 cm and ≤5 cm (or tumor with any of the T2 descriptors, but ≤5 cm) T2b: tumor >5 cm and ≤7 cm T2 >7 cm reclassified as T3 T4 based on additional nodule(s) in the same lobe as the primary tumor, reclassified as T3 M1 due to additional nodule(s) in an ipsilateral lobe other than that of the primary tumor, reclassified as T4 T4 due to malignant pleural effusion has been reclassified as M1a
N	No changes
M	M1 has been subdivided into M1a: separate nodules in a contralateral lobe; tumor accompanied by pleural nodules or malignant pleural or pericardial effusion M1b: distant metastasis

Table 2
Proposed Lymph-Node Zones and Stations

Zone	Lymph-Node Stations
Upper Zone (R)	Highest mediastinal nodes Upper paratracheal Prevascular and retrotracheal Lower paratracheal
Aortopulmonary Zone (L)	Subaortic (aortopulmonary window) Para-aortic (ascending aorta or phrenic nerve)
Subcarinal Zone	Subcarinal
Lower Zones	Paraesophageal Pulmonary ligament
Hilar Zone	Hilar Interlobular
Peripheral Zone	Lobar Segmental Subsegmental

revealed the prognostic importance of the number of zones affected and led to the question of a possible modification of N classification based on these findings. Depending on the number of affected zones, 3 prognostic groups could be established, reflecting involvement of a single N1 zone, involvement of multiple N1 zones or a single N2 zone, and involvement of multiple N2 zones. As these findings could not be validated by geographic region, type of database, or T category, no changes in classification were recommended. Nevertheless, the findings are of potential clinical importance since they are useful for prognosis and may be of use in planning therapy.[4]

The M component was studied by comparing the survival of patients with additional nodule(s) in another lobe in the same lung as the primary tumor to those with pleural involvement, to those with contralateral nodules, and to those with extrathoracic metastases. As observed in the analysis of the T component, the first group of tumors was associated with a prognosis similar to that of T4 tumors and were, therefore, reclassified. Likewise, patients with pleural dissemination or contralateral pulmonary nodules had a significantly better prognosis than those with distant metastasis; this was the main reason for the subclassification of M1[5] (Table 1).

The changes recommended for this seventh edition of the lung cancer classification system were based on differences in survival, were carefully scrutinized in a process of internal and external validation,[6] and resulted in changes in the placement of the various TNM subgroups within stages.[7] Thus, T2bN0M0 tumors were switched from stage IB to IIA; T2aN1M0 tumors, from stage IIB to IIA; and T4N0 or T4N1M0 tumors, from stage IIIB to IIIA. In comparison with the sixth edition of the classification, the changes in staging of the T and M components of the seventh edition provide for better prognostic distinctions. The recommended changes are applicable to both non-small cell and small cell carcinomas. For small cell carcinoma the recommendation is to use TNM classification in future clinical trials instead of grouping cases according to limited vs extended disease or stratifying by stage.[8] Despite the limitations of TNM classification owing to changes over the course of its history, this system has been studied in relation to 520 carcinoid tumors in the IASLC database and has been found to be applicable to such tumors. For the first time, this seventh edition of the TNM staging has been recommended for use in conjunction with this type of tumor.[9]

Since the publication of the literature described here, several independent groups have applied the proposed changes to their case series and have validated them with their own data or with data in multicenter tumor registers. Zell et al[10] observed that the changes proposed represent an improvement in the classification of advanced bronchioalveolar carcinoma compared with the sixth edition. Oliaro et al[11] found that the most accurate prognoses corresponded with the seventh classification when they studied a series of patients with additional nodules. Lee et al[12] came to the same conclusion on observing that additional nodules in the same lobe share a prognosis with T3 tumors, whereas those with nodules in another lobe in the same lung have a prognosis similar to T4 tumors. Both studies lend support to the proposed IASLC reclassification. Lee and colleagues[13] also validated the prognostic differences of the 3 groups of patients with lymph node disease identified in the IASLC study, thereby reinforcing the prognostic importance of lymph node tumor load. Ruffini et al[14] validated both the proposed changes for the T component and the prognostic differences of the 3 groups with lymphadenopathy. Filosso et al[15] found the most accurate prognoses to coincide with the current classification of T4 tumors based on additional nodules in the same lobe.

The seventh edition of the TNM lung cancer classification is the first one based on truly international data for patients very heterogeneously treated. It places more importance on tumor size than did previous editions. It reconciles the classification of tumors accompanied by additional nodules with their real prognosis. Finally, it adapts the classification of pleural dissemination to prognosis as well as to usual clinical practice, in which such cases are considered to be disseminated disease. The shifting of some TNM classifications to different stage categories from the ones previously occupied means that new clinical trials on adjuvant therapy will be necessary and, until new evidence is obtained, clinical judgment will have to be exercised when applying this therapy to treat tumors for which it has thus far not been indicated, but which we now realize have a worse prognosis than was suggested by the sixth edition of the classification. The seventh edition has its limitations: most of the descriptors for T2, T3, and T4 tumors still lack validation owing to lack of data, to discrepancies between the clinical and the pathologic classifications, or to lack of validation of those classifications. However, even with these limitations, the seventh edition better distinguishes between prognostic groups. The new edition is not perfect or definitive, but it is the one we will be using until the next one appears in 2016. That edition will be the result of analysis of the prospective IASLC staging project, which begins in 2009 and aims to complement the retrospective study by filling gaps that remain.

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