Review

The Revised TNM Staging System for Lung Cancer

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The International Staging Committee (ISC) of the International Association for the Study of Lung Cancer (IASLC) collected 68,463 patients with nonsmall cell lung cancer and 13,032 patients with small cell lung cancer, registered or diagnosed from 1990 to 2000, whose records had adequate information for analyzing the tumor, node, metastasis (TNM) classification. The T, N, and M descriptors were analyzed, and recommendations for changes in the seventh edition of the TNM classification were proposed based on differences in survival. For the T component, tumor size was found to have prognostic relevance, and its analysis led to recommendations to subclassify T1 tumors into T1a (≤ 2 cm) and T1b (>2 – ≤ 3 cm) and T2 tumors into T2a (>3 – ≤ 5 cm) and T2b (>5 – ≤ 7 cm), and to reclassify T2 tumors > 7 cm into T3. Furthermore, with additional nodules in the same lobe as the primary tumors, T4 tumors would be reclassified as T3; with additional nodules in another ipsilateral lobe, M1 as T4; and with pleural dissemination, T4 as M1. There were no changes in the N category. In the M category, M1 was recommended to be subclassified into M1a (contralateral lung nodules and pleural dissemination) and M1b (distant metastasis). The proposed changes for the new stage grouping were to upstage T2bN0M0 from stage IB to stage IIA, and to downstage T2aN1M0 from stage IIB to stage IIA and T4N0-N1M0 from stage IIIB to stage IIIA. The proposed changes better differentiate tumors of different prognoses. (Ann Thorac Cardiovasc Surg 2009; 15: 4–9)

Key words: tumor, node, metastasis classification, staging system, tumor size, nodal involvement, metastatic disease

Introduction

The recommendations of the fifth edition of the tumor, node, metastasis (TNM5) classification of lung cancer, published in 1997,[1,2] remained unaltered in the sixth edition (TNM6), published in 2002.[3,4] The revisions included in 1997 were based on the analysis of data from 5,319 patients in North America, nearly all of whom had undergone surgical treatment from 1975 to 1988.[5] This revised classification meant an improvement in the grouping of tumors with similar prognoses (stage I was divided into stages IA and IB; stage II into stages IIA and IIB; and T3N0M0 tumors were moved from stage IIIA to stage IIB). However, there were evident limitations. It was based on a selected population of patients who had undergone surgical treatment, but

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did not represent the entire population of patients with lung cancer. All tumors had both clinical and pathological classifications, but none of the descriptors had been validated; the revised classification was not really international because the patients had been collected in only one geographic region; and the series of patients on which the classification was based was becoming historical. Considering all these limitations, in 1998 the International Association for the Study of Lung Cancer (IASLC) created an International Staging Committee (ISC) of multidisciplinary members. The objective of this committee was to collect data worldwide from lung cancer patients for analysis. With the agreement of both the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), the results of these analyses would be released for inclusion in the seventh edition of the TNM classification (TNM7) scheduled for publication in 2009.[6)]

The objective of this review is to summarize the work of the ISC and the proposals for changes in the TNM classifications that were derived from analyses of the IASLC database.

The IASLC Database and Methodology

The ISC collected data on 100,869 patients diagnosed or registered with lung cancer from 1990 to 2000. The patients were from more than 20 countries in Asia, Australia, Europe, and North America, and their data originated in 45 different databases. Fifty-three percent of these patients had undergone surgical treatment, either alone or in combination with chemotherapy or radiotherapy. After we excluded the patients who had not been diagnosed within the established time, those whose tumors could represent a recurrence and those with tumors other than bronchogenic carcinoma, 68,463 patients with nonsmall cell lung cancers and 13,032 with small-cell lung cancers (SCLCs) (totaling 81,495) fulfilled the inclusion criteria and remained valid for analyses. The IASLC database is stored, managed, updated, and analyzed by Cancer Research And Biostatistics (CRAB).[6)] The findings of the data analyses that could become recommendations for change in every component of the TNM classification had to be internally validated by geographic region and type of database. They also had to be externally validated by being tested against the Surveillance, Epidemiology, and End Results (SEER) registries for the relevant period.[7)] For those exploratory analyses where huge amounts of data were available, the database was randomly divided into a training set, consisting of 2/3 of the cases from which the recommendations were developed and 1/3 of those that formed the validation set.

The T Component

There were enough patients with staging data to analyze tumor size, additional nodules in the same lobe of the primary tumor, additional nodules in a different ipsilateral lobe, and pleural dissemination (malignant pleural effusion and metastatic pleural nodules). Because most contributing databases did not have the objective to validate TNM classification, there were insufficient tumors with staging information for study of the remaining T descriptors.

Regarding tumor size, survival analysis was done in the population of 7,335 patients with pathological (p) T1 and T2N0M0 completely resected (R0) tumors who had not received induction therapy. Running log-rank statistics produced for each cutpoint of the data were graphed against tumor size and tested for statistical significance via permutations of the data. The tumor size that coincided with the highest log-rank statistic was considered the optimal cutpoint. In patients with pT1N0M0R0 tumors, the optimal cutpoint occurred at the pathological tumor size of 2 cm. In patients with pT2N0M0R0 tumors, the highest log-rank statistic was at the pathological tumor size of 7.3 cm (rounded off at 7 cm for practicality); there also was a second highest log-rank statistic at 5 cm. So these three cutpoints, together with the classic 3 cm cutpoint that separates T1 from T2 tumors, generated five groups of tumors of different sizes and significantly different survival. Five-year survival rates for the five different tumor-size groups were pT1 ≤ 2 cm, 77%; pT1 > 2 cm but ≤ 3 cm, 71%; pT2 > 3 cm but ≤ 5 cm, 58%; pT2 > 5 cm but ≤ 7 cm, 49%; and pT2 > 7 cm, 35%. These differences were maintained when the less-selected population of patients with any type of resection (complete and incomplete) and with tumors with any type of nodal involvement were analyzed. When the same analysis was done in patients with clinical (c) T1 and T2 node negative cases and cT1 and cT2 N cases, the same differences were found, except in the two smallest tumor sizes; the differences between cT1 ≤ 2 cm and cT1 > 2 cm but ≤ 3 cm were not statistically different, though the 5-year survival rate for the smallest cT1 tumors was higher than that for the largest ones: 53% vs. 47%. The largest T2 tumors,

Table 1. Proposed changes for the seventh edition of the TNM classification of lung cancer

Component of the classification	Proposed changes
T	To subclassify T1 according to tumor size in - T1a: ≤ 2 cm and - T1b: > 2 cm but ≤ 3 cm
	To subclassify T2 according to tumor size in - T2a: > 3 cm but ≤ 5 cm (or tumor with any other T2 descriptors, but ≤ 5 cm) and - T2b: > 5 cm but ≤ 7 cm
	To reclassify T2 tumors > 7 cm as T3
	To reclassify T4 tumors by additional nodule/s in the same lobe of the primary tumors as T3
	To reclassify M1 tumors by additional nodule/s in another ipsilateral lobe as T4
	To reclassify T4 tumors by malignant pleural effusion as M1a
N	No changes
M	To subclassify M1 in - M1a: separated tumor nodule/s in the contralateral lung; tumor with pleural nodules or malignant pleural (or pericardial) effusion; and - M1b: distant metastasis

those larger than 7 cm, were compared with T3 tumors. Their 5-year survival was similar in all clinical and pathological populations studied, except for those of patients with completely resected pN0 tumors, in whom the 5-year survival rate for pT3 tumors was even better than that for pT2 > 7 cm: 41% vs. 35%.[8] Lastly, to elucidate survival differences among pT3 tumors (1,224 patients), pT4 tumors by additional nodules in the same lobe of the primary tumor (363 patients), pT4 tumors by other factors (340 patients), pM1 by additional nodules in a different ipsilateral lobe (180 patients), and pT4 by pleural dissemination (245 patients), survivals were calculated and compared. Their 5-year survival rates were 31%, 28%, 22%, 22%, and 11%, respectively. Statistical comparisons showed that pT3 and pT4 tumors by same-lobe additional tumors had the same survival rate; that pT4 by other T4 factors and pM1 by same-side additional nodules also had the same rate; and that pT4 by pleural dissemination had the poorest survival. This was even more evident when *c*T4 tumors by pleural dissemination were compared with *c*T4 tumors by other T4 factors: the 5-year survival rates of these patients with any cN category were 2% and 14%, and these differences were statistically significant.[8]

In view of the above findings, the ISC of the IASLC recommended the subclassification of T1 and T2 tumors according to tumor size; the upstaging of large T2 tumors; and the downstaging of T4 and M1 tumors so described by additional nodules in the same lobe of the primary tumor or in another ipsilateral lobe, respectively, and the upstaging of pleural dissemination (Table 1).

The N Component

From the total of 68,463 patients with nonsmall cell lung cancer, 38,265 had information on the clinical status of the lymph nodes, and 28,371 who underwent surgical treatment had information on the pathological N status. In the population of patients with tumors with cN status, the expected degradation of survival as nodal involvement increased was observed, and differences among the different cN categories were statistically significant. Five-year survival rates for cN0, cN1, cN2, and cN3 were 42%, 29%, 18%, and 7%, respectively. The same degradation of survival was observed among patients who underwent surgical treatment and whose tumors had both cN and pN staging. Five-year survival rates for patients whose tumors were classified as cN0, cN1, cN2, and cN3 were 50%, 39%, 31%, and 21%, respectively. The corresponding 5-year survival rates for pN0, pN1, pN2, and pN3 were 56%, 38%, 22%, and 6%, respectively. All differences were statistically significant.[9]

A group of 2,876 patients had specific details on pN1 and pN2 involvement, and this information was used to compare the prognostic impact of individual nodal stations. When compared among them, no single N1 or N2 nodal station had significantly better or worse prognosis

Table 2. Proposed nodal zones with their nodal stations

Proposed nodal zones	Nodal stations
N2 nodes	
Upper zone	Highest mediastinal (#1) Upper paratracheal (#2) Prevascular and retrotracheal (#3a, #3p) Lower paratracheal (#4)
Aortopulmonary zone	Subaortic (aortopulmonary window) (#5) Para-aortic (ascending aorta or phrenic (#6)
Subcarinal zone	Subcarinal (#7)
Lower zone	Paraesophageal (below carina) (#8) Pulmonary ligament (#9)
N1 nodes	
Hilar zone	Hilar (#10) Interlobar (#11)
Peripheral zone	Lobar (#12) Segmental (#13) Subsegmental (#14)

#, nodal station number.

than the others. This result prompted the ISC members to amalgamate the traditional nodal stations into nodal zones for further exploratory analyses (Table 2). Survival differences among the different zones were not statistically significant, though the single involvement of the peripheral zone had the longest median survival (51 months) compared with the combined involvement of peripheral and hilar zones (median survival from 28 to 48 months, depending on how many nodal stations were involved). No significant differences were found in the median survival of the different N2 zones.[9)]

When survival was analyzed by the number of involved nodal zones, three different prognostic groups were found: single N1 zone, with a 5-year survival rate of 48%; multiple N1 zone or single N2 zone, with 5-year survival rates of 35% and 34%; and multiple N2 zones, with a 5-year survival rate of 20%. Survival differences among the three groups were statistically significant.[9)] However, these findings could not be validated by geographic area because most patients with specific details in the nodal status came from Asia, or by T categories because of the few patients in each category. Therefore no recommendations for changes in the N component could be made.

The M Component

For an analysis of the M component, a total of 6,596 patients with best-staged tumors and having additional nodules in another ipsilateral lobe (1,106 patients), with pleural dissemination (771 patients), contralateral lung nodules (369 patients), and distant metastasis (4,350 patients), could be analyzed. Five-year survival rates were 16%, 6%, 3%, and 1%, respectively. Statistical analyses showed that tumors with additional nodules in another ipsilateral lobe had the best survival; that pleural dissemination and contralateral lung nodules had similar survival; and that distant metastases had a significantly worse survival compared with contralateral lung nodules and pleural dissemination. Consequently, the recommendations of the ISC were to subclassify metastatic spread into intrathoracic and distant, based on the significant differences in survival[10)] (Table 1).

Stage Grouping

As a consequence of the recommendations for changes in the T and the M components of the classifications of lung cancer, changes were also suggested for the stage grouping. A survival tree was generated by the recursive partitioning and amalgamation analysis of 17,726 patients with best-staged tumors. After all possible

combinations had been considered, the final stage grouping recommended was the one that showed the best gradation of survival with increasing stages and the clearest separation of survival curves with no overlapping of curves of adjacent stages. Here are the proposed changes for the new stage grouping: large T2 tumors (T2b) N0M0 were upstaged from stage IB to stage IIA; small T2 tumors (T2a) with N1M0 disease were downstaged from stage IIB to stage IIA; and T4 tumors with no nodal involvement or with N1 disease were downstaged from stage IIIB to stage IIIA. The 5-year survival rates for the new clinical stages were IA 50%, IB 47%, IIA 36%, IIB 26%, IIIA 19%, IIIB 7%, and IV 2%. The corresponding 5-year survival rates for their pathological counterparts were IA 73%, IB 58%, IIA 46%, IIB 36%, IIIA 24%, IIIB 9%, and IV 13%.[11)]

Small-Cell Lung Cancer

From the 13,032 patients with SCLC, 12,620 were eligible for study and 8,088 had information on the TNM classification: clinical TNM 3,215 patients, pathological TNM 128, clinical and pathological TNM 215, and clinical M1 4,530. Because of the few patients with pathological classification, no attempt was made to study pathological staging. Survival analysis found a progressive degradation of survival as T and N increased. Clinical T1 with any N category had better prognosis than T2, T3, and T4 with any N category. Their 5-year survival rates were 29%, 15%, 11%, and 10%, respectively; although differences in 5-year survivals among T2, T3, and T4 were small, they were statistically significant. When the N component (any T) was analyzed, N0 and N1 were found to have similar prognoses, but N2 had a worse one than N0-N1, but better than N3. Five-year survival rates for N0, N1, N2, and N3 were 24%, 20%, 12%, and 9%, respectively. So it seems that in the N component there are three prognostic groups: N0-N1, N2, and N3. When the survivals of clinical T categories were analyzed according to the N component, it was found that survival curves tended to converge as the N increased. Pleural effusion, with positive or negative cytology, had an intermediate survival between limited disease and extensive disease. Stage grouping by the proposed IASLC stages also differentiated tumors with different prognoses. Five-year survival rates for the different clinical stages were IA 38%, IB 21%, IIA 38%, IIB 18%, IIIA 13%, IIIB 9%, and IV 1%. Except for the paradoxically high survival of patients with stage IIA tumors (this group has only 55 patients), the expected worsening in prognosis is observed as the tumor stage increases.[12)]

Based on the above findings, the TNM classification and staging system was recommended for SCLC, and stratification by stage I–III also was recommended in clinical trials of early-stage disease. The TNM classification and staging system differentiate more specific prognostic groups than the dichotomous system, which considers only limited disease and extensive disease.

Conclusion

The proposed changes for the seventh edition of the TNM classification of lung cancer emphasize the prognostic relevance of tumor size much more than in previous editions. They assign tumors with additional nodules in the same lobe of the primary tumor and in another ipsilateral lobe a classification that is more in agreement with their prognosis. They reconcile the classification of pleural dissemination with both its real prognosis and clinical practice. They separate metastatic disease into two prognostic groups. Therefore these proposed changes better differentiate tumors with different prognoses, which is one of the objectives of the TNM classification.

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