Editorial

The "N"—factor in non-small cell lung cancer: staging system and institutional reports

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Lymph node (LN) status is a highly significant component of staging of non-small cell lung cancer (NSCLC). Staging of NSCLC provides prognostic data related to the risk of recurrence as well as overall survival (1). Lymph node metastasis alters the treatment decisions, including surgical resectability and appropriateness of adjuvant interventions.

According to the TNM rules, at least six lymph nodes need to be removed, three from N1 and three from N2 stations. This is the minimum requirement for a diagnosis of N0 when lymph nodes are negative (2).

Currently, the 7th edition of NSCLC staging system defines the nodal status as N0 (no nodal involvement), N1 (peribronchial, interlobar, hilar node involvement), N2 (ipsilateral nodal involvement), N3 (contralateral mediastinal, contralateral hilar or supraclavicular nodal involvement) depending only on the location of the metastatic lymph nodes and the actual definition of nodal categorization not varied in the last revision from the 6th to the 7th edition.

Differently from other organs, in the case of lung cancer, the principle that the nodal status is based on the location of the nodal metastasis and not on the number of metastatic nodes has been maintained.

The principle that raise the N staging of lung cancer on the base of the anatomic location of the involved nodes is accepted because: the lymph nodes location is easy to be determined on CT-scan or PET/CT (that is fundamental for the determination of the clinical N status), it has an high prognostic impact, and its categorization is anatomically reasonable from the perspective of a lymphatic pathway from the lung parenchyma through the hilum, the mediastinum and the supraclavicular fossa.

Whereas the IASLC Staging and Prognostic Factors Committee was analyzing the collected database to define the above cited staging system, many authors from single institutions researched about the impact on long-term outcome of the number of involved nodes coming up to interesting results.

In a recent study by Smeltzer *et al*. (3), "Missed intrapulmonary lymph node metastasis and survival after resection of non-small cell lung cancer", a specialized technique of intrapulmonary LN sampling is utilized to identify possible previous not detected LN metastasis; the impact on overall survival of the presence of cancer metastasis to the intrapulmonary LNs is analyzed too. In their study, the initial pathological staging after routine dissection was pN0 69%, pN1 16% and pN2 15%. After re-dissection, additional LN metastasis was found in 23% patients. This caused a lowering of the pN0 rate from 69% to 65% and an augmented rate of pN1 cases from 16% to 22%. As second end-point the above mentioned paper reported an augmented risk of death for patients with more than two missed metastatic nodes at intrapulmonary stations.

Despite some limitations due to the small number of patients and the short follow-up period, the paper, like others in the recent literature (4-7), has the great value to instill two doubts: the number of metastatic LNs should be of better prognostic value than the location itself and, the pathologist with an accurate dissection of the resected specimen should help a better definition of the N status, particularly when the LNs dissection by the surgeon is not highly accurate.

During the last decade, other authors investigated

the value of missed LNs metastasis at re-dissection of pulmonary specimens with curative intent (8,9), and others studied the prognostic impact of the number of metastatic LNs and their relative location after hilar-mediastinal nodal dissection (10,11).

Maeshima *et al*. described the prognostic implications for N1 status; they stratified N1 nodal status based on hilar/interlobar zone (level 10–11 nodes) versus the peripheral zone (level 12, 13 and 14 nodes) in 230 patients affected by pN1 disease from a Japanese population. Their study supported previous data that metastasis to high level nodes alone, level 13 or 14, may have a better prognosis and those patients with level 11 or 12 nodal metastasis had a worse 5-year disease-free survival compared to level 13 or 14 involvement alone (8). Rena *et al*. investigated the prognostic significance of segmental and subsegmental (level 13 and 14) lymph nodes metastasis in 124 patients with resected NSCLC. Significant differences were recorded in long-term outcome when different nodal levels of metastatic spread were compared: the higher the nodal level, the higher the long-term survival rate (9). The above studies conclude that the level of pulmonary lymph nodes involved is related to the long-term outcome and the increased risk of death after surgery should be related to the progression of the metastatic spread along the lymphatic pathway from the peripheral lung to the hilum.

On the other hand, other authors reported the possibility of the number of involved nodes instead of the location-based cN or pN in lung cancer (10,11). These studies compared the two categorizations, by location and number of metastatic nodes and showed that the number of involved nodes is a better prognostic determinant than the location-based pN classification. Wei *et al*. addressed the problems of the number of involved nodes in practical use: it is very difficult to determine the number of involved nodes before treatment by low-resolution imaging diagnosis and on a PET/CT image, metastatic nodes are not clearly separated for accurate counting.

During the decade 1999–2010, the IASCL collected a new database the analysis of which will inform the 8th edition of the TNM classification of lung cancer. The database consists of 94,708 patients collected from Europe, North and South America, Australia and Asia and information on the N categorization was available for 31,426 pN status (12). As for the previous series that supported the used classification, unfortunately, the present database once again did not include information regarding the number of involved nodes and information of nodal status are limited to the nodal station(s) involved (single *vs.* multiple).

Recently, Asamura *et al*. (12) reported about the proposal of a new classification of the N descriptor in NSCLC. The analysis of the collected database allowed to conclude that the utilization of the currently used descriptors (N0, N1, N2, N3) are highly prognostic even in clinical and pathological staging. The analysis was extended to explore if the combination of location and number of involved stations (single *vs.* multiple) may be useful to better stratify patients survival. The new analyzed groups are pN0 (absence of nodal involvement), pN1a (metastasis at single station N1 level), pN1b (metastasis at multiple station N1 level), pN2a1 ("skip metastasis"—metastasis at a single N2 station without involvement at N1 level), pN2a2 (metastasis at a single station N2 level without skip), pN2b (metastasis at multiple station N2 level). The analysis of survival revealed that pN2a1 has better prognosis than pN2a2 and pN2b, but pN1b has similar prognosis than pN2a1.

Unfortunately, once again the database utilized for the definition of the N descriptor of the incoming 8th edition has some important limitations.

Two different lymph nodes maps were used when the database was constructed [the MDATS in Europe/America (13) and the Naruke lymph node map adopted by the Japan Lung Cancer Society in Japan (14)], and the use of different maps might have caused a stage shift, with a different prognosis for the same pN status. There was a considerable imbalance in the origin of the data too: most of the data, especially those for pN status came from Japan (23,463 patients, 75%). The present analysis of pN factor was mostly an evaluation of nodal categorization based upon Japanese-Naruke map and it is not clear if it can be concluded that nodal categorization according to MDATS is also prognostic.

Second, the method used to evaluate harvested lymph nodes at today is still not standardized. It has been noted that the incomplete retrieval of lymph nodes from a resected specimen seriously affects nodal categorization (7,8,15). There is still a question regarding the minimum number of lymph nodes that should be assessed pathologically. Usually, when systematic lymph node dissection is performed, the lymph nodes are dissected "en bloc" together with surrounding adipose tissue. Whereas ideally pathologist or surgeon should remove these nodes out as distinct nodes, in the reality some of the nodes can be missed without undergoing a pathological assessment.

The analysis of the 1999 to 2010 IASLC database that

should support the proposals for the N descriptor of the 8th edition has shown that the actually used N categories are still useful for distinguishing between tumors with significantly different prognoses in both clinical and pathological settings (12). The results added that the number of involved nodal stations was found to have prognostic impact too, although this finding was derived from pathological staging and could not be validated in clinical staging.

In the 7th edition of the TNM classification of malignant tumors, there are some tumors (i.e., breast or penis cancer) that have different descriptors for the clinical and pathological N categories. Clinical staging uses some characteristics as mobility and fixation, whereas the number of involved nodes is used to define the pathological N categories. The cited examples reflect the difficulty of counting the number of involved lymph nodes in the clinical staging and, at the same time, acknowledge the importance of the number of involved lymph nodes at pathological staging. The tests currently available for clinical staging in lung cancer are not accurate enough in counting the number of involved nodes but there is strong evidence that the number of involved nodes has a significant prognostic impact. It should be seriously considered if NSCLC will benefit of two different staging systems (clinical and pathological) in the future classification.

In the discussion of his last paper, Asamura suggests that "…the N descriptors of the 7th edition should be maintained not varied in the incoming 8th one. According to the results of the additional analyses the combination of location of metastatic nodes, the number of nodes (single station *vs.* multiple stations), and absence versus presence of skip metastasis (pN0, pN1a, pN1b, pN2a1, pN2a2, pN2b) may give a more accurate prognosis: this classification requires prospective evaluation before being considered for future revisions of the TNM staging system for lung cancer" (12).

Concluding, it is clear that the actual staging system of non-small cell lung cancer may be ameliorated with future efforts and the following suggestions may affect the results.

First of all, it should be desirable that in the collection of future data bases, physicians will use the same nodal map and anatomical definitions to describe regional lymph node involvement in lung cancer, the IASLC map being a useful option (16).

Secondarily, future staging system should provide guidelines or suggestions regarding a standardized method for evaluating dissected/removed lymph nodes by the surgeon during the resection and by the pathologist during the specimen dissection to correctly report the number of dissected nodes and the number of metastatic ones from each lymph node station.

These data will be of great value to define the future categorization of the pN factor.

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Footnote

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