Commentary

Clinical value of nodal micrometastases in patients with non-small cell lung cancer: time for reconsideration?

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Lung cancer is the leading cause of cancer-related mortality worldwide (1). Surgery is the treatment of choice in early-stage and in selected locally-advanced non-small cell lung cancer (NSCLC). However, a significant number of patients die due to cancer recurrence even in the early stages of the disease. Accurate staging and definition of prognostic factors are therefore mandatory to identify patients at higher risk of recurrence with the aim of refining therapeutic strategies and improve overall survival.

Nodal status is one of the major prognostic factors in lung cancer. However, it encompasses a wide spectrum of disease extent, which may vary from microscopic to macroscopic nodal metastases, intra- and extracapsular extension, single or multiple involvement of lymph nodes or nodal stations and presence of skip metastases. In particular, one of the issues that still need to be investigated in detail is the role of nodal micrometastases. The prognostic role of micrometastases has been clearly assessed in tumors as breast cancer and melanoma and is specified in the current TNM staging manuals (2). Conversely, the role of nodal micrometastases in lung cancer is still a matter of debate. In the current AJCC Cancer Staging Manual isolated tumor cells (ITC) in lymph nodes are defined as single tumor cells or small clusters of cells smaller than 0.2 mm in their greatest diameter without mitoses, vascular or lymphatic invasion. The presence of ITC does not modify tumor stage. Micrometastases, on the other hand, are defined as clusters of cells measuring between 0.2 and 2 mm in their greatest diameter, usually with mitoses and vascular or lymphatic invasion, and when identified are considered similarly to other nodal metastases with consequent tumor upstaging.

The results of previous studies analyzing the prognostic role of nodal micrometastases are extremely heterogeneous. In some of them the presence of nodal micrometastases had a negative prognostic influence on recurrence and survival, but on the contrary other studies have failed to confirm these data. The role of micrometastases has been more frequently analyzed in stage I and II tumors. Nosotti *et al*. observed that the presence of micrometastases, detected by carcinoembryonic antigen mRNA, was a predictor of cancer recurrence in stage I patients (3). The results of the American College of Surgeons Oncology Group Z0040 trial recruiting 1,047 patients with tumor stages varying from Ia to IIIb, 66% of whom with stage I disease, also showed that occult nodal metastases were associated with a significantly worse prognosis (4). On the contrary, Marchevsky *et al*. observed that the presence of ITC or micrometastases detected with serial histologic sections and keratin AE1/AE3 immunostaining in the lymph nodes of 266 patients with stage I NSCLC were not associated with a decreased survival. A meta-analysis performed by the same authors in 835 NSCLC patients confirmed these results and did not show a significant correlation between nodal micrometastases and survival. These Authors therefore suggested that microscopic involvement of N1 and N2

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nodes (pN1mi and pN2mi) may not necessarily lead to an upstaging of the tumors and to an indication to adjuvant treatments (5). In another study Rena *et al*. also found that the presence of ITC or nodal micrometastases (pN1mi) did not influence disease free and overall survival (6).

The prognostic role of micrometastases in N2 and N3 nodes of clinical N0 tumors has been evaluated less frequently. Herpel *et al*. observed that occult metastases in N2 nodes were associated with a reduced survival, data that were confirmed by the results of the CALBG 9761 trial (7,8). The role of nodal micrometastases has been recently re-assessed by Garelli *et al*. in a study analyzing a group of 982 surgically-treated patients with stage IIIA-N2 NSCLC, 352 of whom had been submitted to neoadjuvant treatments (9). In this study residual microscopic N2 disease was observed in 32% of the patients, and did not have a significant influence on long-term survival. In comparison to macroscopic N2 disease, microscopic N2 involvement was associated to a significantly better prognosis (39% *vs*. 21% 5-year overall survival and 36% *vs*. 18% disease-free survival). Interestingly, in this study adjuvant treatments in patients with microscopic N2 disease had a detrimental effect and were associated with a lower long-term survival. The results of the study by Garelli *et al*., although potentially conditioned by a lack of randomization and by the heterogeneity of pre- and postoperative adjuvant treatments, confirm the need to raise awareness on the role of nodal micrometastases in lung cancer staging and prognosis, and to wonder whether patients with microscopic nodal involvement should be staged and treated in the same way as patients with macroscopic nodal metastases.

In fact, a different prognostic impact of microscopic and macroscopic N2 involvement was also demonstrated in previous studies based on a smaller number of patients. Meacci *et al*. observed in a group of 40 patients that the persistence of nodal micrometastases following induction treatment was associated with a significantly better prognosis in comparison to macroscopic N2 disease (10). Similarly, Cerfolio *et al*. also observed that the presence of microscopic N2 residual disease after induction treatments was associated to a relatively better prognosis (11). Dooms *et al*. found that stage IIIA patients with residual microscopic N2 disease after induction chemotherapy (defined as less than 10% nodal involvement) had a 43% survival after surgery, similar to that of patients with complete nodal clearance and significantly better than the survival of patients with persistent macroscopic N2 disease (0%). However, these Authors also observed that in patients with microscopic or absent residual N2 disease other factors had a significant prognostic role, as the reduction of PET scan SUV max of the primary tumor following chemotherapy, and that a cut-off value of 60% in SUV max decrease allowed to further stratify the patients according to their prognosis (12).

Other issues are of paramount importance when analyzing the role of nodal micrometastases in patients with lung cancer. An essential point concerns the techniques used in the detection of micrometastatic involvement. In fact, in this setting the use of standard hematoxylin-eosin staining is associated with a relatively low detection rate. Several reports have shown that the use of immunohistochemistry (IHC) analysis significantly increases the detection rate of occult micrometastases (7). Molecular techniques as polymerase chain reaction (PCR) for p53 and K-ras and reverse transcriptase polymerase chain reaction for CEA, MUC1, CK7, CK19, VEGF and other targets have also been used (3,7,13-15). Verhagen *et al*. re-assessed the lymph nodes of patients who had had tumor recurrence after surgery and observed a higher prevalence of micrometastases when using serial node sectioning and immunohistochemistry (16). In another study by Herpel *et al*. the use of serial sectioning of the lymph nodes and immunohistochemical staining with keratin and epithelial markers led to the detection of micrometastases in 48.2% of the patients analyzed, with a subsequent upstaging in 20.5% of them. One significant limitation to the diffusion of a more complete analysis of the lymph nodes and immunohistochemical analysis are the time and costs required. According to Herpel *et al*. a selective approach focused on N2 nodal stations could be an adequate compromise in order to improve nodal staging and limit the costs (7).

Other points may also be noteworthy, as the histology of the primary tumor. Roh *et al*. suggested a relationship between micropapillary adenocarcinoma and nodal micrometastases, since in their experience stage I patients with micropapillary adenocarcinoma had a higher incidence of microscopic nodal involvement in comparison to other histological subtypes. Rena *et al*. also observed a higher incidence of micrometastases in patients with adenocarcinoma (6). Another interesting issue concerns the specific molecular and morphological differences that characterize nodal micro- and macrometastases, related to phenotypic changes that happen in cancer and stromal cells during the process of transformation from microscopic to macroscopic metastases. A study by Aramaki *et al*. showed

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that dynamic microenvironmental changes happen during the transformation from micro- to macrometastases with epithelial-mesenchymal transition of cancer cells and structural changes in stromal cells. A lower microvessel density was also observed in micrometastases. On the basis of such findings the transition between micro- and macrometastatic nodal involvement may not be considered as a mere growth of tumor tissue but rather as distinct phases of the process of metastatization (17).

In conclusion, these points raise the issue whether time has come to reconsider the role of micrometastases in the current staging criteria. However, in the International Association for the Study of Lung Cancer (IASLC) recommendations for the forthcoming 8th Edition of the TNM classification of lung cancer other parameters are suggested for due consideration, as the location and number of stations involved (single versus multiple nodal stations) and the presence of skip metastases (18). Nevertheless, considering the trend towards a more personalized approach of cancer treatment, the definition of the role of micrometastatic nodal involvement certainly deserves additional investigation, in order to more accurately stratify the tumors according to prognostic parameters. Standardization of the diagnostic approaches for the identification of nodal micrometastases and planning of further studies are therefore warranted to clarify the role of micrometastatic nodal involvement in lung cancer.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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