Lymph nodal micrometastases in NSCLC: where do we stand?

“...various authors have been trying to elucidate the role of microscopic tumoral foci, whose identification lies beneath the power of resolution of common pathological techniques.”

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NSCLC remains the first cause of cancer-related death worldwide. Prognosis depends mainly on pathological stage. However, even in the cohort of early stage NSCLC, a high percentage of patients would experience relapse and eventually die owing to recurrent disease. For instance, overall survival for stage Ia according to seventh edition of tumor node metastasis (TNM) staging system (namely a tumor whose major diameter is <2 cm, without lymph nodal metastases) has been shown to be 82% [1]. In order to disclose the factors affecting survival in early stage lung cancer, various authors have been trying to elucidate the role of microscopic tumoral foci, whose identification lies beneath the power of resolution of common pathological techniques.

The role of lymph nodal micrometastases has been thoroughly studied in the field of breast cancer. The International Breast Cancer Study Group underlined the role of micrometastases in ipsilateral axillary nodules in determining early relapse [2]. When it comes to NSCLC,

the concept of micrometastasis has been addressed since the nineties. In particular, Izbicki and coworkers evaluated the incidence and prognostic influence of micrometastases [3]. In a series of 93 patients with pathological N0–N1 resected NSCLC, the revision of the specimens with employment of immunohistochemistry (IHC) managed to identify 29 patients with micrometastatic foci in mediastinal lymph nodes (LN; 2 mm or less). Those patients then displayed a survival pattern very similar to pN2 patients. This study, besides confirming the role of occult lymph nodal malignant clusters, underlined the role of IHC. In particular, IHC is able to identify even a single cell within a slide obtained from a lymph node. Unfortunately, although the role of bigger clusters (>0.2 mm) proved to have some prognostic impact, the role of single neoplastic cells is far less certain. In order to evaluate the impact of IHC in the review of lymph nodal specimens from 49 T1–2N0 patients, Nicholson and coworkers employed a simple algorithm:

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• immunohistochemistry
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three almost consecutive sections were taken from five lymph nodes (two from the hilar and three from the mediastinal bunch), the median one was then stained through a broad spectrum antikeratin antibody [4]. IHC provided five positive cases. Two turned out to be false-positive cases, due to cross-reaction with intralymphatic mesothelial cells. In the remaining three cases, neoplastic cells were found also in the two adjacent sections by standard hematoxylin and eosin (H&E) staining. Those micrometastases failed to determine differences in prognosis of the patients. The authors reckon that IHC adds little to standard examinations, unless serial sectioning of the lymph node is provided. Up to now, the term micrometastasis should be limited to tumoral deposits of 0.2 mm in diameter or less, as defined by the American Joint Committee on Cancer [5]. Hence, from a practical point of view, when dealing with micrometastases, maybe the most important factor is the number of slides to be obtained from an harvested lymph node. Theoretically, if we endorse the aforementioned definition, we should perform (at least) a slice every 200 μm . If then we apply this to all the lymph nodes removed during a standard lymphadenectomy, a huge number of slides would then be produced, thereby bringing about an abrupt increase in overall workload and costs. To cope with this burden, given the cost of IHC staining, peculiar procedures had been developed in order to identify the lymph node more likely to be involved by neoplastic spread, which should therefore undergo more careful evaluation. Basing of previous experiences with other cancers, such as melanoma, a reliable and reproducible method for identifying the sentinel lymph node has been sought with interesting, albeit very limited results [6]. The main criticism arises from the high variability of lymphatic drainage of the lung, which could produce false-negative results.

Nonetheless, LN micrometastases remain a major issue. A large prospective study was able to clarify the importance of both micrometastases and IHC. In the CALGB Trial 9761, a total of 193 completely resected cT1–2N0 patients were examined [6]. After H&E, the specimens were re-examined with IHC staining, which unraveled 28 occult metastatic foci, otherwise overlooked by standard staining, thereby upstaging 11 patients. Skip metastases were seen both by H&E and IHC, in 12 patients.

Another issue is represented by the real incidence of occult metastases (OM). In CALGB 9761 OM incidence, as determined by IHC in lymph nodes was 3.47%. The authors underline that there is a wide range of incidence among various studies, probably due to subjective and objective causes, such as the inability to distinguish pivotal cellular characteristics of the cells has been dyed by IHC (i.e., nuclear characteristics of malignancy). Then two critics may be drawn by these early studies: the possibility of inaccuracies when dealing with small foci and the high variability of lymphatic drainage of the lung, which would need a thorough evaluation of all the regional nodes, providing at least a section of the node every 200 μm , hence rising the costs. Nonetheless, more recently, in a quite larger experience, IHC was hugely employed to identify OM to intrathoracic lymph nodes, bone marrow and pleural fluid [7]. Occult LN-metastases were found by IHC in 130 out of 580 pathological N0 patients. This subclinical, occult involvement of LN implied a worse prognosis, both in terms of disease free and overall survival. As a consequence, we must manage to find presurgical characteristics which may help us identify those subsets of tumors more likely to give rise to micrometastatic foci. The introduction of positron emission tomography has completely changed the approach to NSCLC staging and therapeutic approach. In particular, besides identifying nodal metastases during preclinical work up, it has been shown that, also in case of clinical N0, the presence of occult lymph nodal metastases may be predicted by the metabolic features of the primitive tumor. In a recent study, Kim and coworkers showed a strong correlation between maximum standardized uptake value, metabolic tumor volume and total lesion glycolysis and the incidence of occult nodal metastases, in a group of 63 patients [8]. Occult LN-metastases, unforeseen by preclinical workup, were found in 19% of surgically resected cN0 patients. The authors underlined that those patients whose maximum standardized uptake value was 8.8 or more, metabolic tumor volume was 18.8 cm^3 or more and total lesion glycolysis was 88.4 or more, were more likely to present occult LN-metastases. In very recent years, new metabolic parameters have been evolving, which may help to identify those patients with occult LN-metastases. Those indexes, such as entropy and coarseness, are meant to describe the very texture of the

tumor and are probably linked to intratumoral necrosis, microvessel density and other factors that well relate with neoplastic behavior [9]. With the support of those data we might identify subgroup of patients more prone to present subclinical metastases and even micrometastases, thus allowing us to largely apply pathologic techniques such as serial sectioning and IHC onto a specific cohort of subjects, who may deserve a more thorough pathological workup.

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