Commentary

Impact of lymph node occult metastases in stage I non-small cell lung cancer (NSCLC): what is the evidence?

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With the improvement in imaging techniques, and the development of screening protocols for lung cancer, a growing number of patients are expected to be diagnosed with early stage non-small cell lung cancer (NSCLC). The landmark National Lung Screening Trial, gives us a hint: out of 1,060 new cases of lung cancer diagnosed in patients undergoing annual low-dose chest computed tomography screening and 941 cases diagnosed with chest radiography, the proportion of stage I lung cancers was respectively 50% and 31% in the two groups (1). Early-stage lung cancer is also the main focus for the development of minimally-invasive surgical approaches, which constitutes one of the most important challenges of lung cancer surgery over the last years (2). However, despite these improvements in diagnosis and treatment, the outcome remains unpredictable, and patients with stage I NSCLC still experience a 30% risk of recurrence after a curative resection (3).

Given these unsatisfactory survival rates, many researchers have looked for possible factors that could help to predict the behaviour of resected tumour, in order to select those with a worse prognosis and consider the benefit of an adjuvant treatment.

Some of them have focused on clinical parameters, such as carcinoembryonic antigen (CEA) serum levels (4), standard uptake value (SUVmax) in positron emission tomography (5), or performance status (6); others studied histopathologic characteristics such as histological differentiation, vessel and pleural invasion (7,8); lastly, the use of molecular parameters, such as gene expression profiles (9) or epigenetic modifications has provided intriguing results (10).

However, another interesting approach is to look for the presence of occult metastatic tumour cells. In fact, a possible explanation for these high rates of failure might be the presence of occult micro-metastatic sites that remain undetected by standard staging methods, already present systemically at the time of surgery, suggesting that there is an underestimation of the true tumour stage. According to this hypothesis, various studies have been conducted to investigate the presence of occult tumour cells in the pleural lavage (11), peripheral blood (12), bone marrow (13,14) and in the lymph nodes (LNs) (15-18) of patients with NSCLC.

In contrast to the other sites, such as the bone marrow, in which the presence of occult micrometastases (OMs) has not proved its value in predicting survival, various studies have found an association between the presence of OMs in LNs and worse survival.

Passlick *et al*. in 1994 found a significant survival difference in 11 patients out of 72 (15.2%) with completely resected, node-negative NSCLC who had positive LNs to immunostaining with a monoclonal antibody (Ber-ep4) directed against glycoproteins of epithelial cells (15). Similarly, in 2002 Osaki *et al*. analysed LNs of 115 patients with completely resected stage I NSCLC using immunohistochemistry (IHC) with the biclonal anti-cytokeratin (CK) antibody AE1/AE3, and found a positivity in 32 (27.8%) patients, which showed a worse prognosis in both univariate and multivariate analyses (16).

In 2003, Yasumoto *et al*. published the results of a prospective multicenter trial enrolling 351 patients with stage I to IIIA NSCLC from 15 Japanese Institutes. The hilar and mediastinal LNs of 216 patients with stage I NSCLC were stained immunohistochemically with the

same anti-CK antibody AE1/AE3. CK-positive cells in the LNs were detected in 34 (15.7%) out of 216 patients. The patients with CK-positive cells in the LNs had a poor prognosis in both univariate (P=0.004) and multivariate (P=0.018) analyses (17).

Another similar trial was conducted by the American College of Surgeons Oncology Group in 2011 (the ACOSOG Z0040 trial) (18). In this study, 1,047 patients with resectable stage I to IIIB NSCLC were treated with surgical resection and systematic LNs sampling or dissection. LNs of 130 (22.4%) out of 580 patients with histologic N0 disease resulted positive after analysis with CK IHC staining. Again, a statistically significant difference in both overall survival (OS) and disease-free survival (DFS) was found in patients with positive LNs. However, neither the location of IHC positivity within the nodes, nor the total number of OMs-positive LNs, seemed to be associated with a significantly worse OS. Moreover, when dividing by stage, only patients with stage IB and OM-positive LNs showed a statistically significant survival difference, in contrast with patients with stage IA, although this might be due to the different sample size of LN-positive tumours (75 in stage IB patients *vs.* 43 in stage IA).

Recently, Martin *et al*. published "Detection of Occult Micrometastases in Patients with Clinical Stage I Non-Small-Cell Lung Cancer: A Prospective Analysis of Mature Results of CALGB 9761 (Alliance)" (19). Cancer and Leukemia Group B 9761 is a prospective, multicenter trial conducted to test the hypothesis that detection of OMs by IHC or real-time polymerase chain reaction (RT-PCR) in histologically negative LNs is associated with poorer survival among patients with stage I NSCLC.

Between 1997 and 2002, 502 patients with suspected clinical stage I NSCLC were enrolled at 11 institutions in North America. They underwent complete surgical resection and mediastinal lymphadenectomy. Primary tumour and LNs were assayed for OMs using IHC for CK (AE1/AE3) and RT-PCR for CEA.

Three-hundred and four patients (61%) had pathologic stage I NSCLC and were included in the final analysis. IHC resulted positive in LNs of 41 (14%) patients (42% in N1 position and 58% in N2 position), whereas RT-PCR for CEA was positive in LNs of 176 (69%) patients. Neither OS nor DFS were associated with IHC or PCR positivity; however, when separating by LNs position involved, patients who had IHC-positive N2 LNs had statistically significant worse OS (hazard ratio, 2.04, P=0.017) at multivariate analysis.

The results of this last important and well-conducted trial, in the context of existing literature, allow us to make some considerations. First of all, as stated by the authors, CEA probably isn't an adequate marker for NSCLC. The high percentage of patients with positive LNs is difficult to justify in the absence of an association with survival, considering that only 90% of primary tumours tested in this study were positive for RT-PCR.

IHC for CK AE1/AE3, on the other hand, is a commonly employed technique by pathologists for detection of OMs in tissue samples. It remains to understand what is the clinical impact of OMs-positive LNs detected by IHC and consequently, if there could be a role for this assay to be used in routine practice, in the setting of early stage NSCLC.

This study, in contrast with others, did not find a statistically significant survival difference when globally considering patients with IHC-positive LNs compared with IHC-negative patients. This might be due in part to the relatively smaller sample size compared with the ACOSOG Z0040 trial, or to the different choice of CK makers used in the two studies.

Another difference between the two trials is the more homogeneous population of clinical stage I patients of the CALGB 9761 trial compared to the patients of the ACOSOG Z0040 trial, that comprised all resectable, previously untreated NSCLC patients who resulted node-negative at pathologic staging, thus comprising also T3N0 patients, and patients who were suspected clinically to be N1. The difference between these two populations might have contributed to the different outcomes observed.

The finding that only N2-positive, and not N1-positive LNs correlated with worse survival compared to LNs negative patients seems to suggest that, although OMs in LNs have not the same clinical impact as overt LNs metastases, they become more relevant when more distal LN stations are involved. However, the ACOSOG Z0040 trial did not find the same association, and other studies did not analyse the differences between these two sub-categories.

To conclude, we can say that available literature seems to support an association between OMs detected in LNs with IHC and worse survival; however, the impact of this association is not clear, yet. The two most recent and largest prospective trials don't provide enough evidence to state that this factor is more important than others investigated in predicting survival in early stage NSCLC, although it may account in part for the relatively high rates of relapse

in completely resected patients. Further studies are needed to better define the clinical impact of OMs in LNs and if in the future IHC might be of use in selected cases to identify patients with worse prognosis, who may benefit from adjuvant treatment. The clinical variability of early stage NSCLC however, could most likely be due to a combination of different prognostic factors, such as histopathological features, gene expression profiles, epigenetic modifications or soluble tumour markers.

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Footnote

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