

Tracking occult pN2 disease after mediastinal dissection in early stage lung cancer

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Lobectomy with mediastinal lymph node dissection represents the standard treatment approach for patients with resectable non-small cell lung cancer (NSCLC). Defining the stage of a malignant disease is crucial for planning therapy, estimating prognosis and for studies comparison (1). In the latest 3 decades, it has been clearly established that the extent of lymph node involvement in patients with NSCLC is the most important prognostic factor, influencing the therapeutic strategies (2-4). In this regard, N2 disease implies a therapeutic 'shift' from radical curative approaches to multidisciplinary treatment strategies including both chemotherapy and radiotherapy (5). Thus, the accurate staging of a clinical mediastinal N0 disease is crucial for patients and clinicians dealing with loco-regional spread of NSCLC.

To date, a series of accumulating evidence has demonstrated that extensive mediastinal lymph node dissection is prognostic, given that patients undergone more than 11-16 mediastinal nodes live significantly longer (6,7). Nevertheless, while such independent prognostic impact is accepted for node-positive disease, its role for stage I tumors is debatable. Thus, in community based hospitals, the benefits of complete mediastinal lymph node dissection are unclear for such patients (8), although small lung cancers (less than 2 cm in size) show hilar and mediastinal

nodal involvement in more than 20% of cases (9). A series of studies have demonstrated a great anatomical variability in lung lymphatic system, which may represent a possible explanation for the sometimes unpredictable pattern of lymphatic metastatization observed in lung tumors.

Usually, inter-lobar lymph nodes are the site with the greatest incidence of intra-parenchymal lymphatic metastases. From an anatomic perspective, these lymph nodes drain into the hilar nodes and then to the mediastinum. In less frequent conditions, an aberrant drainage pattern bypasses the intrapulmonary and hilar lymph nodes and proceeds directly to the mediastinal nodes, thus resulting in skip metastases, with an incidence rate reported from 18% to 38% in different studies (10,11). Data from anatomic, pathologic and clinical studies indicates that mediastinal drainage tends to be lobe dependent. About 70% of right upper lobe tumors and about 95% of left upper lobe tumors involve just station 2-4 and 5-6, respectively, while more than 50% lower lobe tumors involve only station 7. Thus, the location of the primary tumor may help to identify the mediastinal lymph node stations that are more likely to be involved in case of N2 disease, especially when a single metastatic site is present (11,12).

Although nodal staging of NSCLC should be as accurate as possible, the extent of mediastinal lymph node assessment

during surgery is controversial and a clear consensus has not yet been reached. Different techniques are applied, ranging from simple visual inspection of the unopened mediastinum to an extended bilateral lymph node dissection.

According to the European Society of Thoracic Surgeons (ESTS) definition of systematic nodal dissection (SND) released in 2006, it is recommended to remove all mediastinal tissue containing the lymph nodes within anatomical landmarks, in association with intrapulmonary and hilar nodes. The ESTS guidelines suggest a minimal excision of at least 3 mediastinal nodal stations, always including the subcarinal nodes. A removal of at least 6 lymph nodes from hilar and mediastinal stations is recommended to define nodal staging accurately and to determine pN0 status (13). After these guidelines were released, a series of evidences emerged suggesting that the crucial impact upon staging and prognosis was given by nodal zones and the number of resected lymph nodes as well, but with a higher number of the nodes which are actually required to do not negatively affect outcome (6,7).

The article by Bille *et al.* (14) reports the incidence of occult N2 disease in clinical Stage I lung cancer patients who had undergone lobectomy and SND. Overall incidence of occult N2 disease is 9%, without differences between patients who had just 2 nodal stations removed and patients who had 3 or more nodal stations removed (8.3% *vs.* 9.2%, respectively). Moreover, no statistically significant differences in term of pN2 involvement between T1a and T1b tumors have been reported. In this series, median and 5-year overall survival (OS) is reported to be 75.5 months and 61%, respectively, with no differences between patients with 2 and 3 or more nodal stations resected. As expected, pN0 patients presented an increased median and 5-year OS compared with pN1 and N2 patients (83.7 months and 65.7% for pN0, 48 months and 43.7% for pN1 and 37.9% and 36.4% for pN2, respectively). The 3-year cumulative incidence of recurrence was higher in pN2 compared with pN0/N1 population (49.4% *vs.* 19%, mainly as distance recurrences). According to these results, the authors recommend a systematic mediastinal nodal dissection to be performed even in early, clinical stage I NSCLC. Although the retrospective nature of the analysis, these data are in line with those previously reported, which clearly indicate that the clinical definition of stage I disease simply obtained on the basis of imaging (all patients in this series underwent CT and PET scan), does not allow surgeons to appropriately refine the extension of N2 nodal dissection (in this series, 16% of pN2 patients had mediastinal lymph

node metastasis beyond the theoretical lobe-specific lymphatic drainage). As correctly reminded, although specific biologies and genomic signatures, or featured histologies are more frequently associated to N2 disease, we do not have right now enough evidences to selectively sample N2 lymph nodes, even in stage I disease.

Additional issues in the Bille *et al.* paper deserve to be considered. The surgical technique employed for nodal dissection in this retrospective and single center series was not the same for all patients. About half of the patients had just 2 mediastinal nodal stations removed, while the other half had 3 or more mediastinal stations removed, with a median number of 4 overall, without differences in the incidence of pN2 disease, as reported in additional series (12,15,16). That opens the issue regarding the decision of surgeons in clinical practice in the operative room on how much to extent the nodal dissection, and upon which factors this decision is taken.

In addition, the fact that pN2 disease does not follow a lobe-specific pattern in >15% of patients (with a particular regard to upper lobe tumors) implies that if a lobe-specific lymphadenectomy is routinely performed, a number of patients (in the range of 10% to 20%) might be potentially under-staged, as reported in other series (12). And considering that patients with mediastinal involvement are those who mostly benefit from adjuvant chemotherapy (17), and that the therapeutic benefit of such strategy is really narrowed, with a number-needed-to-treat of 20–25 (i.e., 20–25 patients to be treated for one to benefit), we risk to deny the treatment right to those patients who may benefit the most (18). A further consideration is required about skip metastases, which, in this patients' series, occur in 38% of patients, with no prognostic differences *vs.* patients without. These data underlines that lymph-node sampling, even with negative N1 frozen section, does not guarantee to have a complete dissection.

Lastly, postoperative morbidity and mortality is no longer to be considered an issue for clinical practice. The data reported by Bille *et al.*, together with those reported by Darling *et al.* referring to the ASOCOG Z0030 study, clearly indicate that postoperative morbidity and mortality do not significantly differ between patients undergone systematic sampling and mediastinal nodal dissection, as well as no differences emerge in survival curves (10). According to these data, it appears that a systematic nodal sampling or lobe-specific lymphadenectomy represents a convenient opportunity if surgeons want to reduce operating time of approximately 30 minutes, are we really able to affirm that this represent a real clinical advantage?

Thus, although its retrospective and mono-institutional

nature with all related biases, the study reported by Bille *et al.* once again strengthens that lymph node spread cannot be considered as predictable as lobe-specific drainage anatomy would explain, and that, even if preoperative imaging is accurate (i.e., CT and PET scan) the risk of pN2 disease is not negligible, even in stage I disease. With these perspectives, SND is still strongly recommended in all NSCLC patients candidate to curative surgery, and it represents the highest chance to properly investigate the mediastinum, achieve R0 resection and select those patients who are most likely to benefit from adjuvant treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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