

# Unless I see, I will not believe

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*Comment on:* Bille A, Woo KM, Ahmad U, *et al.* Incidence of occult pN2 disease following resection and mediastinal lymph node dissection in clinical stage I lung cancer patients. *Eur J Cardiothorac Surg* 2017;51:674-9.

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Lymph node status is currently one of the most important prognostic factors for the management of non-small cell lung cancer (NSCLC). According to the current guidelines (1), in case of clinical N2 or N3, patients are not candidate to surgery and they are referred to neoadjuvant or definitive chemotherapy and/or radiotherapy, meanwhile in case of clinical N0/N1 surgery is the treatment of choice. Nonetheless, the definition of both N1 and N2 is still based only on merely anatomical criteria and they therefore enclose a wide range of different pathological situations with different prognosis (2). Moreover, the extent of lymph-node dissection has been debated, but to date no strong evidences are available to support one technique or another.

The European Society of Thoracic Surgeons (ESTS) has proposed the current standard for systematic lymphadenectomy in case of lung resection for NSCLC (3), which encompass to harvest lymph-nodes from at least three mediastinal stations, always including sub-carinal lymph-nodes. Nevertheless, some less extensive techniques for lymphadenectomy have been proposed, namely lymph node sampling, which accounts for resection of only macroscopic and focal lymph nodes, and lobe-specific lymphadenectomy, which is the resection of only stations which are considered as the natural drain for that lobe (4,5).

Bille and his colleagues (6) retrospectively analysed a wide cohort of clinical early stage NSCLC treated with lobectomy, segmentectomy or wedge resection and systematic mediastinal lymphadenectomy in a single centre

focusing on the pattern of lymphatic spread and long-term outcomes. They report 146 cases among 1,667 (9%) of occult N2, of which 16% had a metastasis in a “non-lobe specific station”. Authors conclude that systematic lymphadenectomy should be carried out also in patients who have a clinical N0 in order to avoid an understaging and a R1 resection.

Similar conclusions were drawn by Riquet (7), who found an incidence of pN2 as high as 7.7% on the right side and 8.9% on the left side in patients with a clinical node negative early stage NSCLC of which 14.5% and 27.8% respectively did not follow lobe specific lymphatic drainage. In particular, accordingly to Asamura (8), the authors highlighted a particular propensity of left lower lobe tumors to metastasize to the left lower paratracheal station (4L), which is not considered to be lobe specific. Incidence of unexpected N2 might be reduced by a careful preoperative staging which may include invasive procedures such as EBUS, EUS or mediastinoscopy; Obiols (9) reports his institution’s experience finding a persistent 5% rate of unknown N2 after mediastinoscopy, but these patients had a longer 5-year survival compared to other reports of occult N2. Nevertheless, an American prospective study (10) concludes that invasive staging procedures for clinical node negative patients should be avoided as poorly cost-effective, even though the authors suggested the possibility to understand the possible neoplastic lymph node spreading based on tumor localization, histological features and PET-

CT uptake and therefore guide preoperative staging and intraoperative lymphadenectomy.

Concurrently, a recent meta-analysis of available randomized trials (5) comparing outcomes of mediastinal lymphadenectomy and lymph node sampling during surgery for NSCLC concludes that current evidences are not reliable enough to trustworthily assess the impact of this technique on survival, despite the significant longer survival of patients undergoing mediastinal lymph-node dissection. Furthermore, Matsumura and his colleagues claim that systematic lymph-node dissection should be always carried out also in case of segmentectomy, but it might be avoided only in case of pure GGOs lesions (11). Although some authors support the idea of a routinely lobe specific lymphadenectomy (12,13) in selected patients, its advantages are mainly related only to a shorter operative time, while there are no consistent data supporting an increased rate of postoperative morbidity related to the extent of lymphadenectomy (5,12,14). Nevertheless, all the authors agree that a systematic lymph-node dissection should be offered in all cases if completeness of the resection is in doubt.

Minimally invasive surgical technique is nowadays one of the most popular trend topic in thoracic surgery. Indeed, video-assisted thoracic surgery (VATS) has been gaining a wide consensus, as it allows similar oncological outcomes, with lower postoperative pain and a better view and exposition of anatomical structures compared to open technique (15). Although several single-institution reports find comparable upstaging after VATS compared to open techniques (15,16), the only randomized trial available on this subject concludes that thoracotomy led to a higher upstaging rate in clinical early stage lung cancer (17). As a matter of fact, minimally invasive lymphadenectomy might be challenging and it requires skills, experience and anatomical knowledge. In particular, access to the paratracheal region on the left side can be very difficult also for experienced surgeons. Furthermore, not all the approaches are ideal to perform a correct lymph-nodes dissection. For instance, uniportal sub-xiphoid VATS technique has recently been proposed for lung resection, but some authors stressed the difficulty to perform a correct lymphadenectomy, with special regards to subcarinal station on the left side (18-20).

Since the introduction of fluorodeoxyglucose positron emission tomography (FDG-PET), clinical staging has become more accurate by the exclusion of N or M positive patients that were not positive at CT scan; on

the other hand, the number of false negative can reach a disappointing 18% (21). Inspired by the experiences with melanoma and breast cancer, some authors proposed the use of sentinel lymph-node technique in lung cancer with different methods in order to verify its involvement and take real time decisions on the most suitable surgical treatment and extent of lymphadenectomy. Unfortunately, results are highly inconsistent and both specificity and sensitivity did not seem to be as reliable as it was hoped (22). Furthermore, the anatomy of the lymphatic circulation of the lungs is not constant and hilar stations can be bypassed so that lobes might have a direct drainage to mediastinal nodes; this situation is well-known as skip metastasis (23). Several reports confirmed that skip metastasis have a better prognosis compared to those who have both hilar and mediastinal metastasis (24,25). Although these evidences have not been yet prospectively validated and incorporated in the TNM staging system, this is another important element to confirm the paramount influence that a careful systematic lymph-node dissection might have on patients' therapeutic path and therefore on their prognosis.

Concurrently, recent advances in molecular pathology highlighted that tumor spread might have always been under-estimated due to the dimension of the metastasis themselves. Hence, some authors documented the presence of micro-metastasis, which are defined by the UICC as single or small number of tumor cells that are 0.2 mm in dimension and as a tumor deposit <2.0 mm, but greater than 0.2 mm in dimension (26). Although a standardized method has not been validated so far, the use of polymerase chain reaction (PCR) has been proposed to discover micro-metastasis in lymph-nodes (27). With the use of these more accurate methods, the presence of micro-metastasis in otherwise node negative early stage NSCLC is significantly associated with a worse survival and a shorter disease-free interval. These results have been confirmed also in a recent meta-analysis (28), but still need a prospective confirmation and a standardization of the technique in order to be validated.

Recently, two trials (29) suggested the use of radiotherapy for the definitive treatment of early stage lung cancers advocating a less invasive approach with less morbidity and mortality; their results were criticized for the inclusion criteria and conclusions that were inconsistent. We can speculate that, based on the results of the study of Bille and co-authors, if radiotherapy was used as definitive treatment, 16% of patients with clinical node-negative early stage NSCLC would have received an under-treatment and their

N positive status would have remained unknown leading to a probable early disease recurrence.

In conclusion, these data confirm the paramount prognostic power of lymph-node status and the necessity of a careful and precise definition, which is only possible by a radical yet systematic dissection of mediastinal tissues. In the era of minimally invasive surgery, every effort must be done to enhance and improve the quality of instruments and surgical technique as well as training of junior surgeons to reach these results. Concurrently, multicentric randomized trials (30) are urgently needed to confirm with large and prospective cohort of patients the role of lymphadenectomy.

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### Footnote

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

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