



The importance of correct regional lymph node removal as part of surgical treatment of non-small cell lung carcinoma: could it be a therapeutic strategy?

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Surgical treatment including lymphadenectomy combined with adjuvant chemotherapy (aCT), and in case of an epidermal growth factor receptor (EGFR) mutation, adjuvant tyrosine kinase inhibitor, is the treatment of choice for operable patients with early stage or locally advanced (stage IB–IIIA) non-small cell lung cancer (NSCLC) (1). An appropriate lymphadenectomy permits more precise staging as well as better survival. However, no consensus has been reached on the extent of intraoperative mediastinal lymph node dissection necessary to adequately stage the disease or benefit survival outcomes.

The current article by Li *et al.* (2) reports that the number of harvested regional lymph nodes (RLNs) not infiltrated by tumor cells (pN0) can affect survival outcome of operable patients at stage IIA NSCLC. Their key finding is that a higher resected lymph node count is associated with better survival, and that the more tumor negative nodes dissected, the more significant the improvement in survival. But how does lymphadenectomy of nodes not infiltrated by tumor cells positively affect survival? The

exact nature of the proposed relationship remains unclear. As the authors have pointed out, it seems compelling to assume that incorrect staging due to missed metastasis in the form of free nucleic acids or even early microscopic dissemination (micrometastasis or isolated tumor cells), likely to be missed by standard histopathological evaluation, is one of the reasons as to why the removal of draining lymph nodes is beneficial to the patient's prognosis. In other words, cancerous nodes have been resected unknowingly, resulting in a more radical resection and better staging. One could thus debate whether there is a true benefit on survival when nodes are supposedly free from metastasis, or that lymphadenectomy is merely useful for proper staging and thus better treatment [Fisher view (3)]. After all, accurate pN0 diagnosis depends on the number of lymph nodes examined, increasing the negative predictive value, hence the better survival outcome when the patient is diagnosed as truly pN0. The Fisher view can also be corroborated by the systematic review and meta-analysis of Huang *et al.* (4) where they found no difference in overall survival, local

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recurrence rate, and distant metastasis between mediastinal lymph node dissection and sampling, implicating that dissection is not required for better survival, but accurate staging might be.

For accurate staging, adequate removal and histopathological examination of N1 *en bloc* resected lymph nodes is important and should require a standardized approach as Raymond *et al.* (5) has suggested, where they dissected lung specimens centrifugally from the bronchial stump with all lymph nodes at the segmental and subsegmental bifurcations removed. When combined with proper mediastinal lymphadenectomy, this approach is likely to maximize accuracy of the pathologic N descriptor classification and thus also improves treatment decision making.

Besides the inevitable question we all seek answers to, there are several issues in the article by Li *et al.* (2) worth mentioning. The study involves a relatively large cohort but is affected by selection/recall bias. The number of patients excluded from analysis whose number of RLNs removed was unknown (n=220) is high compared to the number of patients included in the 'no RLN removed' group (n=173), and could potentially have a significant influence on their results. Furthermore, it would have been interesting to report the time-to-recurrence and recurrence location in addition to lung cancer specific survival to assess how effective the treatment was. In addition, as the authors righteously pointed out, not only the number of RLNs, also (number of) nodal station(s) has been associated with more accurate nodal staging and better long-term survival (6,7). In the current study, data on nodal station is missing and therefore it is not clear whether a systematic nodal dissection or lobe-specific dissection was performed, according to European guidelines (8). For all is known, only a single station could have been sampled with multiple nodes, indicating poor medical care.

Furthermore, the value of aCT and radiotherapy (RT) in stage IIA NSCLC was discussed. The results of Li *et al.* (2) showed that aCT after resection shows better overall survival than surgery alone and that patients who receive post operative RT have a worse overall survival compared to resection alone. Although these conclusions are interesting, these outcomes are not new. In stage IIA–IIIA NSCLC, aCT after surgery is standard care in case a patient is fit enough, and associated with an absolute survival improvement of 4–5% at 5 years (9). Post operative RT should be considered in case of an incomplete resection (R1) (10). Therefore, it is only to be expected that patients who did not undergo aCT but had an indication for post

operative RT, have worse survival compared to patients who were treated according to the European Society for Medical Oncology (ESMO) treatment guidelines for early and locally advanced NSCLC (11).

In conclusion, it is encouraging to see that the number of lymph nodes evaluated in Li *et al.* (2) has been increasing over the years, indicating adherence to the quality standard for surgical lung cancer treatment, which ultimately will improve the outcome. One must keep in mind though that the biology of the primary tumor also dictates patient outcome and is thus not only influenced by an accurate N descriptor classification. Nevertheless, much work is still needed to unravel the effects of radical lymphadenectomy on survival outcomes and studies like Li *et al.* (2) are valuable contributions.

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