Editorial

Role of intrapulmonary lymph node retrieval for pathological examination in resectable non-small cell lung cancer

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Lymph node (LN) metastasis is a prognostic factor for tumor recurrence and overall survival (OS) in resectable non-small cell lung cancer (NSCLC) patients (1,2). It also affects the decision of prescribing adjuvant or neo-adjuvant systemic chemotherapy or radiotherapy. Current studies and guidelines suggest that systematic LN dissection or sampling should be performed in resectable NSCLC (3,4). It is indicated that mediastinal LN (stations 2–9 or N2) (5,6) should be dissected when performing curative pulmonary resection in order to accurately determine tumor stage. For intrapulmonary LN or N1, stations 10–12 are usually dissected because they are easily identified and collected; however, the dissection of stations 13–14 is quite difficult and requires adequate training (7). A recent study showed that standard pathology practice frequently omitted to examine 60% of intrapulmonary LNs in 90% of lobectomy specimens, and found unexpected LN metastases in 12 % of reported node-negative patients (8). Nodal metastases affect the classification of the case into N2 or N1 disease, which in turn affects treatment strategies, tumor recurrence, and survival. It often happens that in N1 disease stations 13 and 14 are neglected, leading to disease under staging, and lack of prescription of adjuvant therapy. These may contribute to the observation that some of patients with N0 disease develop early tumor recurrence or distant metastases (8).

In the paper entitled "*Impact of Omission of Intrapulmonary Lymph Node Retrieval on Outcome Evaluation of Lung Cancer Patients Without Lymph Node Metastasis*: *A Propensity Score Matching Analysis*" (9), Wang and colleagues retrospectively reviewed 442 clinical early-stage NSCLC who underwent pulmonary resection with systematic LN dissection, pathologically confirmed complete resection and pathologic N0 disease, to test the association between omitting the retrieval of LN from stations 13 and 14 and outcomes [5-year OS and disease free survival (DFS)]. Patients were divided into two groups; the study group (patients whom LN stations 10 to 14 were collected during surgery) and the control group (patients whom LN stations 10 to 12 were retrieved during surgery). They used a matched propensity score analysis to adjust for confounders by indication. The results show that the 5-years OS (89%±3% versus 77%±4%, P=0.027) and 5-year DFS (81%±4% versus 67%±4%, P=0.021) was significantly better when the surgeon collected LN stations 10 to 14. The multivariable analysis demonstrated that intrapulmonary LN 13 to 14 retrieval had a significant impact on OS [hazard ratio (HR), 0.518; 95% confidence interval (CI), 0.298–0.898] and DFS (HR, 0.590; 95% CI, 0.387–0.901). Although the metastatic status of LN stations 13 and 14 in the control group was unknown, it is possible that the omission of the intrapulmonary LN collection might lead to an inferior oncologic outcome. Although intrapulmonary LN dissection was performed by surgeons only in this study, we think that pathologist could play a vital role by dissecting

LNs from lung specimen. The authors were also concerned about this issue and suggested that both surgeons and pathologists handle the intrapulmonary LN dissection after adequate training, and the time required for the procedure was less than 10 minutes (10).

There are some previous studies dealing with intrapulmonary LN examination in NSCLC. Ramirez and colleagues (8) performed a case-control study of a special pathologic examination protocol using thin gross dissection with retrieval and microscopic examination of all LN-like material on remnant NSCLC resection specimens after routine pathologic examination. They retrieved additional LNs in 66 (90%) of 73 patients and found metastasis in 56 (11%) of 514 retrieved LNs from 27% of all patients. There were unexpected LN metastases in 6 (12%) of the 50 node-negative patients. The pathologic stage of 8 (11%) of the 73 patients changed after this special pathologic examination. The time range used for the dissection of the remnant lung specimens was 10–30 minutes. The authors suggested to develop a protocol for dissection and examination of lung resection specimens, performed by surgeons or pathologists to improve LN yield.

Smeltzer and colleagues (11) conducted a prospective cohort study of 110 resectable NSCLC patients to evaluate undissected intrapulmonary LNs from lung resection specimens. They applied a thin-section gross re-dissection protocol to retrieve all material that appeared to be LNs and processed it for histologic examination. They found 25 patients (23%) with additional LNs with metastases. Of these 25 patients, 6 were pN0 after routine pathologic examination. Eleven of the 25 patients had more than 2 additional LNs with metastases. In summary, 6 patients were up-staged (from pN0 to pN1) after re-dissection of the discarded lung resection specimen. Patients with at least one missed metastatic LN had increased risk of death (adjusted HR, 1.4; 95% CI, 0.6–3.7).

Osarogiagbon and colleagues (7) retrospectively reviewed the lung resection specimens over a period of 15 months before and 15 months after the training of the pathologist's assistants on the novel dissection protocol, which included recording the dissection start and end time, and the details of the intrapulmonary LN dissection method. Although there was no difference in nodal stage distribution after using this protocol, they found that the median number of intrapulmonary LNs retrieved increase from 2 to 5 nodes ($P<0.001$) and the 75th to 100th percentile range of detected intrapulmonary LN metastases increased from 0–5 to 0–17 ($P=0.0003$). Osarogiagbon and colleagues (12) re-analyzed the LN dissection arm of the American College of Surgeons Oncology Group Z0030 trial (13) to explore the survival impact in the number of LN dissected in NSCLC patients who underwent pulmonary resection for N0 or nonhilar N1, T1, or T2 disease. The pN category was associated with an increased number of examined intrapulmonary LNs. Patients with pN1 had more non-hilar N1 nodes than those with pN0. Patients with pN0 had better survival with the examination of more N1 nodes. The more intrapulmonary LNs were dissected, the higher was the chance to have a complete nodal staging, and this may achieve the better survival.

In conclusion, for resectable NSCLC patients, adequate intrapulmonary LN dissection should be performed during pulmonary resection or pathologic examination in gross specimen to achieve accurate pathological staging, since this has an impact on adjuvant treatment and survival. Both the surgeons and the pathologists have to consider this and should be encouraged to perform the dissection of intrapulmonary LNs in routine clinical practice of lung cancer surgery.

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Footnote

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

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