Editorial

Controversies of the optimal surgical management for the lymph nodes in non-small cell lung cancer

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Lobectomy with lymph nodal dissection is currently the standard surgical strategy for resectable non-small cell lung cancer (NSCLC). This is largely dependent on the only randomized prospective trial comparing lobectomy with sublobar resections reported by Lung Cancer Study Group in 1995 (1). With regard to the appropriate lymph nodal dissection for surgically resected NSCLC, complete hilar and mediastinal lymphadenectomy, i.e., radical systematic mediastinal lymph nodal dissection, is widely recognized as an essential local management strategy ever since reported by Cahan in 1960 (2). In general, complete hilar and mediastinal lymphadenectomy requires "en bloc" resection of the lymph nodes based on the established anatomical boundaries. It is considered that patients with positive lymph nodal metastases could have a potential risk for the locoregional and/or distant recurrence of lung cancer. Hence, complete lymphadenectomy for NSCLCs plays a pivotal role in that it provides the most reliable information regarding cancer staging and prognosis. In addition, radical lymphadenectomy could reduce the risk of undetected positive lymph nodes which may result in a thorough retrieve of the remnants, and proper delivery of optimal postoperative treatment which may contribute to the survival outcomes (3,4). However, it is still controversial with regard to the actual oncological benefit which the radical lymphadenectomy would provide for.

In this context, how to remove the lymph nodes properly in patients with resectable NSCLC have been widely discussed in the general thoracic surgical community. Several controversies exist with regard to the optimal surgical management of the lymph node for resectable NSCLC. The first is about the concept to decide how to harvest the lymph nodes. Recently, some randomized controlled trials that compared systematic lymph nodal dissection with systematic lymph nodal sampling have been performed (5,6). Although these prospective trials have not demonstrated the definitive survival benefit of systematic lymph node dissection, the current guidelines still recommends systematic lymph nodal dissection for all resectable NSCLC despite the tumor stage or location of the tumor from the point of preventing locoregional recurrence as much as possible after lung cancer surgery (7,8). The second is about the extent of lymph node dissection. Several institutional retrospective studies have recently demonstrated detailed nodal spread patterns in surgically resected early-stage NSCLC (9,10), and lobe-specific lymph nodal dissection has been widely recognized on the basis of these results. Furthermore, previous retrospective studies have suggested that survival and recurrence may be identical between systematic and lobe-specific lymph nodal dissection in early-stage NSCLC (11-13). To elucidate the survival benefit or inferiority regarding the extent of lymph nodal dissection, further study is needed and prospective clinical trial has been conducted for radiologic invasive NSCLC in Japan.

And the third controversy, the topic on this issue, is about a prognostic importance of the number of resected lymph node or positive lymph node number/ratio in patients with NSCLC (14). It is considered that the greater number of examined lymph nodes can reduce the risk of undetected positive lymph nodes, which may contribute to the accurate tumor staging and definite retrieve of remnants,

and subsequent administration of adjuvant chemotherapy to improve survival outcomes. Generally, the number of examined lymph nodes is considered to be a significantly associated with improved survival as shown in breast or several gastrointestinal cancers. Unlike other organ cancers, however, distribution of the lymph nodes is recognized as "station" surrounded by anatomical boundaries in patients with NSCLC based on the IASLC staging rule (15). Hence, the concept of optimal lymph node count prevailed in several organ cancers may somewhat different from that of lung cancer to date. However, the topic on this issue may provide new information for determining the refined N category in the future TNM classification of lung cancer.

In the issue of the *Journal of Clinical Oncology* (*JCO*), Liang and colleagues analyzed the impact of examined lymph node count on precise staging and long-term survival of resected NSCLC using the currently largest data sets from a Chinese multi-institutional registry and the US SEER database on stage I to IIIA resected NSCLC (14). They concluded that a greater number of examined lymph nodes are associated with more accurate node staging and better long-term survival of resected NSCLC. Furthermore, the paper recommended to retrieve at least 16 or more lymph nodes for evaluating the quality of nodal examination or proper stratification postoperatively not only for patients with node positive patient but node negative one. So far, recommendation on the examined lymph node count have not been made in the NCCN guidelines for lung cancer (7), but several retrospective studies have attempted to determine a benchmark of the resected lymph node count (14,16,17). Furthermore, the TNM rules suggest that at least six lymph nodes need to be removed, three from N1 and three from N2 stations. This is the minimum requirement for a diagnosis of N0 when lymph nodes are negative (18). Rigorous examination of the lymph node by the thoracic surgeons would results in more accurate cancer staging and possible survival benefit due to the detection and retrieve of the involved lymph node in patients with NSCLC. Hence, study as for the prognostic importance of examined lymph nodal count will be a new challenge in the thoracic oncology to establish the accurate stage of lung cancer patient, administrate the optimal therapeutic modality and improve the prognosis.

In the field of lung cancer surgery, however, previous analyses on this topic have found somewhat contradictory results (14,16,17,19,20). Several problems exist that should be resolved to discuss this important topic. First, the number of resected lymph nodes would be highly variable from one patient to another, which is relied on the malignant potential of the main tumor and the expected clinical N status (19). Also, extent of the lymph node resection or examined lymph node count would be highly affected by the patient comorbid status (21).

Second, the method used to evaluate harvested lymph nodes needs to be standardized. Usually, when systematic lymph node dissection is performed, the lymph nodes should be dissected en bloc together with surrounding adipose tissue as a lump (15). Ideally, pathologists or surgeons should remove these nodes out as distinct nodes, not as fragments. Otherwise, some of the nodes can be missed without undergoing a pathological assessment (20). It is also reported that missed intrapulmonary lymph node metastasis affect the nodal staging quality gap, which contribute to the poor prognosis (20). More rigorous gross dissection of the resected lung cancer specimens may provide prognostically useful information.

Third, as noted by Liang and colleague, it is interesting to investigate the correlation between the examined lymph node count and the N1/N2 stations based on the 8^{th} N staging. The 8^{th} TNM staging suggests that the combination of location of metastatic nodes, number of involved node (single station versus multiple stations), and absence versus presence of skip metastasis as pN0, pN1a, pN1b, pN2a1, pN2a2, and pN2b may give a more accurate prognosis (15). These classifications require prospective evaluation before being considered for future revisions of the TNM staging system for lung cancer.

The fourth is about the problem of the potential risk in this study; overestimation of unsatisfactory harvesting in patients with a greater number of lymph nodes and underestimation of satisfied lymphadenectomy in patients with a smaller number of resected lymph node (19). This may be a potential bias in this study. To date, systematic lymphadenectomy is accepted as a principle procedure in lung cancer surgery, because the lymph node location can be easily determined on computed tomography (CT) or positron emission tomography (PET). Categorization based on the "station" used in the IASLC staging system is anatomically reasonable from the perspective of a lymphatic pathway from the lung parenchyma through the hilum, mediastinum, and supraclavicular fossa (15). Therefore, in the future, it is necessary to uniform the lymph node counting method to adopt the concept as a new N descriptor.

Finally, we should consider the expected frequencies of pathological nodal involvement in patients with clinically node negative one based on the radiological findings of

the main tumor, which would greatly contribute to the appropriate surgical resection of the lymph node. Because of the refined resolution of thin-section CT scan or the advent of the 18F-fluorodeoxyglucose PET, small-sized or early-stage lung cancer have been detected frequently. Based on the studies of radiological and pathological correlation of lung cancer in Japan (22), we can predict tumor invasiveness and probability of lymph nodal metastasis more precisely on the basis of the preoperative radiologic characteristics. Among them, the presence of a ground-grass opacity (GGO) component, which would represent adenocarcinoma of the lung almost for all, is considered to denote a good prognosis, and in most cases the pathologic features are minimally invasive because of a significant correlation with histologic lepidic growths (23,24). The estimated rate of lymph node metastasis in part-solid lung adenocarcinoma is considered to be about 5% (23,24). Recent studies demonstrated that GGO-dominant tumors are truly localized disease and their pathological features are likely to be indolent, which would be enough with lobe-specific nodal dissection, or may not require nodal dissection in selected cases (11,12). Traditionally, however, a radiologic pure-solid lung adenocarcinoma without any GGO component is assumed to show a highly malignant nature, and postoperative nodal involvement is found in approximately 15% to 20% of clinically node negative cases, even in those with small-sized lesions (23-25). This may be a detection limit in the present day. Therefore, accurate decision for the extent of lymph nodal dissection/resection would be needed in accordance with the tumor invasiveness in reference to the findings on thin-section CT scan or FDG-PET in the future.

At all events, the impact of examined lymph node count on the prognosis would be an important theme that should be addressed intensively in general thoracic surgery. It is still controversial with regard to the prognostic significance of lymph nodal dissection, however, what we have to perform is definite local control by the strict nodal resection. The diagnosis of malignant potential for lung cancers has been refined based on the numerous studies to evaluate the radiological and pathological correlation in thoracic oncology. According to this, further research will be needed to confirm the prognostic impact of lymph nodal resection, considering the several concepts regarding nodal management in patients with NSCLC, such as optimal method to harvest of lymph node, appropriate extent of lymph node, involved lymph node ratio, and importance of examined lymph node count.

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