

The necessity of mediastinal lymph node resection for screen-diagnosed non-small cell lung cancer (NSCLC) manifesting as subsolid nodule

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Dr. Flores and colleagues recently published an article titled “Computed tomography screening for lung cancer” in *Annals of Surgery*, and was presented at the annual meeting of the 16th World Conference on Lung Cancer. Therein, they reported the results of survival differences for patients with and without mediastinal lymph node resection (MLNR) in stage IA non-small cell lung cancer (NSCLC) manifesting as subsolid and solid nodules. They concluded that it is not mandatory to perform MLNR when screen-diagnosed NSCLC manifests as a subsolid nodule.

The Lung Cancer Study Group demonstrated a threefold increase in local recurrence and decreased survival in patients who underwent limited resection. Subsequently, anatomical resection of greater than a lobectomy in combination with MLNR or sampling has become the standard surgical approach even for stage I NSCLC (1). However, advancements in computed tomography (CT) screening technology has allowed for greater detection of smaller-sized tumors in node-negative early stage NSCLC. Moreover, with progress in the quality of high resolution computed tomography (HRCT), the number of cases of ground-glass opacity nodules (GGOs) has been increasing exponentially. As a result, we can begin to question the necessity of standard lobectomy—in favor of limited resection like wedge resection or segmentectomy—for small cancers or subsolid types of cancers.

To address this question, randomized controlled trials with peripherally located NSCLC with 2 cm or less in size were started by the Cancer and Leukemia Group B (CALGB 14053) in the United States and by the Japan

Clinical Oncology Group (JCOG 0802) in Japan. The latter study is a phase III, randomized, multi-institutional study to compare the prognosis and postoperative pulmonary function between lobectomy and limited resection. Importantly, the selection criteria were negative hilar node and consolidation/total tumor size ratio of greater than 0.25 (2). The former—CALGB 140503—study is also a phase III, randomized trial assessing the difference between lobectomy and sublobar resection for peripherally located small NSCLC after the confirmation of N0 status from a frozen section of nodes. It may be the right time to challenge the gold standard for early-stage NSCLC. However, since the present-day indications of limited resection for NSCLC are compromised with limited pulmonary reserve and non-invasive carcinoma, it may be better to consider lobectomy as the gold standard until the two aforementioned multicenter studies—JCOG and CALGB—provide a more conclusive recommendation.

In addition to the extent of resection and the necessity of standard lobectomy, the degree to which MLNR is necessary for the treatment of NSCLC is also a contentious issue. The proponents of MLNR assert that it improves the staging accuracy by increasing LN harvest and enhances the identification of occult N2 disease (3,4). With respect to therapeutic effect, MLNR—according to its proponents—decrease recurrence and increase survival by removing the occult N2 disease. However, it is worth noting the controversial results of improved survival by MLNR (5). Conversely, the opponents of MLNR assert that it could cause potential adverse events, such as ischemic bronchial

stump, chyle leaks, longer operative time, chest tube drainage, and nerve injury (6,7). Due to such dichotomous nature of MLNR, clinicians have always needed to balance the benefits and risks of performing parenchymal resection with MLNR.

In addition, ACOSOG Z30 trial is a multicenter, prospective, randomized trial comparing the efficacy between MLN sampling (MLNS) and MLNR for localized NSCLC. According to this trial, MLNR does not improve long-term survival in patients with early-stage (T1 or T2, N0 or nonhilar N1) NSCLC with pathologically negative mediastinal and hilar nodes after rigorous systematic preresection LNs sampling (8). However, because the current preoperative staging cannot be used to identify patients with mediastinal lymph node involvement, and because patients with known hilar or mediastinal disease N2 or with T3 or T4 tumors may benefit from MLNR, it is still recommended for all patients with resectable NSCLC, since undergoing such procedure does not necessarily increase mortality or morbidity (8).

The appearance of subsolid tumor also raises the question on the necessity of standard MLNR for subsolid cancers. Because the biological behavior of some small NSCLC is aggressive, it is very important to find less aggressive NSCLC preoperatively using radiographic imaging to avoid performing MLNR. Lung adenocarcinomas showing subsolid nodule on CT imaging are usually pathological N0 disease, and they are good candidates for the omission of MLNR. Nomori *et al.* reported that 100% of adenocarcinomas showing non-solid nodule was N0 and 96% of adenocarcinomas showing subsolid nodule was N0. They concluded that MLNR may not be necessary for lung adenocarcinomas with non-solid nodules as well as for those with subsolid nodule (9).

A multicenter analysis of HRCT and PET from Japan has shown that the maximum standardized uptake value (maxSUV) and the proportion of solid components are important in determining the appropriateness of sublobar resection, and they concluded that MLNR is not required for tumors with maxSUV of less than 1.5 in subsolid adenocarcinoma (10).

The study by Flores and colleagues included a total of 203 patients with a subsolid nodule. Among them, 151 patients (74%) underwent MLNR, and only one of these patients (0.7%) had mediastinal LN metastasis. If MLNR was performed in the 52 patients without MLNR, none would have had LN metastasis. There were 74 patients who had no solid component, and among them, 53 patients (72%)

underwent MLNR and had no lymph node metastasis. Contrastingly, in patients whose cancer manifested as solid nodules, there was a 4% of occurrence of mediastinal LN metastases as a result of MLNR. Based on these results, MLNR may not always be necessary.

Unfortunately, due to its retrospective design, there was a lack of randomization to MLNR. Moreover, there was no data about the recurrence at mediastinal LNs during the follow-up period for both groups. Additionally, more detail about solid component ratio in subsolid nodules would have been useful. However, despite some limitations, this study deserves much praise for providing us with a new horizon on MLNR in the era of CT screening for lung cancer.

In efforts to develop standardized guidelines for MLNR in the future, possible predictive factors—like tumor size, solid component ratio in subsolid nodules, tumor location on preoperative CT, and maxSUV on PET—need to be verified through further randomized controlled trials. This would be the only way to conclusively answer the question on the necessity of MLNR.

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Footnote

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