Editorial

Has lobe-specific nodal dissection for early-stage non-small lung cancer already become standard treatment?

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In 1960, Cahan reported the first patients to successfully undergo lobectomy with regional lymph node dissection, which was called radical lobectomy (1). Since then, this procedure has been broadly accepted and has remained as a standard surgery for non-small cell lung cancer (NSCLC). Systematic nodal dissection (SND) has been reported to be important for survival as well as accurate disease staging (2,3). However, the effect of SND on the prognosis remains controversial.

To date, a number of prospective studies for the assessment of SND have been performed. Previous reports (4-6) of randomized trials comparing SND with sampling have presented inconsistent results, leaving the question of whether or not SND improves survival unresolved. Lymph node assessment by SND is also important for the accurate staging of NSCLC. Even peripheral small lung cancers of less than 2 cm show hilar or mediastinal node metastasis with an incidence of more than 20% (7). In addition, N2 lung cancer without N1 involvement has an incidence of approximately 30% (8). If patients do not undergo SND, their evaluation is less complete than those who receive it. Several studies (9,10) have also reported that the prognosis improves if patients receive adjuvant chemotherapy. A meta-analysis showed that cisplatin-based chemotherapy significantly improved the survival of patients with NSCLC (10). If assessment of the mediastinal lymph nodes is not accurate, patients who require adjuvant chemotherapy may not be correctly diagnosed and so the timing of appropriate treatment may be missed. According to a recent population-based study by Yang *et al.* (11), unsuspected pN2 disease was found in 4.4% of patients who underwent lobectomy as the primary therapy for c-stage I–II NSCLC. Their analysis suggested that, in the setting of unsuspected pN2 NSCLC, proceeding with lobectomy does not appear to compromise outcomes if adjuvant chemotherapy with or without radiation therapy can be administered following surgery.

On the other hand, some reports (7,12-14) stated the identification of distinct patterns of metastatic spread through the lymphatic system that depend on the location of the primary tumors. They reported that right upper lobe and left upper segment tumors tend to metastasize to the superior mediastinum, but rarely metastasize to the subcarinal nodes without concomitant metastasis to the hilar or superior mediastinal nodes. Moreover, Aokage *et al.* (12) reported that upper lobe tumors with subcarinal metastasis were associated with a poor 5-year survival rate of 9.1%. They reported that lower lobe tumors seldom metastasize to the superior mediastinal nodes without concomitant metastasis to the hilar or subcarinal nodes. Asamura (14) reported that tumors of the right lower lobe with superior mediastinal metastasis were associated with a poorer 5-year survival rate of 4.1%. Based on the results of the lobe-specific patterns of nodal metastases, lobe-specific nodal dissection (LSD) has been developed (15-18).

In the SND group, lobectomy was combined with radical systematic en bloc mediastinal lymph node dissection, as described by the International Association for the Study of Lung Cancer (19). In the LSD group, lymph node dissection was performed on the basis of lobe-specific lymph node metastasis patterns. When the tumor was located in the right upper lobe, the upper mediastinal lymph nodes (upper and lower paratracheal nodes) and hilar lymph nodes were systematically removed. When the tumor was located in the left upper lobe, the aortopulmonary window nodes,

aortic nodes, tracheobronchial nodes, and hilar lymph nodes were systemically removed. In these cases, dissection of the lower mediastinum was omitted when the nodes in the hilum and upper mediastinum or aortic nodes were free from metastases. Of course, intraoperative frozen section analyses were employed when lymph node metastases were suspected. On the other hand, when the tumor was located in a lower lobe, the subcarinal, lower mediastinal nodes, and hilar lymph nodes were dissected; dissection of the superior mediastinum was omitted when the intraoperative diagnosis was negative.

There have been some reports comparing LSD with SND (15-17) at single institutions. Okada *et al*. (15) performed SND in 377 patients between 1985 and 1996 and LSD in 358 patients between 1997 and 2002, and they reported that LSD for stage I NSCLC was as effective as SND. They also reported that the morbidity of the patients undergoing LSD was less than that for those undergoing SND. In addition, the pattern of recurrence was not significantly different between the 2 groups. Ishiguro *et al*. (16) compared LSD for resectable NSCLC with SND using propensity scores. They reported that LSD did not worsen the survival. However, they did not investigate tumor recurrence. We also compared survival, morbidity, and the recurrence pattern between the clinico-surgical N0 NSCLC patients who underwent lobectomy with SND and LSD (17). When we excluded part-solid tumors with a small area of consolidation resulting in a consolidation/tumor ratio of <0.5 from the analysis, there were no significant differences in postoperative complication rates, 5-year overall and disease-free survival rates, or overall recurrence rates between SND and LSD groups. The only significant differences were a shorter operative time and higher recurrence rate at mediastinal nodes for the LSD group. It is noteworthy that mediastinal node recurrence occurred in only one patient with SND but in three with LSD (P=0.005). These three recurrences occurred outside of the LSD area. From these results, lobectomy with SND appears to be the most effective treatment.

In 2010, the Japanese Joint Committee of Lung Cancer Registry (JJCLCR) conducted a nationwide registry study project to clarify the clinicopathologic profiles and prognoses of patients who underwent surgery for primary lung cancer in 2004 (20). In the registry, a total of 5,392 patients underwent R0 resection for c-stage I–II NSCLC by lobectomy and mediastinal lymph node dissection (SND or LSD). Hishida *et al*. (18) assessed the surgical outcomes according to the extent of mediastinal lymph node dissection (SND versus LSD) using this database. LSD and SND were performed in 1,268 (23.5%) and 4,124 (76.5%) patients, respectively. The 5-year overall survival rate was 81.5% in the LSD group and 75.9% in the SND group. Pathological N2 disease was observed more frequently in the SND group than in the LSD group (12.7% *vs*. 8.4%, respectively). Extended pN2 outside the LSD area was found in 3.2% of the SND group, which resulted in a poorer prognosis. In the comparisons between LSD and SND groups after propensity score matching, they showed that LSD did not have a negative prognostic impact, and instead was associated with favourable survival (hazard ratio =0.68, 95% CI: 0.60–0.77). However, the authors indicated some limitations in their study. First, they could not conduct a preoperative radiological evaluation, such as, assessing the proportion of ground glass opacity on thin-section computed tomography (TSCT), known as an indicator of tumor invasiveness. Second, they could not show the actual conversion rate from planned LSD to SND based on the intraoperative findings.

We suggest that the important problem is the recurrence in mediastinal nodes only in the LSD group. It may be impossible to know the accurate site of local recurrence in the 77 patients (6.1%) of the LSD group and clarify the risk factors for lymph node metastasis from their database. How many patients developed recurrence outside of the LSD area? As one alternative procedure to overcome this problem, researchers may try to collect the original data of individual patients at each institute, clarify the clinic-pathological characteristics, and analyse the risk factors associated with lymph node metastasis. Of course, large multi-institutional prospective randomized studies are needed to clarify whether LSD is applicable for clinical stage I–II NSCLC.

Hishida *et al*. (18) reported that, in the SND group, pN2 disease outside of the LSD area and accessible only by SND (non-LSD pN2) was found in 1.6% of patients with upper-lobe tumors and 5.5% of those with lower-lobe tumors. According to the revised ESTS guidelines for preoperative mediastinal lymph node staging for NSCLC (21), modern techniques such as positron emission tomography (PET)-CT and endoscopic ultrasonography (EBUS) were showed the highest sensitivity and negative predictive value. However, the working group considered a rate of unforeseen pN2 disease of 10% as acceptable. When compared with this rate, that of non-LSD pN2 is minimal, especially in patients with upper-lobe tumors. As one of possible explanation that patients with pN2

disease outside of the LSD in lower-lobe tumor were more often than those in upper-lobe tumor, the difference in lymphatic drainage pathways between the two lobes was highlighted. According to the study by Watanabe *et al.* (22), basal segment tumor of the lower-lobe metastasizes to the superior mediastinum mostly through the subcarinal node. However superior segment (S6) tumor often metastasizes directly to the superior mediastinum without concomitant metastasis to the subcarinal node. It potentially metastasizes to the superior mediastinum via the lymphatic pathways around the upper-lobe bronchus. Therefore, LSD may be inadequate surgical procedure for S6 segment tumor.

Thus, the suggestion by Hishida *et al.* (18) that LSD is an alternative to SND for selected c-stage I–II NSCLC patients might be justified except for S6 segment tumor.

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Footnote

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