



# The role of lymph node assessment along with sublobar resection is now evident, but what about the role of sublobar resection in small non-small cell lung cancer?

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Yendamuri *et al.* published an important work in the *Journal of Thoracic and Cardiovascular Surgery* in July 2018 on the effects of the number of resected lymph nodes (LNs) on the survival of patients with small-sized ( $\leq 2$  cm) non-small cell lung cancer (NSCLC) who underwent sublobar resection (1). This retrospective analysis was based on the Surveillance, Epidemiology, and End Results (SEER) database in the United States with more than 3,900 cases (study period: 2004–2013). The study showed that the increased number of lymph nodes examined (LNE) was associated with favorable survival in patients with sublobar resection for small NSCLC that was declared node negative after surgery. We need to clearly understand that the improved outcome resulted not from the procedure (i.e., sampling LNs) itself, but from the fact that a greater number of LNE made more accurate staging possible by identifying occult N1 or N2 disease; a smaller number of patients with occult LN-positive disease in the group with a greater number of LNE, leading to a superior post-surgical outcome than those with a smaller number of LNE that might include more misdiagnosed (i.e., occult LN-positive) cases. Nodal upstaging rates in those who underwent wedge resection for clinical T1-2N0M0 NSCLC were recently reported by Ajmani *et al.* (2). Overall upstaging rate with at least 1 LNE was 5.2%, and understandably, the rate increased as the LNE increased; from 4.4% in those who

had 1 to 5 LNE to 8.1% who had more than 10 LNE. The Yendamuri's study reassures that a LN assessment reduces the risk of understaging, which has been shown in the previously published series (3-5). On the other hand, despite the known importance of adequate LN assessment, the study also revealed that a significant proportion of patients with sublobar resection did not have any LN assessment during surgery; no LNs were assessed in 49% of wedge resection, and 23% of segmentectomy (1). This reflects the trend of clinical practice during the study period, i.e., between 2004–2013, in the United States as the SEER database covers 28% of its population. The American College of Surgeons then endorsed LN removal at least 10 as a quality metric for Stage IA-IIIB NSCLC surgery (6).

The role of LN assessment along with sublobar resection now seems evident, but what about the role of sublobar resection in small NSCLC? Do we have enough evidence for that? To date, sublobar resection is generally recommended only for those who are not suitable for lobectomy. Dai *et al.* reported better survival for lobectomy (N=11,520) than sublobar resection (N=4,240) in patients with NSCLC where tumors measure 2 cm or smaller, using the same SEER database with similar study period (the Dai's study: 2000–2012, the Yendamuri's study: 2004–2013) (7). In clinical practice, however, we often see patients who are not suitable for lobectomy because of comorbidity, advanced

age, limited cardiopulmonary reserve, and other issues. We also see more frequently those with small ground-glass opacity with minimal solid component and/or very small (<1 cm) NSCLC that may benefit from sublobar resection to preserve lung function while achieving a complete removal of the lesion. Although a debate on sublobar *vs.* lobar resection was not in the scope of the Yendamuri's study, the result needs to be carefully interpreted and applied to our decision-making process. Yendamuri *et al.* demonstrated an interesting result that in those who had at least one LNE at the time of surgery (1,615 cases with wedge resection and 547 with segmentectomy), the survival benefit of segmentectomy over wedge resection was not seen in multivariate analysis, suggesting again, the importance of LNE in sublobar resection. Based on the result, the authors questioned the necessity of choosing segmentectomy that is a more technically complex procedure than wedge resection with longer surgical time. However, there is a clear difference between segmentectomy and wedge resection in terms of the quality of assessing the intersegmental/lobar or hilar LNs. Wedge resection is technically less suited for exploring those LNs compared to segmentectomy because it does not require segmental bronchial dissection that affords better LN assessment. Therefore, so far, it can be said that only those patients with non- or minimally-invasive, small, peripheral NSCLC would be good candidates for wide wedge resection. Suzuki and his colleagues reported a prospective study to assess the tumor invasiveness by thin-section computed tomography (CT) images, and showed that radiologically small ( $\leq 2$  cm) tumors with consolidation/tumor ratio  $\leq 0.25$  was reliable sign of pathological non-invasiveness (i.e., there was good correlation with no nodal involvement, vascular invasion, or lymphatic invasion) (8). Evidence in support of sublobar resection was reported by Tsutani *et al.* who showed that small (<0.8 cm) or low SUVmax (<1.5) nodule on FDG-PET/CT was predictive of pN0, thus those cases may be good candidates for sublobar resection (9). The authors reported a 3-year disease-free survival rate of 100% in those who met the criteria, which provides an evidence of not only tumor size, but also less aggressive tumor biology (reflected by the low SUVmax) could allow us to perform lesser resection. Yoshida *et al.* proved the concept in the early 2000's in a small (N=50), but a meaningful prospective trial (10). We also acknowledge that sublobar resection could be equivalent to lobectomy for clinical stage IA NSCLC shown by Altorki *et al.* (11), based on a subgroup, propensity-scoring matched analysis of the International Early Lung Cancer Action Program

database (294 lobectomy and 53 sublobar resection), and by Schuchert *et al.* (12) from the University of Pittsburgh group (246 lobectomy and 182 segmentectomy), although both are retrospective. The trend over the past two decades in the SEER database showed improved post-surgical outcome of sublobar resection that was equivalent to lobectomy, partly owing to the liberal use and better access of refined diagnostic tools such as high-resolution computed tomography (HRCT), positron emission tomography (PET), and minimally-invasive nodal staging techniques (13). All the diagnostic modalities improve sensitivity not only to avoid mis-staging, but also to evaluate tumor biological aggressiveness, both of which contribute to the decision-making on the extent of resection.

There are some more important factors that need to be considered in choosing sublobar resection either simple wedge resection or anatomical segmentectomy, as opposed to lobectomy for patients with small NSCLC. Firstly, wedge resection would be limited its capacity to remove intrasegmental LNs or microscopic tumor cell spread around the main tumor while anatomical segmentectomy or lobectomy may have a higher chance to do so. In a recent study by Eguchi *et al.* from Memorial Sloan Kettering Cancer Center (MSKCC) with around 1,500 surgical cases of pT1 ( $\leq 3$  cm) N0 adenocarcinoma, an almost three-fold higher risk of recurrence was seen in patients with "spread through air spaces (STAS)"-positive adenocarcinoma (median tumor size, 1.5 cm) who underwent sublobar resection compared to those who did lobectomy (14). The MSKCC group also found a benefit of achieving a surgical resection margin wider than the tumor size in patients with STAS-negative adenocarcinoma in protecting locoregional recurrence, but the benefit was not seen in those with STAS-positive adenocarcinoma. More importantly, sublobar resection as opposed to lobectomy led to a higher chance of not only locoregional recurrence, but also distant metastasis and cancer-specific death in patients with STAS. Therefore, lobectomy, not even segmentectomy, is still a better choice of surgical procedure for patients with T1 adenocarcinoma with STAS. Because STAS is associated with several, although not specific, CT features such as central low attenuation, ill-defined opacity, air bronchogram, and percentage of solid component (>90%), sublobar resection should be carefully considered even for small tumors if the radiological findings exist on the preoperative CT images (15). Secondly, an adequate surgical margin is critical to obtain complete cancer removal, which would be achievable

more likely by segmentectomy or lobectomy than wedge resection, especially in cases of centrally located tumors, tumors with microvessel invasion, or tumors with lymphatic permeation. Koike *et al.* reported independent risk factors of locoregional recurrence in clinical stage IA NSCLC after sublobar resection (216 wedge resection and 34 segmentectomy), and identified the following ones: wedge resection, visceral pleural invasion, lymphatic permeation, and microscopic positive surgical margin (16).

To summarize, the body of recent evidence reassures that any type of resection as an intent-to-cure surgery for small NSCLC requires LN assessment, but for the definitive answer to the ongoing debate as to whether sublobar resection could be equivalent to lobar resection, we still await the two large, randomized trials led by the Japan Clinical Oncology and West Japan Oncology Groups (JCOG0802/WJOG4607L) (17), and the Cancer and Leukemia Group B (CALBG140503) (18).

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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