



Radical segmentectomy as a potential alternative surgical treatment with curative intent in early-stage non-small cell lung cancer

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Since the Lung Cancer Study Group (LCSG) reported the results of a prospective, randomized, and comparative trial of sublobar resection *vs.* lobectomy for non-small cell lung cancer (NSCLC) measuring ≤ 3 cm in 1995 (1), lobectomy has been the standard surgical procedure for NSCLC, even for small tumors. In the LCSG study, a three-time higher locoregional recurrence rate was seen with relatively lower overall and cancer-specific survival in patients who underwent sublobar resection, including both segmentectomy and wedge resection, compared to those who underwent lobectomy. In the 2000s, some studies demonstrated favorable postoperative outcomes after segmentectomy in patients with early-stage NSCLC (2-5). These studies focused on relatively smaller tumors compared to those investigated in the LCSG study and focused solely on segmentectomy in sublobar resection surgeries. In a recently published review article, titled “Are segmentectomy and lobectomy comparable in terms of curative intent for early stage non-small cell lung cancer?” by Mimae *et al.* (6), the authors specifically referred to radical segmentectomy for early-stage NSCLC and discussed the possibility of segmentectomy as an alternative to lobectomy for the surgical treatment with curative intent for early-stage NSCLC.

Difference between segmentectomy and wedge resection

In the review article by Mimae *et al.* (6), the authors

first discussed the extent of pulmonary resection in sublobar resection surgery. As mentioned above, the LCSG demonstrated a significantly higher locoregional recurrence rate with relatively lower postoperative survival in patients undergoing sublobar resection, compared to those undergoing lobectomies for clinical stage IA NSCLC (1). However, the LCSG study enrolled patients who underwent segmentectomy and wedge resection in the sublobar resection group; in fact, 40 of the 122 patients (32.8%) in the sublobar resection group underwent wedge resection. It is considered that anatomic segmentectomy is a superior oncologic approach compared to non-anatomic wedge resection, and that segmentectomy has the theoretical advantage of a more radical resection. Anatomic segmentectomy achieves appropriate margins by reducing the technical limitations and involves wider resection of the draining lymphatics existing in intersegmental planes that are considered a source of residual cancer cells (7). Many previous studies about sublobar resection in early-stage NSCLC focused solely on segmentectomy, and favorable postoperative outcomes after segmentectomy have been reported (5-year overall survival rates of 87–90%, 10-year overall survival rates of 81–84%, and an overall recurrence rate of 17%) (2-5). In fact, in our previous retrospective study involving patients with clinical stage IA NSCLC (≤ 3 cm) who underwent sublobar resection, wedge resection was identified as a significant independent risk factor for locoregional recurrence and poor disease-specific survival [hazard ratios (HRs) of 5.787 and 3.183, respectively]

compared to segmentectomy (8). Similar results were reported in the United States (9), and segmentectomy was associated with a significantly better overall (HR: 0.80) and lung cancer-specific survival (HR: 0.72) in patients with stage IA NSCLC who underwent sublobar resection. Mimae *et al.* mentioned in their review article (6) that anatomic segmentectomy involving lymph node dissection, but not wedge resection, allows hilar nodal dissection and a wider surgical margin. Although both segmentectomy and wedge resection are classified as sublobar resections, anatomic segmentectomy with systematic lymphadenectomy must be clearly differentiated from wedge resection and segmentectomy without lymphadenectomy. Moreover, it is considered that intentional radical segmentectomy and segmentectomy for lobectomy intolerable patients need to be independently discussed. Intentional radical segmentectomy should be compared with lobectomy for the curative intent treatment of early-stage NSCLC.

Preoperative radiologic assessment of early-stage NSCLC for segmentectomy

In the LCSG study, the enrolled patients were diagnosed with clinical T1N0 disease (≤ 3 cm) by posteroanterior and lateral chest roentgenogram, and computed tomography (CT) for detecting occult distant metastasis, such as the brain, lung, liver, and adrenal glands metastasis was not routinely performed (1). Thus, the disease stage might have been underestimated compared to the current preoperative staging, which is evaluated by high resolution CT and ^{18}F -fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT). Moreover, tumors that general thoracic surgeons often encounter in recent times, such as small tumors with ground glass opacity (GGO) components, might not have been included in the LCSG study. In the current TNM staging system (10), the solid component size is one of the factors determining the T-factor whereas a GGO component is not involved in tumor diameter and the T-factor. Because the solid component size reflects an extension of the invasive component size, oncological feature is considered more precisely defined in the 8th, rather than in the previous versions of TNM classification (11). However, Mimae *et al.* mentioned in their review article (6) that the entire tumor size including the GGO component is more important for determining the surgical indication for segmentectomy in stage I NSCLC. The results of previous studies about sublobar resection (12-14) suggested that the entire

tumor size ≤ 2 cm might be a good indication for sublobar resection, and the entire tumor size and tumor location on preoperative high resolution CT should be assessed to secure an appropriate surgical margin and to avoid local recurrence after segmentectomy. In fact, in our recent analysis of risk factors for the recurrence of early-stage NSCLC in patients who underwent anatomic segmentectomy (15), some patients with small solid component size developed surgical margin recurrence, despite having a lower overall risk of recurrence. Mimae *et al.* recommended lobectomy or more extended resections, including sleeve lobectomy, bi-lobectomy, and pneumonectomy even for small tumors that are difficult to secure an adequate margin by segmentectomy, such as centrally located tumors and those located around the root of the lobar bronchus.

Mimae *et al.* also referred to some preoperative radiologic parameters which are associated with the malignant potential of early-stage NSCLC (16,17), such as the consolidation to tumor (C/T) ratio on CT and the maximum standardized uptake value (SUVmax) on FDG-PET/CT (6). The C/T ratio is defined as the maximum solid component diameter divided by the maximum tumor diameter on high resolution CT (18). Since tumors with a high proportion of GGO components reflect a high proportion of non-invasive adenocarcinoma, a low C/T ratio could indicate low malignant adenocarcinomas, such as adenocarcinoma in situ and minimally invasive adenocarcinoma (11). Many previous studies about intentional sublobar resection addressed small NSCLC with a low C/T ratio, and excellent postoperative survival was seen in patients with such tumors (19,20). Although such less aggressive tumors are considered a good indication for sublobar resection, Mimae *et al.* suggested that small tumors with a low C/T ratio are not suitable for a comparative prospective study of lobectomy *vs.* segmentectomy because these tumors can be cured even with wide-wedge resection (18).

The SUVmax of 1.5 on FDG-PET/CT was reported as a threshold to predict lymph node metastasis (16), and our previous study indicated a predictive effect of SUVmax ≥ 6.10 on the pathological metastasis and involvement in clinical stage IA NSCLC (21). However, Mimae *et al.* suggested that currently, an SUVmax on FDG-PET/CT cannot be relied on to decide the indication for segmentectomy for early-stage NSCLC. This is because FDG-PET/CT modalities continue to be evolving, thus improving the sensitivity (6). Moreover, the meaning of actual value of SUVmax differs between modalities,

institutions, and generations.

Preserved pulmonary function after segmentectomy

Compared to lobectomy, segmentectomy has the theoretical advantage of preserving the postoperative pulmonary function because of the smaller extent of excised lung parenchyma. Although the LCSG study concluded that sublobar resection did not preserve the postoperative pulmonary function because the forced vital capacity (FVC) or maximum voluntary ventilation were not significantly better [but the forced expiratory volume in 1 second (FEV₁) was better] relative to sublobar resection (1), some previous studies, including our study, suggest significantly better preservation of FVC and FEV₁ in patients who underwent segmentectomy than in those who underwent lobectomy (14,22). Mimae *et al.* (6) also mentioned that although some segmentectomies create several intricate intersegmental planes and are considered a complex segmentectomy, both simple and complex segmentectomy may contribute to better postoperative pulmonary function than lobectomy for early-stage NSCLC patients (23).

Radical segmentectomy as a potential alternative surgical treatment with curative intent in early-stage NSCLC

In the review article by Mimae *et al.* (6), the authors discussed whether radical segmentectomy can be an alternative to lobectomy as a surgical treatment with curative intent for early-stage NSCLC patients. They stated that segmentectomy is more valuable than wedge resection in terms of an oncological perspective; thus, anatomic segmentectomy with lymph node dissection needs to be independently examined compared to lobectomy. Moreover, even in small NSCLC, the entire tumor size and tumor location on preoperative high resolution CT should be carefully assessed to secure an adequate surgical margin after segmentectomy, and other preoperative radiologic factors, such as C/T ratio and SUVmax might be necessary to determine an indication for segmentectomy in the future. This is because segmentectomy will likely become the standard surgical procedure for early-stage NSCLC following the results of ongoing prospective, randomized trials of lobectomy *vs.* sublobar resection in patients with

early-stage NSCLC, such as Cancer and Leukemia Group B 140503 (24) and Japan Clinical Oncology Group 0802/ West Japan Oncology Group 4607L (25). Thus, Mimae *et al.* concluded that general thoracic surgeons will need to master segmentectomy because the opportunity to encounter patients with small NSCLC who need surgical treatment continues to increase (6).

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