including tumors with a peripheral location within the outer third of the lung. Tumors considered for segmentectomy should be confined to the anatomic segmental boundaries without crossing intersegmental planes. Anatomic resection of multiple segments of one lobe is technically feasible, but its functional advantage may be questionable if compared with lobectomy. There is also a strong recommendation for a systematic hilar and mediastinal lymph node harvesting to exclude occult metastases and ensure accurate staging which is mandatory for the appropriateness of sublobar resection.[13]

There is no doubt that only the conclusion of the two ongoing randomized trials (CALB-140503 and JCOG-0802) for peripheral NSCLC ≤ 2cm will definitively clarify the role of segmentectomy as a potential operation of choice for early-stage NSCLC. However, there is currently a large amount of data that have contributed to define a subset of patients for whom segmentectomy is likely to become the standard of treatment.

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COUNTERPOINT:

Should Segmentectomy Rather Than Lobectomy Be the Operation of Choice for Early-Stage Non-small Cell Lung Cancer? No

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In recent years, many factors have reintroduced an interest in anatomic segmentectomy as the favored procedure for early lung cancer. This is due to technical advances in imaging and the use of low-dose CT imaging in various screening programs, a larger number of elderly patients and those with limited pulmonary reserve being treated with minimally invasive techniques, and the epidemiologic rise in multiple or bilateral lung nodules. Thoracic surgeons will likely encounter the dilemma of how to manage a significantly increased number of small peripheral tumors. The main advantage of segmentectomy over lobectomy is obviously the parenchyma-sparing effect, but it is still debatable whether the oncologic outcomes are comparable in early-stage non-small cell lung cancer (NSCLC).[1] The Lung Cancer Study Group completed the only available phase III prospective randomized controlled trial (RCT) of sublobar resection vs lobectomy in peripheral NSCLCs ≤ 3 cm.[2] Ginsberg

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and Rubinstein[2] demonstrated an unfavorable postoperative prognosis (threefold increase in the locoregional recurrence rate) for sublobar resections. The Lung Cancer Study Group study had several limitations: CT imaging was not routinely performed, 32.8% of the limited resections were wedge resections with high locoregional recurrence rates and poor survival compared with segmentectomies, and PET studies were not accessible.[3] In contrast, in two recent surveys of propensity-matched comparisons, noninferior survival and recurrence rate in segmentectomies was demonstrated in clinical stage I NSCLC.[3,4] More data will be available after the completion of the two ongoing RCTs: Cancer and Lymphoma Group (CALBG140503) and the phase III Japan Clinical Oncology Group/West Japan Oncology Group (JCOG0802/WJOG4607L) studies. CALGB140503 and JCOG0802/WJOG4607L[5] have large sample sizes (target accrual of 1,297 and 1,100 patients, respectively), and the primary end point will investigate the noninferior outcomes of segmentectomies. However, it should be noted that the inclusion of a large number of patients with noninvasive or minimally invasive adenocarcinomas (as well as the maintenance of a generic "sublobar" treatment arm as the comparator to lobectomy) might represent potential confounding factors.[3] Interestingly, during the CALGB140503 trial, as many as 39% of patients were ineligible for randomization as the result of understaging or misdiagnosis. In fact, a substantial number of clinically suspected T1a NSCLCs had more advanced or benign disease mimicking malignancies. This finding highlights another potential confounding factor and strongly supports recommending preoperative biopsy procedures for all patients with suspected small lung cancers before randomization.[6,7]

While we are awaiting direction from the RCTs mentioned earlier, some of the potential benefits of segmentectomies should be redefined and critically evaluated. Surgeons should consider the anatomic complexity of segmentectomy, that is dealing with nonpalpable lesions (dissecting the inner part of the lobe and fissures, tackling small structures without clear landmarks) with the goal of ensuring resection margins and full hilar lymph node dissection. Preoperative evaluation of resection margin by three-dimensional imaging and intraoperative frozen sections has been recommended.[8] One of the most challenging aspects is how to identify the intersegmental plane,[9] and this could explain why the type of segmentectomy itself could represent an independent risk factor for regional recurrence, leading to a prognosis that is not equivalent for all segments.[10] Left upper lobes and superior segmentectomies have significantly less local recurrence. In contrast, right upper lobe and basal segments have shown a considerably higher recurrence.[8] In right upper lobectomies near the segmental border, resection margins tend to be insufficient even with extended segmentectomies, because it could be difficult to resect one adjacent subsegment. A right upper bisegmentectomy to ensure surgical margins would spare only a single segment, and the surgeon may then prefer a lobectomy.[8] Moreover, segmentectomy and larger tumor size were independent significant clinical factors of recurrence. Therefore, even in cases of small-sized NSCLC, segmentectomy should be applied with great caution, especially for radiologically pure solid nodules.[11]

A sublobar resection may appear a more reasonable alternative to lobectomy in elderly patients (shorter life expectancy and worse pulmonary reserve). A single-center experience found that segmentectomy and lobectomy had comparable disease-free and overall survival.[6] In contrast, the large Surveillance, Epidemiology, and End Results (SEER) database showed that segmentectomy had significantly worse overall and lung-cancer-specific survival. Thus, older age alone should not justify segmentectomy in early-stage NSCLC.[12] A recent meta-analysis, focused on patients with medical comorbidities or cardiopulmonary limitations, discovered that overall survival was equivalent only in patients who could tolerate segmentectomies or lobectomies, whereas it was significantly worse in compromised patients and could represent a reflection of noncancer-related deaths in a frail cohort who could not tolerate lobectomy.[8] Segmentectomies proved to have a more favorable prognosis due to variables other than the volume of resection only (tumors < 2 cm, peripherally located, ground-glass opacity on imaging).[13]

Given that in the new International Association for the Study of Lung Cancer lung cancer staging system T1a (< 2 cm) cancers are classified into two subgroups with 1-cm cut points, considerable interest has been raised about theoretical differences in surgical management for NSCLC lesions < 1 cm and those 1 to 2 cm. In the meta-analysis of Zhang et al,[14] segmentectomies had an intimate relationship with inferior overall or cancer-specific survival, whereas Dai et al[15] found that the superiority of lobectomy extends to both subgroups.

Interestingly, for tumors < 1 cm, wedge resections also have a role in anatomic segmentectomy, and surgeons could rely on surgical skills and patient profile to decide between segmentectomy or wedge resection.[16]

Likewise, sublobar resection may understage NSCLC because of inadequate lymphadenectomy of N1 nodes.[10] Nevertheless, Dembitzer et al[17] found no statistically significant difference in survival between lobectomy and sublobar resection regardless of histologic type, even with other negative prognostic factors such as lymphatic invasion, suggesting that sublobar resection may be suitable for NSCLC with more extensive invasive components.

A significant number of patients cannot tolerate a lobectomy because of limited pulmonary reserve. Since segmentectomy can preserve more lung parenchyma, in theory it should have an advantage for pulmonary function.[15] Several retrospective studies have shown that the extent of the resected parenchyma directly affects the loss of pulmonary function and that segmentectomy offers better functional preservation.[9] Nevertheless, this technical advantage in early-stage lung cancer lasts only for the preliminary period after surgery and to a lesser extent than expected. Authors found significant benefit for postoperative FEV_1 but not for postoperative FVC.[16] Another study comparing postoperative CT functional lung volumes found no significant difference between the techniques after 6 months.[9]

The literature on segmentectomy has only proved that selected subsets of patients with desirable characteristics might be appropriately treated without adversely affecting disease-free survival, but lobectomy remains the gold standard for early-stage NSCLC. We should be aware that most of the meta-analyses are performed using summary data and are a statistical examination of the studies included; therefore, the results are as good as the studies included. Although the bias sources can be controlled with Forest and Funnel plots, an excellent meta-analysis of imperfectly designed studies will still lead to confounding results and misinterpretations; for example, studies pooling together all the sublobar resections (without separated data on segmentectomy) would probably introduce bias, as estimated hazard ratios derived from survival curves regularly involve extrapolation and assumptions about censoring patterns.[18]

In conclusion, despite the growing literature on segmental resections for early-stage NSCLC, there is still a lack of evidence to support similar long-term outcomes. Based on available results, lobectomy should still be considered the gold standard. There may certainly be a subset of patients who might benefit from sublobar resections, but this group needs to be identified. For any recommendations, we should realistically expect the results of the ongoing RCTs, always taking into account that the volume of lung parenchyma excised is only one of the variables affecting long-term results (together with the histologic subtype and the biological characteristics of the tumor) and that in the present scenario, stereotactic ablative radiotherapy is an emerging competitive tool for small lung cancers.[19]

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Rebuttal From Drs D'Andrilli and Rendina

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Drs Bertolaccini and Solli report some important considerations suggesting caution in the use of segmentectomy as the operation of choice for early-stage lung cancer.[1] From a functional point of view, they maintain that the advantage related to segmental resection is present only in the preliminary period after surgery and to a lesser extent than expected.

It is true that some retrospective studies show a functional preservation after sublobar resection that is lower than the predicted postoperative value estimated preoperatively and that sometimes the advantage with respect to lobectomy declines over time. However, we point out that most data in the literature confirm a better preservation of pulmonary function after segmentectomy even in the long term. The postoperative reduction in pulmonary function test results after segmentectomy was evaluated at 6 months in the analysis by Saito et al[2] and at 1 year in the studies by Keenan et al[3] and Macke et al,[4] showing significant benefit compared with lobectomy.

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Furthermore, our opponents argue that an indication for segmentectomy should be critically evaluated and defined, taking into account independent risk factors leading to a prognosis that is not equivalent for all segments and for every type of lesion. Based on data in the literature and our clinical experience, we agree that anatomic segmentectomy should not be considered the operation of choice for all stage I non-small lung cancer (NSCLC) and that patients with larger tumors and tumors not confined within the segmental boundaries are not good candidates for this operation. This is because such neoplasms are at increased risk for local recurrence and may require multiple segmental resections, whose functional advantage with respect to lobectomy is questionable.

Drs Bertolaccini and Solli conclude that based on published results including only one available phase III trial published by the Lung Cancer Study Group in 1995,[5] lobectomy should be still considered the gold standard for early-stage NSCLC, because there is still a lack of evidence to support the role of segmental resection in this setting for patients who are not functionally compromised.

We reply that the previously mentioned phase III trial shows significant methodological limitations, principally related to the obsolete study design, and that there is a growing amount of recent data suggesting similar oncologic efficacy for anatomic segmentectomy and lobectomy in the treatment of tumors up to 2 cm in diameter with a peripheral location.

Therefore, while awaiting future indications from the two ongoing randomized controlled trials, we believe that current data no longer support the role of lobectomy as the operation of choice for all patients with stage I NSCLC. The introduction of a further subgroup with a 1-cm cut point among stage I tumors (stage IA1) in the new International Association for the Study of Lung Cancer staging system would probably stimulate increasing interest in establishing different surgical management for smaller cancers.

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