

## POINT: Should Segmentectomy Rather Than Lobectomy Be the Operation of Choice for Early-Stage Non-small Cell Lung Cancer? Yes



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**ABBREVIATIONS:** CSS = cancer-specific survival; NSCLC = non-small cell lung cancer; OS = overall survival; RCT = randomized controlled trial; RFS = recurrence-free survival; VATS = video-assisted thoracic surgery

Although the functional advantages of parenchymal sparing have been sufficiently proved in lung cancer surgery, the role of anatomic segmentectomy in the treatment of early-stage non-small cell lung cancer (NSCLC) has been not yet standardized, and lobectomy still represents the first choice even for stage I tumors.

The main reason for this is provided by the only available prospective randomized trial comparing lobectomy with sublobar resections (segmentectomy or wedge) for early-stage NSCLC, which was published in 1995 by the Lung Cancer Study Group.<sup>1</sup> In a statistical sample of 247 low-risk patients with T1N0 tumor, this study showed a significant increase (75%) in the recurrence rate for patients receiving sublobar resection, although the observed 30% increase in overall death rate and 50% increase in death with cancer rate had only a borderline value for statistical significance. However, the study has some limitations that need to be emphasized more than 20 years after its publication. First, the Lung Cancer Study Group trial was conducted throughout the

1980s with patient inclusion based on lung cancer detection by simple chest radiography without the routine use of CT and PET scanning as standardized tools for preoperative staging and follow-up controls. This may suggest the possibility of undetected metastatic disease either in the preoperative or the postoperative setting for some of these patients. Second, one-third of patients in the “limited resection arm” received only a wedge resection instead of an anatomic segmentectomy. Finally, there was not a specific analysis to assess the recurrence and death rate for tumors < 1 or 2 cm.

There is currently general agreement that anatomical segmentectomy represents a more effective option than wedge resection since it allows to join functional advantages with oncological reliability for the treatment of early-stage NSCLC. From a technical point of view, the main reason is that the hilar dissection required for segmentectomy allows more adequate N1 lymph node harvesting and larger resection margins.

Modern advances in diagnostic means and screening programs based on CT imaging have contributed to an increase in the number of patients presenting with small tumors. Also, improvement in perioperative management has increased the rate of elderly and medically high-risk patients undergoing lung resection. These developments have prompted increased interest in better defining the role of segmentectomy in the treatment of small tumors, especially those < 2 cm.

In the past decade, several retrospective studies from national or international registries<sup>2-5</sup> and from single-center or multicenter studies<sup>6,7</sup> have suggested that sublobar resection may be equivalent to lobectomy regarding recurrence rate and survival if performed in adequately selected patients with tumor size  $\leq$  2 cm and a noncentral location.

An analysis from the US Surveillance, Epidemiology, and End Results registry has compared the results of 688 patients who underwent limited resection (segmentectomy or wedge resection) with those of 1,402 patients treated with lobectomy for stage I NSCLC < 1 cm finding equivalent overall survival (OS) and cancer-specific survival (CSS).<sup>2</sup> Similar results were published in 2015 from the same registry analyzing data

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from 2,008 patients > 65 years with stage I NSCLC < 2 cm. About one-third of these patients were treated with limited resection. Among patients with adenocarcinoma, those undergoing segmentectomy showed survival rates similar to those of patients treated with lobectomy after adjusting for propensity score, whereas patients undergoing wedge resection did not.<sup>3</sup>

Similarly, investigators from the International Early Lung Cancer Action Program retrospectively analyzed the role of limited resection (segmentectomy and wedge resection), especially for stage I tumors up to 2 cm in diameter. For patients with cancers  $\leq 20$  mm, the 10-year survival rates were 88% after sublobar resection and 84% after lobectomy when adjusted for propensity score.<sup>5</sup> In this study, all recurrences observed in patients receiving limited resection were after wedge resection, whereas there was no recurrence after segmentectomy, thus suggesting a better oncologic reliability with such an operation.

Most of the previously mentioned studies provide useful information to explore the role of limited resection for smaller tumors ( $\leq 2$  cm) but have the limitation of reporting cumulative results for both anatomic segmentectomy and wedge resection without a specific analysis of each procedure.

Two recent meta-analyses have addressed this issue by evaluating only studies reporting specifically on the outcome of anatomic segmentectomy for early-stage NSCLC. Bao et al<sup>8</sup> in 2014 analyzed the results of 22 studies and reported equivalent efficacy regarding OS and CSS for segmentectomy compared with lobectomy. In contrast, for tumors > 2 cm, segmentectomy showed OS and CSS rates that were inferior to those of lobectomy.

Zhang et al<sup>9</sup> in 2015 included 31 comparative studies in their meta-analysis. They showed no significantly higher recurrence rate after segmentectomy compared with lobectomy in a sample size of 4,658 patients. In particular, no significant difference in local recurrence was observed if considering only the six studies that had patients with stage IA disease. Also, for distant recurrence, anatomic segmentectomy was not associated with a significant increase. Similarly, no significant difference was found in recurrence-free survival (RFS) and OS between segmentectomy and lobectomy in patients with stage IA tumors receiving complete lymphadenectomy, even when considering only the four studies that included patients who underwent video-assisted thoracic surgery (VATS). In comparison,

patients with larger tumors did not show equivalence in RFS and OS if comparing segmentectomy with lobectomy.

Results of both these meta-analyses suggest that anatomic segmentectomy may be particularly effective for small peripheral tumors  $\leq 2$  cm located within anatomic segmental boundaries if associated with systematic hilar and mediastinal node dissection.

Other single-institution retrospective studies have focused on comparative analysis of anatomic segmentectomy and lobectomy, finding results in line with those of the previous meta-analyses.<sup>7,10</sup> Kodama et al,<sup>10</sup> using a propensity-matched model, compared the outcomes in 69 patients for each treatment arm finding no significant difference in 5-year OS rates (97.1% vs 89.7%) and RFS rates (97% vs 97.1%) between segmentectomy and lobectomy for patients with T1aN0 NSCLC.

Given the increasing interest in minimally invasive approaches, recent investigations have focused on the assessment of safety and efficacy of VATS segmentectomy. A systematic review considering either retrospective comparative studies or prospective observational studies has concluded that anatomic video thoracoscopic segmentectomy is a feasible operation with at least equivalent levels of morbidity, recurrence, and long-term survival compared with open segmentectomy.<sup>11</sup> Furthermore, several studies report significant differences in the length of hospital stay, postoperative complications, and duration of chest tube placement, suggesting that in selected cases, thoracoscopic segmentectomy may confer additional perioperative benefit compared with the thoracotomy procedure.<sup>11</sup>

Moreover, a recent retrospective study comparing thoracoscopic segmentectomy with thoracoscopic lobectomy after propensity-score matching has shown equal short-term surgical results and long-term oncologic outcomes between the two procedures.<sup>12</sup>

In conclusion, it is now clear that although segmentectomy is still largely reserved for patients with compromised cardiopulmonary status, recent evidence supports the intentional use of such an operation even in low-risk patients with tumors < 2 cm.

This operation is safe and can be performed using VATS with a similar risk profile and long-term outcome. Moreover, although segmentectomy can be performed for central tumors, the bulk of evidence supporting this procedure with curative intent comes mainly from series

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.<sup>13</sup>

There is no doubt that only the conclusion of the two ongoing randomized trials (CALB-140503 and JCOG-0802) for peripheral NSCLC  $\leq$  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).<sup>1</sup> The Lung Cancer Study Group completed the only available phase III prospective randomized controlled trial (RCT) of sublobar resection vs lobectomy in peripheral NSCLCs  $\leq$  3 cm.<sup>2</sup> Ginsberg

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