

# Sublobar Resection Ongoing Controversy for Treatment for Stage I Non–Small Cell Lung Cancer



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## KEYWORDS

- Adenocarcinoma in situ • Minimally invasive adenocarcinoma • Non–small cell lung cancer
- Sublobar resection

## KEY POINTS

- Improved imaging technology over the past 20 years may have rendered results of the only randomized trial on intentional sublobar resection for stage IA non–small cell lung cancer (NSCLC) outdated.
- Single-institution and population-based analyses suggest sublobar resections have equivalent outcomes to lobectomy in patients with tumors less than 2 cm and in whom adequate resection margin can be achieved.
- Data suggest sublobar resection may be a superior surgical option choice for those 75 years of age and older and those with ground glass nodules.
- Additional randomized trials exploring the intentional use of sublobar resection for stage IA NSCLC are underway, but results are many years away.

## HISTORY

The optimal surgical management of early-stage non–small cell lung cancer (NSCLC) is continuously in a state of evolution. Some of the recent considerations in surgical decision making include open versus minimally invasive approaches, extent of mediastinal lymph node evaluation, use of adjuvant and neoadjuvant therapies, and extent of resection. Recent randomized trials have addressed many of these issues, but the only randomized trial comparing lobectomy to sublobar resection for stage IA NSCLC was the 1995 publication by the Lung Cancer Study Group (LCSG).<sup>1</sup> That trial was conducted at a time when intentional sublobar resection for good-risk patients was gaining in popularity. It was designed to prove that sublobar resections would not be inferior to lobectomies with regard to local recurrence and

cancer-free survival, but reported a 3-fold increase in local recurrence and a nonsignificant decrease in overall survival following sublobar resection. Despite the fact that a subsequent analysis decreased the significance of these differences,<sup>2</sup> this study standardized lobectomy as the treatment of choice for stage IA NSCLC and has guided surgical care for the past 20 years. There is a slow recognition that the findings from the landmark trial may now belong to a different era. The trial completed enrollment in 1988, before the introduction of PET with fludeoxyglucose and the widespread use of computed tomographic (CT) scans for diagnosis and staging. Improved resolution of CT scans have also allowed for detection and precise identification of subtle changes in ground glass nodules (GGNs), which paired with an improved understanding of tumor biology has

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Disclosures: None.

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introduced histologic subgroups with indolent behavior and favorable outcomes. Low-dose CT scans have also served as the basis for new lung cancer screening guidelines by the US Preventive Services, which aims to detect cancers that are smaller and at an earlier stage. Simultaneously, advances in surgical technique, which allow for better tolerated resections, have brought older and poorer risk populations into consideration for anatomic resection. Each of these factors has continued to fuel the controversy over the intentional use of sublobar resection for medically fit, good-risk patients with stage IA NSCLC.

### PROSPECTIVE RANDOMIZED TRIALS

There are now 2 large, multi-institutional prospective randomized trials investigating the intentional use of sublobar resections for stage IA NSCLC: one is underway in North America, Alliance/CALGB 140503,<sup>3</sup> and the other recently completed accrual in Japan, JCOG0802/WJOG4607,<sup>4</sup> but it will be many years before significant conclusions can be made from either. These trials are similar in design to the trial from the LCSG, but much larger in size and with subtle differences in inclusion and exclusion criteria (**Table 1**). The most significant difference may be the limitation in tumor size lesions less than 2 cm.

In the meantime, there is a tremendous amount of data from single-institution retrospective series and population-based analysis to help drive the controversy. Outcomes from retrospective analysis of sublobar resections can be difficult to interpret because sublobar resections are used in 2 divergent clinical settings. They can be used intentionally/electively as a parenchymal sparing option in good-risk patients with small, peripheral, or indolent tumors who would tolerate lobectomy, but they are also used as a compromise procedure in frail and debilitated patients who do not have adequate cardiopulmonary reserve to tolerate lobectomy. One of the most important questions that needs to be asked when embarking on a comparison of outcomes between lobectomy and sublobar resection for early-stage NSCLC is: “what is the specific indication for sublobar resection in this population?” Evaluating surgical outcomes in a heterogeneous population that contains both medically fit and unfit patients has limited utility because short- and long-term outcomes are significantly impacted by medical comorbidity.

### POPULATION-BASED ANALYSIS

Population-based analyses are incredibly informative in situations where randomized data are

lacking. They validate findings from small retrospective reviews and help define cohorts for prospective evaluations. Over the past 5 years, there have been a multitude of articles investigating the role of sublobar resection for NSCLC from the Surveillance Epidemiology and End Result (SEER) registry and the National Cancer Data Base (NCDB). SEER and NCDB are large and powerful oncologic databases, but the information collected may not be granular enough to adequately address the question of intentional sublobar resection for early-stage NSCLC because data on the indication for sublobar resection are not collected. Specifically, was a sublobar resection applied as a compromise procedure in a debilitated patient or as a parenchymal sparing option in an otherwise healthy individual? Both situations represent “curative-intent surgery,” but anticipated outcomes are different. Propensity-matched analysis is frequently used to help circumvent the issue of surgical intent, but neither SEER nor the NCDB is explicit enough with regard to pulmonary disease, the primary source of comorbidity following thoracic surgery. Pulmonary function tests are not reported, and commonly used comorbidity indexes are not specific with regard to pulmonary disease. **Table 2** outlines results of recent population-based studies comparing survival between lobectomy and sublobar resections for early-stage NSCLC. At first glance, results seem contradictory, but on closer inspection, important trends become apparent. Broad comparisons of all stage I or even all stage IA patients seem to favor lobectomy over sublobar resections,<sup>5-8</sup> even in propensity-matched comparisons,<sup>8</sup> but refinements in the study populations related to older age, smaller tumor size, more indolent histology, and more recent year of treatment result in a different conclusion regarding equivalence of outcome.<sup>5,9-12</sup> These population-based analyses serve as important indicators that sublobar resection is likely not appropriate for all stage I NSCLC patients, but in small tumors (<2 cm), well-staged patients, and those with indolent histology, or advanced age, survival results may be equivalent.

### RETROSPECTIVE ANALYSIS

Shortly after the publication from the LCSG, the University of Pittsburgh shared the results of their prospective, multicenter, nonrandomized trial of lobar versus sublobar resection. They demonstrated decreased perioperative mortality for sublobar resections, equivalent 1-year survival, and 5-year actual survival favoring lobectomy (70% vs 58%). Most deaths in this cohort were due to nonlung cancer-related causes, but they also

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