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CALGB 140503: Is it time to turn the page on LCSG 821?

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Abbreviations

NSCLC – non-small cell lung cancer
SBRT – stereotactic whole body radiotherapy

Central Message

Is sublobar resection a viable alternative to lobectomy for small peripheral lung cancer?
Question asked and answered but the devil is in the details.

Central Picture Legend

Nasser K. Altorki, MD (left) and Oliver S. Chow, MD (right)
In 1962, Michael Shimkin, then the Chief of the Biometry and Epidemiology Branch at the National Cancer Institute, reported in this *Journal*, the results of a “systematic analytical comparison” of the survival of patients with non-small cell lung cancer (NSCLC) treated by either lobectomy or pneumonectomy at the Overholt Clinic in Boston and the Ochsner Clinic in New Orleans. Shimkin and colleagues concluded that in the absence of randomized trials “the available evidence suggests that less extensive surgical procedures were related to survival rates that were at least as good as, and perhaps better than, those recorded following more extensive surgery”. This report almost single handedly transformed the surgical standard of care for NSCLC from pneumonectomy to lobar resection. In the following decades several investigators reported results of sublobar resections (wedge or segmentectomy) performed initially in patients with limited pulmonary function and subsequently in patients with stage I disease who had adequate cardiopulmonary function. The putative benefits of sublobar resection included preservation of pulmonary function, a reduction in perioperative mortality, and the ability to offer patients further resections in the event of the development of a second primary lung cancer. In 1995, the Lung Cancer Study Group reported the results of a randomized trial (LCSG 821) comparing lobectomy with sublobar resection in patients with clinical T1(≤3 cm)N0 NSCLC. In their initial report, Ginsberg and Rubinstein reported that compared to lobectomy, sublobar resection was associated with a three-fold higher frequency of recurrence and a 50% increase in lung cancer–related mortality. These results established lobectomy as the standard of surgical care for patients with clinical T1N0 NSCLC.

In the decades since, advances in imaging and staging methods have allowed the detection of smaller and earlier tumors, prompting renewed interest in sublobar resections for patients with...
Clinical stage IA NSCLC (≤2 cm) who might otherwise be candidates for lobar resection. Most recently, two large, randomized trials comparing lobectomy to sublobar resection have been reported\(^7,8\). Japanese investigators reported the results of JCOG 0802, a large randomized trial comparing lobectomy with anatomical segmentectomy in patients with clinical stage IA NSCLC with a tumor size of 2 cm or less\(^8\). Shortly thereafter, the much anticipated North American trial (CALGB/Alliance 140503) also reported its primary results\(^9\). Both trials met their primary endpoint of non-inferiority of sublobar resection to lobectomy, thus establishing sublobar resection as a standard of care for the surgical treatment of a subset of patients with clinical stage IA NSCLC. In this featured expert opinion piece, we will focus on reviewing the available data from the North American trial and will share our interpretation of the data and how they might be optimally disseminated into routine clinical practice.

CALGB 140503 was a multicenter randomized trial designed to determine whether sublobar resection is non-inferior to lobectomy for patients with peripheral clinically node negative NSCLC two centimeters or less in size. The primary end point was disease-free survival, defined as the time between randomization and disease recurrence or death from any cause, whichever occurred first. Secondary end points included overall survival, locoregional and systemic recurrence, and expiratory flow rates 6 months postoperatively. Overall survival was defined as the time between randomization and death from any cause. Locoregional recurrence was defined as recurrent disease in the lung or the hilar nodes of the index lobe. Regional recurrence was defined as isolated mediastinal nodal recurrence. All other recurrence was deemed to be systemic. The trial was activated in June 2007 and completed target accrual in March 2017. Eligible patients were preoperatively registered for the trial and intraoperatively randomized.
after frozen section examination confirmed the absence of metastatic carcinoma in one major hilar and at least two mediastinal nodal stations. For practical sample size considerations, the type of sublobar resection was not randomly assigned but left to the discretion of the surgeon. If the choice was wedge resection, surgeons were encouraged to obtain at least a two centimeter margin or a margin equivalent to the clinical tumor size as determined by the preoperative CT scan. Failing either, a frozen section examination of the resection margin was strongly encouraged. Patients with a positive margin could have either an additional wedge resection or conversion to anatomical segmentectomy if possible or to lobectomy if necessary. Since activation, the trial was monitored by the CALGB/Alliance data and safety monitoring board (DSMB) twice a year. On the basis of interim analyses conducted up to November 2021 and an independent validation analysis in March 2022, the DSMB recommended unanimously to release the data and terminate further monitoring of the trial by the DSMB, noting that there was a minimal chance that the trial may yield a different conclusion at the planned final analysis.

A total of 697 patients were randomized to either sublobar resection (340 patients) or lobar resection (357 patients). After a median follow-up of 7 years, sublobar resection was non-inferior to lobar resection for disease-free survival (hazard ratio for disease recurrence or death, 1.01; 90% confidence interval [CI], 0.83 to 1.24). Five year disease-free survival was 63.6% (95% CI, 57.9 to 68.8) after sublobar resection and 64.1% (95% CI, 58.5 to 69.0) after lobar resection. Exploratory subgroup analysis showed that disease-free survival was similar between arms across age groups, sex, tumor location, tumor size, cell type and ECOG performance score. Additionally, the key secondary endpoint of overall survival was similar between the two arms of the trial (hazard ratio for death, 0.95; 95% CI, 0.72 to 1.26). Five year overall survival was
80.3% (95% CI; 75.5 to 84.3) after sublobar resection and 78.9% (95% CI, 74.1 to 82.9) after lobar resection. No substantial intergroup differences were seen in the incidence of locoregional or distant recurrence. Locoregional recurrence was observed in 10% of patients after lobar resection and 13.4% after sublobar resection. At 6 months postoperatively, a between-group difference of 2 percentage points was measured in the median percentage of predicted forced expiratory volume in 1 second, favoring the sublobar resection group. Although these results from CALGB 140503 are generally consistent with results reported by JCOG investigators, there are important differences in outcomes between the two trials. Perhaps most strikingly, both five-year overall and relapse free survival reported by JCOG 0802 investigators were numerically superior to those reported in CALGB 140503. However, beyond potential ethnic based differences in disease biology, there are important differences between the two trials in baseline demographic and clinical characteristics that may well have contributed to the different survival outcomes (Table 1). Regardless, the results of both trials definitively established sublobar resection by either anatomical segmentectomy or wedge resection as an effective and in our opinion a preferred treatment strategy for a highly selected cohort of patients with clinical T1aN0 NSCLC in whom the absence of metastases to the major hilar and mediastinal lymph nodes is pathologically confirmed.

Although CALGB 140503 may well be a practice changing trial, it leaves us with several unanswered questions. For example, could sublobar resection be best suited for patients beyond 70 years of age? Is it still a good option for patients with tumors approaching 2 centimeters in size? What about patients with poorly differentiated tumors or those with large cell or pleomorphic histology? And of course, last but not least, what is the optimal modality of sublobar resection. While all these are important clinically relevant questions, all large trials are
designed to answer one or at most two research questions that dictate sample size and power calculations. And so it is with CALGB 140503. The trial was adequately powered to test for noninferiority of sublobar resection for the primary end point of disease-free survival. With a hazard ratio (sublobar resection vs. lobar resection) of 1.01 and a p-value for noninferiority of 0.02, the trial met its primary endpoint. All comparisons beyond the primary endpoint including those from post-hoc and unplanned exploratory analyses should be regarded as hypothesis generating and not construed as the result of hypothesis testing. That said, we cannot ignore the elephant in the room: are wedge resections and anatomical segmentectomy oncologically equivalent procedures? Contrary to canonical thoracic surgical teaching, the short answer is a definite: may be. We have recently conducted a post-hoc analysis of CALGB 140503 and reported differences between patients treated by wedge resection and segmentectomy in recurrence rates and survival outcomes. Overall recurrence occurred in 31% after each modality. Although locoregional recurrence was numerically higher after wedge resection, the difference was not statistically significant (segmentectomy: 12%; wedge resection: 14%; p=0.295). Despite the numerically higher locoregional recurrence rate after wedge resection, five year disease-free survival was 63.8% after segmentectomy and 62.5% after wedge resection (p=0.88). Five year overall survival was 81.9% and 79.7% after anatomical segmentectomy and wedge resection respectively (p=0.87). These results suggest that wedge resection and anatomical segmentectomy may be oncologically equivalent in this specific subset of highly selected patients with clinical stage IA NSCLC in whom node negative disease has been pathologically ascertained. Here it is important to emphasize that since the type of sublobar resection was not randomly assigned, rather than advocate for a specific type of sublobar resection, we simply suggest that either modality is acceptable within the constraints defined by the trial. The integration of these results
into clinical practice should be guided by the surgeon’s training, preferences and expertise. At our institution, we have data-driven equipoise for the utilization of wedge and segmental resection for most tumors ≤ 1.5 cm in size. However, we are generally biased in favor of anatomical segmentectomy in younger patients and in those with tumors over 1.5 centimeters in diameter. In this regard, it is essential that thoracic surgeons should possess sufficient versatility in their surgical tool box to convert a wedge resection to anatomical segmentectomy if necessary rather than adopt lobectomy as the default procedure.

We also posit that an important contribution of CALGB140503, is the strong recommendation by trial investigators for implementation of quality metrics that govern the conduct of sublobar resection especially wedge resections. One such metric is the use of frozen section examination to assess the parenchymal margin after both wedge resection and segmentectomy. A positive margin on frozen section was found in 8 of 204 patients who had wedge resection and 2 of 131 who underwent a segmentectomy and in all 10 patients additional parenchymal resection was performed at the index operation. The overall incidence of a positive margin was 5% after wedge resection and 1.5% after segmentectomy. In aggregate, the findings from this trial make it possible to suggest quality metrics for wedge resection that include definition of the specific subset of patients in which it may be appropriate, the associated minimum requirement of mediastinal and major hilar nodal assessment and intraoperative frozen section examination of the parenchymal margin. Establishing quality metrics for wedge resections is critically important since it remains the most common type of sublobar resection reported in the General Thoracic Surgery Database of the Society of Thoracic Surgery\textsuperscript{10}.  


The findings of this study, particularly those related to wedge resection, will inevitably raise questions regarding the role of competing ablative strategies particularly stereotactic whole body radiotherapy (SBRT). To our knowledge, there are no data from randomized trials supporting the use of SBRT in this patient population or indeed in patients with NSCLC who are otherwise good surgical candidates. A more comprehensive review of this topic is beyond the scope of this communication and in our opinion, the role of SBRT in this cohort of patients remains unproven.

**Future directions**

A sobering finding from CALGB 140503 is that 30% of patients with stage IA NSCLC two centimeters or less in size, developed recurrent lung cancer even after lobar resection. Therefore, it is no longer tenable to exclude these patients from clinical trials exploring novel adjuvant or neoadjuvant treatment strategies. Additionally, there are ongoing plans to create a task force that will evaluate the impact of pathological variables such as adenocarcinoma subtypes, lympho-vascular invasion or spread through the airspaces on survival and recurrence. While it is extremely unlikely that a randomized trial of the size and duration of CALGB 140503 will ever be conducted again, thoracic surgeons could (and perhaps should) collaborate to perform prospective controlled observational studies that aim to fill in the knowledge gaps left by this important trial.
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open-label, phase 3, randomised, controlled, non-inferiority trial. Lancet 2022;

399: 1607-17.


Table 1. Differences between JCOG 0802 and CALGB 140503

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<tr>
<th></th>
<th>JCOG 0802</th>
<th>CALGB 140503</th>
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<tbody>
<tr>
<td>Never smokers</td>
<td>55%</td>
<td>10%</td>
</tr>
<tr>
<td>ECOG 1/2</td>
<td>2%</td>
<td>26%</td>
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<tr>
<td>Adenocarcinoma</td>
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<tr>
<td>% with GGO</td>
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