



We Asked the Experts: Minimally Invasive Segmentectomy for Early Stage Lung Cancer—Will it Replace Lobectomy?

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At the International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer in August 2022, Dr Nasser Altorki presented the results of the Cancer and Leukemia Group B 140,503 (Alliance) phase III randomized study comparing lobar versus sublobar resection for clinical stage IA non-small cell lung cancer (NSCLC) with tumor size ≤ 2 cm [1]. In conjunction with the results of the Japanese JCOG0802/WJOG4607L phase III randomized study comparing lobectomy versus anatomical segmentectomy for a broadly similar category of disease [2], the findings suggested to lung cancer physicians worldwide that sublobar resection might henceforth be regarded as the standard of care for early stage lung cancer.

These studies represent two of the largest, highest quality randomized trials in the history of lung cancer surgery. They conclude that 5-year overall survival (OS) and disease-free survival (DFS) were not inferior with sublobar resection vs lobectomy for patients with peripheral cT1aN0 NSCLC and tumor size ≤ 2 cm [2]. Strictly speaking, the findings merely reconfirm the already acknowledged inference from accumulated published data over the years that segmentectomy was acceptable treatment for this selected subcategory of patients [3]. They also do not alter the fact that sublobar resection is already established in multiple guidelines as a preferred treatment

option for selected ‘compromised’ patients who cannot tolerate a lobectomy [3]. In this context, are the largely well-expected results from these two studies really sufficient to mandate switching to sublobar resections for all elective surgery for small, peripheral, early stage lung cancer from now on?

What is the cost?

To become the new gold standard, sublobar resection must be demonstrated to offer better cost–benefit considerations than lobectomy. The CALGB and JCOG/WJOC studies only demonstrate equivalent OS and DFS for sublobar resection versus lobectomy, but do not definitively address some key issues regarding costs:

- The reported rates of mortality (competing deaths) and serious complications were similar in the 2 study arms in both the CALGB and JCOG/WJOC studies. However, most operations were performed by expert surgeon investigators at leading thoracic surgery centers in North America and Japan. Given that segmentectomy is a technically more challenging procedure than a lobectomy, it is unknown whether similar levels of safety can be maintained in real-world settings should segmentectomy be broadly performed worldwide.
- In published interim results from both the CALGB and JCOG/WJOC studies, segmentectomy was associated with higher rates of postoperative air leak and a certain proportion of patients requiring conversion to lobectomy due to bleeding or other causes [4, 5]. It is unclear how much patient harm was incurred as a result and whether this may offset any purported benefits from segmentectomy.

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- In the Japanese trial, almost twice as many patients receiving segmentectomy experienced local recurrence than those receiving lobectomy [2]. Even though OS was not compromised, the cost/harm to the patients related to management of the recurrences is not known.
- The overall added monetary costs of sublobar resection (if any) are unknown, including costs related to: additional resources for pre-operative planning/lesion localization; different operation durations; use of advanced equipment and consumables; management of complications; and management of recurrences.

What is the benefit?

It is generally accepted that the one key advantage of performing a sublobar resection is the preservation of the patient's lung function [3]. The CALGB and JCOG/WJOC studies do not definitively resolve some key issues regarding the benefits of sublobar resection:

- Both studies showed a statistically significant difference in the reduction in spirometry values after surgery in favor of sublobar resection [2]. However, in absolute magnitude, these differences were in terms of a few percentage points only—which are almost imperceptible to patients in most real-world situations. Is this small ‘benefit’ sufficient to justify sublobar resection replacing lobectomy when the costs are not fully known and the survival is similar? It is important for surgeons to remember that the only real reason for selecting a sublobar resection over a lobectomy—especially in the face to the potential harms as outlined above—is the preservation of lung function [3]. With both the CALGB and JCOG/WJOC studies showing that this benefit is so limited, surgeons must consider carefully for each individual patient whether they are offering more good than harm when choosing to perform a sublobar resection.
- The JCOG/WJOC study surprisingly found a small but statistically significant difference in 5-year OS in favor of segmentectomy over lobectomy [2]. However, most of the excess deaths in the lobectomy arm were due to the occurrence of a new cancer (not recurrence of the original lung cancer) during the study period. As these are not explainable by the use of lobectomy per se, and lung cancer-related deaths were similar in both arms, it is not logical to conclude that segmentectomy is a superior lung cancer operation based on current data.

What are the remaining issues?

There are also some questions that the CALGB and JCOG/WJOC studies have left unanswered, but which are important before sublobar resection is embraced as the standard of care:

- Surgeons recognize that not all segments are equally easy to resect. The two studies have not demonstrated whether simple and complex segmentectomies each offer equivalency to lobectomy and to each other in terms of safety and survival.
- In the CALGB study, 58.8% of the sublobar resections were wedge resections rather than segmentectomies [1]. It has not been shown whether wedge resections are equivalent to segmentectomy. This is in fact a critical issue—especially when a preponderance of previous evidence suggests that segmentectomy should yield superior oncological results [3]. Where both are equally feasible, a wedge resection is obviously technically less challenging than a segmentectomy. There is understandably an urge amongst some surgeons to consider that the CALGB study gives license to elect to perform a wedge resection more liberally in future. This would be potentially problematic. The CALGB study has not analyzed the relative pros and cons of wedge resection versus segmentectomy in sufficient detail to reach such a conclusion. Future studies are essential to study this issue in depth before equivalency can be declared.
- Following from the above point, it has been postulated that the previous observations of the superior oncological results of segmentectomy over wedge resection may be due to a greater likelihood of achieving wide resection margins with the former [3]. The hypothesis that follows from this would be: if a wedge resection were performed to match a segmentectomy in terms of resection margins, would the difference in oncological outcomes be null? Future studies to address this are particularly relevant in light of the CALGB study results.
- Given the marginal observed benefits of sublobar resection in terms of lung function preservation, it

remains to be demonstrated whether it is preferable in difficult cases to convert from a minimally invasive segmentectomy to a minimally invasive lobectomy or to an open thoracotomy segmentectomy.

Is it time to switch to sublobar resection now?

Considering the costs, benefits and unresolved issues exposed by the CALGB and JCOG/WJOC studies, this author does not subscribe to the view that all small, peripheral NSCLC should henceforth be resected by sublobar resection—at least for now. There are too many unanswered but critical questions to give a blanket endorsement of sublobar resections in elective situations where lobectomy is feasible. At present, this author still regards lobectomy as not (yet) usurped as the ‘gold standard’ in such situations, but stands ready to change positions should future evidence indicate it. Sublobar resection, however, is indisputably still an essential choice in niche situations, such as in ‘compromised’ patients who cannot tolerate lobectomy or in patients with multifocal NSCLC [3].

What are the future prospects?

The destiny for sublobar resection perhaps lies beyond replacing lobectomy for early stage lung cancer. Instead, its potential for reaching patients with situations beyond lobectomy should be explored, including:

- As lung cancer screening becomes increasingly adopted, will the effectiveness of sublobar resection demonstrated by the CALGB and JCOG/WJOC studies prompt a more proactive approach toward offering surgery for screening-detected lung lesions?
- With the development of increasingly effective neoadjuvant and adjuvant therapies, how will sublobar resection fit in? For example, will segmentectomy be more or less difficult to attempt after neoadjuvant therapy, and will it better complement the start and completion of adjuvant therapy?
- There is now greater understanding of particular subcategories of lung cancer, including: multi-focal lung cancer; oligometastatic disease; salvage surgery

after definitive chemo-/radio-therapy; and so on. The role of sublobar resection for these niches remains to be defined, especially vis-à-vis lobectomy.

Conclusion

The CALGB and JCOG/WJOC trials are landmark studies in lung cancer surgery, confirming the oncological efficacy of sublobar resection for early stage lung cancer. However, they do not provide the answers to all the key questions regarding the costs, benefits and technical considerations about sublobar resection. Hence, it is premature to conclude at this time that lobectomy should be immediately replaced as the standard of care. Future studies should address these questions, but also investigate the role of sublobar resection in therapeutic niches beyond the reach of lobectomy.

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