Peer Review File

Reviewer A

Comments: Segmentectomy is a topic in chest surgery and this paper provides an accurate view on its current status and problems. As the author states, I think it is important to unify the definition of predicates regarding anatomic sublober resection.

Reply 1: Thank you for your comments. We have emphasized on the issue of nomenclature and definition and have changed the title to reflect this.

Changes in the text: Title: The Evolving Field of Sublobar Resection: In Search of the Optimal Operation or the Optimal Definition

Reviewer B

Comments: Nice commentary. I was wondering if this article would be suitable to discuss what your opinion is about redo ipsilateral thoracic surgery after a complex segmentectomy. I cannot imagine how the procedure would look like if we need to do a lower lobectomy following a "proper" anatomic S8+9 segmentectomy.

Reply 1: Thank you for the comment. I have added a statement reflecting this possible challenging situation, which is likely to occur as these surgeries are more frequently being performed.

Changes in the text: It would be interesting to elucidate from those patients who had rescue operations for relapsed ipsilateral disease, what is the feasibility of a completion lobectomy or repeat segmentectomy after a prior anatomic segmentectomy.

Reviewer C

Comments: The commentary discusses the evolving landscape of surgical treatments for

lung cancer, mainly focusing on the outcomes and experiences associated with anatomical partial lobectomy (APL). The introduction highlights the historical shift in the perception of sublobar resection, from being considered a compromise operation to now being recognized for its equivalent or superior oncologic outcomes compared to lobectomy in select early-stage patients. It emphasizes landmark trials such as JCOG 0802/WJOG4607L, which demonstrated improved overall survival with segmentectomy compared to lobectomy but noted higher local recurrence rates.

One weakness of the commentary is the lack of critical appraisal regarding potential biases or limitations in the studies referenced, mainly JCOG 0802/WJOG4607L and CALGB 140503. While these trials are pivotal in shaping current understanding, a more thorough analysis of their methodologies, potential sources of bias, and generalizability of results could provide a more robust foundation for the discussion.

Additionally, the commentary could benefit from a more comprehensive discussion of the potential clinical implications and practical challenges associated with implementing standardized terminology for sublobar resections. While the importance of agreement on terminology is acknowledged, further exploration of how this standardization could be achieved in practice, considering the diversity of surgical practices and regional variations, would enhance the depth of the commentary.

Furthermore, the commentary could expand on the potential implications of the findings from the study by Qiu and colleagues beyond the scope of surgical technique and outcomes. For example, exploring the broader impact on patient quality of life, healthcare resource utilization, and long-term survival trends could provide a more holistic perspective on the significance of the research.

Lastly, the commentary could discuss future research directions in this field. Identifying knowledge gaps and areas requiring further investigation, such as the optimal management of specific patient subgroups or the role of emerging technologies in refining surgical approaches, would enrich the discourse and offer insights into potential avenues for advancement in clinical practice.

Reply 1: Thank you for the review and the thoughtful comments. We have incorporated a more in-depth review of the recent randomized trials (1)We have also expanded on the sublobar terminology and definition debate and expanded on potential implications or solutions for standardization, recognizing the challenges of a systematic universal approach(2). We expanded on our interpretation of Qui and colleagues' current article, but are unable to expand on quality of life, resource utilization or regional variation since this was not published in the manuscript. However, we made comments regarding these

considerations and how these concepts are adopted into real world practices (3). Finally, as suggested, we have expanded on the potential new advances and technology to help surgeons in the optimal adoption of sublobar resection and complex segmentectomy.

Changes in the text:

(1) Over the subsequent decades, we have witnessed a transition in the role of sublobar resection from a compromise operation appropriate for patients unable to tolerate a lobectomy, to that of an equivalent (non-inferior) or potentially superior oncologic results compared to a lobectomy in appropriately selected early-stage patients [2,3]. In a large multicenter phase III randomized prospective trial, the JCOG 0802/WJOG4607L demonstrated for the first time that there is an overall survival advantage in patients undergoing segmentectomy compared to a lobectomy (5-year OS 94.3% vs 91.1%, p=0.0082 for superiority), shifting the paradigm, and establishing anatomical segmentectomy as the procedure of choice for early-stage tumors ≤2 cm in size [2]. However local recurrence occurred more frequently in the segmentectomy arm (10.5% versus 5.4% for lobectomy, p=0.0018). Despite excellent oncological and perioperative results, there are a few limitations of this study which may limit its applicability to everyday practice. There was no reporting of the surgical margins of resection achieved in the cases. Despite a recommended 2 cm margin, smaller margins were acceptable if they were negative on frozen section. Furthermore, the disease biology seemed to be favorable with an outstanding 5-yr disease free survival of 88% in both groups. However, with only 50% of cases had pure solid nodules (CTR of 1.0) and a large proportion of patients were never smokers (44%), suggestive of a less aggressive disease biology in this population.

In another important prospective randomized trial, the CALGB 140503 study also demonstrated excellent oncologic results in patients undergoing sublobar resection (which included wedge resection in 58.8% of cases) with equivalent disease-free survival compared to lobectomy (5- year DFS 63.6% versus 64.1%, p=0.0176)[3]. In this study, the sublobar procedure of choice (segmentectomy or wedge resection) was left to the discretion of the surgeon and systematic nodal dissection was not mandatory. In addition, the recommended margin of resection was larger than 2 cm or at least equal to the size of the lesion, but smaller margins were also acceptable and margin extent was not reported in the results. Despite these limitations, there was no difference in the locoregional disease recurrence between sublobar or lobar resection (13.5% vs 10%, p=NS). We eagerly await more analysis between the outcomes and recurrence between wedge resection or segmentectomy in this study or subsequent prospective trials to add further clarity regarding patient selection and the

performance of a non-anatomic sublobar resection.

With an increased prevalence of smaller tumors detected in lung cancer screening as well as the increased presence of multifocal disease, the importance of lung parenchyma preservation has come to the forefront in lung cancer surgery discussions. Despite the incredibly important contribution of these large, randomized trials, significant questions remain. Are all segmentectomy options equivalent regardless of the tumor location? Given that there is not a clinically significant difference in pulmonary function between segmentectomy or lobectomy, what are the specific tumor or patient factors predictive of a worse post operative or oncologic result that would warrant a lobectomy? Among the segmentectomy options, is the anatomical intersegmental plane enough? Or is the margin achieved the main consideration regardless of performing a wedge resection or a complex segmentectomy?

(2) The increasing use of 3D software, artificial intelligence, and other intraoperative adjuncts such as augmented reality will likely make anatomical identification easier and the consistency of reporting and definitions of sublobar resections will likely become more standardized and uniform across institutions and studies.

(3) One of the major limitations of this study is the lack of oncologic results such as survival or disease recurrence data. Despite this being a retrospective single institution study, the oncologic results will provide further understanding of the locoregional control of sublobar resection and expand on the potential value of the definition of APL compared to a standard anatomical simple or complex segmentectomy.

(4) Improvements in tumor preoperative diagnostics and localization with advanced robotic bronchoscopy and tumor localizing intravenous agents will facilitate further the intraoperative nodule localization, assessment of complete resection and likely improve the selection of optimal sublobar resection approach. As not all institutions will have access to all this technology, considerations of costs, resource management and patient selection will also need to be considered as we take all these innovative approaches into clinical practice.

Reviewer D
Comments:
The Authors commented an interesting manuscript published by Qui et al. which discussed the role of anatomical partial lobectomy (APL) in one of the largest case series

available in literature and the 3D planned reconstruction cases performed that are impressive.

The commentary correctly highlights two of the most important criticisms that are still open questions regarding sublobar resections: what should be considered as a safe surgical margin distance in lung surgery and the unsolved problem of local recurrence after sublobar resections. Qui and colleagues increased the layer of difficulty as concerning resection nomenclature. In this perspective a clear consensus is urgently needed to avoid discrepancies among studies and to make comparisons among sublobar resections' literature more clear. This is maybe the only suggestion I encourage to add into the manuscript, that is clear and extremely well-written.

As reported in the commentary, an important question about this manuscript remains unsolved: is APL considerable also in terms of survival and disease free survival expectancies? In fact, Qui and Colleagues discussed their manuscript in terms of safety and feasibility, that are of primarily importance when performing a surgical procedures, in order to guarantee a safe procedure. Despite this, the postoperative middle and long-term outcomes remain unsuperseedable especially in a control arm (lobectomies). Another criticism is related to benign histologies included, that implemented the difficult interpretation of the results and in this sense the lack of survival and disease free survival analyses appears to be a valuable point of the study. It is clear that a such large cohort is extremely valuable and that, as underlined in the commentary, and survival data and recurrence parameters are already available in other large studies.

Reply 1: Thank you for the kind comments. We have emphasized the issue of margin adequacy and pointed this out as a critique of the recently published randomized trials on sublobar resection. As mentioned above, we have expanded on the issue of segmentectomy definition and consistency as the field evolves as we agree this is an important problem as we try to compare studies and results. We completely agree with your assessment of the incredible potential that this study cohort has in contributing to our understanding of disease recurrence and survival of a well performed anatomical segmentectomy with very wide margins. We eagerly await a follow up manuscript addressing these issues.

Changes in the text:

Despite the incredibly important contribution of these large, randomized trials, significant questions remain. Are all segmentectomy options equivalent regardless of the tumor location? Given that there is not a clinically significant difference in pulmonary function between segmentectomy or lobectomy, what are the specific tumor or patient factors predictive of a worse post operative or oncologic result that would warrant a lobectomy? Among the segmentectomy options, is the anatomical intersegmental plane enough? Or is the margin achieved the main consideration regardless of performing a wedge resection or a complex segmentectomy?

Although obtaining a negative margin is the primary goal of all types of sublobar resection, that fine balance of functional parenchymal preservation with margin size is subject to inherent surgeon bias and creates significant technical challenges. The authors clearly recognized this challenge as their performance of APL gradually increased over time and case volume increased and they found surgeon experience was an important predictor of postoperative complications in the multivariate analysis.

One of the major limitations of this study is the lack of oncologic results such as survival or disease recurrence data. Despite this being a retrospective single institution study, the oncologic results will provide further understanding of the locoregional control of sublobar resection and expand on the potential value of the definition of APL compared to a standard anatomical simple or complex segmentectomy.