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Review Comments

Reviewer A

This review report aimed to provide a concise overview of the surgical treatment of superior sulcus tumors, with particular emphasis on chest wall resection.
This report is wonderfully organized.
I have several suggestions.

We would like to thank reviewer A for his/her kind comments.

Comment 1:
If possible, it would be better to have a Table or something about morbidity or mortality that summarizes the reports so far.

Reply 1:
In line with the reviewer's suggestion, we have added Table 1 to the manuscript, in which we describe the outcomes of studies including more than 40 patients resected for superior sulcus tumors.

> Added Table 1:
> Table 1: surgical and oncological outcomes for patients with superior sulcus tumors (studies including >40 patients)

Comment 2:
In focusing on the technique of combined resection of the chest wall, it would be easier for the reader to understand if there were illustrations of specific approaches.

Reply 2:
We agree with the reviewer, however, there are several textbooks and articles that have excellent drawings and pictures of the several approaches. Instead of reproducing these once more, we have decided to refer to the specific articles: references 23-26.
In addition, we have contacted the Editorial Board of Journal of Thoracic Diseases whether there was some kind of a picture-library owned by the journal, in which copyrighted illustrative material is stored, that would be available for use in the manuscript. Unfortunately, no such database exists.

Comment 3:
References 17 and 18 are duplicated, please delete one of them.

Reply 3:
We have changed the text, and deleted ref 18.

I hope this manuscript will be better and published in the future.

Reviewer B

This is an excellent overview of the basic tenets of SST treatment. Well-written and easy to read. Unfortunately, there simply is not that much new information that cannot be found in any thoracic surgery textbook chapter. I understand the purpose of a review is to summarize the existing literature, and you have done that well. Bottom line is that multiple book chapters have done the same and I am not sure our readership will find that much additional value in this article. If more innovative or novel components could be incorporated (maybe a focus on 3D printing instead of the chest was reconstruction in general), it may be of more interest.

We would like to thank reviewer B for her/his time to critically read our manuscript. We agree with the reviewer's comment that there is a lot in common with existing literature and book chapters. However, we have tried to cite as much recent references as possible. Nevertheless, we have added some more on preoperative planning techniques and reconstruction, and a reference was added:

Added text: page 8, lines 191-196:

The use of 3D-printing reconstructions in the preoperative planning for SST has not yet extensively been investigated, but might be of additional value in planning of complex, high-risk thoracic resections when compared to conventional CT scans and MRI, and may even reduce operating room time (21,22). Although promising, this technique currently is only available in a few highly specialized thoracic centers.

Added text: page 12, lines 285-288:

3D-printing techniques for reconstructive and restorative use, to replace resected structures such as chest wall or vascular structures with biomaterial, will facilitate surgery for complex thoracic tumors and overcome the disadvantages of synthetic material (20-22).

Reference added:

21. Gillaspie EA, Matsumoto JS, Morris NE, et al. From 3-Dimensional Printing to 5-Dimensional Printing: Enhancing Thoracic Surgical Planning and Resection of Complex Tumors. Ann Thorac Surg. 2016 101:1958-62.
22. Pavan Kalyan BG, Kumar L. 3D Printing: Applications in Tissue Engineering, Medical Devices, and Drug Delivery. AAPS PharmSciTech 2022;23:92

Reviewer C

Dear authors, Thank you very much for the excellent review on superior sulcus tumors. I have no major comments to make. The review is well-written and clear.

We would like to thank reviewer C for his/her nice words and comments.

Comment 1:
The only thing that is perhaps missing is a summary table of the main cases and the main authors.

Reply 1:
We agree with the reviewer that a Table with the most important studies may add informative data to the review. We have added Table 1.

Added Table 1:
Table 1: surgical and oncological outcomes for patients with superior sulcus tumors (studies including >40 patients)

Comment 2:
If it's possible should be helpful a table with some key information. It's not obligatory but maybe it could be made more complete your review

Reply 2:
As suggested by the reviewer, we have added a Table 2, with some bullet points for the readers.

Added Table 2:
Table 2: bullet points

Reviewer D
The authors submitted an invited review on superior sulcus tumors. I appreciate the efforts of the authors to summarize the state of the art on the management of these challenging, rare tumors.

We would like to thank reviewer D for his/her comments and suggestions.

Major Comments:
1. The intent of the review was "particular emphasis on the chest wall resection" (line 161) yet less than two paragraphs (lines 263-292) were devoted to the primary aim of this review. I too use PFTE most of the time when performing a chest wall resection through a Paulson-Shaw approach. This is nothing novel that can't be read in any major thoracic surgery textbook. It's reasonable to briefly indicate when chest wall reconstruction should be performed to avoid scapular impingement and traditionally PFTE and Marlex were used. However, also describe newer techniques that have been published using plating systems and highlights the patient centered outcomes

associated with and the pros and cons of each reconstruction material. Finally, go into greater depth on patient selection, management and outcomes of vertebral body resection and reconstruction, as described by the USC, MA Anderson, and Dartevelle groups among others.

Reply 1:
The need for chest wall reconstruction in superior sulcus tumors is rarely needed. For patients that do need restoring chest wall integrity, which we have described in the review, we did several recommendations (…page 10-11, lines 249-255): In most patients with SST, 3 or fewer ribs have to be partially removed to obtain radical surgical margins. For patients with posterior located tumors, this can be performed without the need for chest wall reconstruction. However, in patients with an anterior tumor invading larger parts of the chest wall, requiring 3 or more ribs to be removed, or more than 4 ribs for posterior tumors with risk of scapular impingement (Figure 1), restoration of the integrity of the chest wall is recommended to preserve chest wall stability, mechanics and respiratory function…).

We like the suggestion of going into greater depth of patient selection, management and outcomes of vertebral body resection ad reconstruction. Therefore, we have added the following to the surgical technique section:

Added text: page 11, page 258-263:
Patients with SST invading the spine represent a challenging group, especially for those whose tumor invades the vertebral corpus and spinal canal. Curative intent treatment with partial or complete, single or multilevel vertebrectomy, has been reported with considerable 5-year overall survival rates (43-61%), and acceptable and manageable morbidity in high volume, specialized centers (37-38).

References added:
37. Collaud S, Waddell TK, Yasufuku K, et al. Long-term outcome after en bloc resection of non-small-cell lung cancer invading the pulmonary sulcus and spine. J Thor Oncol. 2013;8:1538–1544.
38. Collaud S, Fadel E, Schirren J, et al. En bloc resection of pulmonary sulcus non-small cell lung cancer invading the spine: a systematic literature review and pooled data analysis. Ann Surg. 2015;262:184–188.

2. I strongly disagree with your comment that "resection in patients with limited N2 may be considered" (lines 187-188). This is in stark contrast to data from INT 0160 which showed that patients with N2 disease did poorly after surgical resection. In fact, N2 disease based on current NCCN guidelines is a contraindication to surgery. Though the current era of chemoimmunotherapy may alter this paradigm, we don't have data to support such a change in clinical practice at this time.

Reply 2:

We agree with the reviewer, resection of patients with N2 disease remains an issue of debate. However, as far as we know from the eligibility data reported, the INT0160 trial did not include patients with N2 disease (T3-4N0-1 only). Induction treatment (CRT) and staging modalities (FDG-PET, EBUS, MRI) all have significantly improved over the years since then, which may result in better outcomes for patients with N2 in recent years: higher dose of RTx on the nodes, improved systemic control with chemotherapy, better exclusion of patients with occult metastases in the brain (MRI instead of CT).
In addition, for patients with SST, locoregional recurrence can cause debilitating pain with severe impact on quality of life. This may be a reason to decide for surgery in selected cases of N2 to establish maximal change for local control.

3. Describe any insight you have on the role of 3 printing for planning (eg, Gillaspie, Ann Thorac Surg. 2016).

Reply 3:
As suggested by the reviewer, which we believe is an important suggestion, we have added the following:

Added text: page 8, lines 191-196:
The use of 3D-printing reconstructions in the preoperative planning for SST has not yet extensively been investigated, but might be of additional value in planning of complex, high-risk thoracic resections when compared to conventional CT scans and MRI, and may even reduce operating room time (21,22). Although promising, this technique currently is only available in a few highly specialized thoracic centers.

Added text: page 12, lines 285-288:
3D-printing techniques for reconstructive and restorative use, to replace resected structures such as chest wall or vascular structures with biomaterial, will facilitate surgery for complex thoracic tumors and overcome the disadvantages of synthetic material (20-22).

Reference added:

21. Gillaspie EA, Matsumoto JS, Morris NE, et al. From 3-Dimensional Printing to 5-Dimensional Printing: Enhancing Thoracic Surgical Planning and Resection of Complex Tumors. Ann Thorac Surg. 2016 101:1958-62.
22. Pavan Kalyan BG, Kumar L. 3D Printing: Applications in Tissue Engineering, Medical Devices, and Drug Delivery. AAPS PharmSciTech 2022;23:92

4. It should be noted that lobectomy is the standard of care resection for Pancoast tumors (lines 225-229).

Reply 4:
This is stated in the manuscript, lines 200-201. For clarification, we have added:

Added text, page 9, line 201:
(e.g. lobectomy + mediastinal lymph node dissection)

Minor Comments:
1. Describe the sensitivity and specificity of MRI and CT for detecting chest wall and vertebral body invasion.

Reply 1:
We have added to the text some more information on the value of CT and MRI in detecting invasion of the chest wall and vertebral body

Added text: page 7, lines 150-160:
A CT scan detects chest wall invasion with a sensitivity and specificity of 38-87% and 40-90%, respectively (11). Although this is a wide range, sensitivity increases with the presence of symptoms, such as pain and muscle atrophy on the ipsilateral side. The sensitivity for detecting chest wall invasion with MRI is 63-90%, and is comparable with CT, although specificity is more consistently, and is reported in the range of 84-86% (12,13), To determine vascular invasion, as well as the relationship of the tumor with the brachial plexus, an MRI is of additional value (14). Although CT scan is superior in identifying vertebral bony involvement iIn patients with an SST in close proximity to vertebral structures, an MRI may help to differentiate between reactive inflammatory changes and true vertebral invasion (15).

Reference added:

11. Quint LE, Francis IR. Radiologic staging of lung cancer. J Thorac Imaging 1999;14:235-46
12. Padovani B, Mouroux J, Seksik L, et al. Chest wall invasion by bronchogenic carcinoma: Evaluation with MR imaging. Radiology 1993;187:33-8
13. Webb WR, Gatsonis C, Zerhouni EA, et al. CT and MR imaging in staging non–small cell bronchogenic carcinoma: Report of the radiologic diagnostic oncology group. Radiology 1991;178:705-13

2. The standard of care for superior sulcus tumors is concurrent chemoradiation. Indicate the pathologic complete response rate

Reply 2:
We have added pCR and MPR rates to Table 1. In addition, pCR has repeatedly been identified as predicting factor for improved survival (Table 1).

Added Table 1:
Table 1: surgical and oncological outcomes for patients with superior sulcus tumors (studies including >40 patients)

3. Highlight some of the larger series on superior sulcus tumors, noting the 5-year survival rates and prognostic factors.

Reply 3:
We agree with the reviewer this is of interest for the readers. We added a table (Table 1) in which we describe the outcomes of studies including more than 40 patients resected for superior sulcus tumors.

Added Table 1:
Table 1: surgical and oncological outcomes for patients with superior sulcus tumors (studies including >40 patients)

Reviewer E
Summary

This invited review article for the Series "Chest Wall Resections and Reconstructions" of the journal deals with current management of complex reconstruction due to surgical resection of sulcus superior tumors invading the chest wall. A trimodality treatment concept with induction chemotherapy followed by surgery is recommended by international guidelines. As en bloc resections of the thoracic outlet with invasion of crucial structures such as nerve roots/plexus, vessels and vertebral bodies are highly challenging, the authors aim to give an overview of operative planning, surgical options and prevention of treatment-associated morbidity.

There are several issues that have to be addressed regarding this manuscript:

1. As with all systematic reviews, this study should follow the PRISMA 2020 statement. Its guideline helps to improve the quality for reporting systematic reviews.

Reply 1:
This manuscript was not intended as a systematic review, but a concise review of the current aspects of surgery for superior sulcus tumors and chest wall reconstruction.

2. Main Body: I would advise you to name your cited guideline (ESMO Clinical Practice Guidelines), in which country this guideline was developed etc. Are there any more guidelines all over the world or is this the only one? This is important since different countries have different resources – is there any difference in patient outcome, local control or overall survival? What exactly is the benefit if one follows this guideline in the context of your specific scientific question?

Reply 2:
We have referred to two guidelines (ESMO and ACCP guidelines), covering large parts of Europe and United states:

2. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv1–iv21.
3. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e314S–e340S.

These recommendations were largely based on the results of the highly cited trials by Rusch and Kunitoh, setting the current standard of care, which is induction chemoradiotherapy and surgery for fit patients with superior sulcus tumors.

3. Page 12, materials used for chest wall reconstruction: which materials are more prone to develop a bacterial biofilm that supports chronic infection and thus cannot be treated by i.-v. antibiotics? How low (in %, range) are "low infection rates" of mentioned synthetic resorbable meshes, biological meshes, etc.?

Reply 3:
We have added to the text:

Added text: page 12, lines 280-288:
With the use of synthetic meshes, a relatively high infection rate (6–22%) in chest wall reconstruction in non-contaminated defects is reported, with up to 42% requirement of removal of synthetic mesh (41).

Reference added:
41. Weyant MJ, Bains MS, Venkatraman E, et al. Results of chest wall resection and reconstruction with and without rigid prosthesis. Ann Thorac Surg. 2006;81:279–285.

4. On page 11, you state "This is in line with the recent expert consensus on resection of chest wall tumors and chest wall reconstruction, in which rigid
implants for chest wall reconstruction is recommended once the maximum diameter of the chest wall defect exceeds 5 cm" – on the following page, you state that rigid reconstruction rarely needed in patients with chest wall resection. Please specify and make it more clear what the benefits and flaws of rigid reconstructions are, when and how often (in %) they are used and why.

Reply 4:
In patients with superior sulcus tumors with dorsal involvement, scapular coverage will

mostly be sufficient, except when more than 4 ribs have to be (partially) removed, with the risk of scapular impingement. However, in our own experience, the need for resection of more than 4 ribs is rare. More specifically, in our series of more 123 patients with superior sulcus tumors resected, only 8 patients had more than four ribs resected [Ünal S, et al. Longterm outcomes after chemoradiotherapy and surgery for superior sulcus tumors. JTO Clin Res Rep. 2023;4:100475]. In anterior located SST, rigid reconstruction is necessary in smaller defects, in line with the recent recommendations from the expert consensus on chest wall reconstruction.
We have discussed the benefits (to preserve chest wall stability, mechanics and respiratory function) and the flaws (infection, scattering) of rigid chest wall reconstruction throughout the manuscript.

5. What about the material used when performing en bloc resection of vertebral bodies?

Reply 5:
This is an issue that has our interest and is depending on the size of vertebral involvement, the number of levels involved, and the need for vertebral corpus replacement /reconstruction: In case of a complete vertebral resection, a cage is placed between the adjacent vertebrae, with dorsal stabilization rods, and sometimes, anterior plate or rod stabilization. A detailed outline of vertebral resection and reconstruction is not within the scope of this review, but will be published in the very near future, as a paper by our group has been accepted pending minor revisions.
We have added the following to the text:

> Added text: page 11, lines 258-263:
> Patients with SST invading the spine represent a challenging group, especially for those whose tumor invades the vertebral corpus and spinal canal. Curative intent treatment with partial or complete, single or multilevel vertebrectomy, has been reported with considerable 5-year overall survival rates (43-61%), and acceptable and manageable morbidity in high volume, specialized centers (37,38).

References added:

37. Collaud S, Waddell TK, Yasufuku K, et al. Long-term outcome after en bloc resection of non-small-cell lung cancer invading the pulmonary sulcus and spine. J Thor Oncol. 2013;8:1538–1544.
38. Collaud S, Fadel E, Schirren J, et al. En bloc resection of pulmonary sulcus non-small cell lung cancer invading the spine: a systematic literature review and pooled data analysis. Ann Surg. 2015;262:184–188.

6. How high are the percentages of impaired healing due to radiotherapy? Are there any numbers regarding implant failure (dislocation, fracture, non-union…)?

Reply 6:
We do not exactly know these numbers, but we do know that radiotherapy can cause

rib fractures, even long after the last radiotherapy dose. In addition, rates of impaired wound healing and infection are higher in irradiated tissue. As a consequence, implants may fail due to infection (e.g. loosening screws in spinal reconstruction) or in case of fixation-site fractures.

7. One of the main goals of your study was to identify factors that prevent morbidity. I can find only 2 of those: antibiotic prophylaxis and specialized rehab programs. Please elaborate more and create an own sub-section in your manuscript, which clearly shows the reader which actions he/she can take to address this issue.

Reply 7:
One of the main goals of this review was to give an update on the contemporary treatment of superior sulcus tumors and chest, with input of an expert team combined with the recent literature. Preventing morbidity is important, as morbidity of this complex type of surgery should not outweigh the oncological benefit from such approach. Therefore, we have made a subheading titled: *Surgical technique and preventing morbidity.* In this section we have discussed several morbidity-preventive measures: limiting pulmonary resection in patients with impaired pulmonary function, the optimal surgical approach, buttressing the bronchial stump to prevent fistula formation, the two-day instead of one-day approach, …etc.

8. Regarding the presentation of current literature: take e.g. George et al. 2017 /ref. #17: since 2018, there are 71 hits in PubMed regarding the implementation of 3D models. Please elaborate more the role of this technique and its currents status in planning such complex therapies.

Reply 8:
We agree with the reviewer this is of interest for the reviewer.

> Added text: page 8, lines 191-196:
> The use of 3D-printing reconstructions in the preoperative planning for SST has not yet extensively been investigated, but might be of additional value in planning of complex, high-risk thoracic resections when compared to conventional CT scans and MRI, and may even reduce operating room time (21,22). Although promising, this technique currently is only available in a few highly specialized thoracic centers.
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> Added text: page 12, lines 285-288:
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21. Gillaspie EA, Matsumoto JS, Morris NE, et al. From 3-Dimensional Printing to 5-Dimensional Printing: Enhancing Thoracic Surgical Planning and Resection of Complex Tumors. Ann Thorac Surg. 2016 101:1958-62.
22. Pavan Kalyan BG, Kumar L. 3D Printing: Applications in Tissue Engineering, Medical Devices, and Drug Delivery. AAPS PharmSciTech 2022;23:92