

Peer Review File

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Review comments

Reviewer A:

The authors have submitted a manuscript on Pancoast tumors.

1. In lines 64-65 the authors reference mediastinoscopy as a valuable preoperative staging method. The authors should mention that endobronchial ultrasound has largely replaced mediastinoscopy and is an acceptable form of mediastinal lymph node evaluation in these situations.

Dear reviewer, thank you for your comments. We will add the following text to the manuscript. EBUS allows access to most mediastinal, hilar, interlobar, and selected intralobar lymph nodes because the lymph nodes are anatomically closely associated with the airways. This explains why EBUS-TBNA was more accurate than mediastinoscopy for staging NSCLC in certain studies.

Reference: Detterbeck FC, et al. Executive summary: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):7S–37S.

Reviewer B:

Congratulations to the authors for the work. I think it has the potential to be published, but certain aspects are worth improving.

Thank you!

-The title has a typo: Pancost.

We changed the title to “Pancoast Tumors” and revised the typos .

-I don't understand very well the structure of the work. The headings Introduction, Evaluation, Staging, Treatment, and VATS for Pancoast tumors appear. There is no concluding heading.

This Manuscript is Pancoast tumors in a journal specialized in VATS. This paper is an invitation for a special issue on Advanced Uniportal VATS. Which why we concluded that VATS should be the focus of the text. However, utilizing VATS for pancoast resections is not a common procedure and the data about this topic is very limited. Thats why we added more description and discussion about the pancoast tumors in general to enrich the script

-In the introduction there is no reference to the objective of the article. In the evaluation and staging, I believe that concepts are mixed and it is not clear what

should be the way to study and evaluate these patients. The conclusion is only one paragraph and exclusively refers to the VATS approach.

We have edited the article accordingly.

Evaluation

-Line 39 ...biopsy is essential for histological confirmation, assessment of operability, and treatment planning...

The concept of operability is relative to the patient, not to the tumor. Tumors are or are not resectable, while patients are or are not operable. I do not understand that the biopsy determines the operability of the patient. I also take this opportunity to say that I am missing some comment regarding the operability study that should be performed on patients (spirometry, diffusion, stress test, cardiology study...).

Thank you for your remark. We will change it accordingly.

Preoperative physiologic evaluation should begin with cardiovascular assessment and spirometry to determine FEV1 and diffusing capacity for carbon monoxide. The anticipated postoperative pulmonary functions (PPO)

should be calculated. If the %-PPO-FEV1 and %-PPO-Dlco are both greater than 60%, the patient is considered to be at minimal risk for anatomic lung resection and no further testing is recommended.

If the % PPO FEV1 or % PPO Dlco are within 60% and 30% of expected values, respectively, a low technique exercise test should be performed as a screening test. The risk of anatomic resection is considered low if patients perform well on the low-tech exercise test (stair climbing > 22 m or shuttle walk distance > 400 m).

A cardiopulmonary exercise test is recommended if the PPO FEV1 or PPO Dlco (or both) are less than 30% or if the stair-climb or commute walk test is inadequate. A peak oxygen consumption (o₂peak) of less than 10 ml/kg/min or 35% indicates a significant risk of death and long-term impairment after major anatomic resection. In contrast, expecting an o₂peak of greater than 20 mL/kg/min or 75% indicates a low risk.

References (23,24) where added

-Line 42 ...Video-assisted thoracoscopy (VATS) may be indicated for tissue diagnosis when other methods are inconclusive, and EBUS and mediastinoscopy, especially on the right side, and/or anterior mediastinotomy may help determine the extent of the disease and should be strongly considered...

I do not see a high probability that VATS can help in the diagnosis of a Pancoast tumor, except if what you want to do is perform an incisional biopsy of the tumor with the consequent risk of pleural dissemination.

I think it should be clearer that the objective of techniques such as EBUS, mediastinoscopy, and mediastinotomy is to rule out or confirm mediastinal lymph

node involvement.

We agree with the editor about his comment. However, we still use VATS in some cases when the tumor is not accessible for CT guided biopsy or other non surgical methods especially in the high apical tumors and we found ourselves needing to perform VATS in these situations.

-It strikes me that authors talk about CT and MRI, but not about PET-CT, when the most frequent cause of Pancoast syndrome, as the authors say, is bronchogenic carcinoma. I think that is where it should be said that PET-CT can help determine the extent of the disease, and that it should be accompanied by a cranial CT/MRI.

We agree with the reviewer and added the following text to the manuscript:

Over the recent decade, the utilization of positron emission tomography (PET) has seen a marked escalation as an integral component of the preoperative evaluation for lung cancer. Within the context of Pancoast tumors, its relevance manifests in dual capacities. Primarily, it facilitates the preoperative staging of lymph nodes and aids in the detection of occult metastases in patients with non-small cell lung cancer (NSCLC) (1). Secondly, PET is instrumental in re-stratifying tumors subsequent to neoadjuvant therapy (3). However, its limitations include an inability to offer precise topographical details regarding the initial lesion, except in the presence of coincident atelectasis. Lymph nodes that display positivity on a PET scan necessitate verification via mediastinoscopy or endoscopic EBUS. Moreover, a negative PET-CT scan does not conclusively negate nodal engagement, hence, invasive staging remains indispensable. For cases presenting with intrinsic hand muscle atrophy, a rigorous neurological assessment is mandated to discern nerve root compromise. (references 17,18 were added)

Staging

-Line 69 ...In a large study of SSTs at Memorial Sloan-Kettering Cancer Center... I understand that SSTs is Superior Sulcus Tumors, but the authors should specify the abbreviations they use. In fact, only VATS is specified. Others such as CCD (line 133) are not defined either. There are more undefined acronyms but I can accept that they are in common use (NSCLC, CT, MRI, EBUS).

We agree with you all the abbreviations will be addressed in a separate paragraph.

-Line 69 ...In a large study of SSTs at Memorial Sloan-Kettering Cancer Center, patients treated with bimodal therapy (preoperative radiotherapy followed by en bloc resection) had a 5-year survival rate of 46% for stage IIB tumors, 0% for stage IIIA tumors, and 13% for stage IIIB tumors. T and N status and completeness of resection influenced survival, with accurate staging significantly impacting survival. However,

pathologically complete resection was achieved in only 64% of T3 N0 and 39% of T4 N0 tumors (24)...

I think just as remarkable as that work cited by the authors (Rusch VW, Parekh KR, Leon L, Venkatraman E, Bains MS, Downey RJ, Boland P, Bilsky M, Ginsberg RJ. Factors determining outcome after surgical resection of T3 and T4 lung cancers of the superior sulcus. J Thorac Cardiovasc Surg 2000;119:1147-53), would be another later one (Rusch VW, Giroux DJ, Kraut MJ, Crowley J, Hazuka M, Winton T, Johnson DH, Shulman L, Shepherd F, Deschamps C, Livingston RB, Gandara D. Induction chemoradiation and surgical resection for superior sulcus non-small cell lung carcinomas: long-term results of Southwest Oncology Group trial 9416 (Intergroup trial 0160. J Clin Oncol 2007;25:313-8). The work of the Intergroup Trial 0160 (SWOG 9416) of the year 2001, evaluated patients in stage T3-4N0-1 after 2 cycles of cisplatin-etoposide plus 45 Gy of concurrent radiotherapy, achieving complete resections in 91% of T3 patients and 87% of the T4 with a post-surgical mortality of 2.3%. Pathologic complete remissions were achieved in one third of cases, microscopic residual disease remained in one third, and macroscopic viable tumor remained in one third, pathologic complete response being the main prognostic factor for survival.

We agree with you and will add this important data to the manuscript with references (30-32)

Treatment:

-Line 98 ...inoperable, or medically inoperable disease...

I think the authors confuse inoperable with unresectable again.

We will change according to your note.

-A reference could be made to a treatment guideline for patients with bronchogenic carcinoma, such as the nccn guidelines, in which the treatment scheme for pancoast tumors appears in detail.

definitely we will add The nccn guidelines to the references (44).

VATS for pancoast tumors:

-I can understand that the authors intend to emphasize the minimally invasive treatment of these tumors, but I believe that dedicating paragraphs 139 to 153 to describe the evolution and development of the VATS uniportal seems unnecessary given that it does not seem to be the objective of the work of according to the title (Pancoast Tumors). Likewise, they talk about the benefits of VATS surgery compared to open surgery, citing retrospective studies when we now have the results of a randomized study presented at the World Congress on Lung Cancer and the European Congress on Thoracic Surgery (VIOLET, Eric Lim et al). .

definitely we will cite this important study and add the references (47).

-Line 127 ...VATS approach demonstrated similar oncologic efficacy compared with the standard technique for the resection of Pancoast tumors...

I would like to know what studies the authors are relying on to make this claim.

We will edit the text as there is still no such comparative study in the literature, the text should be (VATS must be performed only when maintaining the oncological principles as in open surgery).

Bibliography:

-Ref 9 does not contain the number, volume or pages of the study. Authors and journal publication only.

Reference: (9) Shahian DM, Neptune WB, Ellis FH., Jr Pancoast tumors: improved survival with preoperative and postoperative radiotherapy. *Ann Thorac Surg* 1987;43:32-8.

-The title of the studys are missing from ref 25 to 36.

-Some refs have numbers in parentheses with uncertain meaning (33, 25 and 18).

-Some refs have doi and others (most) don;t. The same format should be used in all references.

We have revised and edited all the bibliography according to the reviewers remarks.

Figures

-Figures 1 and 2 do not have identifiable elements.

SUMMARY: I think it can be a good review of Pancoast tumors, but it needs a major review. There is too much information on VATS surgery (and uniportal VATS) and important details of the study and treatment of these patients need to be better defined. The bibliography also deserves a full review.

Reviewer C:

The topic of this paper is really interesting, because highlights the potential usefulness of minimally invasive approaches such as UniVATS for traditionally open-approached tumors like Superior Sulcus Tumors.

After careful review of the manuscript, it seems to deserve a comprehensive review.

General

- Authors have not clearly defined the type of paper they submit. As these papers are an invitation for a special issue on Advanced Uniportal VATS,

many authors have submitted Clinical Practice Review, but authors should decide first which type of article meets their purpose and then adjust the sections according to the guidelines

(<https://vats.amegroups.com/pages/view/guidelines-for-authors>)

Introduction

Thank you for your comment and remarks.

This article is an invited paper for a special issue on advanced uniportal VATS.

We have wrote a Clinical Practice Review and tried to review the topic in brief then to add our initial experience in this kind of surgeries. The journal guidelines will be considered in the revised manuscript.

- “These symptoms are attributed to the invasion of different structures such as the parietal pleura, endothoracic fascia, bony skeleton of the apex, and nerves such as the brachial plexus, sympathetic chain, and stellate ganglion”. I think that authors should include subclavian vessels as other structures that potentially can be affected in superior sulcus tumors (SSTs), and their clinical Symptoms.

We have edited the manuscript according to the reviewer comments.

Evaluation

- Diagnosis of SSTs has been lightly described, but deserves more accurate description. For diagnosis, imaging tests that have been described (Chest x- ray, CT, MRI) could be accompanied by diagnostic accuracy in terms of sensitivity and specificity. For cito/histological diagnosis, transthoracic needle aspiration (TTNA) or core biopsy are the most common approaches, but fiberbronchoscopy should also be performed, and their accuracy could be shown and summarized. VATS is usually performed for treatment, for exploration in order to rule out pleural implants or assess resectability, for mediastinal lymph node assessment, but is not commonly performed for primary tumor diagnosis due to the risk of pleural seed.

We have will edit the text according to the reviewer comments. We spare VATS biopsy for few cases when the tumor is non accessible via non-Invasive methods.

Staging

- SSTs usually deserve specific section in NSCLC clinical guidelines, depending on if they show T3 or T4 component. More information regarding staging methods can be included. PET-CT scan is mandatory in order to rule out distance disease and for hilar/mediastinal ipsi/contralateral nodal involvement. Invasive mediastinal assessment is mandatory because only N0- I SSTs benefit for surgical modality within multimodal treatment. EBUS and EUS are considered nowadays the first line techniques for mediastinal

assessment. In cases of positive CT/PET-CT but negative EBUS-NA, mediastinoscopy, mediastinotomy, VAMLA or VATS should be performed to rule out lymph node metastasis. We will edit the text according to the reviewer comments.

Treatment

- Standard treatment for SST is induction chemorradiation followed by radical resection + adjuvant treatment, or definitive concurrent chemorradiation followed by Durvalumab in non-resectable cases. As this paper aims to illustrate the use of Uniportal VATS in these cases, a brief description of traditional surgical approaches for SST should be included (Dartavelle, Grunenwald, Hemiclamshell, Shawn-Paulson...)

We have edited the text according to the reviewer comments and added the relevant references.

VATS:

- General background and description of VATS is beyond the aim of this paper (lines 116-128). Authors should focus in how VATS could approach SST resection.

- Comparative results of VATS or Uniportal VATS and open approach for SST resection has been mentioned, but should be shown and referenced.

We have edited the text according to the reviewer comments and added the relevant references.

- General background and description of uniportal VATS is beyond the aim of this paper (lines 143-158). Authors should focus in how uniportal VATS could approach SST resection.

- Digital assessment of the resection field seems not to be an accurate method for assessing the type of resection. If doubts, intraoperative frozen section of samples in the margins is mandatory.

We have edited the text according to the reviewer comments and added the relevant references.

- Authors have just mentioned but not clearly described the hybrid approach step by step.

Authors could include more figures and specifically videos to illustrate their technique of combined open approach for the superior sulcus and uniVATS for the lobectomy and lymph node dissection.

We will add illustrative video to describe the technique.

Lymph node dissection is similar to the technique that we usually perform in any other standard lobectomy.

- Do the authors have their own data analysis of the cases performed through this hybrid approach? Can they compare or show published case series or comparative studies? Which are the benefits of a hybrid or combined approach compared to traditional open approach?

Our experience with the hybrid approach is initial and limited for few cases, it's not suitable for conclusive studies.

Conclusion

- Conclusion section should be clearly identified out of other sections

Figures and Videos

- Video and Figure legends have not been included

- Figure 2 is low quality, do the authors have higher quality one?

I think the paper deserves MAJOR REVISION with important changes before Publication.

We have edited the text according to the reviewer comments an added Videos and the relevant references.

Further review comments

Reviewer B:

1- Eric Lim's work was published in NEJM Evidence last year, in case the authors prefer to change the reference and include the final work instead of the project. It can be accessed at <https://evidence.nejm.org/doi/10.1056/EVIDoa2100016>

Answer 1: We have changed the citation according to the reviewer recommendations.

2- I think it would improve the surgical part of the work to include some reference to works that already talk about hybrid approaches in cases of Pancoast tumors. I cite some that may serve as examples:

*Uchida S, Suzuki K, Fukui M, Hattori A, Matsunaga T, Takamochi K. Hybrid robotic lobectomy with thoracic wall resection for superior sulcus tumor. *Gene Thorac Cardiovasc Surg*. 2022 Aug;70(8):756-758. doi:10.1007/s11748-022-01839-x. Epub 2022 Jun 6. PMID: 35666358.

*Hireche K, Moqaddam M, Lonjon N, Marty-Ané C, Solovei L, Ozdemir BA, Canaud L, Alric P. Combined video-assisted thoracoscopy surgery and posterior midline incision for en bloc resection of non-small-cell lung cancer invading the spine. *Interact Cardiovasc Thorac Surg*. 2022 Jan 6;34(1):74-80. doi: 10.1093/icvts/ivab215. Epub 2021 Jul 30. PMID: 34999810; PMCID: PMC8932506.

*Oka S, Ono K, Kajiyam K, Yoshimatsu K. A minimally invasive and safe surgical approach to resect anterior superior sulcus tumors. *Int J Surg Case Rep* 2020;68:148-150. doi: 10.1016/j.ijscr.2020.02.047. Epub 2020 Feb 28. PMID: 32145568; PMCID: PMC7058854.

*Kawai N, Kawaguchi T, Yasukawa M, Watanabe T, Tojo T. Less Invasive Approach to Pancoast Tumor in a Partitioned Incision. *Ann Thorac Cardiovasc Surg*. 2017 Jun 20;23(3):161-163. doi: 10.5761/atcs.nm.17-00019. Epub 2017 May 9. PMID: 28484150; PMCID: PMC5483865.

Answer 2: We have changed the citation and the text according to the reviewer recommendations.

3- -Figure 2 is confusing to me. Would it be possible to identify structures in some way?

Answer 3: We have added some marks to the figure according to the reviewer recommendations and will be attached.

Reviewer C:

1- Treatment section: authors have summarized the protocols of treatment for SST based on clinical guidelines but this section appears a bit confusing and messy. I'd recommend they re-structure again this section for better reader's understanding trying to concisely summarize the outcomes after the different historical treatment regimens used in SST.

Answer 1: We have restructured the section in a more simple language according the reviewer recommendations.

2- VATS for Pancoast tumors: the manuscript takes part into an Advanced Uniportal VATS special issue. I think the section should be re-labeled Uniportal VATS for Pancoast Tumors. In this sections, author's are encouraged to describe the potential application of Uniportal VATS for SST's resection. As in SST's there is a need for chest wall resection, in some cases including spinal or vascular resection and reconstruction, uniportal VATS can only be performed in the context of a hybrid approach. The purpose is to describe the hybrid approach including brief description of the open techniques for chest wall involvement (Dartavelle, Grunnenwald, Shaw Paulson...) and then description of technical aspects of uniportal VATS for pulmonary resection after open technique. Conventional closed or assisted multiportal VATS are beyond the aim of this review. I would suggest authors to include more detailed surgical pictures illustrating the findings of uniVATS after open approaches for chest wall involvement. I'd also suggest inclusion of surgical videoclips reflecting the combination of the open and uniportal VATS approaches. It would also be great if authors briefly review the evidence of uniportal VATS in combined hybrid approach for SST resection, if available, and if not clearly remark the lack of this information. The aim of this special issue including this chapter, is to provide reader's with scientific data and technical details for safely performing the described procedures.

I encourage authors to review the manuscript again and provide the missing expected information for better understanding and educational purpose.

Answer 2: We have edited the section according the reviewer recommendations.