

Peer Review File

Article Information: <https://dx.doi.org/10.21037/vats-23-80>

Review Comments

Reviewer A

Dear Authors,

General Comment: This is a basic review article. Although it is interesting, many papers have already been published and the authors missed important papers in the references. Moreover, there is no future perspective. The authors wrote a strong message about the indication for metastasectomy “We also review the indications for minimally invasive metastasectomy and perform a critical assessment of the associated literature. The choice of which technique remains at the discretion of the surgeon and their respective institution”. This need further discussion as things are not so simple.

General Reply 1: Thank you for the thorough review of our work. We appreciate the reviewer’s critique as well as the push to offer for more definitive recommendations. We have made several changes throughout the text in light of these recommendations.

Specific changes include:

- a. Additional discussion of indications for metastasectomy (see response to comment 1 below)
- b. A more focused description of the aims and framework of this review (see response to comment 2)
- c. Addition of references indicated by the reviewer (see response to comment 1 and comment 3)
- d. Addition of future directions subheading (see response to comment 4)

We believe that these revisions have strengthened this work and appreciate the reviewer’s comments and insight.

Changes in text: Please see below for the in-text changes specific to each comment.

COMMENT 1: Line 107 Indication for Minimally Invasive Metastasectomy The choice of which technique remains at the discretion of the surgeon and their respective institution. I think that in this chapter more innovation is necessary and a window should be open toward the future. The dogma to operate at the discretion of the surgeon and their respective institutions is old, and should be changed. There are sign where a personalized treatment could be performed on the basis of a proposed staging/classification for lung metastases which can help

in the future to make the decision who operate or not (1,2). Authors are encouraged to further discuss this concept.

Response 1: We agree with the reviewer that personalization of treatment should be based on individual risk factors and tumor biology. This should be incorporated into a shared-decision making process between clinicians and patients. We have rewritten the sections identified by the reviewer to better reflect this point and included the two suggested references.

Changes in Text 1:

Highlight Box:

What is the implication and what should change now?

- Patient characteristics and tumor biology determine who is most likely to benefit from pulmonary metastasectomy. Minimally invasive metastasectomy can prolong overall and disease-free survival in well-selected patients. There are a variety of highly-effective localization techniques that can be used to facilitate minimally invasive metastasectomy and spare patients from the morbidity of a thoracotomy.

Line 137-153:

“More recently, other considerations for metastasectomy have been evaluated to help select patients most likely to benefit from pulmonary resection. Together these factors comprise a proposed TNM classification system for pulmonary metastasectomy and include primary tumor activity, nodal involvement, and number of metastasis (10). Additional risk factors for recurrence after pulmonary metastasectomy include age less than 70 and presence of extra-thoracic metastases. The type of primary tumor is also an important consideration (11). The timing of pulmonary metastasis relative to the original date of diagnosis can be considered as well. Synchronous pulmonary metastases are identified at the time of original primary cancer diagnosis. These are associated with a worse prognosis overall than metachronous pulmonary metastases which develop later as a site of progression or recurrence (12). In general, the number of pulmonary metastases should not be increasing in patients where pulmonary resection for disease control is planned. The ongoing appearance of new sites of disease within the lung suggests more diffuse and systemic disease than what is currently visualized on a chest CT scan and local control of pulmonary disease in these patients is less likely to improve overall survival. Together, these works speak to the need to personalize treatment based on individual risk factors and the biology of tumor.”

Conclusions (Line 548-556):

“The decision to proceed with minimally invasive pulmonary metastasectomy should be based on a patient’s individual risk factors, likelihood of successful local control, absence of other sites of systemic disease, and tumor biology. Minimally invasive pulmonary metastasectomy in conjunction with localization procedures is associated with a >95% success rate. The choice of localization technique is at the discretion of the surgeon and their institutional practice. Understanding the advantages and disadvantages of different methods can help guide the thoracic surgeon towards better patient outcomes based on the available

resources. Direct comparison of systemic targeting and traditional image-guided labeling through randomized trials is needed to determine the optimal modality.”

Comment 2: Line 103 Herein, we review the indications for minimally invasive Which method has been used for this review? Where the guidelines for one of the review articles of the journal followed? (<https://vats.amegroups.org/pages/view/guidelines-for-authors#content-3-7>) How the studies included in the paper have been chosen? I think that readers should know how the references have been chosen.

Response 2: We followed the journals guidelines for a clinical practice review as outlined below. We have clarified this point in the introduction section of the manuscript which is excerpted below. In short, our aim for this manuscript is a focused clinical assessment and overview of available localization techniques. We did not aim for comprehensive systematic or scoping review.

2.2.4 Clinical Practice Review

A clinical practice review is often shorter than a systematic review, a scoping review, or a narrative review. It mainly provides a summary of clinical issues involving clinical manifestations, diagnosis, treatment, prognosis, etc. It often requires perspective and expert opinion along with evidence-based review and may include early or unpublished observations. For example, it can be a detailed step-by-step and **empirical summary of certain surgical techniques or approaches**; **it can be a comparative summary of several treatment approaches; it can also be a review of a controversial clinical issue to sort out the controversy and the possible best approach, and so forth.**

Changes in Text 2: See introduction lines 120-124

“Herein, we provide a brief review of the indications for minimally invasive pulmonary metastasectomy and in-depth comparison of the effectiveness and safety of each localization method. Our aim is to provide the reader with a focused clinical review of the available techniques and the limitations of the current literature.”

Comment 3: Line 242-257. paragraph 99mTc

The british experience with 99mTechnetium and methylene blue (3) has been missed from the list of references.

Response 3: The reviewer is correct and the omission of this reference is an error on our part. The reference has been added and the text/tables modified appropriately.

Change in Text 3: See lines 336-344 and Table 2

“99mTc radiotracer has a success rate of 95-100% in localizing and resecting lesions (60–71). The marker remains localized at the site of injection up to 24-36h after injection (53), allowing for flexibility in scheduling operations. Intraoperatively, the handheld gamma probe provides continuous reassessment of location to confirm accurate resection. This

technique can be combined with injection of methylene blue to provide an additional visual guidance (71). The procedure is well-tolerated and has minimal risk of complications and morbidity; however, pneumothorax has been reported during radiolabeling (63). Spillage of radiotracer into pleural space is possible, especially if the injection site is near the pleural surface of a major fissure.”

Excerpt of Table 2:

Radiotracer (99mTc, 99mTc-MAA)	Detection of radioactivity with gamma probe	Percutaneous or navigational bronchoscopy	VATS or RATS	36 hours	-Hand-held gamma probe can be used with docked robot -Can be combined with dyes and other visualization techniques	-User dependence -Special precautions with use of radiotracer	Case series, prospective trials, retrospective cohort studies
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Comment 4: Localization of the nodule intraoperatively could take advantage of using 3D reconstruction and intraoperative navigation (4). What the authors think? You should add few lines, discuss further development.

Response 4: This an interesting and emerging technology. We agree that it is worth discussion but given that it is at the pilot stage we have placed it in subsection focused on Emerging Technologies rather than the main body. In this subsection we discuss other developing techniques that have not yet reached widespread clinical practice.

Change in text 4: See lines 502-520.

“In addition to the more established techniques described above, there are emerging technologies being evaluated in animal models and early pilot studies. This includes augmented reality and navigational systems, in which pre-operative CT-scans and localization markers are used to generate a 3-dimensional projection of the lung and an associated nodule, which can be viewed on a surgeon worn headset during the resection (94). This technology has shown promise in animal models and human trial with a 70% success rate (95). It has the advantage of streamlining the localization process but its cost and benefit over existing technologies has not yet been evaluated.

The use of artificial intelligence is also being evaluated. This technology is already used in the radiologic identification of pulmonary nodules, but may soon be available for intraoperative assessment (96,97). Broadly, this technology can aid surgeons by predicting intraoperative pathology and helping ensure adequate margins (97). It has been used to in neurosurgery and endocrine surgery to help identify residual malignancy and the likelihood for nodal metastasis (98–100). The introduction of artificial intelligence to thoracic surgery is likely eminent, although the exact manner in which it will be employed is uncertain.”

Comment 5: Have the guidelines for a review article of VATS journal been followed? References have not been written according to the Vancouver reference style as requested by the journal

Response 5: We have followed the VATS journal Clinical Practice Review guidelines outlined in response 2. We have corrected the references, and they are in the Vancouver reference style as requested.

Change in Text 5: Please see revised reference section.

Reviewer B

Comment 1: I would like to compliment the authors on developing this well written manuscript.

I recommend that the manuscript be accepted for publication

It provides a thorough overview of the existing literature

As a suggestion a Figure can be added that provides clinical images of the use of several techniques.

Response 1: Thank you very much for the review of our work. We have added an additional figure (figure 2-3) with some examples of the described techniques.

Change in Text 1: See figure 2-3.