

Peer Review File

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Review comments

Reviewer A

Comment 1: We very much appreciate the possibility to review this article on the topic of local therapy of pulmonary metastases. Even though we very much enjoyed reading this article, we must admit the manuscript does not add much to the currently available literature on this topic.

Reply 1: Thank you for this comment, however a narrative review need not necessarily provide new information. It is a comprehensive rundown of current available literature on the topic. Likewise, it provides a quick reference review on the topic for practitioners.

Comment 2: Furthermore, in line 171 the STS expert consensus (PMID 30476477) is used to claim that a thoracotomy should be recommended to achieve a complete resection. However, the consensus document states that open techniques are appropriate when a R0 and parenchymal-sparing resection cannot be accomplished by minimally invasive surgery. This is a misrepresentation of the current literature and not in line with the current practice, as shown in a recent publication of a ESTS survey on this topic (PMID: 36847670).

Reply 2: Line 173-176 statement revised as follows

“However, according to the 2019 Expert consensus on pulmonary metastasectomy, in cases where complete and parenchymal-sparing surgical resection is not achievable via minimally-invasive techniques, open surgery is still appropriate. (33).”

Comment 3: Also, we believe that the evidence on local treatment of early-stage NSCLC does not belong in a narrative review on the local treatment of pulmonary metastases, Line 287.

Reply 3: Upon consideration of reviewer comment, line 287 MISSILE-NSCLC trial result statement omitted because this is not in line with the objectives of the review and might confuse readers. References 76-84 numbers and references list adjusted accordingly.

Comment 4: Lastly, we believe that the readability and message of the article can significantly improve by providing recommendations on when to use the different tools in the armamentarium for the local treatment of pulmonary metastases.

Reply 4: As much as the authors would like to provide recommendations on when to apply each modality, this may be beyond the scope of the review seeing as the various hybrid approaches are still in its experimental phase. This point is emphasized by adding lines 419-430 as follows:

“Future plans and studies needed

In summary, the data gathered in this review paint a clear picture of the time lag between large prospective studies that demonstrate the effectiveness of various approaches and the swift advancements in imaging technologies, surgical techniques, and medical treatments for metastasectomy. Identifying this knowledge gap can influence the direction of future research. Although incidental reports and retrospective studies offer some insight into the benefits of combined therapies involving surgical oncology, chemotherapy, and radiotherapy for pulmonary metastases, there is still a lack of clinical trials and large prospective studies investigating the application of these hybrid approaches and their comparison to the current standard of care. Clearly, further exploration is needed regarding indications, contraindications, timing, and sequencing of therapies, but the implementation of hybrid approaches for stage IV lung disease appears promising.”

Reviewer B

Thank you for the opportunity to review.

Overall an interesting article with good research methodology. The focus on hybrid approaches is particularly interesting.

Some points for improvement:

Comment 5: On Page 7 - is it possible to compare the 5-year survival rates to patients who don't undergo surgery to provide a better context to the survival advantage

Reply 5: Unfortunately, since the references cited are systematic reviews, the said reviews did not provide 5year survival rates for patients who did not undergo surgery. Hence, a comparison of 5year survival rates for patients who underwent PM and those who did not undergo surgery cannot be made for this review.

Comment 6: On Page 9 - You mention wedge resections, segmentectomies, lobectomies and pneumonectomies but don't discuss at all. It might be worth a short paragraph comparing the outcomes with these different approaches.

Reply 6: The authors believe that a different review article addressing surgical approaches to pulmonary metastasectomy is assigned for this series by the guest editors to another group of authors. However, to address reviewer suggestion, lines 178-183 briefly discussing the surgical options was added to the manuscript as follows:

“For metastatic lesions presenting as peripheral nodules, wedge resection with adequate margins is employed as a parenchymal-sparing technique. Anatomical resections for complete excision of centrally located or bulky tumors, as well as multiple synchronous lesions in one segment or lobe may be addressed by segmentectomy or lobectomy. The incidence of pneumonectomy for PM is cited at 1.16% and continues to decline due to the availability of modern therapeutic alternatives (34, 35).”

Comment 7: On Page 10 - When discussion small pulmonary nodules: It would be worth discussing intra-operative near-infrared imaging to detect small pulmonary

metastases (a technique that is gaining traction)

Reply 7: Added lines 230-233 to include NIRS for nodule localization as follows:

“Another technique that is gaining traction is the use of near-infrared spectrometry or NIRS in combination with indocyanine green to detect occult nodules as small as 0.2cm within 2cm from the pleural surface (52,53). Precise localization of nodules that are undetectable by PET-CT and manual palpation can now be performed without resorting to open thoracotomy.”

Comment 8: On Page 13/14 - Your discussion about the MISSILE-NSCLC is lacking some detail. You only mention the 60% response to SABR (pre-surgery), but do not discuss the post surgical outcomes of this study. Please add information about post surgical response, complications, etc.

Reply 8: In line with reviewer A comments, we omitted MISSILE-NSCLC study from this review since this topic is not within the objectives of this review and results might confuse the reader.

Comment 9: Page 14 - You say "Neoadjuvant SABR followed by radical-intent surgery after 3-6months as a hybrid approach can potentially..." but there is minimal evidence to support this. Please make it clear that the evidence is poor, and maybe mention newer trials (eg. PSPM) which are aiming to add more information

Reply 9: Added lines 357-361 to emphasize gap in evidence-based information.

“Neoadjuvant SABR followed by radical-intent surgery after 3-6months as a hybrid approach can potentially provide local control and tumor sterilization with minimal toxicity but substantial evidence to support this hypothesis is still wanting. Given the scarcity of data on pCR and underwhelming regional control and survival rates, current efforts are aimed at investigating a hybrid approach which involves the use of neoadjuvant SBRT followed by radical-intent surgery. This technique has the potential to grant improved outcomes while simultaneously providing data on tumor sterilization. The ongoing post-SBRT pulmonary metastasectomy (PSPM) trial is currently examining the efficacy and safety of this method (82).”

Comment 10: Page 15 - Isolated lung perfusion section requires more detail. There are already a few completed Phase II trials (10.1016/j.athoracsur.2019.02.071 , <https://doi.org/10.1097/JTO.0000000000000279>). Please discuss the results of these trials and their implications

Reply 10: Revised lines 381-395 to include results of phase II trials of Isolated lung perfusion and added SPAP as suggested by the reviewer.

“Isolated lung perfusion (ILuP), the intraoperative administration of chemotherapeutic agents through an isolated pulmonary circulation has been extensively studied in animal models since 1983 and phase II trials with agents such as melphalan has been proven to be safe and feasible in humans (85,86). ILuP was founded on the basic principles of isolated limb and liver perfusion and was touted to be an attractive and promising surgical technique for the delivery of high-dose chemotherapy with minimal systemic toxicity in experimental models and phase II human studies (87,88). In patients with

stage IV colorectal carcinoma and sarcoma, ILuP with melphalan combined with PM showed comparable morbidity rates, length of stay with a local recurrence rate of 43% in 3years (89). In theory, locoregional control should be superior with the combination surgical resection for gross disease and isolated lung perfusion for micrometastasis. Building on this concept, selective pulmonary artery perfusion (SPAP) with blood flow occlusion (BFO), an endovascular technique for the delivery of high-dose chemotherapeutic agents to the ipsilateral pulmonary artery via femoral cannula, postulated to achieve tumor and nodal down-staging by enhancing drug delivery (90). Compared to ILuP, this less invasive procedure can be repeated multiple times and has shown promising results in rat models (91).”