

Peer Review File

Article Information: <https://dx.doi.org/10.21037/vats-23-41>

Review comments

Reviewer A:

Comment 1: There are a lot of data and result in the article with support of references, but it needs to be more precise. E.g. evidence of mediastinal lymph node dissection via thoracotomy is not really related to current topic of minimally invasive metastasectomy.

Reply 1: *Thank you for this comment. We agree that mediastinal lymph node dissection via thoracotomy is not really related to the current topic. We have removed that portion of the manuscript.*

Comment 2: The oncological benefit of VATS metastasectomy is not well illustrated. There are spelling and grammar mistakes in line 240 and 242.

Reply 2: *A paragraph has been added to the end of the “Background” section of the manuscript that discusses oncological benefit of VATS metastasectomy. The spelling and grammar mistakes have been corrected.*

Reviewer B:

Drs Sheth and Harano have composed a narrative review of less invasive metastasectomy operations for metastases from colorectal cancer.

Comment 1: It is not stated in the title that this paper is about lung metastases. As it is submitted to a journal of video assisted thoracic surgery it can be assumed by readers but pulmonary or lung needs to be there in the title so that your work can be found by others searching the literature.

Reply 1: *The title of the manuscript has been revised to include the word “pulmonary”.*

Comment 2: I also did not see a methods section. Historically doctors would pull open the drawer of their filing cabinet or riffle through their card index to find their favourite papers to cite in support of their opinions. This provided biased and self-serving reviews. In the present day it is standard to say how the source material for the review was found. What were your search terms, what database(s) did you search and what did you find? These two omissions suggest a need for a better grounding in the fundamentals of reviewing evidence for clinical practice.

Reply 2: *A methods section has been added to the manuscript, including search (MeSH) terms and databases used.*

The abstract opens “Pulmonary metastasectomy is a well-established intervention for the treatment of lung metastases from colorectal cancer” [~L.26] which is true. However, it became established without RCT evidence(2) .

Comment 3: The abstract closes “VATS is a safe and efficacious surgical intervention for the treatment of lung metastases in colorectal carcinoma.” [~L.48] This is often stated in papers about metastasectomy but the words “safe” and “efficacious” are not absolute givens. The word “safe” appears three times in the paper but is never quantified and “risk” appears 15 times but not in the context of death or complications. The authors may feel the matter is covered but I did not find it to be numerically or comparatively analysed.

Reply 3: *The statements including the words “safe”, “efficacious/efficacy”, and “risk” have been revised so as to not overstate the effects and benefits of minimally invasive pulmonary metastasectomy for colorectal cancer.*

Metastasectomy is claimed to be “safe” in surgeons’ self-reports of their work. If supported by data it usually stated that there were no perioperative deaths. In a prospectively collected cohort of patients in 25 international centre 512 patients with CRC were potential candidates for pulmonary metastasectomy. Data were data collected prospectively under trial conditions and returned to the trial centre. Of 292 patients the recorded date of death certification was the same as the date of operation in four patients. A further 5 died in the next six months during which time unoperated patients were very unlikely to die (7) . And deaths are the tip of the iceberg in quantifying harms of interventions. So how “safe” merits quantification and it is not absolute.

Radiation oncologists and thermal ablators also claim safety but prospective studies and trials include a number of cases of pneumothorax, haemorrhage and complications due to lung necrosis. How “safe” is a matter of counting events and you have to ask “compared with what?”

So then let me look at the word “efficacious”. It appears twice and “effectiveness” not at all. The difference may appear nuanced but it the distinction of their use in evidence based medicine is explained in this paper (3) . In terms of removing the metastasis in a sort of “now you see it now you don’t” sense, efficacy can be claimed by radiological observation. But clinical effectiveness — improving survival — requires comparison with what would have been the survival if the metastasis had not been resected.

Comment 4: Within the cohort mentioned above 93 patients had their treatment assigned by randomisation using minimisation to balance the arms for all recorded risk factors. There was no difference in the survival curves (5). The statistical power was insufficient to prove absolutely that there was no survival difference but it brings into question the generally held belief that lung metastasectomy for CRC is of benefit to patients.

Reply 4: *A paragraph has been added to the end of the “Background” section of the manuscript, that specifies that there is no difference in survival for patients who receive pulmonary metastasectomy for colorectal cancer vs. those who do not; the citation in this comment is referenced.*

The Society of Thoracic Surgeons published a consensus statement which included “metastatic disease survival is assumed to be zero” from which the publishing authors distanced themselves adding “a contention not supported by the literature” (2). The myth has been exploded (4). The zero assumption has been found to be wrong. This work has been widely cited (8). These papers would have been discovered by a simple search of the literature.

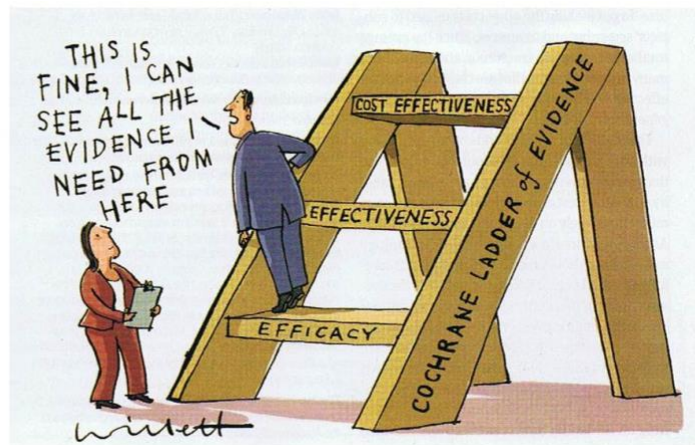
This lack of clinical effectiveness in improving survival was also found in a SEER big data analysis (6).

I do not challenge the advantages to patients of less invasive treatments. The introduction of VATS transformed the management of a number of thoracic surgical practices. Examples are the management of pneumothorax, pleural effusion, early empyema and haemothorax. Observation alone was enough to convince surgeons, their teams and their patients of the advantages of avoiding thoracotomy. Once they had mastered the technology, surgeons would not return to routine thoracotomy. There are many examples in the history of surgery: Thomas's split for fractured femur, Blalock Taussig Thomas shunt for cyanotic heart disease, water-seal drainage for pneumothorax. The criteria for when a controlled study is not needed have been codified (1). I would put the introduction of VATS in that list for the examples I have given.

Comment 5: But lung metastases from colorectal cancer — that are amenable to surgical removal — are typically asymptomatic and rarely contribute to death. There are very many factors influencing the time to death of a CRC patient with lung metastasis. These factors are used to select those most likely to survive for a while longer. A causative link between removal of a metastasis and the length of survival is, on available evidence, improbable.

Reply 5: A paragraph has been added to the end of the “Background” section of the manuscript, that specifies that there is no difference in survival for patients who receive pulmonary metastasectomy for colorectal cancer vs. those who do not.

- **Efficacy**
 - Can it work
- **Effectiveness**
 - Does it work
- **Cost effectiveness**
 - Is it worth it?



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BMJ 2011;342:d2175

(3)

Reference

- (1) Glasziou, P., I. Chalmers, M. Rawlins, and P. McCulloch. 2007. "When are randomised trials unnecessary? Picking signal from noise." *BMJ* 334 (7589): 349-351. <http://www.ncbi.nlm.nih.gov/pubmed/17303884>.
- (2) Handy, J. R., R. M. Bremner, T. S. Crocenzi, F. C. Detterbeck, H. C. Fernando, P. M. Fidias, S. Firestone, C. A. Johnstone, M. Lanuti, V. R. Litle, K. A. Kesler, J. D. Mitchell, H. I. Pass, H. J. Ross, and T. K. Varghese. 2019. "Expert Consensus Document on Pulmonary Metastasectomy." *Ann Thorac Surg* 107 (2): 631-649. <https://doi.org/10.1016/j.athoracsur.2018.10.028>. <https://www.ncbi.nlm.nih.gov/pubmed/30476477>.
- (3) Jarvinen, T.L., H. Sievanen, P. Kannus, J. Jokihara, and K.M. Khan. 2011. "The true cost of pharmacological disease prevention." *BMJ* 342: d2175. <http://www.ncbi.nlm.nih.gov/pubmed/21505222>.
- (4) Macbeth, F., and L. Fallowfield. 2020. "The myth of pulmonary metastasectomy." *Br J Cancer* 123 (4): 499-500. <https://doi.org/10.1038/s41416-020-0927-2>. <https://www.ncbi.nlm.nih.gov/pubmed/32541870>.
- (5) Milosevic, M., J. Edwards, D. Tsang, J. Dunning, M. Shackcloth, T. Batchelor, A. Coonar, J. Hasan, B. Davidson, A. Marchbank, S. Grumett, N. R. Williams, F. Macbeth, V. Farewell, and T. Treasure. 2020. "Pulmonary Metastasectomy in Colorectal Cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed." *Colorectal Dis* 22 (10): 1314-1324. <https://doi.org/10.1111/codi.15113>. <https://www.ncbi.nlm.nih.gov/pubmed/32388895>.
- (6) Siebenhuner, A. R., U. Guller, and R. Warschkow. 2020. "Population-based SEER analysis of survival in colorectal cancer patients with or without resection of lung and liver metastases." *BMC Cancer* 20 (1): 246. <https://doi.org/10.1186/s12885-020-6710-1>. <https://www.ncbi.nlm.nih.gov/pubmed/32293337>.
- (7) Treasure, T, V Farewell, F Macbeth, T Batchelor, M Milosevic, J King, Y Zheng, P Leonard, N Williams, C Brew-Graves, and L Fallowfield. 2021. "The Pulmonary Metastasectomy in Colorectal Cancer cohort study: Analysis of case selection, risk factors and survival in a prospective observational study of 512 patients." *Colorectal Dis* 23 (7): 1793-1803. <https://doi.org/10.1111/codi.15651>. <https://www.ncbi.nlm.nih.gov/pubmed/33783109>.
- (8) Williams, N. R., H. Patrick, F. Fiorentino, A. Allen, M. Sharma, M. Milosevic, F. Macbeth, and T. Treasure. 2022. "Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) randomised controlled trial: a systematic review of published responses." *Eur J Cardiothorac Surg*. <https://doi.org/10.1093/ejcts/ezac253>. <https://www.ncbi.nlm.nih.gov/pubmed/35415756>.