Peer Review File

Article information: https://dx.doi.org/10.21037/asj-21-59

Reviewer A

The authors present an overview of current treatment and results of resection of lung metastases from colorectal cancer. Most important topics are addressed providing an overall interesting review for daily clinical practice.

Comments:
- due to the absence of large randomised trials, this is a narrative review and the majority of included studies are retrospective; so, a selection bias is present as recognized by the authors
- the authors present no general diagnostic and therapeutic algorithm for patients with lung metastases from colorectal cancer; no evidence-based recommendations are possible, but the authors could provide algorithms they currently apply in their center; this would increase the clinical value and applicability of this review
→ Reply: Thank you for your comments. I added the algorithms we applied in our center.
→ Changes in the text: Page 4, line 130-137
- a common problem encountered in clinical practice is differential diagnosis with primary lung adenocarcinoma, especially in patients with presumed lung metastases who are current smokers: this should be addressed and commented by the authors (in case of doubt: lobectomy or segmentectomy or wedge excision?)
→ Reply: Thank you for your comments. I added the practice in our center if we are not sure about the histology of lung nodule.
→ Changes in the text: Page 8, line 268-273
- line 98: 5-year "mortality": do the authors mean "overall survival"?
→ Reply: Thank you for your comments. We corrected the mistake.
→ Changes in the text: Page 3, line 98
- line 106: year of publication was 2020 (instead of 2000)
→ Reply: Thank you for your comments. We corrected the mistake.
→ Changes in the text: Page 3, line 106
- line 108: "unresectable" is not correct; better mention "in patients with pulmonary metastases who did not undergo resection and"
→ Reply: Thank you for your comments. We rephrased the sentence.
→ Changes in the text: Page 3, line 108-109
- lines 253-54, 289, 308: when ablative techniques as laser resection, radiofrequency ablation or stereotactic radiotherapy are used, there is no pathological proof of metastatic disease or lymph node involvement, this is a limitation which should be mentioned. Also, how to judge local response, as these techniques give rise to inflammation of surrounding lung parenchyma?
- the English language needs thorough revision; examples include:
line 208: on (instead of in)
line 213: patients undergoing (instead of patient received)
line 263: had a (instead of were associated with)

line 264: undergoing wedge resection (instead of with wedge resection performed)
line 267: showed that (instead of showed)
line 317: results (instead of result)
line 338: determined (instead of deteremined)
Reply: Thank you very much for your comments. We corrected the mistakes.

Reviewer B

Thank you for asking me to comment on the review:
Lung metastases from colorectal cancer [CRC]: a multidisciplinary approach and role of local treatment.

I entirely agree with the intention of the sentence in the conclusion:
"The role of local treatment to colorectal lung metastasis needs further randomized controlled trials to define" but to *define* what?

I think it is agreed that other than the PulMiCC trial there have been no randomised trials. (1) That has been acknowledged by the US Society of Thoracic Surgeons.

If — as they write — "local treatment to colorectal lung metastasis needs further randomized controlled trials" are the authors going to play an active role in leading the way to such trials? This will require a clear declaration that there is *some* evidence that there is no benefit. This will help define the trial question and the estimated of possible benefit would be useful for the sample size calculation. (2)

Contrary to Line 110, there was in fact good recruitment with 512 patients in the cohort study. (3) The data have been analysed in full and the difference in survival between those selected to have or not have metastasectomy was much smaller than believed and might all be accounted for by selection for known risk factors from Gonzalez et al. (4)

In the absence of a trial it would be useful to know what is the mortality without operation.

The STS are willing to assume it would be zero. This was always implausible and is now exposed to be a myth. (5) The most informative systematic review with a meta-analysis states that survival is worse than 5% (4) which is derived from a study of 5FU in very advance CRC reported 32 years ago. (6) This is total neglect of the scientific method. If you operate on a disease you should have worked to find out what is the untreated natural history. This gap in knowledge was filled by self-serving guess work.

Few reports report even the denominator. A prospective Spanish study found that maybe 3% of people with CRC lung metastases had an operation (7) and in the English National Health Service it has been <2% until the latest few years. (8)

There is now a SEER study (9) which found no benefit from lung metastasectomy for CRC.

Prominent recent publications have made an important shift in the objective of treatment which as been for a long time “cure” which was progressively claimed with increasing realism to “improve survival” but has now shifted to “local control”. (10) This means that the outcome is non-progression in the lung as established by imaging. This is welcomed of course by radiation oncologists and those using image guided thermal ablation (IGTA). They are “treating the X-ray”.

This approach is supported by statement such as this which is now being cited.

“If patients do not receive timely and effective treatment, they may die as a result of respiratory failure.” (11)

This is not true. Lung metastases very rarely cause symptoms even in terminal stages. Respiratory failure due to lung metastases from CRC has never been reported to my knowledge. So this is complete invention and if patients are told that, it is false information encouraging them towards an ineffective treatment.

In the PulMiCC trial there was a net loss in lung function after metastasectomy (12) and no difference in overall health utility. (13, 14)

Although there are 105 publications cited, there are important references that were not cited. I provide them here below.

(9)

1. Handy JR, Bremner RM, Crocenzi TS, et al. Expert Consensus Document on Pulmonary Metastasectomy. Ann Thorac Surg. 2019;107(2):631-49.
2. Fiorentino F, Treasure T. Sample size calculations for randomized controlled trials and for prediction models. Colorectal Dis. 2021;23(1):316-9.
3. Treasure T, Farewell V, Macbeth F, et al. 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. 2021;23(7):1793-803.
4. Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol. 2013;20(2):572-9.
5. Macbeth F, Fallowfield L. The myth of pulmonary metastasectomy. Br J Cancer. 2020;123(4):499-500.
6. Poon MA, O'Connell MJ, Moertel CG, et al. Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol. 1989;7(10):1407-18.
7. Embun R, Fiorentino F, Treasure T, Rivas JJ, Molins L. Pulmonary metastasectomy in colorectal cancer: a prospective study of demography and clinical characteristics of 543 patients in

the Spanish colorectal metastasectomy registry (GECMP-CCR). BMJ Open. 2013;3(5):5 e002787 doi:10.1136/bmjopen-2013-.
8. Fenton HM, Finan PJ, Milton R, et al. National variation in pulmonary metastasectomy for colorectal cancer. Colorectal Dis. 2021;23(6):1306-16.
9. Siebenhuner AR, Guller U, Warschkow R. Population-based SEER analysis of survival in colorectal cancer patients with or without resection of lung and liver metastases. BMC Cancer. 2020;20(1):246.
10. Antonoff MB, Sofocleous CT, Callstrom MR, Nguyen QN. The roles of surgery, stereotactic radiation, and ablation for treatment of pulmonary metastases. J Thorac Cardiovasc Surg. 2021.
11. Qi H, Fan W. Value of ablation therapy in the treatment of lung metastases. Thorac Cancer. 2018;9(2):199-207.
12. Treasure T, Farewell V, Macbeth F, et al. Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC): a multicentre randomised clinical trial. Trials. 2019;20(1):718.
13. Brew-Graves C, Farewell V, Monson K, et al. Pulmonary metastasectomy in colorectal cancer: health utility scores by EQ-5D-3L in a randomized controlled trial show no benefit from lung metastasectomy. Colorectal Dis. 2021;23(1):200-5.
14. Treasure T, Dunning J, Williams NR, Macbeth F. Lung metastasectomy for colorectal cancer: The impression of benefit from uncontrolled studies was not supported in a randomized controlled trial. J Thorac Cardiovasc Surg. 2021.

Reply: Thank you for your comments. Changes are performed according to your suggestion.

Reviewer C

The authors are summarizing the interdisplinary treatment of colorectal lung metastases with focus on pulmonary metastasectomy.

For my opinion the manuscript is actually just touching the surface of the issue and needs a revision.

1. A Long the whole manuscript the term metastases and metastasis is changing. The authors should clarify when they are writing about one or multiple metastases.
Reply: We are writing about multiple metastases. We corrected the text.

2. The manuscript should be revised by a native English speaker.

3. Line 98: The authors are writing 5-year mortality rate. Do they mean 5-year overall survival?
Reply: Thank you for your comments. We corrected the mistake.

4. Line 106: The PulMiCC Trial was not published in the year 2000. Furthermore, the authors should also mention that the cohort of operated patients had a survival of 38%. The only finding of the study was that patients without therapy did not have a 5-year Survival rate of zero percent.

Reply: Thank you for your comments. We corrected the mistake.
Changes in Page 2-3, line 109 - 111

5. Line 124: The authors are writing that there should be no extrathoracic metastases. Further in the text they are writing that additional liver metastases are not a contraindication for an operation. Please clarify.
Reply: Thank you for your comments. Some centers reported their results of pulmonary resection for patients with history of completely resected liver metastasis but not synchronous liver and lung metastases.

6. Regarding perioperative and additional chemotherapy: Due to the reason that this article is regarding the multidisciplinary treatment, the authors should for my opinion differ between chemotherapy in patients with synchronous or metachronous lung metastases. Furthermore, it should be mentioned that some studies did not find a benefit of additional postoperative chemotherapy. It should also be differed between patients with single or multiple metastases, between additional liver or lymph node metastases. The issue is complex and should be described and discussed as clearly as possible.
Reply: Thank you for your comments. We've included study showing no benefits from additional postoperative chemotherapy.
Changes in the text: page 6, line 213-217

7. Line 243: The authors are writing about involved margin, this is not a R0-resecion please clarify. Regarding the type of resection the authors should mention that it is important to know about tumor spread cells (7mm around, Welter et al.). For this reason also a wedge resection should have enough resection margin. Furthermore is a pneumonectomy obsolet. The authors should describe why and that it only should be taken to consideration in palliative situations.
Reply: Thank you for your comments. We included the study you mentioned.
Changes in the text: Page 7-8, line 262 – 263.

8. Line 131-132: The authors are mentioning that the studies are from the 1990s; regarding their references all studies are published after the year 2000.
Reply: Thank you for your comments. We've included study in the 1990s. References are added.

9. SBRT: Nelson DB et al. demonstrated that wedge resection has a better uutcome than SBRT, (Nelson DB et al. JTCVS Oct. 2019) this should be discussed.
Reply: Thank you for your comments.
Changes in the text: Page 9, line 343-348.

10. Summary: Here the authors are writing that pulmonary metastasectomy is mostly safe. I do not find any comment about the postoperative morbidity and mortality rates in the text. Please clarify your summary or the text.

Reviewer D

o The introduction is synthetic. In my opinion there are several controversies in CRC lung metastasectomy that should be discussed.
o In method section must be indicated the searching PubMed date. Who decided and what criteria were used to determine which studies to include? There is lack of important papers in this area, hence a selection criterion should be indicated.
o Discussion: I really appreciate the subdivision into paragraphs; however, the discussion seems to be scholastic without specified results (e.g. there aren't comparative data on survival of tumours harbouring mutations versus the once that have not). In my opinion survival percentages should be useful to the readers to better understand the question.
Moreover, several problems as resection margins distance, the possible role of immunotherapy, the optimal timing for pulmonary metastasectomy and the necessity to perform lymphadenectomy in lung metastases can be discussed more properly.

I really appreciate the interest and the efforts of the authors; however, several amendments are mandatory to make the paper useful for readers. Recently, thanks to improvements in systemic therapies and rapidly evolving era of immunotherapy, surgeons need to be focused on patient's selection.

Reply: Thank you for your comments and changes are performed according to your suggestion.
