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**Reviewer A**

Overall reply: We thank Reviewer A for a detailed review of our paper and respond as follows.

Comment 1: The authors provide a rather personal opinion on the present and future role of resection of lung metastases. They provide some historical data unrelated to oncology, give a view from the future and conclude that “we anticipate that lung metastasectomy will also be consigned to history”. - this introduction is quite provocative and focussed on one side of the coin arguing in different ways against surgery for lung metastases

Reply 1: Of course. That is what we intended. This was as agreed with the commissioning editors at the outset and our understanding is that these issues of the journal will have other pieces — the majority or probably all — claiming benefit from lung metastasectomy. The historical examples were chosen to illustrate how clinical practice changes over generations using illustrations from diseases and treatments familiar to thoracic surgeons.

Comment 2a- lung metastases cannot be considered to a single disease entity; in fact, lung metastases are characterized by heterogeneity related to number, volume, disease-free interval, primary tumor, biological behavior;

Reply 2a.True.

Comment 2b - so, general statements by the authors as made in their conclusions referring to a single trial on colorectal metastases, cannot be applied to every type of lung metastatic disease

Reply 2b. But in the absence of any other RCT, it is legitimate to extrapolate because the biological principles underlying the metastatic process are unlikely to be radically different for other epithelial tumours.

Comment 3 - even in disease entities where large randomized controlled trials (RCT) are available as e.g. non-small cell lung cancer (NSCLC) with N2 involvement, guidelines for treatment are not uniform and this topic remains a controversial issue at every major thoracic oncological conference. An EORTC task force is currently discussing the definition of resectable stage IIIA-N2 disease. So, RCTs are not always the holy grail as stated by the authors.

Reply 3. For determining the relative value of clinical interventions, well conducted RCTs are the most reliable form of evidence. To claim otherwise is simply wrong. Incidentally, we did a meta-analysis of RCTs of management of N2 nodes in lung cancer. (Mokhles et al. 2017) We think more reliance should be placed on that form of evidence than the discussion of a task force’s opinion.

Comment 4. - nowadays, pulmonary surgery can be performed with a low morbidity and mortality, mostly by minimally invasive techniques. In case of malignancy, detailed molecular analysis may provide a specific personalized treatment. How to determine adjuvant treatment if no surgery is performed and no histology is obtained? So, surgery can be at least to be considered diagnostic and provide individualized treatment opportunities.

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Reply 4. This shifts the ground to metastasectomy as a diagnostic procedure. If there is likely to be a significant change in histology from the primary tumour, and molecular evidence is essential to determine the best choice of systemic treatment then a biopsy might be justified. This is not an argument for resecting metastases. Present practice is based on hope of prolonging life and even the possibility of cure. The evidence indicates that is rarely if ever the case.

Comment 5 - what is the authors' treatment algorithm in patients with a single indeterminate nodule in a smoker with a previous history of cancer? This could be a primary lung cancer or metastasis. Would they still advocate conservative treatment in such a case?

Reply 5. This should be managed as for any indeterminate nodule. FNA or excision biopsy.

Comment 6 - quite surprisingly, the authors don't discuss or even mention the D. Gomez trial [J Clin Oncol 2019; 37:1558-1565]. In this randomized (!) phase II trial evidence is provided that in case of limited oligometastatic disease of NSCLC, local ablative therapy (high-dose radiotherapy or surgery) not only prolongs disease-free survival but also overall survival.

Reply 6. This is a small randomised Phase II trial (of RT or not to a range of metastatic sites) which does indeed show a significant survival advantage.(Gomez et al. 2019) We know the study and comment on it here. (Macbeth and Treasure 2022) It should be seen as hypothesis generating and needs to be repeated in a larger definitive Phase III. But it is being interpreted as clear evidence of benefit when it could be a chance finding. We still have not cited it because it was not about lung metastasectomy.

Comment 7 - one should also realize that "absence of evidence" is not "evidence of absence" as the authors seem to suggest. There is no large and confirmatory RCT clearly demonstrating that there is no role for surgery in patients with suspected lung metastases from any primary tumor. In the PulMiCC trial the control group consists of selected patients which may artificially raise the overall survival in this group.

Reply 7. That is a specious argument. The onus is on those advocating a surgical intervention with uncertain benefit and known risk to demonstrate its effectiveness rather than claim because there is 'absence of evidence' that it is justified. But in this case there isn't an absence of evidence because there is PulMiCC!

Comment 8 - although the authors claim to have performed a thorough literature review, at least 20/49 references are self-citations (40.8%) which results in a skewed reference list.

Reply 8. I can't find that in our manuscript. We do not make that claim. "a systematic review of the responses to PulMiCC" was made. (Williams et al. 2022) We do write "a systematic search was made of the contents of the British Medical Journal and the Lancet from the 1890s to the 1920s".The reference list is relevant to the whole article which is not itself a systematic review.

## **Reviewer B**

I am very pleased to have received this invitation to peer-review this manuscript for a special edition devoted to lung metastasectomy by the AME Surgical Journal. These are my comments for both the authors and the editors.

100 Comment 1. I assume this manuscript is part of a pro/con debate for this special edition on  
101 pulmonary metastasectomy. And if that is the case, I think the editors could not have chosen a better  
102 research group to advocate the con side. The authors have again shown their passion and dedication  
103 to the field of pulmonary metastasectomy in this thorough review.  
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105 Reply 1. This is a question for the editors really. Our understanding was that the other articles would  
106 be in support of lung metastasectomy. Thanks for you kind remarks about our work.  
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108 Comment 2. The manuscript is well-written and has a nice build-up with a clear message. Many of  
109 the original reports by this research group have been used in their argumentation. Using the  
110 perspective of researchers in the future helps in making bold statements, which was a very nice idea  
111 when writing the manuscript.  
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113 Reply 2. Thanks. We pleased that you appreciated the approach we have taken.  
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115 Some general remarks.  
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117 Comment 1. Treatment of colorectal liver metastases, which is much more frequently performed, is  
118 not touched, but the notion that an oligometastatic concept exists is challenged. Do the authors also  
119 consider that local treatment of colorectal liver metastases should be consigned to history? Or is the  
120 first-pass effect for liver metastases used to argue that these metastases can be treated locally? And if  
121 so, does the same first-pass effect apply to pulmonary metastases from a rectal primary?  
122

123 Reply 1. This is not relevant to an article on pulmonary mets and at the outset we decided to not  
124 engage with the question of liver metastasis. TT questioned the whole basis of liver metastasectomy  
125 when first questioning CRC metastasectomy (Treasure, Utley, and Hunt 2007) and again more  
126 recently (Morris and Treasure 2017, 2018) and studied the history of its introduction (Grunhagen et  
127 al. 2013). If you can find a copy of this little book (Gray 2007) the opening pages are fascinating.  
128 We can send you the relevant pages.  
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130 Comment 2. Recently, and following the publication of the PulMICC trial, the ESTS survey on  
131 pulmonary metastasectomy was published. <https://pubmed.ncbi.nlm.nih.gov/36847670>. In this  
132 survey, 97% of surgeons consider that pulmonary metastasectomy for colorectal pulmonary  
133 metastases improves disease control, and 92% state that it improves patients' survival. Are the  
134 authors interested in incorporating these results in the manuscript, given that these results are not in  
135 line with their view on the topic?  
136

137 Reply 2. Thanks. We had not seen it but is cited up front now. It is a shining example of optimism  
138 bias and competing interests at work.  
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140 Changes in the text: L.96-8 1.3  
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142 Comment 3. If this manuscript is not part of a pro/con debate, then I can appreciate some limitations  
143 of the published results. The authors have published the international community's reactions to their  
144 trial and felt a widespread disregard and misinterpretation/misrepresentation of the results  
145 (<https://pubmed.ncbi.nlm.nih.gov/35415756/>). Therefore, it would be interesting to read some  
146 limitations of the authors given that, based on current practice and following the publication of the  
147 PulMICC trial, metastasectomy is still performed on a daily basis for colorectal pulmonary  
148 metastases.  
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150 Reply 3. We are not sure what the question is. That lung metastasectomy continues is evident but  
151 each time we see a report we look at the start and end dates and the number and the calculation  
152 shows that “a daily basis” may be globally true, but for (Casiraghi et al. 2011) it was about weekly  
153 and in some published series we have seen recently it is more like monthly.

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155 Some details.

156 Reply Thanks for these specific comments. These are very helpful

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158 Comment 3 Line 190. The STS expert consensus document was published in 2019, not in 2022.  
159 Even though this number might be a bit high, the authors decided to refer to this article.  
160 (<https://pubmed.ncbi.nlm.nih.gov/30476477>)

161  
162 Reply 3. Correct but if there were more than 1000 in 2019 by 2022 — when we were writing the  
163 paper — it would have been more, but better to not make it appear that we haven’t got the dates  
164 right! Thanks for pointing it out as confusing.

165  
166 Comment 4. Line 205-206. Is it correct to quote clinical sites if they did not include any patients?

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168 Reply 4. Good pick up. The “trial” should have been “study”. The full cohort study is a vital part of  
169 the PulMiCC evidence.

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172 Comment 5 Line 216, 271, 277, 309. The chronological order of the Figures is incorrect. Also,  
173 Figure 3 consists of a Figure 2 and a Figure 3, this is a bit confusing.

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175 Reply 5. Thanks. Quite right on both points and now fixed - I hope.

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177 Changes in the text: Figures renumbered and cited correctly.

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179 Comment 6. Line 259-261. I would say that the largest single institutional follow-up study  
180 originates from Milan and was published in 2011 (<https://pubmed.ncbi.nlm.nih.gov/21642869>).

181  
182 Reply 6. It wasn’t the size but the included factors that led to the use of these two reports in the  
183 model. I hope that is now clear. Now at 324-338.

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186 Comment 7. It is probably obvious that I recommend accepting this manuscript, and the remarks  
187 serve as suggestions, not as required revisions.

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189 Reply 7. Thank you!

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192 **Reviewer C**

193 Comment 1. A nicely written piece, and a timely reminder that surgical oncology is only the  
194 beginning of wisdom when it comes to cancer treatment.

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196 Reply 1. Many thanks

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