

Manuscript No: 34647, "Different clinical presentations of metachronous pulmonary metastases after resection of pancreatic ductal adenocarcinoma. Retrospective study and review of the literature."

### Author's response to the Reviewer's Comments

Authors would like to thank Reviewers for looking over our manuscript. The comments from the reviewers indicate that all four reviewers found the article of a very good quality and acceptable for publication to their minds, aside from few minor but generally very supportive, consistent and relevant comments which helped us to substantially improve the contents and soundness of the manuscript.

We tried to respond to all of the comments and made appropriate changes (in red in the revised manuscript), which mainly consist of clarification on details, some editing, explanations for the assessment of R0/1 resection and minor typos. Please find below our responses and description of changes made to the manuscript. Moreover, the manuscript was again edited by native speaker (co-author Tharani Yogeswara from UK).

We would be very grateful if you could re-consider this again in light of the reviewer's comments, and hope that the revised version of the paper would be found acceptable for publication. Thanks very much for your consideration.

Reviewer #1: The manuscript by Martin Lovecek and colleagues analyzes the outcome of metachronous pulmonary metastases after resection of pancreatic ductal adenocarcinoma. It is a retrospective study on 159 consecutive patients operated on between 2006 and 2013. The authors show that patients with isolated pulmonary metastases (oligometastases and multiple metastases) had better survival compared to metachronous pulmonary metastases with other metastases or non-pulmonary metastases This is an interesting, valid, and well written analysis. There are a few points, the authors might want to address:

- "One-hundred and fifty patients (94.2%) were operated with R0 resection". This is an impressive rate of R0 resections, especially considering that the Leeds protocol was utilized. How can the authors explain this high rate?

Author's response: We completely agree with the Reviewer 1 that 94% R0 resection would be really impressive considering the Leeds protocol. Unfortunately, it has to be noted that „Histopathological diagnosis of PDAC was performed according to the standard classification, and **all specimens were evaluated before the implementation of the Leeds protocol**" (page 4). As this note may be rather confusing, we point out this fact and change the Result part to: "R0 and R1 resection is not rated as the samples have been evaluated before the Leeds protocol and the results concerning R0 resection could be overestimated (page 5)".

- As the authors state and discuss, only 5 patients had isolated lung metastasis, and only 3 could be considered candidates for surgery. Any statistical analysis is critical in this setting. The authors should further tone down their conclusions.

Author's response: We completely agree with the Reviewer 1 and toned down the conclusion.

- The discussion is rather long and could be shortened.

Author's response: The discussion was shortened in the revised version of the manuscript.

Reviewer #2: The authors studied a special subgroup of PDAC patients who suffered from metachronous pulmonary metastasis after surgery in a Central European population. They identified three different patterns of metachronous pulmonary metastasis and found much better prognosis in such subgroup compared to non-pulmonary metastatic patients. This clinical finding is important and valuable to clinical practice. Moreover, the study indicates the needs of identifying this subgroup beforehand and will guide future basic studies in the relevant field. The manuscript is generally well organized, and I have only some minor comments.

- The reason that female has high risk of metachronous pulmonary metastasis should be discussed.

Author's response: The most recent European study by Decoster et al. reported 22 of MPM, 3 of them were solved surgically, and showed a female predominance. Our study also showed marked predominance of women among patients with isolated pulmonary metastases. Female predominance in both studies is quite interesting as there are no evidence based facts to explain this observation. The effect of sex hormones is one of the potential mechanisms, but without supporting in vitro or in vivo data this remains only a speculation. Future studies should investigate whether MPM cases are characterized by specific molecular pathogenesis and biology that could explain this particular metastatic pattern.

- In table 1 and related text, the neoadjuvant and adjuvant therapies should be specified. Were they radiotherapy, chemotherapy, or others?

Author's response: We added the specification to the text in part Results (page 5): "Two patients (1.3%) had neoadjuvant therapy consisting of concomitant radiotherapy with continuous 5-fluorouracil administration. Adjuvant chemotherapy consisting of nucleoside analogues (gemcitabine and 5-fluorouracil) was administered in 111 (69.8%) patients."

- In the Methods, why only cases with R2 resection were excluded? What about R1 resection?

Author's response: All specimens were evaluated before the implementation of the Leeds protocol" (page 4). As this note may be rather confusing, we point out this fact and change the Result part to: "R0 and R1 resection is not rated as the samples have

been evaluated before the Leeds protocol and the results concerning R0 resection would be overestimated (page 5)". According to up to date knowledge, R0/R1 resection had no impact to prognosis of PDAC patients before the Leeds protocol. R2 resection when macroscopic residuum remains means that tumor was in a fact inoperable so out of our criteria.

- The authors implicated a possible association between PDAC in the head of pancreas and higher metachronous pulmonary metastasis as well as higher incidence of perineural invasion of the tumors. This possibility also needs further discussion.

Author's response: Because the difference was not statistically significant in comparison with non-pulmonary metastatic patients we added the remark that this observation is not statistically significant and needs to be evaluated in larger cohort or meta-analysis (page 8).

- The authors stated, "PDAC patients with MPM exhibit a metastatic pattern consistent with the Paget hypothesis". The association between the metastatic pattern and the Paget hypothesis is not straightforward. Please explain this.

Author's response: We completely agree with the reviewer that this statement has to be explained in more detail. But as 2/4 reviewers found out the discussion too long and this clarification would make it much longer we decided to delete this sentence as it is not crucial for this manuscript.

- By saying "there is a subgroup of patients with metastatic PDAC who would benefit from surgical therapy", do the authors mean the subgroup is patients with metachronous pulmonary metastasis or one of the three scenarios mentioned in the text?

Author's response: We agree completely with the Reviewer and clarify this in conclusion and abstract with regards also to Reviewer 1 and 4 by the sentence: "Surgery should be considered for all patients with solitary pulmonary metastases, but this has to be carefully weighted individually for each patient."

Reviewer #3: Pancreatic cancer is a very aggressive disease with high incidence of developing metastasis and limited therapeutic options. This retrospective study reported different clinical presentations of metachronous pulmonary metastases in a cohort of patients underwent a curative -intent surgery from one institute. One of the interesting findings is that patients with metachronous isolated oligometastases could be considered candidates for surgery, and two patients who were radically operated are both currently alive more than one year without recurrence, suggesting that there is still therapeutic option for PDAC patients with presentations of metachronous pulmonary metastases.

Minor issue: Tables 1-5 should be organized in the format required by the journal.

Author's response: Tables were reorganized to the appropriate format.

Reviewer #4: Hereby I would like to comment on the article entitled: "Different clinical presentations of metachronous pulmonary metastases after resection of pancreatic ductal adenocarcinoma. Retrospective study and review of the literature" by the authors Martin Lovecek et al. The authors present a retrospective analysis of the prevalence and treatment of solitary pulmonary metastasis after curative surgery for pancreatic adenocarcinoma. This study has been well-written and performed well. Comments:

1. As the authors point out the low number of patients that had metachronous pulmonary metastases following curative treatment for pancreatic adenocarcinoma is an important limitation. Although the effort of the authors to further characterize this group need to be appreciated, I think it is not possible to draw any conclusion from this or relate it to a specific treatment protocol. Surgery was undertaken in these patients with success and I think that the most important message is that it can be considered, but this has to be outweighed for each patient on an individual basis.

Author's response: We completely agree with the Reviewer 4 and toned down the conclusion according to proposed recommendation and add it to abstract and conclusion part (page 2, 11)

2. The number of Tables and figures may be reduced to improve readability

Author's response: Tables 1,2, and 4 were add to Supplementary material. There is only 1 figure and 2 tables in the revised version of our manuscript.

3. In the discussion, results are frequently repeated, I would limit this. Furthermore, the discussion can be compacted.

Author's response: The discussion was shortened in the revised version of our manuscript.