

## **Response to reviewers:**

Reviewer 00729478- “very well written”

Response- Thank you

Reviewer 02460781- “This article is to investigate the importance of a three-tiered histologic grade on outcomes for patients with mucinous appendiceal adenocarcinoma. The study is good. However, the conclusion is not enough. In the result department, “Tumor grade and PCI were the only independent predictors of both DFS and OS.” But, in the conclusion, “Our data strongly supports the distinction of an intermediate histological grade for mucinous appendiceal adenocarcinoma. Including the three-tier grade classification provides improved prognostic stratification.”

Response- Thank you. In response to your suggestion, we have revised the conclusion in the abstract to “Our data demonstrates that moderately differentiated MAA have a clinical behavior and outcome that is distinct from well- and poorly differentiated MAA. The three-tier grade classification provides improved prognostic stratification and should be incorporated into patient selection and treatment algorithms.” In addition, we have revised the conclusion in the discussion to state “This classification best stratifies survival outcomes and should be incorporated into patient selection and treatment algorithms and potentially into future AJCC staging updates. The 8<sup>th</sup> edition of the AJCC staging system currently groups grade G2 and G3 (moderate and poorly differentiated) mucinous appendiceal adenocarcinoma into the same Stage IVB group. Our data suggests a separate Stage IV for each grade may be more appropriate.” We feel these conclusions are stronger and are supported by the results. These statements are the take home message of this study and hopefully will lead to changes in AJCC staging. We also have now incorporated histological grade into our patient selection and treatment algorithms for mucinous appendiceal adenocarcinoma.

Reviewer 00505440- “This is a very interesting manuscript. While i understand what the point raised by the authors is, namely, the importance of the intermediate stage as a separate entity, their results do not specifically support this. To prove their hypothesis, the authors need to separately analyse the data for well vs moderate, and poor vs moderate in terms of the factors analysed as well as the Kaplan Meier curves. The current analysis of a significant result is likely skewed by differences between well and poorly differentiated. Minor comment 1. In all figures, please provide a complete legend including abbreviations used in the figure, eg PMP, etc.”

Response- Thank you. Histological grade was independently associated with both DFS and OS in Cox regression analysis. Furthermore, the OS was significantly different between well differentiated and moderately differentiated ( $p < 0.001$ ) as well as between moderately differentiated and poorly differentiated ( $p < 0.001$ ) carcinomas. The Kaplan Meier graph in Figure 1 shows a very nice stratification of overall survival according to histological grade.

Furthermore, in table 3 the incidence of nodal metastasis is stratified by histological grade as well, suggesting that clinical behavior is also distinct between the three grades. As far as performing separate multivariate analysis for the three histological grades, the bulk of the tumors are well-differentiated (n= 201) there are only 45 moderately differentiated and 19 poorly differentiated and therefore the limited numbers limit further subgroup analysis. However in multivariate analysis when controlling for histological grade, lymph node involvement, previous surgical score and PCI were independently associated with DFS. When controlling for histological grade, PCI and completeness of cytoreduction were independently associated with overall survival. We feel these results support our conclusion that moderately differentiated mucinous appendiceal adenocarcinomas have a clinical behavior and outcome that is distinct from well- and poorly differentiated carcinomas.