

**Editorial Office World Journal of Gastrointestinal Oncology**

Editor-in-Chief – Dr. Ahmed, Dr. Jimenez Rodriguez and Dr. Murtaza Kasi

Amsterdam, 12<sup>th</sup> December 2019

Subject: Revision Ms. No. #52190

Dear Editorial Board, Dear Dr. Ahmed, Dr. Jimenez Rodriguez and Dr. Murtaza Kasi,

Thank you very much for your letter of 6<sup>th</sup> December 2019 and for the opportunity to revise our manuscript entitled “Clinical outcomes of patients with duodenal adenocarcinoma and intestinal-type Papilla of Vater adenocarcinoma” that we have submitted for publication in *WJGO*.

We appreciate the time spent by you and the reviewers evaluating our manuscript and for their constructive comments. We are pleased to inform you that we have revised our study according to the comments that were raised by the reviewers. In particular, we have updated the TNM staging to the 8<sup>th</sup> edition. In addition, we have clarified the involvement of lymph nodes.

Please find the point-to-point reply to the reviewers enclosed in order to identify the modifications to the original manuscript. We have also uploaded an updated version of the manuscript with all changes highlighted.

We sincerely hope the revised manuscript addresses the observations made by you and the reviewers, and meets the quality required for publication in *WJGO*.

We thank you in advance for your kind consideration and we are looking forward to receiving your decision about the revised manuscript.

Yours sincerely,

On behalf of Professor Dr. Geert Kazemier and Professor Dr. Marc Besselink,



**Laura Meijer, M.D.**

Cancer Center Amsterdam, Department of Surgery, Room CCA 1.42



## Point-by-point reply to Reviewer's comments – WJGO Manuscript ID #52190

**We would like to thank the Reviewers for taking time reviewing our paper. We greatly appreciate their thoughtful and constructive comments. Amendments in the manuscript have been highlighted in yellow and the point-to-point reply to the Reviewers, where we indicated the changes in our revised manuscript by page and by line, is enclosed in this letter.**

### Reviewer 1

*It's a well written paper containing interesting and important clinical data. A chosen angle for the clinical decisions and presentation of the data encourage the readers to look at their own data series, systematic literature reviews and plan new clinical trials.*

### Reply

We thank the Reviewer for the positive comments. We agree with the Reviewer and hope that our data will encourage and stimulate further research for these rare tumor types. In the future, clinical trials are indeed needed to confirm the survival benefit of local treatment of oligometastases and provide a framework for optimal treatment options for patients with these rare tumor types.

### Reviewer 2

*The paper reported "Seven (23%) of 31 patients with synchronous stage IV disease underwent resection of the primary tumor combined with local treatment of oligometastases. Local treatment of metastases was associated with in an overall survival of 37 months". The cases are few. We always see the overall survival of stage IV disease was very low. We think it need more case to verity your conclusion.*

### Reply

We acknowledge the considerations raised by the Reviewer and encourage future studies to substantiate our conclusions and, ultimately, to change clinical practice. In our study, we have retrospectively reported our results and outcomes of clinically well-annotated patients. We have carefully included patients with histologically proven duodenal adenocarcinoma and intestinal type Papilla of Vater adenocarcinoma to provide a solid basis for future studies. Until today, this is the largest reported series reporting outcomes for patients with duodenal adenocarcinoma and papilla of Vater adenocarcinoma. We hope that our results will encourage clinicians to accurately diagnosis these patients and register outcomes. In such ways, the clinical outcomes of this study can be substantiated by larger cohorts and eventually clinical trials.

This study provides the first insights into the feasibility to apply local treatment of oligometastases for patients with duodenal carcinoma, which could radically change our current treatment options and improve clinical outcomes for these patients. We have carefully pointed out the limitations of our study in the Discussion section, page 16.



### Reviewer 3

*This is a retrospective study of the outcome of intestinal type ampullary and duodenal carcinoma and found that local curative management led to improved survival. There are some minor points that deserve the author's attention.*

### Comment 1

*AJCC TNM staging 8th edition has been in effect for two years. Please restage all tumors based on AJCC 8th edition and reanalyze the data. Since all data elements are in the path reports, this should not take too much time or effort.*

### Reply

We appreciate the input of the Reviewer and the suggestion to restage the classification based on the AJCC 8<sup>th</sup> edition. To this end, we have carefully checked the pathological reports and revised the staging to the updated 8<sup>th</sup> edition. For duodenal adenocarcinoma and papilla of Vater adenocarcinoma, changes were very subtle compared to the 7<sup>th</sup> edition.<sup>[1]</sup> Thus, this did not change our results. The updated version of the AJCC can be found in the Methods section, page 9.

### Comment 2

*The authors separated liver metastasis from lymph node metastasis. Are those positive lymph nodes regional or distant nodes? If regional nodes, the tumor would be in a lower stage than liver metastasis (stage IV).*

### Reply

We agree with the Reviewer that positive lymph nodes can be either regional or distant nodes. For classification of stage IV disease, the AJCC classification was followed. Involvement of regional lymph nodes was considered as local disease (stage III), while involvement of the celiac nodes was considered M1 (stage IV). All patients included in stage IV demonstrated involvement of distant nodes (**Table 2**).

We have clarified this in the Methods section, page 9, as stated below:

Involvement of lymph nodes was either classified as regional (N1 / 2) or distant (M1), depending on the location of lymph node involvement according to the AJCC staging system.

### Comment 3

*Most regional resection/curative management was performed in one of the two hospitals. When comparing two different hospitals, other factors that potentially affect that data should be considered, such as: difference in pathological interpretation, difference in supporting care, multidisciplinary team, resource and infrastructure.*

### Reply

The Reviewer points out a very valuable comment and we agree that confounding factors should be further investigated. Indeed, many factors could result in optimal clinical outcomes. Unfortunately, due to the low number of patients the factors mentioned by the Reviewer can currently not be thoroughly assessed. We would like to confirm the comparability between the two hospitals, as these are closely related: less than 10 km apart, work together, have the same standardized guidelines (which are nationwide implemented in the Netherlands) and clinicians often consult and collaborate between the two hospitals. Moreover, it is common practice to have



a multidisciplinary team discussion by regional videoconference, in which team members of both hospitals are present. Therefore, we ascertain that the supporting care, multidisciplinary team and infrastructure between the two hospitals is comparable. We strongly encourage further studies to confirm the survival benefit for local resection of oligometastases in (inter)national studies and hope our study will provide a first foundation to stimulate (inter)national collaboration for these rare tumor types.

#### Reference

1 Oweira H, Abdel-Rahman O, Mehrabi A, Reissfelder C. Assessment of the external validity of the AJCC 8 th staging system for small intestinal adenocarcinoma: a time to reconsider the role of tumor location? *Journal of Gastrointestinal Oncology* 2019; **10**(3): 421-428

#### Reviewer 4

*This study investigated the clinical outcome of 155 patients with DA and it-PVA, which is the largest reported series comparing OS for DA and it-PVA. Patients with oligometastases benefited from local treatment, which shows clinical significance for more aggressive and intensified treatment modalities in selected patients with oligometastases from DA and it-PVA. Of course, further prospective investigations would be needed.*

#### Reply

We thank the Reviewers for the appreciation of our manuscript and our large patient series of these rare tumor types. We agree with the Reviewer and hope that our data will encourage and stimulate further research. In the future, clinical trials are indeed needed to confirm the survival benefit of local treatment of oligometastases and provide a framework for optimal treatment options for patients with these rare tumor types