POINT BY POINT RESPONSE

January 21, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: Primary tumor resection in patients with colorectal cancer and unresectable synchronous metastases: a controversial area

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Journal: *World Journal of Gastrointestinal Oncology*

ESPS Manuscript NO: 7425

We really thank the editorial board and reviewers for expressing their interest in our work and for their careful review that allowed appreciable improvements in the manuscript.

As required, the title has been shortened and the manuscript has been revised according to the reviewers' comments and all queries are addressed point by point in the present response. Alterations are in bold characters in the revised version, in green for comments of reviewer #00181023, in blue for comments of reviewer #00068472, in red for comments of reviewer #02573214 and in orange for comments of reviewer #02520050.

Reviewers' comments:

Reviewer #00181023:

The manuscript by de Mestier and colleagues provides a well written in depth review on the pros and cons of primary tumor resection in patients with stage IV colorectal cancer (with unresectable distant metastases). In general, the authors can only be congratulated for this excellent work. I have only two comments.

The manuscript is made up by 11 different chapters, some of them are more relevant (and extremely interesting), some may be "secondary" topics, but I totally accept the authors' choice. Anyway, the manuscript would very much benefit from an additional chapter summarizing the differences that exist between colon and rectum cancers. I have to admit, that this information is mainly included in the different chapters, but it is currently difficult to find. And the local complications for rectal cancer left in situ may differ substantially from those of colon cancer, if we e.g. consider the risk of urinary obstruction and the need for subsequent urological intervention.

We perfectly agree with the present comment of the reviewer #00181023. A dedicated chapter untitled "**Specific issues of rectal cancer**" has been added in the revised version (page 20).

Minor remark: In Table 2 "OR" is not explained, I guess it means odds ratio (this information should be included in the list of abbreviations). But my concern goes further: all ORs are >1, indicating that there is an increase in risk, while all HRs are <1, indicating that there is reduced risk. This, however, cannot be true as the following examples show: Law et al (2004): Resection / OS 7 months; no resection / OS 3 months; OR 2.39 Stelzner et al (2005): Resection / OS 11.4 months; no resection / OS 4.6 months; HR 0.5 It would be much easier for the reader to get the information of this table, if the authors only referred HRs (or ORs) that "go into the same direction", and transform, e.g., the 2.39 OR of the paper by Law et al. in the following way: 1/2.39=0.42=HR.

We really thank reviewer #00181023 for this observation. As proposed, the results in Table 2 (page 36) have been changed for more clarity and readability and the abbreviation “OR” has been explained.

Reviewer #00068472:

The authors address the important area of treatment of patients with colorectal cancer (CRC) with synchronous metastases. Whether primary tumor resection followed by chemotherapy or first step chemotherapy without primary tumor resection is the optimal therapeutic approach in patients with asymptomatic CRC and unresectable metastases is an unanswered, important issue. Well designed, randomized controlled studies are urgently needed. At first sight the manuscript seems impressive. However, overall, the presentation of the topic is a little confused. In my view, the manuscript should be shortened. The English language should be improved. The authors should explain why randomized studies are missing in this topic. The clear-cut indications and contraindications of primary tumor resection should be summarized in a separate table.

As requested by reviewer #00068472, the manuscript has been proofread for grammatical and spelling corrections by one of our colleague who is a native English speaker.

The third paragraph of the “introduction” section has been modified in order to clarify the reasons why randomized trials are missing in this topic (see on page 6).

A last section (page 23) has been added untitled “Summary” that summarizes our review and gives the clear-cut indications and contraindications of primary tumor resection in case of synchronous irresectable metastatic disease.

Reviewer #02573214:

It could be interesting compare also the results, reported in literature, of the cases with asintomatic stenoses, in which endoscopic metal stent was positioned before chemiotherapy.

We thank reviewer #02573214 for the present comment. However, our choice has been to deal only with patients who present with an asymptomatic primary tumor and unresectable synchronous metastases. The palliative management of patients with obstructive stage IV colon cancer (colonic stent vs. surgery) represents a very important topic that need to be adressed in a separated review.

Reviewer #02520050:

This review of a common and difficult clinical scenario—synchronous colorectal cancer with unresectable metastases—is a timely and important contribution to the literature. Not only have the authors worked to perform a thorough review of the literature, but they have also commented on the design of an appropriate randomized trial to address this issue, which is reportedly being planned in France. I believe this is what separates this review from previous meta-analyses/reviews, which have been performed. In general, I think this is a valuable manuscript that would be of interest to many disciplines. I have a few comments:

1. Though the manuscript is readable, I would recommend that a native English speaker thoroughly edit the paper, as there are some syntax and grammatical errors. For example, the last sentence of the abstract needs to be re-worded.

As required, the manuscript has been proofread carefully for syntax and grammatical errors. The last sentence of the abstract has been reworded: "**As no randomized study has been performed to date, we finally discussed how a therapeutic strategy's trial should be designed to provide answer to this issue.**"

2. On page 6, the authors state a survival of 35-60% for patients with resected metastatic lesions. Is this a 5 year survival? Other? Also on page 6, panitumumab is misspelled.

We agree with the present comment. Indeed, the figures reported on page 6 are overall survival data. "Complete surgical resection of metastatic lesions substantially improves survival rates to around 35-60% in selected patients" has been modified by

"**Complete surgical resection of metastatic lesions substantially improves overall survival rates to around 35-60% in selected patients**" for clarification.
"Panitumumab" has been corrected on page 7.

3. I would consider joining sections 4 and 5. They have a similar theme—prognostic variables and how they should be applied to clinical decision making—and individually they don't seem to have enough material to stand alone.
We perfectly agree with the present suggestion. Sections 4 and 5 have been grouped together (see on page 9).

4. The word 'lasts' on line 6 of page 11 does not make sense.
"Lasts" has been corrected by "**they**" (page 11).

5. Though it is stated elsewhere in the manuscript, I think that section 6 should have at least a sentence, if not a paragraph, stating that perhaps there is no survival benefit to PTR—that previous data result from such selection bias that overall survival cannot be interpreted reliably.
We thank reviewer #02520050 for this comment. A paragraph has been added at the end of section 5 (see page 13).

6. Section 7—addressing quality of life—could use some data. Perhaps, for example, a comparison of surgical complications from PTR and grade ? complications from chemotherapy could be made, to give the reader more concrete detail about issues that impact QOL. This seems to be addressed in section 9—perhaps some of these data could be moved to section 7.
Quality of life is an important issue in stage IV CRC patients. We added a sentence at the end of section 6 to explain how this aspect could be evaluated in a future randomized trial (page 14).

7. The statement '…eight patients underwent a surgical resection with curative intent' on page 14 does confuses me. By definition, none of these patients can be cured. Can the authors explain this?
We totally agree with this point. By definition, patients with unresectable colorectal metastases can only be managed palliatively. The NSABP Trial C-10 included only

patient with histologically confirmed adenocarcinoma of the colon with unresectable metastatic disease. However, in their results, McCahill and colleagues reported that: "**In total, eight surgeries were performed with intent to remove the intact primary tumor and all metastatic liver lesions. In three patients, the liver lesions were found intraoperatively to be unresectable, and resection of the primary tumor was performed. One patient had removal of the primary tumor after demonstrating a radiographic complete response in the liver. Four patients underwent resection of all liver metastases and the intact primary tumor, and for three this was performed as a combined surgery. In two of the three combined resections, the patients died of postopera- tive complications. One patient underwent a successful staged resection. In summary, three patients underwent successful resections of both the primary colon tumor and liver metastases without postoper- ative mortality**."
Based on that, we can conclude that some patients in this trial had potentially resectable metastatic disease that became resectable on reevaluation after systemic chemotherapy by mFOLFOX6 and bevacizumab.

8. The sentence on page 18 that starts with 'Indeed, a significative (spelling error) rate of. …. ' is confusing. Can the authors re-state or explain this better?

We apologize for this lack of clarity. This sentence was changed by the following: "**These rates could be even lower with the use of laparoscopic approach, which is known to improve short-term outcomes, including postoperative morbidity, compared to open surgery**" (page 19), with reference to a recent meta-analysis by Othani and colleagues that showed a significant decrease of overall postoperative complications in patients with colon cancer operated on by laparoscopy compared to those who underwent open resection (OR: 0.73; 95%IC: 0.56-0.95; p=0.02).

9. I think a summary paragraph after section 10 may be helpful to wrap up the review.

We thank reviewer #02520050 for this suggestion. As for #00068472, a last section has been added at the end of our manuscript (page 23 in the revised version) to summarize our review.