

November 10, 2018

To the Editorial Board of the *"World Journal of Gastrointestinal Oncology"*.

We are submitting our revised manuscript No 42297, now entitled: "**Predictive factors of histological response of colorectal liver metastases after neoadjuvant chemotherapy**" for your consideration. We would like to thank the reviewers and the Scientific Editor of the Journal for taking the time and effort to assess our initial manuscript so meticulously. Our research group considered all of your recommendations and we modified our manuscript accordingly. Detailed replies to the Editor's and the reviewers' comments are provided below:

### **Replies to the Editor**

**Comment 1:** *"For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies."*

**Authors' reply:** The certificate was established and uploaded in pdf version (the certificate was not an option in the website, so we uploaded it instead of "Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)").

**Comment 2:** *"Please offer the audio core tip, the requirement are as follows:*

*In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:*

***Acceptable file formats:*** .mp3, .wav, or .aiff

***Maximum file size:*** 10 MB

*To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or*

48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS."

**Authors' reply:** The audio core tip has been uploaded, accordingly to these recommendations.

**Comment 3:** *"Please rewrite the "results" sections as the format of Retrospective Cohort Study."*

**Authors' reply:** The results section was modified according to the format of retrospective cohort study.

Moreover, we added the following sentence in the Methods section (p.9): "They were retrospectively analyzed with regard to their pre-treatment characteristics."

**Comment 4:** *"The guidelines for writing and formatting Article Highlights are as follows:*

***1 Research background***

*The background, present status, and significance of the study should be described in detail.*

***2 Research motivation***

*The main topics, the key problems to be solved, and the significance of solving these problems for future research in this field should be described in detail.*

***3 Research objectives***

*The main objectives, the objectives that were realized, and the significance of realizing these objectives for future research in this field should be described in detail.*

***4 Research methods***

*The research methods (e.g., experiments, data analysis, surveys, and clinical trials) that were adopted to realize the objectives, as well as the characteristics and novelty of these research methods, should be described in detail.*

***5 Research results***

*The research findings, their contributions to the research in this field, and the problems that remain to be solved should be described in detail.*

***6 Research conclusions***

*The following questions should be briefly answered:*

*What are the new findings of this study?*

*What are the new theories that this study proposes?*

*What are the appropriate summarizations of the current knowledge that this study provided?*

*What are the original insights into the current knowledge that this study offered?*

*What are the new hypotheses that this study proposed?*

*What are the new methods that this study proposed?*

*What are the new phenomena that were found through experiments in this study?*

*What are the hypotheses that were confirmed through experiments in this study?*

*What are the implications of this study for clinical practice in the future?*

### **7 Research perspectives**

*What experiences and lessons can be learnt from this study?*

*What is the direction of the future research?*

*What is/are the best method/s for the future research?"*

**Authors' reply:** The Article Highlights have been added to the manuscript after the Conclusion section (pages 17 and 18).

### **Answer to the reviewers**

#### **Reviewer 1: Reviewer's code: 01806391**

*"The authors have investigated the existence of factors able to predict the histological response in 150 patients with liver metastases derived from colorectal cancer and receiving neoadjuvant chemotherapy. The results are very relevant showing a set of factors with predictive value for positive or negative histological response. Changes required:*

- 1) The title is incorrect. The predictive information does not come from the histological study but just the opposite, predictive factors would permit to predict the histological response. Accordingly, the title should state: Predictive factors of histological response in patients with colorectal liver metastases after neoadjuvant chemotherapy.*

**Authors' reply:** We changed the title. It is now: **"Predictive factors of histological response of colorectal liver metastases after neoadjuvant chemotherapy"**.

- 2) *Abstract: in the last paragraph of the Results subsection, "respectively" appears twice, however in both cases it is not clear what these comparison refer to. This paragraph must be rephrased to make it clear.*

**Authors' reply:** This sentence was changed by this following sentence (page 4): "The overall survivals were 57% at 3 years and 36% at 5 years. The disease-free survivals were 14% at 3 years and 11% at 5 years".

- 3) *The Discussion section is very long and repetitive of results already described in the Results section."*

**Authors' reply:** We removed repetitive sentences already described in the results sections.

**We removed the following sentences:**

- ⊖ "More than half of our patients had a bilobar affliction (63% of the patients), three or more metastases (69% of the patients), the largest metastasis had a size equal to or greater than 3 cm (80% of the patients), and the primary tumor was lymph node-positive (67% of the patients). "
- ⊖ "Two factors were predictive of a good response: These were a rectal origin of the primary tumor and a liver-first strategy."
- ⊖ "with a significant increase in the median OS: 4.5 years vs. 2.8 years in case of no histological response. On the other hand, in the presence of VNME on the resected specimen, the histological response has no influence on OS."

**Reviewer 2: Reviewer's code: 02742218**

*"In this study authors have analyzed the histological response of colorectal liver metastasis after neoadjuvant chemotherapy and identified that the absence of a radiological response and extended neoadjuvant chemotherapy, comprising more than seven treatment sessions, are the two most pertinent predictive factors of non-histological response. They also confirmed that the histological response of colorectal liver metastases after neoadjuvant chemotherapy has an influence on survival and hence warrants being considered. However, this influence on overall survival was lacking in cases of particularly aggressive disease with microscopic vascular invasion on the histological analysis. Overall the study is very well designed and also well written. However, the data presented in the form of tables is lacking multiple logistic*

*regression analysis. Further, I would advise reduction in the number of tables as much of the information is already included in the text."*

**Authors' reply:** Thank you for this pertinent comment. We removed the table 6 of the manuscript and added the p-value in the manuscript text (p.14)

**Reviewer 3: Reviewer's code:** 01047294

*"The authors evaluated the predictive factors of the histological response of colorectal liver metastases (CRLMs) after neoadjuvant chemotherapy (NAC). And the authors found that a non-radiological response and a number of neoadjuvant chemotherapy > 7 were the two most pertinent predictive factors of non-histological response (TRG 4 or 5) .*

*Please clarify these points described below.*

- *Method Patients for whom the primary tumor was resected or who had chemotherapy at another center were also included. Why the authors included these patients in this study?*

**Authors' reply:** Our center is a tertiary center, an University Hospital where patients are referred for more specialized competences, such has liver resections. Furthermore, many of our patients live far from our hospital and the chemotherapy sessions are provided in a center near their home, accordingly to the chemotherapy plan decided in our multidisciplinary meeting. Despite the distance, we had the follow-up data of these patients.

- *How the authors evaluated the patients who were received chemotherapy at another center?*

**Authors' reply:** We are in contact with the physician of the others centers. They send us letters with the follow-up of the patients. Furthermore, in France, we have a medical and secure regional website which allow us to see the follow-up of the patients who are in another center.

- *And the patients for whom the primary tumor was resected were liver first procedure group?*

**Authors' reply:** The patients for whom the primary tumor was resected first were conventional procedure group.

- *What is ASA score? Please full spelling at the first description.*

**Authors' reply:** ASA score is the American Society of Anesthesiologists' score. The definition was added page 4 (abbreviations) and page 7.

- *Radiological evaluation (e.g., the number of lesions and the response to the treatment) : How did the authors use the radiological evaluation? I cannot understand well only with this "e.g." information.*

**Authors' reply:** The radiological evaluation was made by experienced radiologists on the basis of the morphological criteria of the response to neoadjuvant chemotherapy such as mRECIST criteria.

We added the following sentence in the methods section page 9: "(e.g., the morphological criteria of the response to NAC according to RECIST, mRECIST or CHOI criteria [22–28])".

- *Results repeat liver resections: What were the reasons of repeat liver resections?*

**Authors' reply:** The reasons of repeat liver resections were patients with recurrence of their metastases during the study time period.

- *More than 7 NAC sessions: Was there no rule (how many times should perform) of NAC sessions?"*

**Authors' reply:** The decision of the number of NAC sessions was made in multidisciplinary meeting, according to the radiological response to the neoadjuvant chemotherapy. The pursue of neoadjuvant chemotherapy sessions was initially reevaluated after 4 NAC cycles. The NAC was pursued if there were need for more response to NAC to perform surgery in better conditions.

**Reviewer 4: Reviewer's code: 03475120**

*"This paper is well-written. Histological response after neoadjuvant chemotherapy may show the discrepancy from radiological response, because some viable tumors after NACs showed necrotic changes without size changes. Please discuss this point, even if your results of*

*histological response were similar with radiological responses. How to recognize the tumor viability by image study should be described in detail."*

**Authors' reply:**

Effectively, histological response after neoadjuvant chemotherapy may show the discrepancy from radiological response, because some viable tumors after NACs showed necrotic changes without size changes. However, our experienced radiologists who analyzed the imaging exams to evaluate the response to neoadjuvant chemotherapy used sizes criteria and also density criteria which are correlated to the necrosis of the metastases (RECIST, mRECIST and CHOI criteria).

We added the following sentence in the methods section page 9: "(e.g., the morphological criteria of the response to NAC according to RECIST, mRECIST or CHOI criteria [22-28])".