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Editor

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**Re: RESECTION MARGIN INFLUENCES THE OUTCOME OF
PATIENTS WITH BILOBAR COLORECTAL LIVER
METASTASES IN AN ERA OF MULTI-DISCIPLINARY
THERAPY**

We would like to re-submit this manuscript titled above for publication in your journal – World Journal of Hepatology.

All the authors have approved the corrections for this manuscript and there is no conflict of interest.

If there is any further information you require, please contact us.

Thank you for your cooperation.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'D. Gomez', enclosed within a thin rectangular border.

Reviewer: Comments to the Author

This article is interesting but I think epidemiological data are more interesting than univariate and multivariate analysis, which is the part highlighted by the authors. Structure of the manuscript is correct. The message of this article is not very clear. It missed something important to hold about this article. But the content of the manuscript have value for publication all the same.

1) It is unclear why the non-operated but down staging patients, have not been finally operated. What are the criteria used?

Unfortunately, these patients did not response to neo-adjuvant therapy. The criteria used for resection was based on response to neo-adjuvant therapy and the ability to remove all macroscopic disease. All radiological imaging were reviewed in our MDT pre- and post- down-staging therapy prior decision on surgical resection. We have explained this in the Methods and Results section.

Please refer to page 6, second paragraph, and highlighted section:

..... Patients were then re-discussed at the MDT and considered for surgery based on absence of new disease, tumour response and extent of disease.Resectable disease was defined as excision of all macroscopic CRLM to achieve a clear margin while preserving sufficient liver parenchyma based on pre-operative radiological imaging.

Please refer to page 9, second paragraph, and highlighted section:

.....These patients did not respond to their down-staging therapy, which included: (1) having new metastases; (2) disease progression; and (3) inability to remove all macroscopic liver disease whilst leaving sufficient remnant liver. This

decision was based on MDT review of up to date radiological imaging following down-staging therapy.

2) It lacks a clear table of epidemiological characteristics of all patients. To add an overall survival curve of all patients and the number of > 5 years survivors would be interesting. The survival curve could show too: operated patients, down staging patients, inoperable patients. Maybe it would be interesting to look precisely risk factors to lead to operate patients?

We have corrected this.

We have added Table 1, which includes clinical data for all patients in this study.

Please refer to Table 1.

Table 1: Clinical data of patients with bilobar colorectal liver metastases in this study.

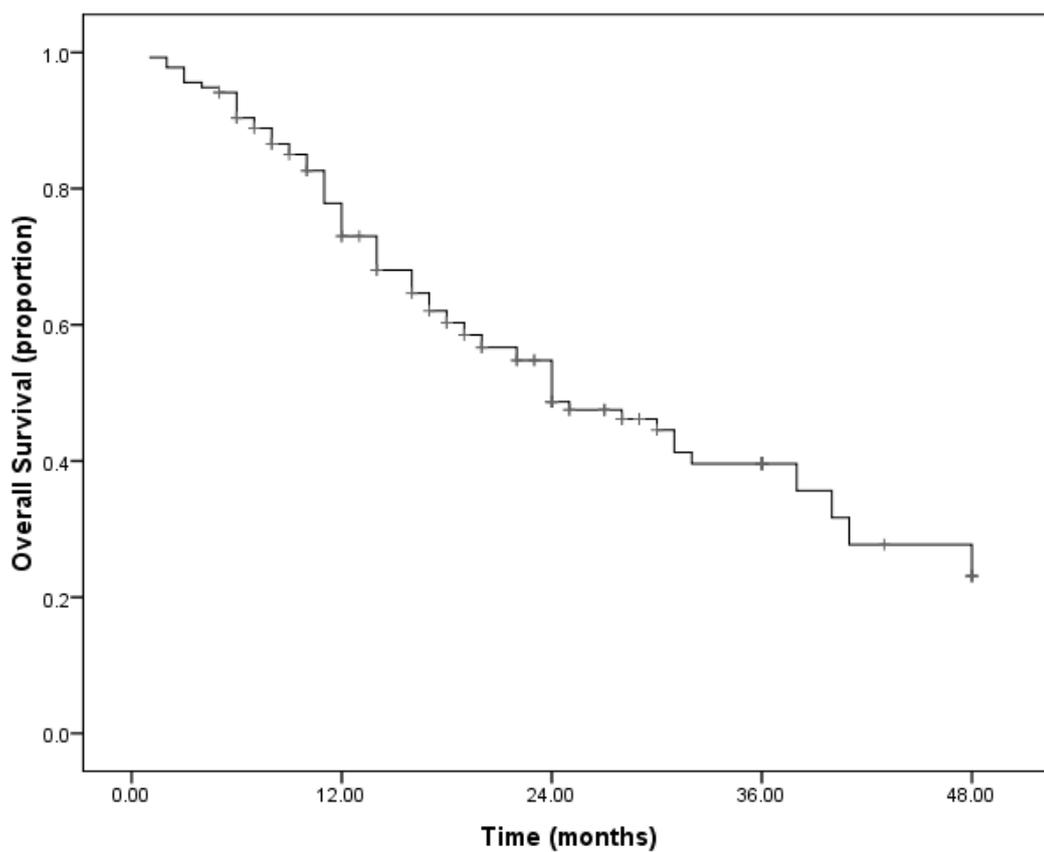
Demographic, clinical and pathological factors All patients (n = 136); All surgery patients (n = 71)	Total (n)
Demographic factors	
Age \geq 65 years	68
Male Gender	99
Synchronous Presentation	80
Down-staging therapy	70
Oxaliplatin-based regimen	60
Irinotecan-based regimen	10
Addition of Biological agent	30
Surgical factors (n = 71)	
Hemi-hepatectomy or more	22
Histo-pathological factor (n = 71)	
Largest tumour size \geq 5 cm	11
Number of metastases $<$ <u>4</u>	44
Lymphatic invasion present	15

Vascular invasion present	28
Peri-neural invasion present	9
Biliary invasion present	25
Resection margin (R0)	40

We have added two new survival curves as suggested by the reviewer.

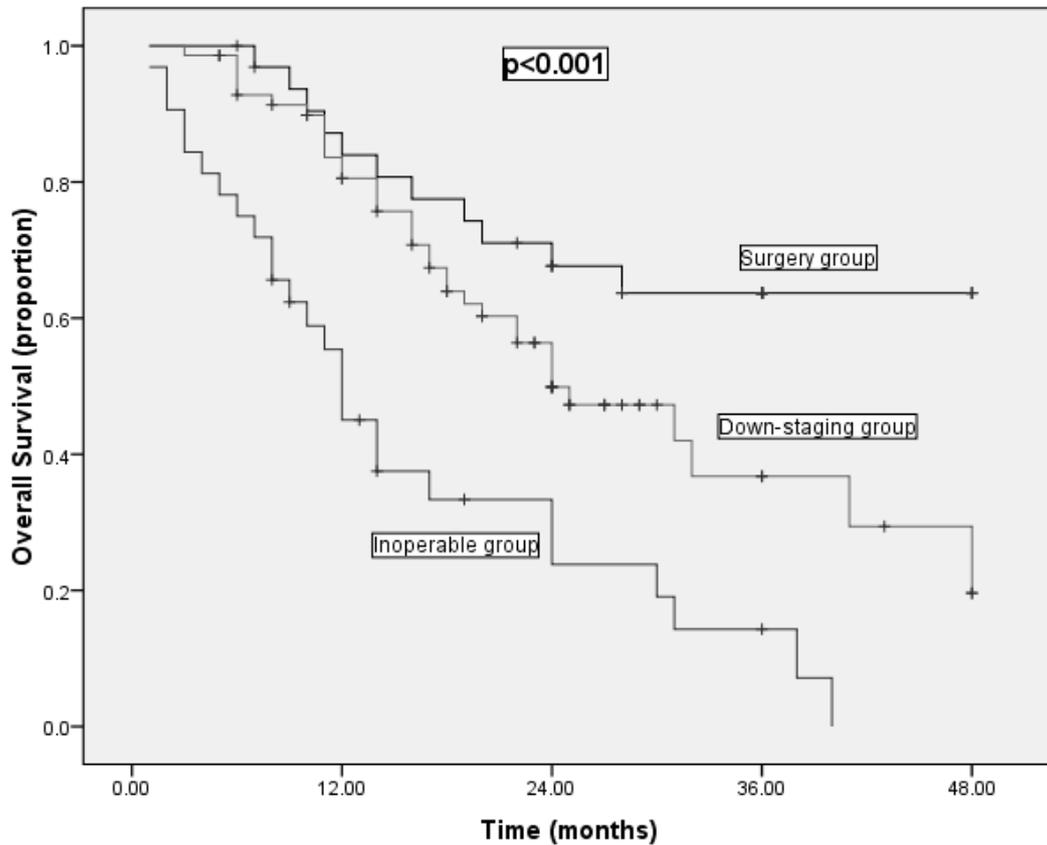
Please refer to Figures 2 and 3.

Figure 2: Overall survival of patients with bilobar colorectal liver metastases in this study.



All patients (n = 136): 18 (1 – 48) months

Figure 3: Difference in overall survival in patients that underwent surgery, down-staging therapy followed by surgery or palliative therapy and inoperable patients.



Surgery (n = 34): 28 (7 – 48) months

Down-staging therapy (n = 70): 18 (3 – 48) months

Inoperable (n = 32): 11 (1 – 40) months

As stated above, the operability was dependent on MDT review of radiological imaging to enable removal of all liver metastases whilst preserving sufficient liver parenchyma.

3) Data on treatment (chemotherapy) are not clear enough.

We have explained in detail the chemotherapy regimens used in this Unit in the Methods section.

Please refer to page 5, last paragraph, and highlighted section.

Down-staged therapy and Adjuvant chemotherapy

Patients scheduled for preoperative systemic chemotherapy had 3 – 6 months of neo-adjuvant treatment. The regimens used were either Oxaliplatin based: two weekly FOLFOX [5-fluorouracil (FU) 400mg/m² bolus, and 2400mg/m² over 46 hours, Leucovorin and Oxaliplatin 85mg/m²] or three weekly CAPOX (Capecitabine 1000mg/m² BD for 14 days and Oxaliplatin 130mg/m²).

However, in patients tested and found to be *RAS* wild-type, two weekly FOLFIRI (Irinotecan 180mg/m², 5-FU 400mg/m² bolus, and 2400mg/m² over 46 hours) was administered with concurrent Cetuximab (400mg/m² cycle 1, then 250mg/m² cycle 2 onwards).

We have added chemotherapy data in the Results section, and included these details in Table 1.

Please refer to page 9, 2nd paragraph, highlighted section and Table 1.

.....Besides receiving either an Oxaliplatin-based (n = 60) or Irinotecan-based (n = 10) regimen, 30 (42.8%) patients also had biological agents as part of their down-staging treatment.

4) Discussion provides interesting insights into article's outcome. Strengths and limitations of this study are not expressed by the authors.

This has been addressed in the Discussion section.

Please refer to page 14, highlighted section.

There are limitations in this study. This is a retrospective study, and focused on a group of patients with bilobar liver metastases. These are patients with bad tumour biology and in most cases, will require down-staging therapy. Nevertheless, although these group of patients have a higher tumour burden; their prognosis can be improved with a MDT approach that focuses on multi-modal therapy.

5) I find some English mistakes...

This has been corrected throughout the manuscript.