

February 21, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (Manuscript 16518-review.doc).

Title: *Liver-First Approach of Colorectal Cancer with Synchronous Hepatic Metastases: A Reverse Strategy*

Author: Jaques Waisberg and Ivan Gregório Ivankovics

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 16518

Revision has been made according to the suggestions of the reviewer.

The authors thank the reviewers for their valuable suggestions offered. The authors state that **all the suggestions** of the reviewers were incorporated into the manuscript text.

Reviewer 02663375

In symptomatic patients the liver-first option is not suitable [Ref. #2]. In the systematic review of Lykoudis PM et al [Ref. #2] no subgroups of patients who would clearly benefit from a particular approach were recognized. It should be clearly stated in this review.

Authors

The manuscript has been improved according to the suggestion of the reviewer.

"Lykoudis et al.[2] in a systematic review suggested that none of the three surgical strategies (primary first, liver first or simultaneous resection) is inferior to the others. All of them should be considered for patients with synchronous colorectal liver metastases, with the exception of those with symptomatic primaries, in whom the liver-first approach is not suitable.[2]" 4th paragraph, page 8.

Reviewer 02663375

Please, explain why the combined strategy may have a negative effect on the progression of disease-free survival. In a systematic review that included 4 studies Jegatheeswaran S et al [Ref. #6] report that the liver-first approach for patients with colorectal cancer with synchronous liver metastases is possible but is associated with a wide range of survival outcomes, despite protocol similarities between studies.

Authors

The manuscript has been improved according to the suggestion of the reviewer.

De Haas et al.[12] studied 228 patients undergoing hepatectomy for synchronous colorectal liver metastases, 55 (24,1%) had a simultaneous colorectal resection and 173 (75,9%) had delayed hepatectomy. They observed disadvantages of the combined strategy as the morbidity of complex liver resection, combined with major bowel resection, is likely to be considerable, and there is some evidence that this combined strategy has a negative effect on progression free survival. Actually, disease recurrence was observed more often in patients treated by a simultaneous strategy, and three-year overall survival rates did not significantly differ according to the surgical strategy, but progression-free survival was significantly better after delayed hepatic surgery. Three independent predictive factors of disease recurrence were: three or more colorectal liver metastases at diagnosis, initial unresectability of colorectal liver metastases, and simultaneous colorectal and hepatic resection. After case matching for age, sex, number and location of colorectal liver metastases, the morbidity rate remained lower and the recurrence rate higher in the simultaneous strategy group. Furthermore, progression-free survival was also significantly lower in the simultaneous strategy group. Unfavorable recurrence rates for simultaneous colorectal

and hepatic resection were confirmed in the LiverMetSurvey cohort. **2nd paragraph, page 4.**

Jegatheeswaran et al.[6] performed another systematic review about the liver-first approach. Of 121 patients starting treatment, 90 (74%) completed the specified treatment protocol. Disease progression during the protocol period occurred in 23 patients (19%). De Rosa et al. reported the outcomes of 82 patients with synchronous colorectal liver metastases following the reverse strategy. Overall, the morbidity and mortality rates were low. The recurrence rate ranged from 25 to 70 % and the overall 5 year survival ranged from 31 to 41 %. **1st paragraph, page 8.**

Reviewer 00057521

I suggest that data regarding overall survival, disease free survival, surgical morbidity, etc, should be included in the discussion. It is true that there are NOT randomized trials however, published retrospective series provide this numbers and should be stated in the manuscript

Reviewer 02822870

Convincing data should be cited in the manuscript, instead of tedious narration.

Authors

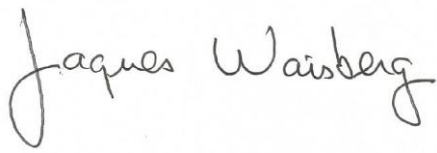
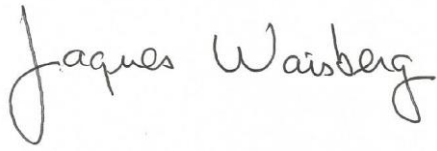
The manuscript has been improved according to the suggestions of the both reviewers.

Brouquet et al.[10] retrospectively evaluated the outcomes of 156 patients with synchronous CRLM managed by three different surgical approaches: traditional (n = 72); combined (n = 43); and reverse strategy (n = 27). Patients treated with the reverse strategy had a significantly higher number and larger colorectal liver metastases than patients treated by the combined and traditional strategies. All 27 patients that completed the reverse strategy treatment had preoperative chemotherapy. Major liver resection was performed in 24 patients in the reverse strategy group, with a R0 resection rate of 85% (n = 23). Postoperative mortality rates in the combined, classic, and reverse strategies were 5%, 3%, and 0%, respectively. The postoperative cumulative morbidity rates were 47%, 51%, and 31%, respectively. Cumulative postoperative morbidity and mortality rates were not statistically different between the groups. There was no significant difference in 3-year and 5-year survival between the three groups, and the median disease-free survival was 11 months in all three groups. **First paragraph, page 6**

Andres et al.[21] performed a survival analysis of the liver-first reversed management of advanced simultaneous colorectal liver metastases based on the LiverMetSurvey (January 1, 2000 to December 31, 2010), and included patients with resection of two or more colorectal liver metastases. All patients had irinotecan and/or oxaliplatin-based chemotherapy before liver surgery, and patients undergoing simultaneous liver and colorectal surgery were excluded. A total of 787 patients were included: 729 submitted on resection of the primary colorectal cancer (with or without neoadjuvant radiotherapy for rectal cancer), following by colorectal liver metastases, and subsequent resection of all colorectal liver metastases (classical approach) and 58 patients submitted on reverse management defined as a sequential management including colorectal liver metastases directed chemotherapy, the resection of all colorectal metastases, and the subsequent resection of the primary colorectal cancer (with or without neoadjuvant radiotherapy for rectal cancer). Patients in the two groups had similar numbers of metastases and Fong scores of 3 or more. Rectal cancer, neoadjuvant rectal radiotherapy, and the use of combined irinotecan/oxaliplatin chemotherapy were more frequent in the reverse management group ($P < 0.001$), whereas colorectal lymph node involvement was more frequent in the classical management group ($P < 0.001$). Overall survival and disease-free survival were similar in both groups (48% vs 46% at 5 years, $P = 0.965$ and 30% vs 26%, $P = 0.992$). **4th paragraph, page 6**

Kelly et al.[22] reported a network meta-analysis review comparing classical, combined, and liver-first strategies. Eighteen studies were included in this review, reporting on 3,605 patients. Network meta-analysis and pair-wise meta-analysis of the 5-year overall survival did not show significant difference between the three surgical approaches: combined versus colorectal-first, liver-first versus colorectal-first, liver-first versus combined. In addition, network meta-analysis of the 30-day mortality among the three approaches also did not observe statistical difference. Analysis of variance showed that mean post-operative complications of all approaches were comparable. **5th paragraph, page 7.**

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

A handwritten signature in black ink, reading "Jaques Waisberg". The script is fluid and cursive, with the first letter of each name being capitalized and prominent.A second handwritten signature of "Jaques Waisberg" in black ink, identical in style to the one above.

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