

Buenos Aires, December 10, 2015

Jin-Xin Kong,
Science Editor, Editorial Office.
World Journal of Gastrointestinal Surgery

Dear Sir:

We have received your letter with the comments about our manuscript ***“Parenchymal-sparing liver surgery in patients with colorectal carcinoma liver metastases”*** (ESPS manuscript No. 21718) and we are glad to know about the interest expressed in reviewing the paper again if certain revisions are made in the manuscript.

We have modified the paper according to the referee’s suggestions as well as the editorial comments and hope that all the concerns have been appropriately addressed. The changes were made using the Track Changes function in the manuscript and were highlighted in yellow.

All the authors have seen this version of the manuscript and agree with the modifications that have been performed.

Specific answers to comments:

Reviewer #1 (Reviewer’s code: 00183251): We thank the reviewer comments highlighting the value of our manuscript.

Reviewer #2 (Reviewer’s code: 03317096): As requested by the reviewer, in order to increase the discussion we added more updated data in the section *“Tumor biology”* specifically regarding intrahepatic lymphatic invasion of colorectal liver metastases as a recently introduced feature translating tumor biology. Two references were added to the text and the reference list was updated:

- New reference 29: Lupinacci RM et al. Intrahepatic lymphatic invasion but not vascular invasion is a major prognostic factor after resection of colorectal cancer liver metastases. World J Surg. 2014;38(8):2089-96.
- New reference 31: Korita PV, Wakai T, Shirai Y, Sakata J, Takizawa K, Cruz PV, Ajioka Y, Hatakeyama K. Intrahepatic lymphatic invasion independently predicts poor survival and recurrences after hepatectomy in patients with colorectal carcinoma liver metastases. Ann Surg Oncol 2007;14: 3472–3480.

Reviewer #3 (Reviewer's code: 00057645):

- As requested for the “*Hystorical Perspective and Oncological Basis*” section of the manuscript, we included and discussed important experimental and pathological studies regarding micrometastasis and the potential implications of the so-called “dangerous halo” after discontinuing chemotherapy before two-stage liver resections:

- New reference 28: Wakai T, et al. Appraisal of 1 cm hepatectomy margins for intrahepatic micrometastases in patients with colorectal carcinoma liver metastasis. *Ann Surg Oncol*. 2008; 15(9):2472-2481.
- New reference 30: Wakai T, et al. Histologic evaluation of intrahepatic micrometastases in patients treated with or without neoadjuvant chemotherapy for colorectal carcinoma liver metastasis. *Int J Clin Exp Pathol*. 2012; 5(4):308-314.
- New reference 21: Mentha G, et al. Dangerous halo after neoadjuvant chemotherapy and two-step hepatectomy for colorectal liver metastases. *Br J Surg*. 2009; 96:95-103

- As well, as suggested by the reviewer we added in the section “*Imaging techniques*” the role of MRI especially with Diffusion-Weighted sequences.

- Regarding the use of contrast enhanced intraoperative ultrasound (CE-IOUS), in our opinion even though unfortunately it is not available everywhere, we agree with the reviewer on its transcendental value. Therefore, following the reviewer suggestion we provided more information regarding CE-IOUS, specifically adding the interesting findings of the study by Ruzzenente A, et al. Usefulness of contrast-enhanced intraoperative ultrasonography (CEIOUS) in patients with colorectal liver metastases after preoperative chemotherapy. *J Gastrointest Surg*. 2013;17(2):281-7. This reference was added as the new reference 46 and the reference list was updated in the text.

Please do not hesitate to contact me if there is any further revision of our manuscript needed. Looking forward to a favorable response, I thank you in advance.

Sincerely,

Eduardo de Santibañes, MD, PhD
Professor and Chairman, Liver Transplant Unit & General Surgical Service
Hospital Italiano de Buenos Aires.
Juan D. Perón 4190. C1181ACH. Buenos Aires, Argentina.
Tel: +54-11 4981 4501. Fax: +54-11 4981 4041
E-mail: eduardo.desantibanes@hospitalitaliano.org.ar