Peer Review File

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Reviewer A

Current article is based on relevant experience with liver resection in the patients with HCC. Data is well presented and analyzed. Conclusions are sound and based on presented info. Authors should be congratulated on providing important evidence in quickly developing field of HCC resection in patients with chronic liver diseases.

Excellent article adding to mounting evidence that is time to expand liver resection for patients with contraindications in the past.

A: We thank the reviewer for the comments.

Reviewer B

Multinodular HCCs may attribute to intrahepatic metastasis or multicentric occurrence. Intrahepatic metastasis is associated with portal system invasion. This means that multinodular HCCs may have a same meaning of portal system invasion. How do the authors consider this point?

A: We thank the reviewer for the comments.

Of 8 patients with more than one nodule, 3 (37.5%) had macroscopic portal vein invasion. The other cases could be a multicentric occurrence of HCC. Survival was similar in both groups (median survival = 18 months, with and without portal vein invasion). This information was added to the text (Discussion).

There is no way to know the origin of other nodules in multinodular presentation of HCC, whether multicentric disease or due to portal invasion. Both negatively impact prognosis.

Reviewer C

1. The title of this study is “Liver resection for hepatocellular carcinoma beyond the BCLC: are multinodular disease, portal hypertension, and portal system invasion really contraindications?” Of the three factors discussed as risk factors, multinodular disease is included in only 5.3%.

A: Thank you for your question.

From the three main BCLC contraindications, multinodular disease was the least frequent. Liver resection for multiple HCC nodules is a very controversial subject. There is data showing benefits of resection for up to 3 nodules (Ruzzenente et al. J Gastrointest Surg. 2009; Glantzounis et al. Eur J Surg Oncol. 2018). Just a few patients were included (5.3% of patients) because we were very selective for the indication of resection in patients with multiple HCCs. We opted for the resection of 2 or 3 nodules only in patients in which nodules were restricted to the same sector of the liver and outside the Milan criteria (no indication for liver transplantation).

2. What their analysis shows is a prognostic factor analysis of 150 HCC resected cases, which we believe cannot be used as material to discuss the validity of BCLC guidelines.

A: Thank you for your comment.

This paper did not try to validate the BCLC; what we wanted to show is that for a reasonable number of patients, a curative treatment would not be offered if BCLC was adopted. In our series, if the BCLC 2010 and 2018 recommendations had been followed, 70 patients (46.7%), and 40 patients (26.7%) respectively would not have undergone a potentially curative treatment. Our experience with HCC resection (195 cases; 150 selected for this study) is similar to other large referral centers in the Western world.

Our results showed that there is room for a more liberal indication of HCC resection allowing potentially curative treatment to several patients that would receive palliative therapy.

3. The 90-day mortality rate of 6.7% is extremely high.

A: Thank you again for your comment.

In our series, 84.7% had chronic liver disease, and in more than half of the patients the main cause was Hepatitis C.

The mortality rate presented in this series is relatively high, however it is similar to other western series as: Bartolini I et al. (8.3% - Italian multicentric study - Am J Surg 2021); Cauchy F et al. (6.4% - 450 patients - Beaujon Hospital – France - Best Pract Res Clin Gastroenterol 2014); Chapman BC et al. (8.5% - 11259 patients – US National Cancer Database US – Liver cancer 2021).

4. The authors described in Results section, “The mean follow-up was 32.1 months (median 23.95 months, range 5 to 136.28 months)", and “Median OS was 57.4 months”. That is strange. There are similar concerns regarding DFS.

A: It is important to clarify the difference between median follow-up time and median overall / disease-free survival.

While the median follow-up time considers the median time that patients are followed-up independently of the events (death or not; recurrence or not), the median overall / disease-free survival considers patients without death or recurrence, respectively, as censored, changing the number of subjects at risk. Thus, median overall / disease-free survival is quite different of median follow-up time.

Since median is more important and representative than mean, we changed the order of appearance of mean and median in the Results section.

5. The authors evaluated number and size of the lesions, and the presence of satellite nodules. Please clearly describe the difference between number of the lesions and satellite nodules.

A: According to the US-National Cancer Institute, we called a satellite nodule a nodule located within 2cm of the primary tumor (this information was inserted in the methods section). Satellite nodules were not considered as another lesion.

6. Fig 1-4 should be grouped together as Fig 1A-D. It should be expressed exactly which Figure represents what.

A: Thank you for this suggestion. It was corrected in the text.

7. English and structure are not suitable for publication.

A: The paper was sent to a professional English revision. Thank you.