Peer Review File

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Reviewer A

This paper compares the oncologic outcomes of AR in PET-positive versus PET-negative patients with HCC in a quite large cohort of patients. The paper is well written and u nderstandable however I have the following main concerns:

1. Since it is already well known that AR performs better than NAR and the prognostic role of positive PET in the setting of numerous cancer including HCC finally the authors just confirmed a scenario already described in the literature adding nothing new to the surgical approach of HCC

Reply 1: We totally agree with your comment that oncological benefit of AR and the prognostic role of positive PET are already described in the previous studies. However, our hypothesis is that while the outcome of AR may be similar with NAR in PET-negative HCC where there may not be a vascular invasion, AR certainly shows better results than NAR in PET-positive HCC where there may be a vascular invasion.

In the total study patients, AR for PET-positive or-negative HCC did not show a better RFS or OS than NAR (Figure 2).

However, in subgroup analysis based on tumor size, the RFS of AR was found to be better tha n NAR at PET-negative HCC or 3cm or more and PET-positive HCC of 3cm or less (Figure 4). The significance of this study is that tumor size and P ET positivity, clinically representing the tumor aggressiveness, can be used to define HCC pat ients whose AR is superior NAR, although somewhat rough.

2. The criteria for performing AR or NAR are not clearly defined and left to surgeon's preference

Reply 2: Since this study is a retrospective study conducted on patients who have undergone surgery by five surgeons in multi-center, it is true that the preference of surgeons, along with the condition of the liver function and the location of the tumor, has affected the selection of AR or NAR. However, the criteria for AR or NAR selection are defined as follows: AR was defined as complete resection of an anatomic region demarcated by preceding ischemia, along with division of the Glisson associated with tumor location. With solitary HCC located peripherally or presenting with exophytic growth, NAR was performed when patients required limited resection due to insufficient liver function or remnant liver volume.

Changes in text: we removed this expression ‘according to the surgeon’s preference’, and add ed the sentence regarding evaluation of resection type. (see Page 6, line 8)

3. The finding that PET correlated with increased PIVKA, MVI and PV invasion is clearly expected since are all same aspects of more aggressive presentation of HCC and is not new to the literature.

Reply 3: As reply 1 about comment1, it started with the question of whether there would be any difference in oncological outcomes of HCC patients depending on the results of preoperative PET and the type of resection; AR versus NAR. Our study shows that AR is superior to NAR when the tumor is PET-negative HCC of 3cm or more, or PET- positive HCC of 3cm or less. In other words, in HCC patients whose tumors are too aggressive or too mild, AR may not be superior to NAR. Therefore, although there is selection bias due to the nature of the retrospective study, it can be said that this study has clinical implications to help the surgeon choose the resection type (AR vs NAR) by assessing the biological characteristics of the tumor shown in preoperative tests including PET.

Changes in text: we added above sentences in the discussion section. (see Page 12, line 8)

4. Multivariate analysis failed to show any role of PET and AR as independent factor for HCC recurrence

Reply4: PET positivity and NAR are known to be associated with more HCC recurrence after hepatectomy. However, first, in the paper I reviewed in the study of PET, none of the studies showed that PET positivity was an independent prognosis factor of more than five years of long-term (more than five years) outcomes in multivariate analysis (Reference 11-14).

Next, for AR, previous studies have shown that NAR conducted with sufficient resection mar gin do not differ significantly from AR in terms of oncological long-term outcomes. In our study, there was no difference in tumor-free margin between each subgroup (P=0.863, Table 5). Multivariate analysis revealed that hi gher E-S grade, MVI, intrahepatic metastasis, and multicentric occurrences were significantly associ ated with HCC recurrence (P=0.001, P=0.037, P=0.004, and P=0.001, respectively; Table 2). This implies that HCC recurrence after hepatectomy may be influenced by tumor biology rath er than the procedure of anatomical resection, provided a sufficient surgical margin was achie ved.

5. Although the authors stated that no clear definition of PET positivity (SUV cut-off) was given this remains a major concern for the entire evaluation of this paper

Reply5: Unfortunately, the definition of PET positivity using SUV cutoff value was not conducted in this study. This related topic will be carried out as a follow-up study.

Reviewer B

Very well written. Relevant findings.

I suggest the following revisions:

- improve the literature review for the Introduction by adding and citing the following references:

1) Hepatocellular carcinoma (HCC) patients listed in short wait regions remain advantaged for liver transplant (LT) following 2015 HCC policy change.

Brondfield MN, et al. Liver Transpl 2019.

2) Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases.

Marrero JA, et al. Hepatology 2018.

3) HEPATOCELLULAR CARCINOMA: DIAGNOSIS AND OPERATIVE MANAGEMENT

Chedid MF et al. Arq Bras Cir Dig 30 (4), 272-278.

4) Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis.

Kulik L, et al. Hepatology 2018 - Review.

5) Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases.

Marrero JA, et al. Hepatology 2018.

Reply: I reviewed the reference paper mentioned above in detail. However, reference No. 1 and No. 4 were not related to this study as papers on LT as HCC treatment.

Changes in the text: We added two references (see Page 14)

Reviewer C

The authors in their paper titled "Clinical impact of anatomical resection on long-term outcomes after hepatectomy for primary solitary hepatocellular carcinoma with or without preoperative positron emission tomography positivity" reported the result from their recent research on the prognostic value of AR and PET negativity to predict postoperative outcomes in in patients with solitary hepatocellular carcinoma. With significant implications for clinical practice, the importance of the present study should never be over emphasized. However, some issues should be furthered discussed.

1. Line 97: "259 naïve HCC patients" -------"naïve" means what?

Reply 1: "naïve"HCC refers to HCC that has never been treated.

Changes in the text: We added "treatment-" before "naïve"to prevent confusion and ensure its meaning. (see page 5, line 11)

2. Line 135: It should be noted that the "T test" is only used for continuous variable of normal distribution.

Reply 2: We agree with your comment. When the dependent variable is continuous, but not normally distributed, we analyzed the data using a Mann-Whitney test.

Changes in the text: we add "or a Mann-Whitney test".(see page 7, line 6)

3. "liver-related OS rates" and "liver-related mortality" should be defined in the Method Section.

Reply 3: Liver-related mortality was defined as death from HCC recurrence after hepatectomy, as well as death caused by hepatectomy-related complications including hepatic failure, sepsis due to bile leakage, and postoperative bleeding.

Changes in the text: we add above definition (see page 6, line 1)

4. Line 227: In discussion section, the authors said that "the present study revealed that PET positivity was significantly associated with higher PIVKA-II (P=0.025), portal vein invasion (P=0.031), and MVI (P=0.012)."

However, I didn't found strong evidence that can be used to support the authors' conclusion.

Considering the article is a retrospective study, the selection bias shouldn't be ignored.

If the authors want to explore whether PET can predict MVI, patients should be grouped according to "the status of MVI".

Then, the univariate and multivariate analyses should be carried out.

Reply 4: We agree with your comment. However, since the aim of this study is not to explore whether PET can predict MVI, but to compare the oncological outcomes of AR and NAR in PET positive HCC, it seems inappropriate to group patients according to the status of MVI. However, the sentence you mentioned in the discussion section may show that the PET positivity is strongly related to the MVI, so we revised it as follows in the discussion to avoid this confusion.

Changes in the text: In the present study, patients with PET-positive HCC tended to have significantly higher PIVKA-II (P=0.025), portal vein invasion (P=0.031), and MVI (P=0.012) than patients with PET negative HCC. (see Page 11, line 1)