

Date: 17th Nov 2022

To
The Chief Editor
World Journal of Gastrointestinal Surgery

Re: Manuscript NO: 80745

Title: Does size matter for hepatic resection of giant (≥ 10 cm) versus non-giant (<10 cm)hepatocellular carcinoma? A meta-analysis

Dear Sir

Many thanks for seeking peer review of our submission and please accept the revised manuscript along with the response letter addressing reviewer comments.

Reviewer 1:

This work proposes a meta-analysis aimed to investigate whether oncological outcomes and safety profiles of resection differ between giant and non-giant HCC. The authors have given important results that resection of giant HCC is associated with poorer long-term outcomes. The corresponding suggestions are given in this paper : HCC staging systems should account for the size difference. However, the paper has several limitations.

Comment 1: Authors compared the short-term perioperative outcomes and safety profiles in two groups, only measured by 30-day mortality and postoperative complications between the two groups, authors deduced that HCC size may not affect the safety and efficacy of surgical resection in the short term, however, these indexes may not enough to accurately reflect the safety profile of surgical resection, we required more evidence to proposed that giant HCC have different tumor characteristics from non-giant HCC.

Response 1:

We agree with this view that 30-day mortality and postoperative complications are not the sole determinants of safety and efficacy. I shall deal with the issue of giant and non-giant HCC along with comment 2. For the postoperative complications, three issues are relevant: (a) 90-day mortality (b) post-hepatectomy liver failure,

and (c) one-year survival outcomes. Further, there will be situation-specific and patient-specific outcomes; for example for elderly patients, discharging to their own home or admission to a nursing home, % of patients operated by minimal access route, etc, and so on. For the purpose of this manuscript and the response, we shall address the earlier three issues.

- (a) 90-day mortality is a key performance indicator for liver resection and in general, the 90-day mortality statistic is higher than the 30-day mortality statistic. We are advocates of reporting 90-day mortality. However, when we conducted a systematic review on this topic, we encountered a majority of authors reported 30-day mortality. Thus, we cannot report 90-day mortality data as the included studies did not report this. The current draft already contains this issue in the discussion on page 15 and we borrow from our manuscript the short segment of paragraph that addresses this issue:

“Although both groups had similar 30-day postoperative mortality and major complication rates, these may not accurately reflect the safety profile of surgical resection in each group. As the 90-day postoperative mortality rate has rarely been reported, only the 30-day mortality rate could be used as an indicator of postoperative mortality. However, a review by Egger et al. found that most studies reported an approximate doubling of mortality rates between 30 and 90 days following surgery [48]. As the findings of this study were based on 30-day mortality rates, they may not accurately reflect the safety profile of surgical resection. “

- (b) Post-hepatectomy liver failure is another key performance indicator of liver resection outcomes in patients with HCC. There are varied definitions of PHLF and thus there is inherent heterogeneity in the reported studies about this variable. With regards to PHLF, we have included on page 15 of our manuscript the following:

“Additionally, many studies did not specify which postoperative complications the patients experienced, and only 6 of the 24 studies [22, 27, 30, 31, 34, 37] specified if the patients developed PHLF. Since PHLF has been found to be an independent predictor of mortality [2], the development of PHLF after HCC resection may be more indicative of the safety profile than complication rates alone. Thus, to improve the safety profile assessment of surgical resection, more precise reporting of major postoperative complications, particularly PHLF, and reporting of the 90-day mortality rate are required. “

For giant HCC, it is very likely that major liver resections are warranted with significant large liver volumes removed and high risk of small FLR (future liver remnant); thus, increasing the risk of PHLF. However, high quality studies are necessary to prove this conjecture.

(c.) One-year survival outcomes: In our opinion, this is a hybrid outcome that is applicable and relevant as short-term outcome (largely applied to perioperative outcomes) and long-term outcome (oncologic or survival outcomes). We have reported that one-year outcomes of patients undergoing liver resection for HCC are inferior compared to 90-day mortality (citation 2 in our manuscript); however, there is absolute paucity of such data in literature. Simplistically speaking, 1 year mortality is double than 90-day mortality which is double than 30-day mortality. Again, I do not have high quality studies to back this statement; but the data out there does suggest that mortality is a continuum of follow-up and within 1 year mortality could be considered broadly as perioperative mortality rather than lumping as survival statistic. Again, due to lack of data, this is not reported, but we have done some discussions along these lines. It is essential to understand this cautiously with the following case example. For instance, a patient sustains bile leak following hepatectomy and needs percutaneous drains, ERCP's etc to control bile leak and passes away of sepsis after few months and within a year – the mortality is actually perioperative and related to surgery. In another instance, a patient develops a recurrence and metastases after an uneventful surgery. Such mortality is not in fact perioperative but an oncologic outcome due to tumour biology. Thus 1-year outcomes should be a hybrid of perioperative and oncology both.

Comment 2: Some factors that have been shown to be associated with poorer outcomes of giant HCC in this manuscript, this study concluded that giant HCC have different tumor characteristics from non-giant HCC. However, the difference between giant and non-giant HCC may be related to other surgical factors such as the expansion of surgical resection due to different tumor diameter, which should be discussed in this paper.

Response 2: We entirely agree that the difference in perioperative and oncologic outcomes could be due to tumour characteristics based on size as well as operative surgical factors that could be directly or indirectly related to size, or simply independent (e.g., skill of surgeon, skill of operating team, quality of anesthesia to reduce blood loss, use and availability of technology like energy devices or stapling devices, etc). Intuitively, what you say is very true – larger tumour is likely to need expansion of surgical margins and this may mean proximity to hilum or major vessels and propensity for bleeding or bile leak. Also, FLR would be smaller and this risk of PHLF may be higher. All these issues make size as indeed a factor that contributes to complications and outcomes; but entire literature is silent on this matter. Size is known to matter in other body cancers like breast, colon, lung, etc and thus it should matter in HCC too! But existing guidelines do not report this; hence this study was conducted. In our draft on page 15 we have included the following – “From a technical perspective, the surgical resection of

giant HCC is challenging. A large tumor size limits the surgical working space, increases the risk of tumor seeding from surgical manipulation, and distorts liver anatomy, thus potentially increasing operative difficulty.”.

We have added the following: Further, it is likely that resection of large tumor entails dissection zone in proximity to hilum or major vessels, thus increasing the likelihood of bleeding or bile leak. In addition, surgical resection of giant HCC is in general entails major hepatectomy with small future liver remnant and associated risk of PHLF.

Comment 3: There are not detailed explanation of differential and diagnostic criteria between giant and non-giant HCC in the manuscript. The inclusion and exclusion criteria need to be improved.

Response 3: Thanks for these insightful comments. We have excluded studies published before 2000 and also excluded case reports and case series. We have included comparative studies that compare outcomes of HCC resection based on tumor size cut off at 10cm. This increases the validity and generalizability of our results. With technological advances and better understanding of surgical technique and familiarity, surgical outcomes have improved over last 2 decades and thus older studies are likely to have inferior clinical outcomes, that should not be forming benchmarks for future. This we excluded studies before 2000.

With regards to diagnostic criteria, each study has its own way of diagnosing HCC before surgery and all studies mentioned had histologically confirmed diagnosis of HCC.

Reviewer 2:

The authors presented a well-organized meta-analysis. Size differences should be considered in HCC staging systems.

Response: Thanks for your comments.

Thanking you

Sincerely

Dr Vishal G Shelat

Senior Consultant

Tan Tock Seng Hospital

Singapore 308433

E-mail: vgshelat@rediffmail.com