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Outcomes of surgical resection of super-giant (≥ 15cm) hepatocellular carcinoma: Volume does matter, if not the size

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Ref.: Ms. No. JCTRes-D-22-00027
Outcomes of surgical resection of super-giant (≥ 15cm) hepatocellular carcinoma: Volume does matter, if not the size.
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Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Apr 23, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This paper summerizes the experience of a center with the resection of very larger HCC's measuring 15 cm or greater. The series is small, but does show acceptable short term results.

I think the introduction can me more consise, the etology of HCC is not really relevant for the paper or introduction.

The paper is well written, and easy to understand.

Age should always be truncated to whole numbers. with 18 patients providing a decibal with percentages is not appropriate.

The authors use the Clavien-Dindo classification for complications, which is fine, but do not use 'Clavien grade II'. Keep it consisent, so leave the Clavien out after first mention.

Please report on the location of distant recurrences.

The authors compare median OS to treatement alternatives, however, is there data on long term survival for instance at 3 years for alternative therapies. Median OS is a bit longer with resection, suggestd in the discussion, but when resection results to 29% 3 year OS and other therapie shave no 3-year OS, the relevance increases.

And please state that resection for HCCs > 15cm should be left to experienced centers.

The discussion is adequate, but perhaps a bit long.

Reviewer #2: This study has small sample; but i also agree that most surgeons would not operate many patients with 15cm and more size tumours in liver; so there js some value⁰ in this report.
I have some comments and observations that authors need to address.
1. Authors operated 1 child B patient. I would consider such patient for tace or sirt therapy.
2. Authors dont consider adjuvant theray after surgery. Why so?
3. Authors report poor long term outcomes. What is ur view about not operating these patientz but just offering locoregional treatment?
4. Any patient had paraneoplastic syndrome like erythrocytosis, hypoglycemia etc.?

Reviewer #3: Authors conducted study about surgical resection of super-giant (≥ 15cm) hepatocellular carcinoma. The study was very carefully designed and the paper is quite clear.

I have no more comment about minor and major concern.

Excellent and important study which i enjoyed to read.

Authors' affilation
To

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Ref.: Ms. No. JCTRes-D-22-00027
Outcomes of surgical resection of super-giant (≥ 15cm) hepatocellular carcinoma: Volume does matter, if not the size.

Many thanks for seeking peer review of our manuscript and we are grateful to reviewers for time and inputs to enhance our manuscript. We provide a point-by-point response to reviewer comments as well as highlight in red font the edits that are made in the manuscript.

Reviewer #1:

Comment 1: This paper summarizes the experience of a center with the resection of very larger HCC's measuring 15 cm or greater. The series is small, but does show acceptable short term results. I think the introduction can me more concise, the etology of HCC is not really relevant for the paper or introduction.

Response 1: Many thanks for comment. We have removed the following 2 statements related to aetiology of HCC from the introduction section. "Part of the differences in recommendation is related to the etiology of HCC, with hepatitis B virus (HBV) predominant in Asia. This is reflected in a retrospective study by Selby *et al* on 766 HCC patients with predominant HBV etiology."

Comment 2: The paper is well written, and easy to understand. Age should always be truncated to whole numbers. with 18 patients providing a decibal with percentages is not appropriate.

Response 2: Thanks for the comment, the median age is 65 years and we have edited this in table 1 as well as first statement in the result section.

Comment 3:

The authors use the Clavien-Dindo classification for complications, which is fine, but do not use 'Clavien grade II'. Keep it consistent, so leave the Clavien out after first mention.

Response 3: Thanks for this suggestion. We have done the edits in result section and deleted the Clavien after first mention.

Comment 4:

Please report on the location of distant recurrences.

Response 4: Thanks for this suggestion. We have added the following - The most common site of distant metastases was lung (n=7), including one patient with clinical features suggestive of Pancoast's syndrome. In addition, one patient each developed metastases to brain, left adrenal gland, left chest wall and rib cage.

Comment 5:

The authors compare median OS to treatment alternatives, however, is there data on long term survival for instance at 3 years for alternative therapies. Median OS is a bit longer with resection, suggested in the discussion, but when resection results to 29% 3 year OS and other therapies shave no 3-year OS, the relevance increases.

Response 5: Thanks for this comment. You are right to state that the relevance increases in favor of surgical resection when we don't have any 3 yr OS in alternative therapy options while surgery offers 29% 3-year survival. Our study is unable to comment as there is no comparator group. However, in local experience, the survival of TACE or Y90 therapy is about 2-3 years in patients who are Child A and good functional status. In super-giant HCC, there is no literature to compare outcomes of surgery versus no-surgery. In our opinion, surgery offers some palliation to right sided abdominal discomfort and symptoms of early satiety due to space occupying lesion in right abdomen.

We have included the following in limitations - A comparative group of patients with super-giant HCCs who underwent non-surgical treatment will also be helpful to compare the survival between both groups.

We have deleted the following statement as it is not backed by our study results - Long-term outcomes are poor but considerably better compared to locoregional therapy.

Comment 6:

And please state that resection for HCCs > 15cm should be left to experienced centers.

Response 6: This is very insightful thought. Indeed, surgery on supergiant lesions is technically difficult and also pose anaesthesia related challenges. Further, close followup and multimodal therapy are integral. So, such lesions should be managed by experienced centers with established multidisciplinary teams who provide protocolised as well as personalised oncological services. We have added the following - Further, we propose that liver resection for super-giant HCC should be performed by experienced centers.

Comment 7:

The discussion is adequate, but perhaps a bit long.

Response 7: We have removed the discussion on novel therapies including immunotherapies and checkmate trial. This has shortened the discussion without losing relevance. The following is deleted, and along with it the citations are also deleted - It has been shown recently that HCC and HCC-associated Kupffer cells exhibit upregulation of Programmed death receptor-1 (PD-1) and Programmed death-ligand 1 (PD-L1) in the tumour infiltrating lymphocytes, which have generated new interest in using these checkpoint inhibitors as adjuvant therapy following resection. The CheckMate 9DX trial evaluating the use of adjuvant Nivolumab (PD-1 inhibitor) in patients with HCC who are at high risk of recurrence after curative resection or ablation is currently underway and the results are anticipated. We have removed 4 citations.

Reviewer #2:

This study has small sample; but i also agree that most surgeons would not operate many patients with 15cm and more size tumours in liver; so there js some value⁰ in this report.
I have some comments and observations that authors need to address.

Comment 1. Authors operated 1 child B patient. I would consider such patient for tace or sirt therapy.

Response 1. This is acceptable critic. While we carefully select our patients, and majority are Child's A, in this series one patient was Child B. This was largely contributed by albumin due to nutritional compromise and effect on synthetic function of liver due to large tumour. In discussion section we have mentioned one patient with Child score A who we felt on hindsight to have been treated by TACE/SIRT instead of surgery. At same paragraph, we have added the following - Our series also includes one Child's Pugh Class B patient. This patient was deemed suitable for major liver resection due to good performance status and sufficient FLR. The higher Child's Pugh score was solely contributed by low albumin levels, and multidisciplinary teams recommended for liver resection.

Comment 2. Authors dont consider adjuvant theray after surgery. Why so?
Response 2 Adjuvant therapy is not a current standard of care and thus routinely patients undergo surveillance and than receive palliative systemic therapy or local ablation based on pattern on recurrence. Unit has ongoing clinical trials and all patients have an option to participate in clinical trial. However, we do not have any adjuvant trials during the study period. We have added the following in discussion - Our unit actively enrols patient into ongoing prospective clinical trials and we expect that more patients with supergiant HCC will be managed with adjuvant systemic therapy in future.

Comment 3. Authors report poor long term outcomes. What is ur view about not operating these patientz but just offering locoregional treatment?
Response 3 This is very interesting comment. The term "poor outcomes" is a relative term. We believe that without surgery, the outcome is even worse and that too with poor quality of life. Thus, thought the outcomes of operating supergiant patients is not as good as operating

on HCC below 5cm, it is still better to do surgery than not. This is along the lines of operating in situations of ruptured HCC. Eventually operating and resecting is better than not doing so. However, the point is some patients would be harmed by surgery. In our experience, one patient died. Thus, it would be good if we could predict who is at high risk of perioperative morbidity and mortality and avoid surgery and selectively manage such patients with locoregional therapy. This is usually a clinical judgment of primary doctor as multidisciplinary teams would not have the first hand idea and assessment of patient as not every team member has seen and assessed patient clinically. For the patient who died, we have included the following in discussion - In retrospect, due to the large tumour burden associated with poor prognostic features like multiple satellite nodules and portal vein invasion, locoregional therapies or systemic therapies should have been recommended to this patient

Comment 4. Any patient had paraneoplastic syndrome like erythrocytosis, hypoglycemia etc.?
Response 4 No such observation or records in our 18 patients. We have not made any edits in manuscript for this comment.

Reviewer #3:

Comment 1:

Authors conducted study about surgical resection of super-giant (≥ 15cm) hepatocellular carcinoma. The study was very carefully designed and the paper is quite clear.
I have no more comment about minor and major concern. Excellent and important study which i enjoyed to read.

Response 1: Many thanks for this comment. We have not made any edits for this comment.

Thanking you

Sincerely

Vishal G Shelat

2nd Editorial decision
26-Mar-2022

Ref.: Ms. No. JCTRes-D-22-00027R1
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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the

Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: