Dear Editor and Reviewers,

Thank you very much for your letter dated May 1st, 2015. We found the reviewers' kind and detailed suggestions most helpful and have revised the manuscript accordingly. Please find enclosed the revised manuscript, including changes as underlined, and pages with our point-by-point responses to the reviewers' comments. We submit this revised manuscript for consideration for publication in *World Journal of Surgery*.

We sincerely look forward to hearing from you again at your earliest convenience.

Best regards,

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Point-by-point responses to reviewers' comments

Reviewers' Comments:

Reviewer #1

The manuscript by Sasaki et al reported results from a large retrospective series of patients with hepatocellular carcinoma undergoing hepatectomy by using a microwave tissue coagulator in a single institution. The strength of the study is the impressive number of patients included, but it is weakened by the absence of a comparison group and the wide period of recruitment. The following suggestions should be taken into consideration in order to improve the manuscript:

Comment 1- In methods the authors said that before 2003 they used fresh frozen plasma as a protocol, and they divided the analysis of blood transfusion in two time periods (before and after 2003 respectively). In my opinion this is a potential source of bias, and a separate analysis of those patients with hepatectomy before 2003 makes no sense, as the results concerning blood transfusion would not be interpretable. I would suggest excluding those patients having a hepatectomy before 2003. Although the numbers would be significantly reduced, there would be still enough sample size for an appropriate analysis, and the period of recruitment will be also reduced, which will make the results more reliable and applicable to the current clinical scenario (It may well be that the selection criteria, skill of the surgeons, medical care, and surveillance protocols have changed since 1990).

=>

Thank you for meaningful suggestion. We sincerely agree with reviewer's comment and discussed by all authors.

We concluded that we would like to maintain case number and study period. The reasons are as follows;

1) We would like to express all our experience and results of hepatectomies for hepatocellular carcinoma using microwave tissue coagulator, although the operative results would be superior if we limited the cases after 2003.

2) Basically this study was not aimed to show the superiority of the hepatectomy using microwave tissue coagulator to the other liver parenchyma transection techniques. We would like to express merely the results of our 20 years of experience.

3) Although the selection criteria, perioperative patient care, and pre- and post-operative surveillance protocols have been changed during 20 years, the surgeons were all the

same through this study period. All the retrospective studies which consisted of long-term study period have this problem, therefore we included the comparison analysis by time-period.
4) Because of this study did not have comparison analysis, we think the most remarkable point of this study is the largest case number and 20 years of experience.

We sincerely agree with the reviewer's comment of this study, however, please understand our opinion and the study's aim. Alternatively, we added following sentences in the limitation of this study according to the reviewer's comment.

Page 20, Line 9.
With respect to study limitations, the current study was retrospective in its study design
=>
With the wide period of recruitment and it analyzed patients in a single center.

Comment 2- The retrospective design should be stated in methods.
=>
We added the statement about the retrospective study design in the method section as follow;
Page 6, Line 7.
A total of 1118 patients were included in this retrospective-cohort study and data on their clinicopathological characteristics were collected.

Comment 3- In the text, exact percentages should appear whenever possible. Please avoid expressions such as "Three-fourth" or "half of the cases…". Absolute numbers should ever be accompanied by the corresponding proportion. Please revise accordingly.
=>
We completely agree with reviewer's suggestion.
We corrected all the non-numerical expressions to numerical expressions as follows;
Page 11, Line 3
…,approximately 80% were men …
=>
…, 79% were men …
Page11, Line 8.
…one-tenth of patients had grade B.
=>

… 131 patients had grade B (12%).

Page 11, Line 12.

More than 80% of patient underwent hepatectomy for a solitary tumor …

=>

Eighty-two % of patient underwent hepatectomy for a solitary tumor …

Page 11, Line 14.

A poor histological differentiation grade was seen in one-fifth of cases and microscopic vascular invasion was seen in one-fourth.

=>

A poor histological differentiation grade was seen in 21% of cases and microscopic vascular invasion was seen in 24%.

Page 12, Line 1.

Three-fourth of operations were NAR, and as a result, half of the cases had less than 50 g of tissue resected.

=>

Seventy-five % of operations were NAR, and as a result, 49% of the cases had less than 50 g of tissue resected.

Page 12, Line 9

The overall perioperative blood transfusion rate reached approximately 40%.

=>

The overall perioperative blood transfusion rate reached 39%.

Comment 4- In Methods (Statistical analysis) the authors said that “continuous variables were summarized as medians and ranges” and that “the Mann-Whitney U test was used for comparisons”. The authors should restrict the use of median and ranges, and also non parametric tests to describe asymmetric distributions, since non parametric tests are statistically less potent. Taking into account the number of patients included, those continuous variables with normal distribution should be described with mean and standard deviations, and further compared by using student T test or ANOVA. Normality tests such as Shapiro-Wilk’s should be used to test the distribution of continuous variables.

=>

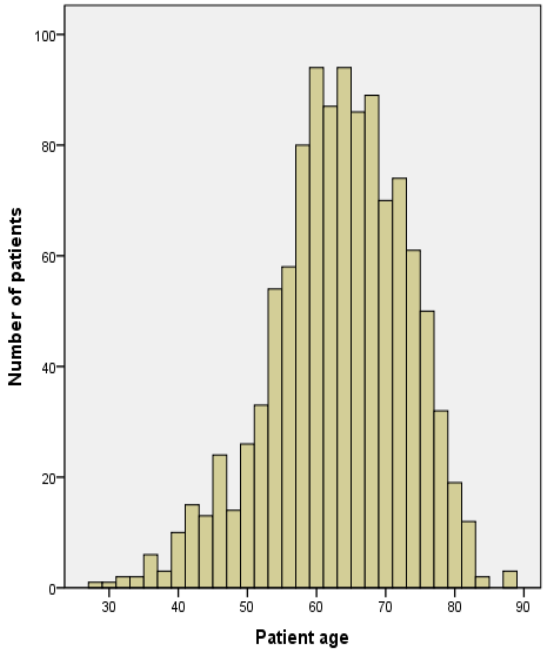
Thank you for good suggestion. I checked all continuous variables including patient age, maximum tumor diameter, operative time, and estimated intra-operative blood loss whether parametrical or non-parametrical by Shapiro-Wilk’s test.

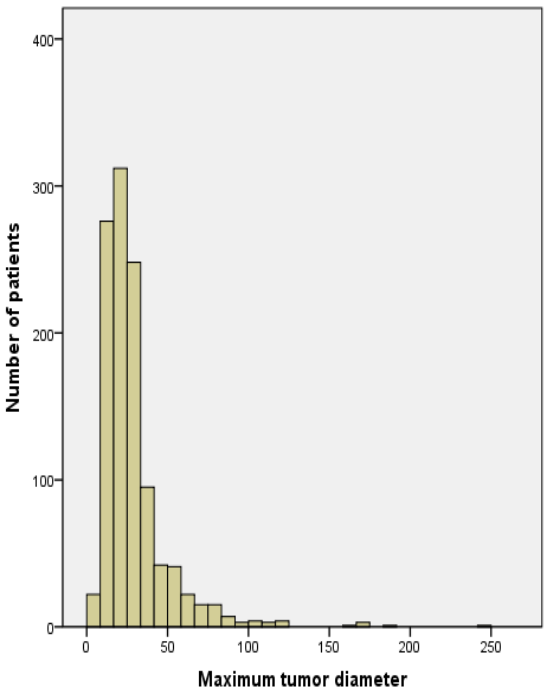
The results of the histogram were as follows and all continuous variables were revealed

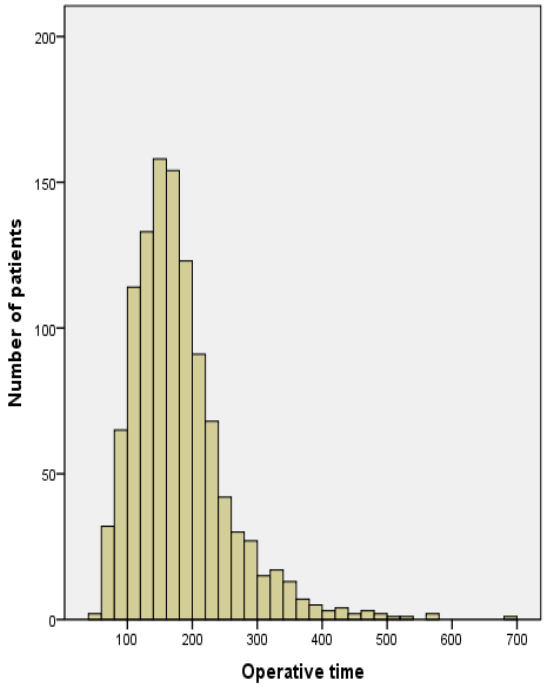
as non-parametrical by statistical analysis.

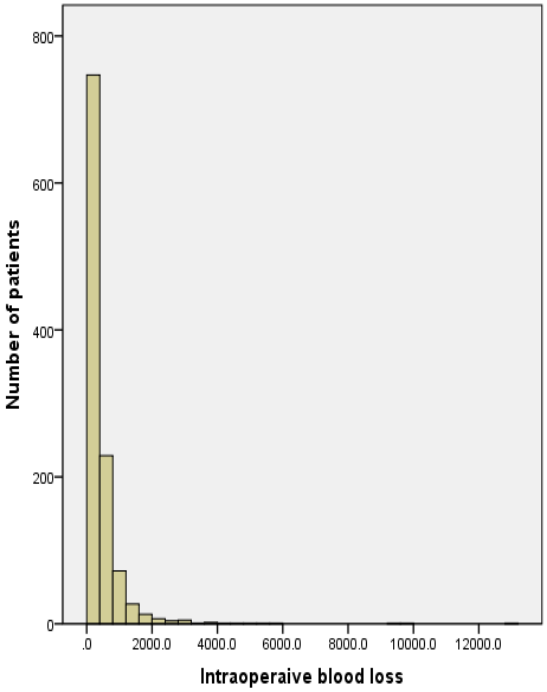
Therefore, express by median and range and using Man-Whitney U for comparison were appropriate for this study.

<Histograms of each continuous variables>









According to the reviewer's suggestion, we changed some sentences as follows.

Page 11, Line 4.

The median age at the time of hepatectomy was 63 years old (mean, 62.7 ±9.7 years)

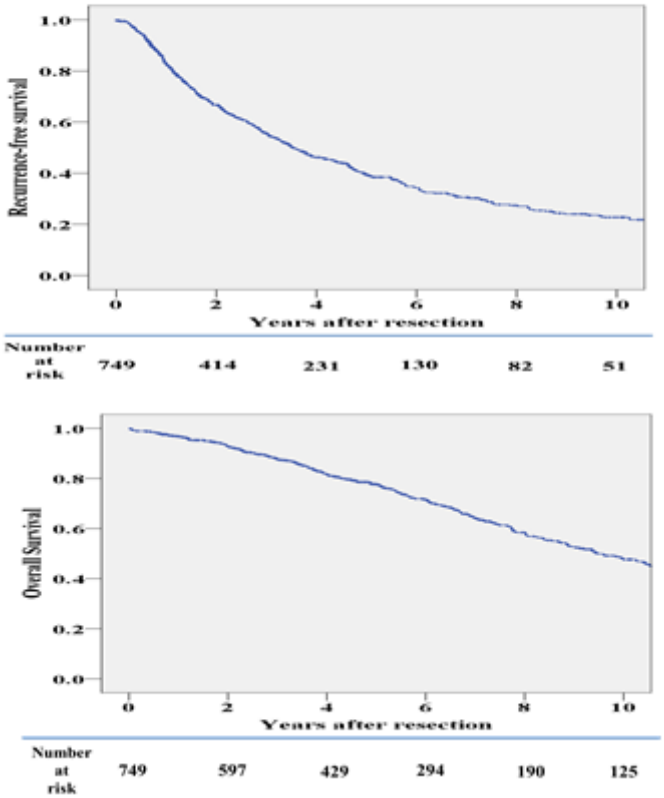
=>

The median age at the time of hepatectomy was 63 years old (range 28-87 years)

Regarding the operative results, many paper presented their results in mean and standard deviation. To compare the operative results with those reports, we used both median and mean. Please understand our intention.

Comment 5- Kaplan Meier curves for recurrence free and overall survival should be included in the manuscript, accompanied by the corresponding censored data.
=>
We completely agree with reviewer's suggestion and added Kaplan-Meier curves for recurrence-free and overall survivals with the number of patients at risk as Figure 3.

Figure 3 .
Recurrence-free and overall survival curves of patients with primary curative hepatectomy



Comment 6- Conclusions both in the abstract and in the discussion (final paragraph) are not supported by the results of the study. As no comparison cohort was included it is not appropriate to say that "using HCN by MTC resulted in less blood loss, and shorter operative time" or "no increase in the incidence of postoperative bile leakage…". To

compare the findings of the present study with other previous reports, although contemporary in some cases, is not appropriate as recognized by the authors earlier in the manuscript. The conclusions should be significantly softened in both the abstract and the discussion.

=>

We agree with reviewer's comments and changed the conclusions both in the abstract and the discussion as follows:

Page 3, Line 6

Hepatectomy using microwave energy showed excellent results in reducing intraoperative blood loss. Although the current study did not directly compare with other devices, the prevalences of postoperative fluid/abscess formation and bile leakage were consistent with those reported in the past.

=>

This study demonstrated the extensive large experience of hepatectomy using HCN by MTC.

Added following sentences to Page 3, Line 1.

Regarding the influence of cirrhosis on intraoperative blood loss, no significant difference was seen between cirrhotic and non-cirrhotic patients (P = 0.38), although cirrhotic patients tended to have smaller tumors and underwent less invasive operations.

Page , Line .

In conclusion, this large-scale study showed that hepatectomy using HCN by MTC resulted in less blood loss, without using inflow occlusion, and a shorter operative time. Moreover, in experienced hands, MTC can be used near the hepatic hilum with no increase in the incidence of postoperative bile leakage and intra-abdominal fluid/abscess formation when compared with the results in other large-scale reports.

=>

In conclusion, this this study demonstrated the extensive large experience of hepatectomy using HCN by MTC. Although the current study did not directly compare with other transection technique, the the prevalence of postoperative fluid/abscess formation and bile leakage seemed to be consisted with other large-scale reported in the past.

In closing, we express our gratitude to the reviewers; their comments gave us the opportunity to provide much detailed information. We believe that their comments were very helpful in cleaning up of the manuscript. Thank you.

The reply for reviewer;

Reviewers comment:

It is a very important study with a large patients population. I have tow suggestions: 1. Remove the following sentence: The study protocol was approved by the Human Ethics Review Committee of Toranomon Hospital to page 3 patients and methods population section in the ned of the first paragraph 2. Delete figures 1 and 2. Are not useful

Comments for reviewer;

Thank you for taking your time and good suggestions for our manuscript.

We changed our manuscript according to your suggestion. Point-by-point replies were as follows;

1. Remove the following sentence: The study protocol was approved by the Human Ethics Review Committee of Toranomon Hospital to page 3 patients and methods population section in the ned of the first paragraph.

Thank you for good suggestion. We moved the comments about IRB approval from end of method section to the page 3 patients and method population section in the end of the first paragraph according to the reviewer's comment.

2. Delete figures 1 and 2. Are not useful

We agreed with reviewer's comment in most part. However, we think some figures were useful for readers to understand the liver resection using microwave tissue coagulator.

We decreased figure number 3 to 2, especially we organized Figure 1 and 2 into one figure.

If you strongly recommend us to remove all of those figures, we are willing to follow your suggestion.

Thank you again for reviewing our manuscript. We sincerely look forward to hearing from you again at your earliest convenience.
Best regards,

Kazunari Sasaki M.D.