

May 27th, 2021

Editors and Reviewers
World Journal of Gastrointestinal Surgery

Dear Editors and Reviewers

Thank you for reading our manuscript and for giving useful comments. In response to the Editors and Reviewers' suggestions, we have revised the manuscript, Manuscript NO 66465 entitled "Outcomes of reduction hepatectomy combined with postoperative multidisciplinary therapy for advanced hepatocellular carcinoma." In response to the Reviewers' suggestions, we have revised the manuscript.

We are feeling that our manuscript improved a lot. We hope that you find our manuscript worthy of publication in *World Journal of Gastrointestinal Surgery*, and thank you in advance for your time and consideration.

Sincerely.

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Our responses to Reviewers' reports are as follows:
Sincerely.

We thank Reviewer #1 for the useful suggestions. The original comments of the Reviewer #1 are as follows.

Reviewer #1: The combination of reduction hepatectomy and multidisciplinary postoperative treatment has been considered the best treatment for advance HCC recently. In this MS, the authors retrospectively analyzed 30 cases of advanced HCC patients performed with reduction hepatectomy. This research has a valuable contribution to the field. However, there are some shortcomings needed to be improved. 1. Abstract: the background in this part is not specific, especially the first sentence. This is not the exact reason why they want to analyze these clinical cases. 2. Introduction: In this part, please give a precise definition of “multidisciplinary postoperative treatment” in the text. Also, more detailed background and outcomes of multidisciplinary postoperative treatment are needed in the treatment of advanced HCC. 3. Discussion: please discuss some preoperative treatments in the treating of advanced HCC combining with hepatectomy. 4. Due to the limited sample size, more and multi-centered cases are needed.

Response

We Thank Reviewer #1 for the useful suggestions. These are our responses for the suggestions.

1. Abstract: the background in this part is not specific, especially the first sentence. This is not the exact reason why they want to analyze these clinical cases.

Thank you for the suggestion. We also considered that the Abstract needs to be changed according to this suggestion. We have made the next change.

BACKGROUND in p.3, 1.3

BACKGROUND

The role of volume reduction hepatectomy in the treatment of advanced hepatocellular carcinoma (HCC) remains unclear. This study aimed to examine the outcomes of combination treatment with reduction hepatectomy and multidisciplinary postoperative treatment for advanced HCC.

was changed to

BACKGROUND

The prognosis of advanced hepatocellular carcinoma (HCC) that is not indicated for curative hepatectomy remains poor, despite advances in the treatment of HCC, including the development of tyrosine kinase inhibitors (TKIs). The outcomes of reduction hepatectomy and multidisciplinary postoperative treatment for advanced HCC that is not indicated for curative hepatectomy, including those of

recently treated cases, should be investigated.

AIM

This study aimed to examine the outcomes of combination treatment with reduction hepatectomy and multidisciplinary postoperative treatment for advanced HCC that is not indicated for curative hepatectomy.

2. Introduction: In this part, please give a precise definition of “multidisciplinary postoperative treatment” in the text. Also, more detailed background and outcomes of multidisciplinary postoperative treatment are needed in the treatment of advanced HCC.

Thank you for the suggestion. We thought this suggestion was important and added next text in p.5, 1.16.

Postoperative multidisciplinary therapy for HCC can include additional surgery, LAT (RFA and MCT), TAI (TACE and IAC), and TKI treatment. A retrospective study reported mean survival times (MSTs) of 31.8 and 18.6 months for Barcelona Clinic Liver Cancer (BCLC) stage B and C HCC after reduction hepatectomy followed by postoperative local therapy targeting the liver, such as additional hepatectomy, LAT, and TAI [8]. In another retrospective study, the prognosis of patients who exhibited remnant extrahepatic lesions after reduction hepatectomy was reported to be poor (3-year overall survival [OS] rate: 0%) [9]. However, the latter study only included 6 cases of HCC with extrahepatic lesions, and postoperative TKI treatment was not mentioned.

and next text was added in p.5, 1.9.

(MCT)

and number of references were changed as next.

Reference 20 was changed to reference 8

Reference 13 was changed to reference 9

Reference 8, 9, 10, 11, 12 was changed to reference 10, 11, 12, 13, 14, respectively.

Reference 14, 15, 16, 17, 18, 19 was changed to reference 15, 16, 17, 18, 19, 20 respectively.

3. Discussion: please discuss some preoperative treatments in the treating of advanced HCC combining with hepatectomy.

Thank you for the suggestion. We were also interested in this point. We have written the next paragraph and added in p.11, 1.16 with new reference 21, 22, 23 listed below.

Some cases that were successfully converted to downstaging hepatectomy after the preoperative administration of the TKIs sorafenib and lenvatinib have been reported [21,22,23]. Although these cases were successfully treated with conversion hepatectomy, the actual conversion rate due to the downstaging effects of TKIs remains unknown, and the response rate of HCC to TKI therapy (a complete response rate of 2% and a partial response rate of 38% can be achieved with lenvatinib [6]) is still insufficient to enable TKIs to be used for downstaging purposes as part of the standard treatment strategy for advanced HCC.

New references are

21 **Kim TS**, Kim JH, Kim BH, Lee YS, Yoo YJ, Kang SH, Suh SJ, Jung YK, Seo YS, Yim HJ, Yeon JE, Byun KS. Complete response of advanced hepatocellular carcinoma to sorafenib: another case and a comprehensive review. *Clin Mol Hepatol* 2017; **23**: 340-346 [PMID: 28633200 DOI: 10.3350/cmh.2016.0070]

22 **Yokoo H**, Takahashi H, Hagiwara M, Iwata H, Imai K, Saito Y, Matsuno N, Furukawa H. Successful hepatic resection for recurrent hepatocellular carcinoma after lenvatinib treatment: A case report. *World J Hepatol* 2020; **12**: 1349-1357 [PMID: 33442460 DOI: 10.4254/wjh.v12.i12.1349]

23 **Ohya Y**, Hayashida S, Tsuji A, Kuramoto K, Shibata H, Setoyama H, Hayashi H, Kuriwaki K, Sasaki M, Iizaka M, Nakahara O, Inomata Y. Conversion hepatectomy for advanced hepatocellular carcinoma after right portal vein transection and lenvatinib therapy. *Surg Case Rep* 2020; **6**: 318 [PMID: 33301055 DOI: 10.1186/s40792-020-01078-3]

4. Due to the limited sample size, more and multi-centered cases are needed.

Thank you for suggestion. As suggested, this point is an important limitation in the present study. We have added next text in p.11, 1.32.

Another limitation of the present study was the small number of cases it included; therefore, a study involving more cases from multiple institutions should be performed in the future.

We thank Reviewer #2 for the useful suggestion. The original comment of the Reviewer #2 and our response is as follows.

Reviewer #2: a good study to show the significance of hepatectomy combining with other treatments, I suggest the clinicalpathological comparision between cPOCR(-)TKI(+) and POCR(-)TKI(-) groups should also be included in this study.

We Thank Reviewer #2 for the useful suggestion. According to the suggestion we have made next changes.

Next text was added in p.9, 1.7.

There were no significant differences between the clinicopathological data of the POCR(-)TKI(+) and POCR(-)TKI(-) groups (Table 5).

Table 5 was added in the last page.

Other changes are listed below

Next text was added in p.1, 1.24.

0000-0002-5238-3678

p.7, 1.22.

Kamiyama T participated in drafting the article and critically revising it.
was changed to

Kamiyama T participated in drafting and critically revising the article.

Next text was added in p.3, 1.11.

Hokkaido University Graduate School of Medicine,

p.3, 1.13.

the evaluable lesions

was changed to

all evaluable lesions

p.3, 1.26.

the POCR(+) group and POCR(-) group

was changed to

the POCR(+) and POCR(-) groups

p.4, 1.10.

Achieving postoperative complete remission (POCR) via multidisciplinary therapy after reduction hepatectomy for unresectable advanced HCC that is not indicated for curative hepatectomy is the key to success,

was changed to

When reduction hepatectomy is performed for unresectable advanced HCC that is not indicated for curative hepatectomy, achieving postoperative complete remission (POCR) via postoperative multidisciplinary therapy is the key to success,

p.5, 1.9.

microwave coagulation therapy+, can also be expected to result in

was changed to

microwave coagulation therapy (MCT), can also result in

p.6, 1.17 and p.11, 1.21.

pertinent
was changed to
important

p.6, 1.24.
the evaluable lesions
was changed to
all evaluable lesions t

Next text was added in p.7, 1.22.
(17-664680)

p.7, 1.23.
prothrombin time (PT) was 90.19±2.75% (69.8-115.8),
was changed to
prothrombin time (PT) was 90.19±2.75% (69.8-115.8);

p.11, 1.35.
Achieving POCR via multidisciplinary therapy after reduction hepatectomy for unresectable advanced HCC that is not indicated for curative hepatectomy is the key to success,
was changed to
When reduction hepatectomy is performed for unresectable advanced HCC that is not indicated for curative hepatectomy, achieving POCR via postoperative multidisciplinary therapy is the key to success,

Next text was added after **CONCLUSION** section.

ARTICLE HIGHLIGHTS

Research background

The prognosis of advanced hepatocellular carcinoma (HCC) that is not indicated for curative hepatectomy remains poor, despite advances in the treatment of HCC

including the development of tyrosine kinase inhibitors (TKIs).

Research motivation

To date, few studies have evaluated combination treatment with reduction hepatectomy and multidisciplinary postoperative treatment for advanced HCC that is not indicated for curative hepatectomy.

Research objectives

To investigate the outcomes of combination treatment with reduction hepatectomy and multidisciplinary postoperative treatment for advanced HCC that is not indicated for curative hepatectomy.

Research methods

Thirty cases of advanced HCC, in which reduction hepatectomy was performed between 2000 and 2018 at the Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, were retrospectively investigated. These 30 cases were divided into two groups, the POCR(+) and POCR(-) groups, according to whether postoperative complete remission (POCR) of the evaluable lesions was achieved through postoperative treatment. Further analyses were performed after dividing the POCR(-) cases into two groups, the POCR(-)TKI(+) and POCR(-)TKI(-) groups, depending on whether TKIs were administered postoperatively.

Research results

The 5-year overall survival rate and mean survival time (MST) for all cases after reduction hepatectomy were 15.7% and 28.40 months, respectively. POCR, tumor size, major vascular invasion, and the number of tumors in the remnant liver after the reduction hepatectomy were found to be related to survival outcomes. In the POCR(+) and POCR(-) groups, the MST was 56.55 months and 14.84 months, respectively ($p=0.0041$). POCR was achieved significantly more frequently when ≤ 3 tumors remained in the remnant liver ($p=0.0025$). The MST was 33.52 months in the POCR(-)TKI(+) group, which was superior to the MST of 10.74 months seen in the POCR(-)TKI(-) group ($p=0.0473$).

Research conclusion

Reduction hepatectomy combined with multidisciplinary postoperative treatment

for unresectable advanced HCC that was not indicated for curative hepatectomy was effective when POCR was achieved through multidisciplinary postoperative therapy. To achieve POCR, reduction hepatectomy should aim to ensure that ≤ 3 tumors remain in the remnant liver. In cases in which POCR is not achieved, TKIs can improve survival outcomes when administered as part of postoperative multidisciplinary therapy after reduction hepatectomy.

Research perspectives

Reduction hepatectomy combined with multidisciplinary postoperative treatment should be considered as a treatment option for unresectable advanced HCC that is not indicated for curative hepatectomy. A well designed and/or larger cohort study is required to further evaluate this treatment strategy.

Next texts were added in Table 4

n=8

was added below

POCR(+)

n=22

was added below

POCR(-)

Next error was corrected on Table 4.

$\leq 200 / > 200$

was changed to

$< 200 / \geq 200$

Next errors were corrected on Table 1, Table 2, Table 3 and Table 4.

well

was changed to
wel

poor
was changed to
por

Number of wel or mod/por on POCR(+) group on Table 4.
3/5
was corrected to
5/3

Number of wel or mod/por on POCR(-) group on Table 4.
11/11
was corrected to
12/10