

January 31, 2014

Dear Editor, Dr. Jin-Lei Wang

We are grateful to you and the reviewers for the decision and helpful comments on the original version of our manuscript. We wish to resubmit the revised manuscript for publication in *World Journal of Gastroenterology*. We addressed all points raised by the reviewer and revised our manuscript accordingly to meet the standards and format of *World Journal of Gastroenterology*.

Please find enclosed the edited manuscript in Word format (file name: 7449-review.doc).

Title: Two-stage treatment with hepatectomy and carbon-ion radiotherapy for multiple hepatic epithelioid hemangioendotheliomas

Author: Shohei Komatsu, Takeshi Iwasaki, Yusuke Demizu, Kazuki Terashima, Osamu Fujii, Atsushi Takebe, Akihiro Toyokawa, Kazuhiro Teramura, Takumi Fukumoto, Yonson Ku, Nobukazu Fuwa

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7449

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated.

- We have marked all new changes in the text using **RED character** (highlighted).
- We have changed the word “liver resection” to “hepatectomy” in the revised manuscript.
- We have revised the contents of the Core tip.
- We have used “LT” as abbreviated word of liver transplantation.

2 Revision has been made according to the suggestions of the reviewer

Answers to Reviewer 02454257

(1) Reviewer's comment “General remark”:

“Twelve authors are listed for the case report regarding the treatment of one patient. Even though the contributions of the respective authors are listed it should be explained why, given the extent of the manuscript, 5 authors were required to perform data analysis; the same applies for the particle therapy. Did these 5 colleagues contribute significantly?”

<Reply>

As per your suggestion, we have deleted 1 co-author (Masayuki Mima), and reconsidered the Author contributions more precisely (Page 2).

Author contributions: Komatsu S wrote the manuscript and performed additional data analysis; Iwasaki T helped by supervising and approving the final manuscript; Demizu Y, Terashima K, Fujii O, Fuwa N performed particle radiotherapy; Takebe A, Toyokawa A were attending doctors of the patient; Teramura K made a pathological diagnosis; Fukumoto T and Ku Y developed a new treatment procedure and supervised the manuscript.

(2) Reviewer's comment “Introduction”:

“Regarding therapy of HEH the authors reflect too much on liver transplantation. The available alternatives like liver resection and TACE should be mentioned as well (see also Grotz TE, HPB 2010 and Wang, WJS 2012).”

<Reply>

We agree with the reviewer's comment. As suggested by the reviewer, we have revised the manuscript in the INTRODUCTION section (Page 4, Line 1-8). The papers kindly indicated by the reviewer were incorporated in the DISCUSSION section as well as in the INTRODUCTION.

Hepatic epithelioid hemangioendothelioma (HEH) is a rare vascular tumor characterized by the presence of epithelioid endothelial cells^[1,2], which presents varying clinical behaviors reflecting borderline malignancy to aggressive disease. Although several nonsurgical modalities such as chemotherapy, radiotherapy, interferon treatment, antiangiogenic chemotherapy, or transcatheter arterial chemoembolization (TACE) has been explored^[3-5], surgical treatments by liver transplantation (LT) or hepatectomy remains the mainstay of treatment for patients with HEH^[1].

(3) Reviewer's comment "Case report":

"The case report is structured clearly. For the sake of completeness it should be mentioned if the infiltrated Fascia Gerota has been resected with an oncological approach."

<Reply>

According to the reviewer's suggestion, we have added the sentences on operative procedure. (CASE REPORT, Page 5, Line 20-23)

We performed right lobectomy with excision of the infiltrated portion of Gerota's fascia as well as partial hepatectomy of segment 3 (Figure 2C) and then placed the omental flap on the cut surface of the liver (Figure 2D) for spacing.

(4) Reviewer's comment "Discussion":

(4-1) Reviewer's comment:

"Most part of the available literature is reflected in the discussion part of the here presented manuscript. Taken together the discussion is focused too much on surgical procedures. In this context the authors should explain why they decided against the parenchyma saving resection of the liver tumors."

<Reply>

i) We are grateful for the reviewer's suggestion. According to the comment, surgical procedures are mentioned more concisely and exclusively in the first paragraph in DISCUSSION. (DISCUSSION, Page 6, Line 20- Page 7 Line 19)

Also, we described why the parenchyma saving resection was impossible in our patient indicating the referral to the legend of Figure 1 as follows. (DISCUSSION, Page 7, Line 19-23)

In any case, our patient had unresectable disease because the presence of the tumor in segment 4 and the central location of multiple tumors in the right lobe hindered parenchyma-saving resection and negatively affected the possibility of curative resection by either right or left hemihepatectomy, respectively (Figure 1).

ii) We have deleted the following sentences in the DISCUSSION section from the first

submitted manuscript.

Multiple bilobar liver cancer is a challenging condition for liver surgery. Two-stage hepatectomy, a combination of partial hepatectomy followed by portal vein embolization and major lobectomy, is an effective strategy.

(4-2) Reviewer's comment:

"For the sake of equilibrium the possibility of TACE should be mentioned. Furthermore, it should be brought up that there are patients in the spontaneous course alive after 5 years without therapy."

<Reply>

We thank the referee for the comment. We have changed the sentences extensively in the second paragraph of DISCUSSION section (page 8, Line 7- page 9, Line 1) including the recent reports of possible effectiveness of TACE along with the fact that there are patients without treatment who are alive after the diagnosis for 5 years.

None of the other nonsurgical therapeutic modalities has been widely accepted since there is little evidence of their efficacy, because of the rarity of this disease. However, TACE was recently recommended by a few researchers. Wang *et al* reported comparable results with hepatectomy (17 patients) and TACE (12 patients), with 3-year survival rates of 74.1 % and 81.6 %, respectively^[13]. Cardinal *et al* reported better results with TACE in patients with metastatic diseases than with LT or hepatectomy in a retrospective study including 25 patients, even though the TACE arm included only four patients^[5].

There are even patients in the spontaneous course alive after 5 years without treatment^[2,14], indicating the borderline malignant nature of the disease resembling neuroendocrine tumors where patients even with metastases maintains stable disease for years. In fact, our patient has been stable for at least 4 years. However, further investigations are needed to clarify whether such nonsurgical interventions indeed influence the patients' natural history. Nonetheless, since the biological and clinical behaviors of HEH are varied and unpredictable, no clinical or pathological prognostic factors have yet been identified. Thus, we opted for the more curative treatment option, and consequently chose to administer particle radiotherapy to the

single residual lesion in segment 4 following right hemihepatectomy and partial hepatectomy.

(4-3) Reviewer's comment:

"The in detail described application of particle radiotherapy in HCC should be shortened since HCC and HEH are different entities regarding tumor biology. Altogether the discussion should be more focused and streamlined."

<Reply>

According to the referee's comment, in order to make our discussion more focused and streamlined, we have deleted the following sentences along with 3 references concerning the treatment of HCC in the DISCUSSION section from the first version of our manuscript.

In contrast, the effectiveness of conventional photon radiotherapy for liver tumors might not be satisfactory because the dose distribution of photon beams is generally inadequate for local tumor control. Although some reports have recently described the efficacy of newly developed modalities such as intensity-modulated radiation therapy for the treatment of HCC, few studies have described data on treatment with a curative intent. Unlike conventional photon radiotherapy, particle radiotherapy is considered a curative treatment.

(4-4) Reviewer's comment:

"The authors are presenting a highly interesting therapy approach which possibly does have the potential to significantly modify the therapy concept of HEH. Even if one may share the delight in the good results for the patient the euphoria in the discussion should be dampened. It should not be forgotten that this is a single case."

<Reply>

The authors appreciated the kind comment of the reviewer in terms of fairness and objectivity of our paper. We have deleted the euphoric word like 'innovative', 'promising', 'novel' and 'in the near future' especially in the last 3 paragraphs.

(5) According to the modification of the context, we have added the following references.

- 5 **Cardinal J**, de Vera ME, Marsh JW, Steel JL, Geller DA, Fontes P, Nalesnik M, Gamblin TC. Treatment of hepatic epithelioid hemangioendothelioma: a single-institution experience with 25 cases. *Archives of surgery* 2009; **144**: 1035-1039 [PMID: 19917940 DOI: 10.1001/archsurg.2009.121]

- 7 **Grotz TE**, Nagorney D, Donohue J, Que F, Kendrick M, Farnell M, Harmsen S, Mulligan D, Nguyen J, Rosen C, Reid-Lombardo KM. Hepatic epithelioid haemangioendothelioma: is transplantation the only treatment option? *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2010; **12**: 546-553 [PMID: 20887322 PMCID: 2997660 DOI: 10.1111/j.1477-2574.2010.00213.x]

- 9 **Rodriguez JA**, Becker NS, O'Mahony CA, Goss JA, Aloia TA. Long-term outcomes following liver transplantation for hepatic hemangioendothelioma: the UNOS experience from 1987 to 2005. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2008; **12**: 110-116 [PMID: 17710508 DOI: 10.1007/s11605-007-0247-3]

- 10 **Mosoia L**, Mabrut JY, Adham M, Boillot O, Ducerf C, Partensky C, Baulieux J. Hepatic epithelioid hemangioendothelioma: long-term results of surgical management. *Journal of surgical oncology* 2008; **98**: 432-437 [PMID: 18792957 DOI: 10.1002/jso.21132]

- 13 **Wang LR**, Zhou JM, Zhao YM, He HW, Chai ZT, Wang M, Ji Y, Chen Y, Liu C, Sun HC, Wu WZ, Ye QH, Zhou J, Fan J, Tang ZY, Wang L. Clinical experience with primary hepatic epithelioid hemangioendothelioma: retrospective study of 33 patients. *World journal of surgery* 2012; **36**: 2677-2683 [PMID: 22890877 DOI: 10.1007/s00268-012-1714-x]

- 14 **Otrock ZK**, Al-Kutoubi A, Kattar MM, Zaatari G, Soweid A. Spontaneous complete regression of hepatic epithelioid haemangioendothelioma. *The lancet oncology* 2006; **7**: 439-441 [PMID: 16648050 DOI: 10.1016/S1470-2045(06)70697-0]

(6) According to the modification of the context, we have deleted the following references from the first submitted manuscript.

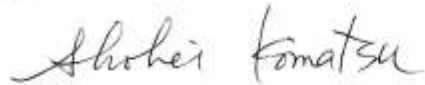
- 3 **Lauffer JM**, Zimmermann A, Krahenbuhl L, Triller J, Baer HU. Epithelioid hemangioendothelioma of the liver. A rare hepatic tumor. *Cancer* 1996; 78: 2318-2327 [PMID: 8941001]
- 12 **McIntosh Cheng JC**, Wu JK, Huang CM, Liu HS, Huang DY, Tsai SY, Cheng SH, Jian JJ, Huang AT. Dosimetric analysis and comparison of three-dimensional conformal radiotherapy and intensity-modulated radiation therapy for patients with hepatocellular carcinoma and radiation-induced liver disease. *International journal of radiation oncology, biology, physics* 2003; 56: 229-234 [PMID: 12694843]
- 13 **McIntosh A**, Hagspiel KD, Al-Osaimi AM, Northup P, Caldwell S, Berg C, Angle JF, Argo C, Weiss G, Rich TA. Accelerated treatment using intensity-modulated radiation therapy plus concurrent capecitabine for unresectable hepatocellular carcinoma. *Cancer* 2009; 115: 5117-5125 [PMID: 19642177 DOI: 10.1002/cncr.24552]
- 14 **Jaeck D**, Oussoultzoglou E, Rosso E, Greget M, Weber JC, Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. *Ann Surg* 2004; 240: 1037-1049; discussion 1049-1051 [PMID: 15570209 PMCID: 1356519]

3 References and typesetting were corrected

We hope that the revised version of our paper is suitable for publication in the *World Journal of Gastroenterology* and we look forward to receiving your reply.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, reading "Shohei Komatsu". The signature is written in a cursive, flowing style.

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