Response Letter

We would like to thank the Editor and the reviewers for their careful consideration and critical reviews of our manuscript entitled *"Technical Advances in External Radiotherapy for Hepatocellular Carcinoma."* The manuscript ID is 26123.

We have revised the manuscript according to the comments and suggestions of the reviewers and provided point-by-point responses.

Detailed response to the comments:

(1) It is better to add the word 'external' to the title of the paper making the title to look like "Technical Advances in External Radiotherapy for Hepatocellular Carcinoma" because there is the technique of internal radiotherapy for HCC.

Response:

Thank you for your suggestion. We have revised the title as recommended.

Revised (P1L5):

"Technical Advances in External Radiotherapy for Hepatocellular Carcinoma"

(2) As stated by the authors, the English needs to improve.

Response:

Thank you for your comment. We had our manuscript edited for the English language using the services of Editage, and have attached the certificate. In addition, we indicated the native English speaker, who helped the English editing of the manuscript and recorded 'audio core tip' in "ACKNOWLEDGEMENTS (P15L21)."

(3) Please clearly state in the Introduction this is not a systematic review on the topic.

Response:

Thank you for your valuable suggestion. We have revised the manuscript to clearly indicate that this manuscript is not a systematic review.

Original:

In this article, recent technical advances in RT for HCC will be highlighted along with their clinical usage.

Revised (P5L22):

In this topic highlight, we focused on the technical aspects of modern RT techniques for HCC along with their clinical applications.

(4) The authors include articles in the review that treated not only HCC, but also other malignant liver tumours with external radiotherapy, e.g. references 6. As the title of the paper clearly stated that this article is on radiotherapy for HCC, this reference should not be included in this paper.

Response:

Thank you for your valuable comment. We have removed reference 6 (Ben-Josef E. J Clin Oncol 2005;23(34):8739-8747) because it reports the results of an analysis in patients with cholangiocarcinoma and metastatic intrahepatic tumor as well as hepatocellular carcinoma. Instead, we have included another article reporting the dose-response relationship for HCC.

Revised (added sentences in P6L11):

Seong et al.[7] treated 158 HCC patients with a dose of 25.2–60 Gy (1.8 Gy/fraction). In their study, the RT dose was identified by multivariate analysis as the only significant factor for survival. The median survival times in patients who received RT doses of <40 Gy, 40–50 Gy, and >50 Gy, were 6, 8, and 13 months, respectively.

<Reference>

7 ***Seong J****, Park HC, Han KH, Chon CY. Clinical results and prognostic factors in radiotherapy for unresectable hepatocellular carcinoma: a retrospective study of 158 patients. International journal of radiation oncology, biology, physics 2003;* ***55****: 329-336 [PMID:*

12527045 DOI: 10.1016/S0360-3016(02)03929-9]

(5) If possible please state the evidence level under each of the topics related to the different technical advances in external radiotherapy for HCC.

Response:

Thank you for your valuable suggestion. It is possible to state the evidence level of radiotherapy itself as described in Page 6 (Korean Practice Guidelines for Management of Hepatocellular carcinoma). However, it is hard to state the evidence levels of the radiotherapy techniques, because studies comparing the clinical outcomes of various radiotherapy techniques except some planning studies have not been conducted. Instead, the appropriate radiotherapy technique should be selected according to the extent, respiratory movement, and/or the specific location of the tumor.

(6) There is no comment on whether the results of external radiotherapy are related to the aetiology of HCC, e.g. hepatitis-B related, hepatitis-C related or alcoholism related HCC.

Response:

To the best of our knowledge, no research suggesting the etiology of HCC in relation to the response to radiotherapy has been conducted. Instead, it was reported that the risk of liver toxicity has increased in patients with Child-Pugh class B or C liver function and in those with hepatitis B carrier status. In this context, more advanced RT techniques are required for the treatment of these patients to minimize the normal liver dose. Accordingly, we revised the following sentence in the 3D-CRT section and added one reference:

Original:

Many factors including poor liver function with Child-Pugh B or C score, prior TACE, PVT are known to be associated with a higher risk of RILD [14].

Revised (P7L3):

Many factors including poor liver function with a Child-Pugh B or C score, prior TACE, PVT, and hepatitis B carrier status are known to be associated with a higher risk of RILD[14, 15]

<Reference>

15 ***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 DOI: 10.1016/S0360-3016(03)00091-9]*