Dear Editors

First of all, we are pleased to inform you that while waiting for the first decision of the manuscript, we had a chance to update the patient information. The total number of patients increased from 35 to 65, and lesions increased from 52 to 95. Accordingly, we also revised the results. We are sure that this revision should draw much more interest of the readers of World Journal Gastroenterology. We would really appreciate it if you would kindly admit this revision.

With reference to your letter regarding the manuscript "**Cyberknife treatment for advanced or terminal stage hepatocellular carcinoma**" submitted for publication to the World Journal Gastroenterology, we hereby convey our explanation in answer to the point of the respected reviewer.

Best Regards, Hiroyuki Kato

This is a study describing the treatment outcome of CyberKnife stereotactic body radiotherapy (SBRT) to primary or metastatic lesions in patients with advanced or terminal hepatocellular carcinoma according to Barcelona Clinic Liver Cancer classification. However, major revision is recommended in order to interpret the result of current study clearly. Major comments:

1. Please clarify how to select targeted tumors eligible for SBRT, especially for those patients with multiple metastases.

We selected tumors eligible for SBRT as follows: intrahepatic tumors invading the hepatic vessels or bile duct without other viable lesions, single extrahepatic tumors, or bone metastases causing pain. In principle, patients with multiple metastases were eligible only for bone lesions.

2. Please clarify if the included patients received other cancer specific therapies other than SBRT.

Although we selected patients who were unsuitable for surgery, TACE, RFA, or other therapies, all the patients had previously been treated for HCC. Twenty-four patients received surgery, 28 patients received RFA, 49 patients received TACE, 7 patients received radiation therapy other than SBRT previously. Seven patients with 15 lesions

were treated along with sorafenib administration. Six patients had been previously treated with sorafenib but discontinued by its side effects. We summarized these results in table 2.

3. Please analyze the relationship between treatment response and patient/tumor characteristics, as well as the change of tumor markers.

Fisher's exact test was used to evaluate prognostic factors for tumor response. Although radiation dose (≧30 Gy) had a favorable tendency regarding tumor response (OR=0.266; 95% CI [0.027 - 1.370]; p=0.119), none of the clinical factors was statistically significant for tumor response (Table 3).

Fisher's exact test and a logistic regression model were used to evaluate prognostic factors for AFP and PIVKAⅡ response. In univariate analysis, radiation dose (≧30 Gy) and fiducial marker implantation were appeared to be factors associated with both AFP and PIVKAⅡreduction. In multivariate analysis, fiducial marker implantation remained to be associated with better control of both AFP (HR=0.152; 95% CI [0.026 - 0.887]; p=0.036) and PIVKAⅡ(HR=0.035; 95% CI [0.003 - 0.342]; p=0.004). Results are shown in Table 4, 5.

4. Please clarify the definition of pain relief in patients with symptomatic bone metastasis.

Response was self-assessed by subjective pain score and was classified in either category: pain relief, exacerbation, or no symptomatic change.

It is true that we should have assessed pain intensity objectively by visual analogic scale ranging from 0 to 10, or scored the analgesic requirement. However, some reports evaluated only on a subjective pain score like in our report. (Arcangeli G et al. The responsiveness of bone metastases to radiotherapy: the effect of site, histology and radiation dose on pain relief. Radiother Oncol. 1989 Feb;14(2):95-101. PMID: 2469105)

Minor comment:

1. In addition to classical radiation induced liver disease (RILD), please document non-classical RILD as well.

We documented non-classical RILD as follows:

In contrast to “classic” RILD, “non-classic RILD” has been proposed as well. Patients with underlying chronic liver disease such as cirrhosis and viral hepatitis may present with liver dysfunction, including jaundice or markedly elevated serum transaminases

(more than 5 times above the upper normal limit) within 3 months after the radiation.