**Peer Review File**

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**Reviewer A**

This paper described about long term clinical result of proton SBRT for liver metastases. Although the median follow-up period is a bit short, this result provides important information to radiologists and gastrointestinal oncologists.

There are some points that should be modified.
Only BED is analysed for local control factors, but primary histology and tumor size should also be analysed.
**Reply:** Local control in terms of tumor size could be analyzed, but the data would be difficult to interpret because of the range of dose and fractionation schemes used. Therefore, this analysis was not completed. Local control in terms of histology could also be analyzed, but there are 12 primary disease sites that have one or two lesions treated and therefore would not provide meaningful data.
**Changes in the text:** None

How many medically inoperable cases are included in this study?
**Reply:** I am unable to provide an estimate on the number of medically inoperable cases.
**Changes in the text:** None

If there is registration number for the Phase II study that you mentioned, please described in the manuscript.
**Reply:** I added the National Clinical Trial (NCT) number of our institutional phase I/II study.
**Changes in the text:** The NCT number was added on page 6, line 76.

**For editor**
It is written in easy-to-understand English, and I think the content is good.
However, It is desirable to perform some additional analysis, so I judged to be a *major revision*.

**Reviewer B**

This is well-written and informative study.
I have few minor revisions.
1) I recommend to add a recent meta-analysis reference (PMID: 31923711) comparing SBRT and RFA at the introduction.
**Reply:** I added a sentence and cited this meta-analysis in the introduction.
**Changes in the text:** The sentence and cited article are on page 3, lines 39-41

2) I understand that univariate and multivaraite analyses might not reveal statistically significant

factors in small studies. However, it is recommended to report uni- and multivariate analyses despite absence of statistically significant factors. In a small study like this, p value between 0,05 and 0.1 might be also meaningful.
**Reply:** I did not conduct a univariate and multivariate analysis with our data because of the small sample size. In addition, the results would be difficult to interpret because of the range of dose and fractionation schemes that were used.
**Changes in the text:** None

3) Authors are reporting valuable and unique clinical experience using proton therapy. Please add some photos of plans or patient treatment methods (e.g. overview of treatment suite, breath holding.. )
**Reply:** Thank you for the suggestion. Images of a sample plan were not included because it was difficult to find images that clearly depicted the treatment of multiple lesions, which were often located in different regions of the liver.
**Changes in the text:** None

**Reviewer C**

This is an inspiring article sharing a pioneering technique of proton therapy treating liver metastases from one of the leading proton centers in the world. Besides their previous experience, the paper also plotted the clinical trial under recruitment, giving oncology clinicians and readers of this journal an updated understanding of this leading-edge treatment. However, there are some parts needed better clarification.

Major
1) Introduction
A. Ln 41. Any solid evidence for TACE and Y90 treating liver metastases?
**Reply:** There is some evidence for treating liver metastases with these other modalities, but further discussion is outside the scope of this paper.
**Changes in the text:** None

B. Ln42-43. These papers suggest surgery for hepatic metastases benefits survival, but not other local therapies.
**Reply:** The purpose of citing these papers is to illustrate that high local control rates of hepatic disease appear to correlate with overall survival. However, a majority of this data is based on resection of hepatic disease. It is hoped that this data can be extrapolated to other modalities that have high rates of local control.
**Changes in the text:** None

C. Ln43-46. Suggest rephrasing why RFA is not considering the local therapy and adding more contraindications for RFA. (So that in certain condition, SBRT in prior to other local therapies.
**Reply:** Discussing the contraindications for RFA is outside the scope of this paper.
**Changes in the text:** None

D. Ln 56-64. Not clear of what it meant. Suggest it could state why we need proton therapy over photon therapy could be 1) lower toxicity because less liver is irradiated, 2) current data of reirradiation of photon therapy and proton therapy, 3) toxicity evaluation of reirradiation using photon therapy, 4) considering systemic therapy for metastasis, how proton therapy could help better than photon therapy, and etc.

**Reply:** I discussed the benefits of proton therapy over photon therapy in the text. I discussed the Bragg peak and the lack of exit dose. The main reason is that "Subsequent courses of treatment may be limited by prior liver radiation exposure with photon therapy. Proton SBRT limits the integral dose to the liver making subsequent courses of treatment more feasible." This is cited on page 4, lines 51-54.

**Changes in the text:** None

2) Methods and materials

A. Ln 100. Considering mRECIST for liver in evaluation treatment response?

**Reply:** mRECIST criteria is used as a way of adapting the RECIST criteria to the particularities of hepatocellular carcinoma. We will continue to use the RECIST criteria in this study since we are only evaluating the response of liver metastases.

**Changes in the text:** None

B. Ln 106. Have you also evaluated non-classic RILD for toxicity evaluation?

**Reply:** Non-classic RILD was not evaluated in this study. Non-classic RILD typically affects patients with underlying liver disease, which our patient population largely does not have. Evaluation of non-classic RILD would be more relevant when evaluating toxicity after radiation in patients with HCC as a majority of these patients will have underlying liver disease.

**Changes in the text:** None

3) Results

A. Ln. 131. Why using GTV for evaluation but not ITV? Since the criteria of creating ITV from 4DCT and DIBH is different, considering ITV shall be better here.

**Reply:** We are not using GTV for evaluation here. This sentence is just reporting on the median size and volume of the GTV. The ITV is used for evaluation. The process of creating the ITV from the GTV based on whether 4DCT or DIBH is used was described in the methods section from lines 94-98.

**Changes in the text:** None

B. Suggest adding recurrence pattern for better result evaluation. In-field or out-field, intrahepatic failure? Or distant metastasis?

**Reply:** The in-field recurrence rates are reported as the local control rates. The out-of-field recurrence rates in the liver are low with only a few patients developing new hepatic lesions. In terms of distant metastasis, 43.5% of patients had distant disease prior to enrollment in the trial. Therefore, tracking new distant disease would be difficult.

**Changes in the text:** None

C. Suggest adding evaluation on viral hepatitis and any victim of progressing hepatitis after irradiation. Evidence suggests hepatitis B virus reactivated after radiotherapy, causing fulminant hepatitis. Fulminant hepatitis is lethal.

**Reply:** There were no reports of reactivated viral hepatitis in our patient population.
**Changes in the text:** None

4) Discussion
A. Ln 180. Lower BED resulting better LC in contradicting previous understanding. Use of chemotherapy is routine clinical practice in treating metastasis, consideration and evaluation of chemotherapy is very important. Meanwhile, different cancer types have different survival. Both with liver metastasis, prostate cancer has better survival but pancreatic cancer is definitely much worse. Different cancer types shall be also into result
**Reply:** Local control was not evaluated by type of cancer as there are 12 primary cancer sites that are represented by 1 or 2 lesions, which will not allow us to report any meaningful data.
**Changes in the text:** None

B. Ln 189-196. Reserving more normal liver is better; could add more materials suggesting how proton therapy could achieve better than photon therapy does. Such as treatment plan comparison and dose-volume histogram between proton therapy and photon therapy, clinical results of literature, or in-house data.
**Reply:** Thank you for the suggestion.
**Changes in the text:** None

C. Ln 197-203. Good LC of local therapies may not be equally translated to good LC of surgery has better survival. Meanwhile, success of systemic therapy shall benefit most in survival.
**Reply:** Thank you for the comment.
**Changes in the text:** None

D. Ln 204. Advantage of proton SBRT in treating two or more liver metastases in one course could be elaborate more.
**Reply:** Thank you for the suggestion.
**Changes in the text:** None

E. Ln 206-207. Respiratory motion management is an important topic and worth a good discussion. Suggest either more discussion of 4DCT and DIBH in proton SBRT or just not. How literature says and your experience in clinical practice (89% using 4DCT and 11% using DIBH) could be a good one.
**Reply:** Thank you for the suggestion.
**Changes in the text:** None

F. Ln 208-213. Suggest to discuss more about the toxicity of this cohort comparing to conventional dose of proton therapy and photon SBRT.
**Reply:** We do not have any data to compare the toxicity between proton and photon-based SBRT. I assume the toxicities are fairly equal between the two modalities as providers in general are following the same set of dose constraints. However, the advantage of proton-based SBRT is the greater potential to stay within these normal tissue constraints over many courses of treatment.
**Changes in the text:** None

G. 1 patient had only 1 months of follow-up. Death due to treatment or cancer progression, infection or other non-cancer related crisis, or just missing data? It could be important to know his or her death cause, just 1 months after proton SBRT.
**Reply:** This patient passed away from infection 5 weeks after the completion of SBRT. The patient had bacteremia and septic shock that appears to be from a urinary source, likely from an obstructing kidney stone.
**Changes in the text:** None

H. Most studies discussed about the feasibility of SBRT of liver metastasis but not survival benefit. Could also compare photon SBRT and your experience of proton SBRT.
**Reply:** We do not have any data to compare survival between proton-based and photon-based SBRT. It would also be difficult to compare between studies given the different inclusion criteria.
**Changes in the text:** None

I. Survival benefit was mostly discussed in colorectal cancer receiving surgery and further standard chemotherapy. SBRT or proton SBRT with less toxicity could be an alternative for medically inoperable patients or patients pursing better quality of life. This could be also worth discussion.
**Reply:** Thank you for the suggestion.
**Changes in the text:** None

5) Reference
A. Proton beam therapy for liver cancers (J Gastrointest Oncol. 2020 Feb; 11(1): 157–165.) has thorough overview of proton therapy in primary and secondary liver cancers. It is worth considering for reference.
**Reply:** Thank you for suggesting this reference.
**Changes in the text:** This reference was added to the text on page 4, line 50.

6) Tables and Figures
A. Table 1. Could elaborate extrahepatic lesions (lung, bone or brain) and prior local therapy (surgery, RFA, or others)
**Reply:** Thank you for the suggestion.
**Changes in the text:** None

B. Table 2. Could have a better chart to demonstrate different side effects and some patients have 2 or more side effects.
**Reply:** Thank you for the suggestion.
**Changes in the text:** None

Minor
1) P2, Ln 8. “Proton” stereotactic body radiotherapy: maybe just “proton”, any specific reason for using capital letter?
**Reply:** “Proton” is capitalized for emphasis.
**Changes in the text:** None

2) P3, Ln 32-37. Could rephrase for better understanding. The idea is "For the patients with oligometastasis to the liver, hepatic resection is the standard treatment with improvement of survival."
**Reply:** Thank you for the suggestion.
**Changes in the text:** None

3) P3, Ln 38. Why the majority of the patients is not suitable for resection, please state the consideration. (And thus, we need safe and effective Tx choices.)
**Reply:** I am unable to provide an estimate on the number of medically inoperable cases, or the reasoning for why the majority of patients were not suitable for resection. My guess is that many patients were not candidates for resection because of multifocal disease in the liver.
**Changes in the text:** None

4) P3, Ln 50. Please clarify 60Gy in how many fractions, or in terms of BED for better understanding.
**Reply:** The protocol for the Rusthoven et al. paper used 60 Gy in 3 fractions.
**Changes in the text:** The sentence now says "…lesions treated with 60 Gy in 3 fractions…" in the introduction on line 44.

5) P4, Ln 55. "higher volumes of liver irradiation with photon therapy." Please be more specific that photon therapy has more volume of lower radiation dose than proton therapy, which is benefited from Bragg effect.
**Reply:** Thank you for the suggestion.
**Changes in the text:** None

6) P5, Ln 78. For general readers of this journal are not specialized in radio-physics, could elaborate "GyE" and its use in proton therapy.
**Reply:** I added an explanation in the text of GyE.
**Changes in the text:** A sentence and reference was added to the text on page 6, lines 77-79.

7) P5, Ln 82. Reference of NRG BR001 protocol.
**Reply:** I added the NCT for the NRG BR001 trial.
**Changes in the text:** NCT added on page 6, line 84.