Supplementary file

This file shows a point-by-point response to the Editor’s comments and/ or reviewers' reports from BMC radiation oncology.

Editors' comments (if any):

**Reviewer #1:** Overall well written paper about a common but poorly described clinical scenario: malignant thrombus in hepatocellular carcinoma.

My underlying criticism is the heterogeneity of the group. There is a very mixed bag of disease states, ECOGs, dose delivered, prior treatment, etc.

Even with a multivariable analysis, this heterogeneity makes it difficult to really buy into the association with of thrombus with survival (even though I agree with it) and it is an even further leap to suggest RT can ulimately lead to improved survival. I would not re-do the analysis but this should be menitoned as a limitation.

**Authors:** Radiation oncologists who don’t major in HCC don’t know how heterogeneous patients with HCC are but Gastroenterologists know how heterogenous. The current study is retrospective and optimal treatment was different from each patient. Even the heterogeneity exists, we demonstrated how the local tumor thrombosis control contributes to OS. And we for the first time analyzed the length of tumor thrombosis by the 3D analyzer before and after the treatment and the result was accurate. So we believe that this study can be a trigger to change how to evaluate the length of the tumor thrombosis and ORRs.

**Reviewer #1:**A few other points:

- ECOG being an independent predictor of overall response rate does not make much sense. Can you please address why you think this is the case int he discussion?

**Authors:** Previous studies on PVTT or IVCTT treated ECOG PS as an independent predictor on OS. We analyzed ORR in the same way. ECOG PS was p < 0.05 in the univariate analysis. Good ECOG-PS patients might tend to receive a dose of 48.75Gy but this is not important. So we don’t mention this in the discussion.

**Reviewer #1: -** There were several important toxicities mentioned which can be helpful to learn from. Please enter the dosimetric data for the grade 3/4 toxicities. Same goes for the 10 patients with Child Pugh progression.

**Authors:** We didn’t irradiate a high dose to the normal liver but the DVH data was lost in half of the patients. Moreover, it’s very difficult to distinguish if a deteriorating liver function was caused by RILD, chemotherapy or HCC progression. So we should not write what we don’t know.

**Reviewer #1:** - Was there any higher risk of toxicity for targets at the hepatic hilum? This is typically an area of concern (sometimes avoidance) but also houses many thrombi.

**Authors:** Again, we didn’t irradiate a high dose to the normal liver or duodenum so we don’t hesitate to irradiate targets at the hepatic hilum.

**Reviewer #1:** - The dose response data is nice, but it's always hard to interpret BED. Was there any difference in response between conventionally fractionated/hypofractionated/SBRT patients?

**Authors:** Only one patient received SBRT in this study. Therefore we cannot mention anything about SBRT. At least, the prescribed dose of SBRT was a high dose.

**Reviewer #2:** The authors report a retrospective analysis of 43 patients with advanced HCC who suffer from tumor thrombosis to major vessels or bile ducts. The cohort is small and heterogenous (it includes also patients with nodal or distant metastases).

**Authors:** In the era of sorafenib, patients including N1 or M1 are not heterogeneous. Pao et al [2] included patients with N1 or M1.

**Reviewer #2:**The treatment included normo- or hypofractionated RT with conventional doses (EQD2 around 40-50 Gy) but was very inhomogenous in total (some received additional TACE, some additional HAIC, some systemtic treatment with sorafenib or regorafenib), therefore drawing any conclusions is generally very difficult.

**Authors:** It’s seemed that reviewer #2 doesn’t understand how HCC with tumor thrombosis was treated in the recent real world. Pao et al [2] included patients treated with surgery, RFA, TACE, or various systemic treatment. Treatment strategies were varied by each patients’ situation.

**Reviewer #2:**The discussion should be more focused on the main results. Extensive language polishing would be needed.

**Authors:** Our message is simple. The local control of tumor thrombosis is important. Therefore, to evaluate the length of the tumor accurately using a 3D analyzer and a dose of 45-50Gy are important. As soon as the tumor thrombosis was found, the tumor thrombosis should be irradiated before the length of tumor thrombosis become more than about 4cm.

**Reviewer #2:**Moreover there are major drawbacks that have to be addressed (if  possible):

Introduction:

"RT can produce survival benefits in patients with advanced HCC and macroscopic hepatic vascular invasion"

Compared to what other treatment ? Mature data exists only for RT vs Sorafenib, in contrast surgery will be beneficial if possible, please specify.

**Authors:** Apologizes for not being precise enough.

In the revised paper we changed the following lines:

Several studies have evaluated the clinical outcomes of RT for inoperable HCC and results showed that RT can produce survival benefits compared to treatment of sorafenib or TACE alone [3, 9-13].

**Reviewer #2:**Methods:

"Patients who were diagnosed with a Child-Pugh class C liver function, an Eastern Cooperative

Oncology Group (ECOG) performance status (PS) of 4, lymph-node metastasis, or distant

metastasis, also had been irradiated with local RT in agreement with the hospital's policy that

it can improve the survival[4]"

The statement does not seem to be fully covered by the reference:

from ref [4]: "Local ablation therapy or subsegmental TACE is performed even for Child-Pugh C patients (CP score 10 and 11) within Milan criteria when transplantation is not indicated. In the case, patients with no hepatic encephalopathy, no uncontrollable ascites, and a low bilirubin level (< 3.0mg/dl) are selected for treatment. Although these are well-accepted treatments in the routine clinical setting, there is no high-level evidence of its survival benefit in Child-Pugh C patients"

Have these patients been inside Milan criteria ? What about the patients with distant metastases or nodal metastases ? This might be covered by the hospital´s policy but not by the reference (please explain or chose another reference).

**Authors:** Apologizes for not being precise enough.

In the revised paper we changed the following lines:

Patients who were diagnosed with a Child-Pugh class C liver function or an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 4 also had been irradiated with local RT in agreement with the hospital’s policy that it would improve the survival even though there is no high-level evidence [4].

**Reviewer #2:**"HCC was diagnosed using CT or MRI"

Please state how many were diagnosed based solely on imaging and how many had biopsy, please state (or reference) which criteria have been used to diagnose HCC solely on imaging

**Authors:** There is no need for biopsy according to the Japanese HCC guideline.

**Reviewer #2:**Please state how image-guidance was performed. Daily cone-beam CT ?

**Authors:** Apologizes for not being precise enough.

In the revised paper we added the following lines:

Cone-beam CT was performed to ensure the relative position of the diaphragm. If the position was found to be not stable, cone-beam CT was performed daily.

**Reviewer #2:**"The gross tumor volume (GTV) included tumor thrombosis, and the primary tumor was also included in the GTV if the tumor thrombosis was close to it."

What does this mean: do you have included patients were the primary tumor has not been included into the GTV ? Please explain.

**Authors:** Apologizes for not being precise enough.

In the revised paper we changed the following lines:

The gross tumor volume (GTV) included only tumor thrombosis in principal, and the primary tumor was partly included in the GTV if the tumor thrombosis was close to it. It’s not necessary for the primary tumor to be fully irradiated.

**Reviewer #2:**Regorafenib or sorafenib is not a chemotherapy.  Please choose another term.

**Authors:** Apologizes for not being precise enough.

The term of systemic “chemotherapy” was changed into systemic “treatment”.

**Reviewer #2:**The authors stated that they used WHO criteria for response assessment. WHO criteria have usually been replaced by RECIST criteria. Please explain why WHO criteria was used instead.

**Authors:** Apologizes for not being precise enough. We used a modified RECIST.

In the revised paper we changed the following lines:

The definitions of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were based on the modified Response Evaluation Criteria in Solid Tumors according to the previous studies [1, 2]

**Reviewer #2:**"A total irradiated dose of the liver was also calculated as a biologically

effective dose 3 (BED3) and an equivalent dose in 2 Gy fractions (EQD2) using a linearquadratic model with α/β ratios of 3, to evaluate acute adverse effects"

What is meant by "total irradiated dose to liver"  ? If it is a mean dose, how did you calculate it biologically ? Did you simply calculate the biological equivalent of the mean dose ?

How did you calculate it without DVH available in half of the patients (see discussion section) ?

**Authors:** We evaluated DVH only in the calculable group. So mean value was evaluated in that group as mentioned in the methods, results and limitation.

**Reviewer #2:**"PVTT was diagnosed in 28 patients and the main PVTT (Vp4) accounted for 59% of them (n = 14). HVTT was diagnosed in 12 patients and IVCTT (Vv3) accounted for 83% of them (n = 10)."

This sentence does not make much sense to me…please give a number an percentage for every subgroup

**Authors:** Please check the table 1, which shows the percentage for every subgroup.

**Reviewer #2:**"Combined chemotherapy was administered to 27 patients. Local chemotherapy was undergone by 12 patients: TACE in 9 and HAIC in 9."

Please explain the timing for those additional therapies, prior to RT, after RT, how many weeks prior or after…

**Authors:** Please check the table 1, which shows the timing of the combined chemotherapy. Combined chemotherapy was done 3 months before or after the completion of RT as mentioned in the method. We think how many weeks… is not important.

**Reviewer #2:**"Systemic chemotherapy with sorafenib was administered to 11 patients"

Was this done simultaneously ? Sorafenib + RT has a higher risk for side effects, please explain why sorafenib was not paused

**Authors:** We don’t use concurrent sorafenib with RT as mentioned in the method.

**Reviewer #2:**Why was 3D-conformal RT used ? Usually those patients would be treated by SBRT or IMRT. Please explain.

**Authors:** We suppose SBRT or IMRT is not always suitable treatments for tumor thrombosis because Vp4 or Vv3 tend to be more than 4cm. And there is a problem with health insurance in Japan. Moreover, it’s often a high risk for normal liver and duodenum to irradiate a high dose if the OAR is close to long GTV. We have to choose patients to apply those treatment case by case. And that would cause selection bias. After all, this study was almost for conventional RT and we don’t have to mention IMRT and SBRT.

(\*) **Reviewer #2:**Results

Did length or tumor thrombosis or tumor size correlate with EQD2 ? This is of major importance because usually smaller lesions are treated to higher doses, therefore it is difficult to find out if higher dose or smaller lesion is the more important factor with regard to prognosis.

**Authors:**

We choose a high dose on the condition that patients are CPA-B, ECOG PS0-2 or mean dose/V30Gy of the irradiated normal liver are not high. If the length of tumor thrombosis is short, EQD2 tended to be high. In the revised paper we added the following lines in the discussion:

Moreover, a small difference of 6.4 Gy in EQD2 unexpectedly resulted in a significant impact on response. This might be because short tumor thrombosis tended to be irradiated in 48.75 Gy of EQD2 and long tumor thrombosis in 42.35 Gy in order to minimize the risk of liver damage.

**Reviewer #2:**"Of the 43 patients, 18 patients (42%) achieved CR, 7 patients (16%) achieved PR, 16 patients (37%) had SD, and 2 patients had PD (5%)"

Did they have a response of the tumor thrombosis, of the primary or  of both ?

**Authors:** Response was evaluated in only tumor thrombosis. The primary tumor is omitted.

**Reviewer #2:**"The one-year OS rates of responders (n = 25) and non-responders (n = 18) were 75% and 35%, respectively, and the difference was statistically significant (p = 0.009, Fig. 2)."

Was response included into the multivariate analysis (MVA) of OS ? As stated in the discussion, previous reports suggest a clearly improved OS in responders after RT which may have influenced the results of the MVA with regard to other endpoints.

**Authors:** Response was included in the multivariate analysis of OS.

**Reviewer #2:**"The median dose of V30Gy of the normal liver was 10% (range of 1-31%)"

Does it mean the median V30 was 10% ? How did you calculate it withouth DVH data in half of the patients.

Please state BCLC stage

**Authors:** We don’t use BCLC stage to choose the treatment as a recent study [2].

**Reviewer #2:**Please state median size and range of the tumors in the characteristics

**Authors:** Please read the result. It’s already written.

**Reviewer #2:**It does not seem likely that a difference of 6 Gy in BED will result in a significant impact on response, therefore a selection bias is very likely and the authors should extensively discuss this possibility and analyze their data accordingly

**Authors:** This comment is more or less the same as the previous comment(\*).

In the revised paper we added the following lines in the discussion:

Moreover, a small difference of 6.4 Gy in EQD2 unexpectedly resulted in a significant impact on response. This might be because short tumor thrombosis tended to be irradiated in 48.75 Gy of EQD2 and long tumor thrombosis in 42.35 Gy in order to minimize the risk of liver damage.

**Reviewer #2:**Moreover, multivariate analysis with 5 parameters in 43 patients does not seem meaningful given the limited number of events.

**Authors:** Even if the parameters are 3, the result is the same.

**Reviewer #2:**Discussion

"In our study, receiver operating characteristic (ROC) curve analysis was used to calculate a threshold value for the length of tumor thrombosis in relation to OS, and that was found to be 3.8 cm."

This method is not described in the methods, please include.

**Authors:** Apologizes for not being precise enough.

In the revised paper we added the following lines in the method and results:

●(in the method) Receiver operating characteristic (ROC) curve analysis was used to calculate a threshold value for the length of tumor thrombosis in relation to response. This value was used in the analysis of OS and ORRs.

●(in the result) A threshold value for the length of tumor thrombosis in relation to tumor thrombosis response was 3.8 cm. This value was used in the analysis of OS and ORR.