Lian-Sheng Ma

**Editor-in-Chief,**

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Dear Dr. Ma,

We have re-evaluated our manuscript according to the reviewers' comments, and our point-by-point responses are provided below. Incorporation of the reviewers' comments has substantially improved our manuscript; we appreciate their time and feedback.

This manuscript was revised by a commercial English-language editing service. All authors participated in the design, execution, and analysis of this work and approved the final version. There are no conflicts of interest related to this study, and the material described has not been published and is not under consideration for publication elsewhere.

Your consideration is greatly appreciated. Thank you for your time.

Sincerely,

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**Reviewers' comments**

Reviewer 1

PVTT is a major problem in the management of HCC. It is expected that radiation therapy would increase the poor survival of patients with PVTT. This review covered conventional RT to particle. The topic was relevant.

Figure 2 was suitable to understand the determination of the irradiation field. It seemed that "RT" was used for photon, such as 10MeV X-ray and gamma ray. It would help to avoid confusion if introduction of radiation therapy was added just before "Application of RT in HCC".

**→ Thank you for your suggestion. We added an "Introduction of RT in HCC" section as you recommended: "Historically, RT was not used in HCC management, especially in the primary lesion of the liver. The main reason for the avoidance of RT in HCC was the low tolerance of liver tissue to RT exposure and concerns regarding radiation-induced liver disease (RILD), which typically presents as anicteric hepatomegaly and ascites 2-3 months after RT[22]. The pathology of radiation-induced liver damage shows changes similar to veno-occlusive disease, including endothelial swelling, terminal venule occlusion, and sinusoidal congestion[67]. RILD is a major concern in liver RT, because there is no established treatment and some patients will die of liver failure, although a few patients may recover[68]. Recently, the incidence of classic RILD has decreased, but non-classic RILD (which appears with jaundice and marked elevation of serum transaminase) is still problematic in the application of RT in HCC[69].**

**Because the treatment options for RILD are very limited, most investigations have focused on identifying predictive factors of RILD development[69-74]. Factors related to RT planning, such as RT dose and liver volume, have been of particular interest. Mean liver dose was demonstrated to be a risk factor of RILD by Dawson et al.[71], and $V_{20\ Gy}$ was suggested to be a dosimetric predictor by Liang et al.[74]. Kim et al. reported that grade 2 or higher radiation-induced hepatic toxicity was significantly related to the percentage of total normal liver volume exceeding 30 Gy irradiation[72]. Our group reported that $V_{30\ Gy}$ was a significant risk factor of Child-Pugh score elevation of two points or greater[69]. There is also a possibility of a higher**

**incidence of liver function deterioration after RT in HCC combined PVTT than in the other, but the dosimetric factors of liver are more important, generally[69,72].**

**With better information regarding RILD development and the application of computed tomography (CT) to RT planning, higher RT doses for local tumor control can be administered with an acceptable RILD risk level[73,75-77]. Further innovative RT technologies, including three-dimensional conformal RT (3D-CRT)[78], intensity-modulated RT (IMRT)[79], stereotactic body ablative RT (SABR)[80], and particle beam therapies[81], have been introduced and actively applied in HCC management (Fig. 2). Additionally, image-guided RT (IGRT)[82], which is used as a supportive/supplementary method with other precision RT techniques, is also standard RT practice. These biological and technical developments have enabled delivery of higher-dose RT with improved precision and better conformation and without an increased probability of normal tissue complications. With these rapid developments in techniques and radiobiology, RT has become an accepted tool in the management of HCC[77].”**

In the new section, RT with photon and particle would be described briefly. Not many readers are familiar with RT, especially particle. Are there any reports on carbon ion to PVTT?

→ **We inserted the following text in the “Clinical outcomes of particle beam RT” section: “Although the application of carbon ion specifically to HCC with PVTT has not yet been documented, several reports reported promising outcomes of 90 to 100% local control and 22 to 35% 5-year OS in HCC patients including combined with PVTT. These results were similar to those of proton beam RT. Komatsu et al. reported that carbon ion and proton therapies for HCC show comparable local control (93%, carbon ion; 90.2%, proton) and 5-year survival rates (36.3%, carbon ion; 38%, proton).”**

Liver function is another factor for patient survival. Based on the literatures, how did the authors think about liver function?

→ **We inserted the following text in the “Limitations of RT” section: “Liver function is one of the most important factors determining the method and purpose of HCC management[16], and is a key concern when considering RT. In patients with a Child-Pugh score ≥8, liver-directed RT is not generally recommended. Thus, there have been**

**few studies in which RT was applied in those patients[36,37]. Culleton et al. reported a prospective study of SABR outcomes in patients with Child-Pugh class B or C HCC, and significantly lower survival was detected in patients with a Child-Pugh score ≥8 (9.9 months in those with scores of 7 vs. 2.8 months with scores of 8 or higher, P=0.01)[116]. In another prospective phase I study of SABR for HCC, three of 11 patients with Child-Pugh class B disease developed grade III hepatic toxicity, while none of the 17 patients with Child-Pugh class A disease did[98]. A significantly higher incidence of grade II or higher liver toxicity in patients with Child-Pugh class B disease was reaffirmed by a large retrospective SABR study (36.0% vs. 11.9% of Child-Pugh class A patients)[117].”**

RT may cause liver damage that resembles veno-occulusive disease. Are there any literatures on radiation liver damage? The liver damage is one of the limiting factors of RT to HCC. What happens in patients with PVTT treated with RT in this regard?

→ **We inserted the following text in the “Introduction of RT in HCC” section: “The pathology of radiation-induced liver damage shows changes similar to veno-occlusive disease, including endothelial swelling, terminal venule occlusion, and sinusoidal congestion[67].” and “There is also a possibility of a higher incidence of liver function deterioration after RT in HCC combined PVTT than in the other, but the dosimetric factors of liver are more important, generally[69,72].”**

Refernece list was absent. It was impossible to refer literatures cited in this manuscript. For example, reference 67, 71, 106, and 107 regarded RT to PVTT.

→ **We added a reference list.**

Reviewer 2

The authors reviewed recent progress in radiotherapy for liver cancer treatment. This topic is important since radiotherapy is much less used in Asian countries compared to western countries. HCC with PVTT is tricky and RT, as they show, can improve certain patients. The review has covered most relevant filed except the limitations of RT, which should be included.

→ We inserted the limitations of RT, as you recommended, in the "Limitations of RT" section:

"Although RT has shown promising results including favorable treatment response and survival rates in HCC with PVTT, treatment decisions regarding RT should be made cautiously because of several remaining limitations[115].

Liver function is one of the most important factors determining the method and purpose of HCC management[16], and is a key concern when considering RT. In patients with a Child-Pugh score ≥8, liver-directed RT is not generally recommended. Thus, there have been few studies in which RT was applied in those patients[36,37]. Culleton et al. reported a prospective study of SABR outcomes in patients with Child-Pugh class B or C HCC, and significantly lower survival was detected in patients with a Child-Pugh score ≥8 (9.9 months in those with scores of 7 vs. 2.8 months with scores of 8 or higher, P=0.01)[116]. In another prospective phase I study of SABR for HCC, three of 11 patients with Child-Pugh class B disease developed grade III hepatic toxicity, while none of the 17 patients with Child-Pugh class A disease did[98]. A significantly higher incidence of grade II or higher liver toxicity in patients with Child-Pugh class B disease was reaffirmed by a large retrospective SABR study (36.0% vs. 11.9% of Child-Pugh class A patients)[117].

Another important obstacle to RT application in HCC is the radiation susceptibility of the bowel, including the stomach and duodenum. The positive correlation between the incidence of symptomatic bowel toxicity and RT dose/bowel volume has been confirmed in several studies[118-120]. Our group also reported that liver function deterioration is related to a higher incidence of symptomatic bowel toxicity[121].

Before applying RT in HCC, these unresolved obstacles need to be considered. Although promising outcomes were achieved in HCC patients with poor liver function (Child-Pugh class C) or adjacent to the bowel in small studies using particle beam RT[122-124], in these high risk patients the use of RT should be carefully restricted or limited to prospective clinical trials.

While acceptable local control using RT in HCC has been reported, especially with SABR, frequent intrahepatic recurrence remains an unresolved issue[88,125-127]. Several studies have suggested that RT may induce intrahepatic metastasis via viral reactivation[128,129] and/or expression of vascular endothelial growth factor[130]. With

**the development and optimal application of antiviral agents and targeted agents like sorafenib, intrahepatic recurrence might be minimized after RT[3-5,130,131]. Further studies on combination treatment with RT are needed. ”**

The structure of the review can be improved. Some sentences lack references.

→ **We inserted additional references.**