MRI-guided radiotherapy for PVTT in HCC patients: evaluation of the efficacy and safety

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Abstract

Purpose This study aims to evaluate the efficacy, feasibility, and safety of the magnetic resonance imaging (MRI)-guided tumor tracking hypofractionated radiotherapy (HFRT) and stereotactic body radiation therapy (SBRT) for portal vein tumor thrombus (PVTT) in hepatocellular carcinoma (HCC) patients.

Methods We retrospectively reviewed the twelve cases of unresectable HCC with tumor thrombus in the main trunk or first branch of the portal vein that were treated with MRI-guided tumor tracking HFRT or SBRT using the ViewRay Linac MRIdian system between June 2019 and January 2021. The HFRT was performed with a total of 50 Gy in 10 fractions, and SBRT performed in a range of 36–50 Gy with 4–5 fractions. The median biologic effective dose (BED) with an $a/b$ ratio of 10 was 75 Gy$_{10}$ (range 68.4–100 Gy$_{10}$).

Results The median follow-up duration was 5.0 months (range 1.9–12.8 months). Ten patients (83.3%) showed an objective response of PVTT. At the time of analysis, ten patients (83.3%) showed local control. The 1-year intrahepatic control rate was 48.9%. Three patients (25%) showed mild gastrointestinal symptoms, and there were no cases of grade 3 or higher toxicity. For hepatic toxicity, there were no cases in which the Child–Pugh score increased by more than two points after RT without disease progression.

Conclusion MRI-guided tumor tracking HFRT and SBRT was a feasible, effective, and safe treatment option in HCC patients with tumor thrombi in the main trunk or first branch of the portal vein.

Keywords Portal vein tumor thrombus · Hepatocellular carcinoma · Hypofractionated radiotherapy · Stereotactic body radiation therapy · MRI-guided radiotherapy

Introduction

Advanced hepatocellular carcinoma (HCC) frequently accompanies the macrovascular invasion of major vessels such as the portal vein and hepatic vein (Li et al. 2019; Wang et al. 2021). Portal vein tumor thrombus (PVTT), which is the most common pattern of macrovascular invasion in HCC patients (Cheng et al. 2016; Li et al. 2019; Lin et al. 2021), is found clinically in 40–60% of HCC patients at the time of diagnosis (Sun et al. 2016; Cerrito et al. 2019; Cheng et al. 2020). The prognosis is very poor, the overall survival (OS) of patients without treatment is 2–4 months (Sun et al. 2016; Cheng et al. 2016; Liu et al. 2021). PVTT cause portal hypertension, deterioration of liver function, and can be a source of tumor dissemination (Sun et al. 2016; Cheng et al. 2016; Lin et al. 2021). In HCC with PVTT, surgical resection or TACE can be used for selective patients, so effective treatment is often limited (Sun et al. 2016; Chen et al. 2021; Mähringer-Kunz et al. 2021). Radiation therapy (RT) has been attempted as a local therapy for PVTT because it can be used regardless of tumor location and vascular invasion (Ohri et al. 2016; Park et al. 2016; Korean Liver Cancer Study and National Cancer Center 2015; Cheng et al. 2020). RT combined with other treatment modalities such as transarterial chemoembolization (TACE) or hepatic artery infusion chemotherapy (HAIC) improved tumor response and survival in previous studies (Huo and Eslick 2015; Im et al. 2017; Zhao et al. 2017; Alrashidi et al. 2021; Kosaka et al. 2021). Several studies have suggested a dose–response relationship between RT and treatment outcomes of PVTT and...
HCC (Lee et al. 2014; Sun et al. 2016; Iwamoto et al. 2019; Byun et al. 2020; Kim et al. 2021). Prescribing a high biologic effective dose (BED) using a large fraction size, such as hypofractionated radiotherapy (HFRT) or stereotactic body radiation therapy (SBRT), might improve the response rate and survival of HCC patients with PVTT (Hong et al. 2016; Holliday et al. 2017; Shui et al. 2018; Choi et al. 2021). Especially in Asian, as HCC is common in patients who had underlying liver diseases such as chronic hepatitis B or C or liver cirrhosis (Kim et al. 2013; Korean Liver Cancer Study and National Cancer Center 2015; Cheng et al. 2020), it is very important to perform RT while maintaining the functional liver volume. However, in the case of RT for PVTT, the treatment volume may be significantly increase to cover the liver motion. Increased treatment volume not only increases the risk of radiation-induced hepatitis or hepatic failure but also is a major cause of the decrease in prescription dose of RT to maintain liver tolerance. Magnetic resonance imaging (MRI)-guided tumor tracking RT makes the delineation of the target lesion more clear and enables treatment even with a small margin on the target by real-time tumor tracking and gating (Boldrini et al. 2021). In this study, we aimed to evaluate the efficacy, feasibility, and toxicity of MRI-guided tumor tracking HFRT and SBRT for PVTT in unresectable HCC patients.

Materials and methods

Patients

Between June 2019 and January 2021, 17 unresectable HCC patients with tumor thrombi in the main trunk or the first branch of the portal vein underwent MRI-guided RT using the ViewRay Linac MRIdian system (ViewRay, Cleveland, Ohio). In our institution, RT on PVTT performed to improve the therapeutic outcome combined with other local therapy or to preserve the portal venous flow and delay the liver deterioration that PVTT can cause. The inclusion criteria of this study were as follows: (1) HCC was diagnosed by histological examination or the imaging criteria of the Korean Liver Cancer Study group (2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma 2019), (2) patients who had liver function of Child–Pugh class (CP class) A or B, (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (4) tumor thrombus in the main trunk or first branch of the portal vein, (5) RT was conducted through the HFRT or SBRT technique using a fraction size of 5 Gy or more. The one patient who did not complete SBRT, two patients who received conventional fractionated RT, and two patients who did not have follow-up imaging after RT were excluded from this study. Twelve out of 17 patients were included in this study. The type of PVTT was evaluated according to the PVTT classification system established by the liver cancer study group of Japan (Ikai et al. 2003): Vp1, presence of a tumor thrombus distal to the second-order branch of the portal vein; Vp2, presence of a tumor thrombus in the second-order branches of the portal vein; Vp3, presence of a tumor thrombus in the first-order branches of the portal vein, and Vp4, presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe of HCC.

Simulation and planning

All patients underwent 0.35 T (T) MRI scan simulation using the ViewRay Linac MRIdian system (ViewRay, Cleveland, Ohio) that consisted of an MRI scanner and a 6 MV flattening filter-free linear accelerator. Patients were immobilized in the supine position with the arm elevated using the Vac-Lok fixation system (CIVCO, Coralville, Iowa, USA). An MRI coil was placed above the patient’s abdomen, and MRI scans were performed with 3 mm thickness slice. For reproducibility and compliance during treatment, MRI scans were acquired for 25 s using an end-exhale breathing hold (EBH) method. Afterward, the physician checked the quality of the MRI scan if delineation of the target lesion and near-normal organ is possible. If the MRI scan was not satisfactory to confirm the target lesion, it was performed again in the same way. MRI scans were performed up to 3 times for patients with poor respiratory coordination, and breathing training was performed on the patient for about 10 min in the middle of scan. After the initial MRI scan was completed, a cine MRI scan was acquired for 10 s with EBH. The most appropriate sagittal plane was selected, the target for PVTT contoured on it by a physician, and the boundary was set with a 5 mm margin of the target. Then, we checked whether the target was recognizable and tracking was possible through cine MRI. Within 30 min after the completion of MRI simulation, the computed tomography (CT) simulation was performed with the same position using the same immobilization system and EBH method. The contrast agent was administered, CT simulation was performed using a LightSpeed RT 16 (GE, Waukesha, WI, USA) CT scanner. The enhanced CT simulation imaging was selected and fused with the MRI simulation image to obtain the electron density data.

The gross tumor volume (GTV) for the PVTT was contoured by a radiation oncologist on the MRI simulation image, referring to the CT simulation image and diagnostic imaging (Primovist (BAYER, Leverkusen, Germany) dynamic MRI, liver dynamic CT). The portion showing a characteristic enhancement pattern (enhancement of the arterial phase and washout of the late portal phase and delayed phase) or the portion showing a low signal

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intensity of the hepatobiliary phase or diffusion restriction of the diffusion-weighted image in dynamic liver MRI were contoured for GTV. The PTV was set at a 5-mm margin on the GTV. The PTV was compromised if the PTV was included or adjacent to the duodenum or stomach. All patients were scheduled to undergo real-time tumor tracking and gating at each RT fraction to maintain the accuracy of the treatment and to control the intra-fractional variability with a small PTV margin. Step-and-shoot intensity-modulated radiation therapy (IMRT) planning was performed using 10–17 beams with the MRIIdian treatment planning system (ViewRay Inc., Mountain View, CA, USA) (Fig. 1). The prescribed dose planned to encompassed at least 95% of the PTV (D95% = 100%) while satisfying the dose constraints of critical normal organs, such as the duodenum and stomach. In the case of four patients who has PVTT near duodenum or stomach, the prescription dose was planned to cover 90% of PTV (D90% = 100%) and at least 95% of GTV (D95% = 100%). The hot spot was limited to less than 110% and allowed within the target. The mean normal liver (whole liver-GTV) dose was maintained at < 23 Gy for planning HFRT and < 15 Gy for SBRT. The volume of normal liver that irradiated less than 15 Gy was set to more than 700 cm³ in all patients. For the stomach and duodenum, the maximum dose was maintained at < 35 Gy and 24 Gy in HFRT and SBRT planning, respectively. The dose calculations were performed using the Monte Carlo computation algorithm.

**Treatment**

During radiotherapy, real-time MRI tumor tracking and gating was performed using deformable image registration-based beam control. At each session of RT, patients underwent 25 s of MRI scanning with EBH method. Alignment adjustment was performed for target lesion compared to the plan imaging. After that, a cine MRI scan was performed for 10 s with EBH. The most appropriate sagittal plane was selected for tumor tracking. The GTV and PTV contoured during radiation planning were set as the target and boundary, respectively. During radiotherapy, the beam was automatically turned off if the target was out of the boundary by more than a threshold of 3% (Fig. 2).

**Follow-up and evaluation**

After radiotherapy, follow-up was performed at 2–3-months intervals. At follow-up, history taking, physical examination, complete blood count, liver function test (LFT), alpha-fetoprotein (AFP), and liver dynamic computed tomography (CT) or MRI were performed, and CP class was evaluated. Tumor response evaluation was performed using dynamic liver CT or dynamic liver MRI according to modified response evaluation criteria in solid tumors (mRECIST) version 1.1. OS was defined as the duration between the first day of RT and the day of death or last follow-up. Local control was defined as a state of maintaining of the lesion in RT field without progressive disease according to mRECIST criteria. Intrahepatic control was defined as a state of maintaining an existing HCC and PVTT lesion without progression and no new occurrence of mass in the liver. OS and intrahepatic control rate were estimated by Kaplan–Meier methods using R version 4.0.0 (R Development Core Team, Vienna, Austria). Toxicity was investigated for 3 months after RT completion for the hepatic and gastrointestinal systems according to the Common Terminology Criteria for Adverse Events (CTACE) version 5.0. To investigate hepatic toxicity, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and bilirubin (LFT), ascites, and Child–Pugh score (CP score) were evaluated. For evaluation of gastrointestinal toxicity, history taking for nausea, dyspepsia, esophagitis, or gastritis less than 15 Gy was more than 700 cm³. *Orange line—95% isodose line, yellow line—90% isodose line, green line—80% isodose line, cyan line—42% isodose line (21 Gy), blue line—30% isodose line (15 Gy)
symptoms were performed. Esophagogastroduodenoscopy was performed in patients with grade 2 or higher gastrointestinal symptoms.

**Results**

The median follow-up duration was 5.0 months (range 1.7–12.8 months). The median age was 61 years (range 50–67 years), and the majority of patients (11 patients, 91.7%) were male. The mean value of alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) of the patients were 23,497.07 ± 48,854.12 ng/ml and 19,061.34 ± 33,565.08 mAU, respectively. Except for one patient, all patients were classified as CP class A. Nine patients (75%) had an HCC mass of ≥ 5 cm, and most of them (8 patients, 66.7%) had multiple HCC lesions. In the PVTT classification, four patients were Vp3 type and eight patients were Vp4 type. At the time of RT initiation, two patients (16.7%) had distant metastases in the diaphragm and lungs, respectively. The details of the patient characteristics are shown in Table 1.

**Treatment**

Four patients received radiotherapy as the first treatment and the other 8 patients received other treatments such as TACE, liver resection, or RFA prior to RT. After RT, eight patients received TACE, and five patients (41.7%) received systemic therapy with a target agent or immunotherapy. Ten patients (83.3%) received combine therapy with TACE within one month before and after RT. The other two patients who did not receive combine therapy were cases in which no viable portion in the liver other than portal vein at the time of RT, or case of sorafenib administered because distant metastasis accompanied. A summary of the treatment is shown in Table 2. Five patients received HFRT, and seven patients received SBRT. The HFRT was performed with a total of 50 Gy in 10 fractions and SBRT performed in a range of 36–50 Gy with 4–5 fractions. The median biologic effective dose (BED) with an \(a/b\) ratio of 10 was 75 Gy\(_{10}\) (range 68.4–100 Gy\(_{10}\)). The median values of GTV and PTV were 30.8 cm\(^3\) (range 13.5–903.7 cm\(^3\)) and 78.4 cm\(^3\) (range 44.4–1540.4 cm\(^3\)), respectively. The median liver volume was 1830.7 cm\(^3\) (range 946.7–3193 cm\(^3\)). The median mean liver dose was 13.43 Gy (range 5.83–21.94 Gy) (Table 2.).

**Tumor response and treatment outcome**

In the response evaluation that was performed at the time of median duration of 2.2 months (range 0.9–3.2 months) from completion of RT, 10 patients (83.3%) showed partial response (PR). The objective response was defined the case that showing complete response or PR. One patient showed stable disease (SD) and the other patient showed progressive disease (PD). At the time of analysis, 10 patients (83.3%) showed local control of PVTT lesions, and five patients died. The 1-year intrahepatic control rate was 48.9%. The median survival time of the patients was 11.6 months (range 1.9–12.8 months). Two patients died due to hepatorenal syndrome, and three died of HCC progression. The patient’s individual clinical characteristics and courses were summarized in Table 3.

**Toxicity**

Until three months after RT completion, seven patients (58.3%) showed elevated levels of liver enzymes (AST and ALT). Of these, three patients showed grade 3 elevation of liver enzymes, 2 patients showed grade 2, and two patients were grade 1. Of the three patients with grade 3 liver enzyme elevation, one was elevated due to TACE and the
other two patients recovered to grade 1 and normal values 3 months after onset. The elevation of ALP was identified in one patient as grade 1. An elevation of the bilirubin level was identified in four patients, of which two were grade 1 and two were grade 3. The grade 3 elevations of bilirubin were due to progression of the hepatic duct invasion lesion and PVTT. An increase in the CP score of 2 or more during the 3 months after completion of RT was identified in three patients. Two patients of them due to disease progression, and one patient showed elevation of CP score at 2 months after RT, and died due to disease progression 3 months later. Three patients showed gastrointestinal symptoms, and none showed grade 3 or higher toxicity. Three patients showed grade 1 dyspepsia, grade 1 nausea, and grade 2 gastric ulcers. The gastric ulcer lesion showed a low correlation with RT, as the lesion was quite distant from the RT field.

### Discussion

HCC with PVTT has a very poor prognosis, and there is no established standard treatment (Chan et al. 2016; Li et al. 2019; Cerrito et al. 2019). Surgical treatment can be considered for types I–II PVTT; however, in the case of types III–IV PVTT is challenging, and the recent postoperative mortality has been reported range of 0–10% (Costentin et al. 2017; Ye et al. 2017; Zhang et al. 2019) and the recurrence rate is high (Sun et al. 2016; Costentin et al. 2017). In addition, TACE alone showed limited tumor response and survival benefit for HCC patients with type III–IV PVTT, and it can be tried in selected patients who have preserved liver function (Zhang et al. 2015; Wang et al. 2016; Silva et al. 2017). Previous RT was mainly performed as a palliative aim due to the low liver tolerance for RT; however, as image-guided RT (IGRT) and IMRT were introduced with the development of techniques, in the recent era, RT has been attempted as a curative aim (Huo and Eslick 2015; Holliday et al. 2017; Yoon et al. 2018; Chen 2019; Lu et al. 2019; Bang and Dawson 2019). The RT combined with local therapy such as TACE and HAIC showed encouraging results for tumor response and survival (Huo and Eslick 2015; Im et al. 2017; Zhao et al. 2017; Yoon et al. 2018; Alrashidi et al. 2021; Kosaka et al. 2021). In this study, 10 patients (83.3%) received RT combined with TACE and showed favorable results, with an objective response rate of 83.3%, local control of 83.3%, and 1-year IHC rate was 48.9%. IHC rate showed consistent results compared with 45.7–45.8% of study by Li et al. (2021) comparing the treatment results of IMRT and SBRT in HCC patients with PVTT. Considering the characteristics of this study that was only for patients with tumor thrombus in the first branch or main trunk of portal vein and included the 5 patients (41.6%) with large HCC mass over 10 cm and 8 patients (66.6%) with multiple HCC, it is thought to be encouraging results.

The tumor response of this study is higher than those of previous studies that analyzed the effect of RT for PVTT (Table 4). The high BED RT of this study through HFRT or SBRT might be attributed to the favorable tumor response. The dose–response relationship between RT, tumor response, and survival in HCC patients with or without PVTT has been suggested in previous studies (Hong et al. 2016; Holliday et al. 2017; Shui et al. 2018; Byun et al. 2020; Li et al. 2021). Holliday et al. (2017) reported that RT with a BED of 75 Gy10 or higher improved tumor response and overall survival (OS) in HCC patients with PVTT. Li et al. (2021) compared the treatment effect between IMRT

### Table 1 Patient’s characteristics

| Factor       | No. (%) |  |
|--------------|---------|---|
| Age          | Median, 61 years (range 50–67 years) |  |
| Gender       | Male 11 (91.7) |  |
|             | Female 1 (8.3) |  |
| Etiology     | HBV 8 (66.7) |  |
|             | HCV 1 (8.3) |  |
|             | Alcoholic 3 (25) |  |
|AFP          | Mean, 23,497.07±48,854.12 ng/ml |  |
| PIVKA-II     | Mean, 19,061.34±33,565.08 mAU |  |
| ECOG         | 0–1 9 (75) |  |
|             | 2 3 (25) |  |
| CP class     | A 11 (91.7) |  |
|             | B 1 (8.3) |  |
| Mass size    | <5 cm 3 (25) |  |
|             | 5–10 cm 4 (33.3) |  |
|             | > 10 cm 5 (41.7) |  |
| Mass number  | Solitary 4 (33.3) |  |
|             | Multiple 8 (66.7) |  |
| PVTT type    | Vp3 4 (33.3) |  |
|             | Vp4 8 (66.7) |  |
| LN metastasis| None 10 (83.3) |  |
|             | Present 2 (16.7) |  |
| Distant metastasis | None 10 (83.3) |  |
|             | Present 2 (16.7) |  |

No number, HBV hepatitis B virus, HCV hepatitis C virus, AFP alpha-fetoprotein, PIVKA-II protein induced by vitamin K absence or antagonist-II, CP class Child–Pugh class, PVTT portal vein tumor thrombus, LN lymph node
and SBRT technique in HCC patients with PVTT; OS and progression-free survival were better when BED 100 Gy\textsuperscript{10} or higher was prescribed, regardless of the technique. High BED RT could be considered as one of the treatment options that may improve tumor response and survival in HCC patients with PVTT. For the feasibility of this treatment, it is important to reduce the treatment volume to preserve the normal organ, especially the functional liver volume. The MRI-guided real-time tumor tracking RT could reduce the treatment volume by controlling intra-fractional motion and variation with a small margin. In particular, it is more useful in organs that have large physiological motions, such as the liver and lungs. Menten et al. compared the PTV between techniques using internal target volume (ITV) and tumor tracking and found that the PTV using the ITV method was 44% higher than that using the tumor tracking method (Menten et al. 2016). In addition, MRI-guided tumor tracking RT may have several advantages over other methods that can decreasing the treatment volume such as respiratory gating method or CT-based dynamic tumor tracking method. Respiratory gating method can reduce the PTV margin by performing RT in a specific respiratory cycle of the patient, but it is not a method that directly monitor the internal tumor movement at the time of RT. Respiratory cycle variation may occur day to day and breath to breath, also geometric variation may exist in the direction in which the center and boundary of the tumor move according to each respiratory cycle (Sawant et al. 2014). In addition, the respiratory gating method has a limitation that it may takes a very long treatment time depending on the patient’s respiratory cooperation. The MRI-guided real-time tumor tracking method can facilitate target delineation using MRI images, and it can improve the accuracy of treatment by directly monitoring the real-time tumor movement through temporal resolution of 4 images/seconds (Cusumano et al. 2018). Through the high soft-tissue contrast of MRI, it is possible to monitoring the entire tumor movement without invasive procedures such as insertion of fiducial marker. And, the patient’s convenience could improve because of RT was performed with free breathing at the time of treatment. And in this study, the

Table 2  Treatment's characteristics

| Previous treatment | No. (%) |
|--------------------|---------|
| None               | 4 (33.3) |
| Surgery            | 1 (8.3)  |
| TACE               | 8 (66.7) |
| RFA                | 1 (8.3)  |
| Post-radiotherapy treatment | No. (%) |
| TACE               | 8 (66.7) |
| RFA                | 1 (8.3)  |
| Sorafenib          | 2 (16.7) |
| Lenvatinib         | 2 (16.7) |
| Aterzolizumab+bevacizumab | 1 (8.3)  |

Radiotherapy

| GTV (cm\textsuperscript{3}) | Median, 30.8 cm\textsuperscript{3} (range 13.5–903.7 cm\textsuperscript{3}) |
| PTV (cm\textsuperscript{3}) | Median, 78.4 cm\textsuperscript{3} (range 44.4–1540.4 cm\textsuperscript{3}) |
| Liver (cm\textsuperscript{3}) | Median, 1830.7 cm\textsuperscript{3} (range 946.7–3193 cm\textsuperscript{3}) |
| Normal liver (whole liver-GTV, cm\textsuperscript{3}) | Median, 1286.8 cm\textsuperscript{3} (range 800.1–2017.7 cm\textsuperscript{3}) |

Prescribed dose

| HFRT | 50 Gy/10 fxs |
| SBRT | 36–50 Gy/4–5 fxs |
| BED\textsuperscript{10} | Median, 75 Gy/10 (range 68.4–100 Gy/10) |
| Liver Dmean\textsuperscript{*} | Median, 13.43 Gy (range 5.83–21.94) |
| Liver V\textsubscript{15} (cm\textsuperscript{3})\textsuperscript{*} | Median, 476.1 cm\textsuperscript{3} (range 67.5–1005.1 cm\textsuperscript{3}) |
| Liver V\textsubscript{21} (cm\textsuperscript{3})\textsuperscript{*} | 276.9 cm\textsuperscript{3} (range 32.8–686.4 cm\textsuperscript{3}) |

\(\text{No. number, TACE transarterial chemoembolization, RFA radiofrequency ablation, GTV gross tumor volume, PTV planning target volume, HFRT hypofractionated radiotherapy, SBRT Stereotactic body radiation therapy, BED biologic effective dose}

\(\text{*Liver Dmean; mean irradiation dose of liver}

\(\text{*Liver V\textsubscript{15} (cm\textsuperscript{3}); liver volume that was irradiated more than 15 Gy}

\(\text{*Liver V\textsubscript{21} (cm\textsuperscript{3}); liver volume that was irradiated more than 21 Gy}

\(\text{and SBRT technique in HCC patients with PVTT; OS and progression-free survival were better when BED 100 Gy\textsubscript{10} or higher was prescribed, regardless of the technique. High BED RT could be considered as one of the treatment options that may improve tumor response and survival in HCC patients with PVTT. For the feasibility of this treatment, it is important to reduce the treatment volume to preserve the normal organ, especially the functional liver volume. The MRI-guided real-time tumor tracking RT could reduce the treatment volume by controlling intra-fractional motion and variation with a small margin. In particular, it is more useful in organs that have large physiological motions, such as the liver and lungs. Menten et al. compared the PTV between techniques using internal target volume (ITV) and tumor tracking and found that the PTV using the ITV method was 44% higher than that using the tumor tracking method (Menten et al. 2016). In addition, MRI-guided tumor tracking RT may have several advantages over other methods that can decreasing the treatment volume such as respiratory gating method or CT-based dynamic tumor tracking method. Respiratory gating method can reduce the PTV margin by performing RT in a specific respiratory cycle of the patient, but it is not a method that directly monitor the internal tumor movement at the time of RT. Respiratory cycle variation may occur day to day and breath to breath, also geometric variation may exist in the direction in which the center and boundary of the tumor move according to each respiratory cycle (Sawant et al. 2014). In addition, the respiratory gating method has a limitation that it may takes a very long treatment time depending on the patient’s respiratory cooperation. The MRI-guided real-time tumor tracking method can facilitate target delineation using MRI images, and it can improve the accuracy of treatment by directly monitoring the real-time tumor movement through temporal resolution of 4 images/seconds (Cusumano et al. 2018). Through the high soft-tissue contrast of MRI, it is possible to monitoring the entire tumor movement without invasive procedures such as insertion of fiducial marker. And, the patient’s convenience could improve because of RT was performed with free breathing at the time of treatment. And in this study, the}
Table 3  The patient’s individual clinical characteristics and course

| Pts., Age/Sex | HCC size (largest, cm) | Number (Solitary/Multiple) | AFP (ng/ml) (Pre-RT) | PVTT type | CP score (Pre-RT → Post-RT) | Pre-RT local Tx. | Post-RT local Tx. | RT dose/Fxs. | Response to RT | LC | Survival/FU duration (mo) | Toxicity | GI | Liver enzyme | Bilirubin |
|---------------|------------------------|-----------------------------|-----------------------|-----------|-----------------------------|-----------------|-----------------|----------------|---------------|-----|------------------------|----------|-----|----------------|----------|
| #1 61/M       | 4                      | S                           | 259.6                 | Vp4       | 5 → 6                       | None            | #5 TACE         | 50 Gy/10 fxs  | PR            | C   | Survival/11.4 mo      | G1, dyspepsia | (–) | (–)             |
| #2 56/M       | 6                      | M                           | 1352.8                | Vp3       | 5 → 5                       | None            | #2 TACE         | 50 Gy/10 fxs  | PR            | C   | Survival/3.7 mo       | G1, G1   | (–) | (–)             |
| #3 63/M       | 3                      | S                           | 22.9                  | Vp4       | 5 → 5                       | #2 TACE         | #1 TACE         | 50 Gy/10 fxs  | PR            | C   | Survival/2.7 mo       | (–)      | (–) | (–)             |
| #4 57/M       | No viable portion in liver | No viable portion in liver | 12.2                  | Vp3       | 5 → 6                       | #9 TACE Segmentectomy #1 RFA |               |                 |                 |                 |     |                       |          |     |                 |
| #5 63/M       | 14.2                   | M                           | 268.4                 | Vp4       | 6 → 7                       | None            | None            | 45 Gy/5 fxs   | PR            | C   | Expire/5.9 mo         | G2, gastric ulcer | G3   | (–)             |
| #6 50/F       | 13.6                   | M                           | 3717.9                | Vp3       | 5 → 5                       | None            | #2 TACE         | 40 Gy/5 fxs   | PR            | C   | Expire/12.8 mo        | (–)      | (–) | (–)             |
| #7 67/M       | 8.3                    | M                           | 96,487.6              | Vp4       | *5 → 8 (Outfield PD)        | #1 TACE         | #2 TACE         | 50 Gy/5 fxs   | PR            | C   | Expire/4.5 mo         | G2       | (–) | (–)             |
| #8 59/M       | 10                     | M                           | 1539.9                | Vp4       | 6 → 6                       | #1 TACE         | None            | 50 Gy/5 fxs   | PR            | C   | Survival/4.5 mo       | G3       | (–) | (–)             |
| #9 55/M       | 7                      | M                           | 153.6.71              | Vp4       | 9 → 9                       | #2 TACE         | #1 TACE         | 50 Gy/5 fxs   | SD            | C   | Survival/3.6 mo       | (–)      | (–) | G1              |
| #10 61/M      | 18                     | M                           | 151,055.7             | Vp4       | *6 → 9 (PD)                 | #1 TACE         | None            | 50 Gy/5 fxs   | PD            | P   | Expire/1.9 mo         | G2, G3   | (–) | (–)             |
| #11 64/M      | 5                      | S                           | 14.4                  | Vp3       | 5 → 5                       | #1 TACE         | #2 TACE         | 50 Gy/5 fxs   | PR            | C   | Survival/12.0 mo      | G3 (after TACE) | (–) | (–)             |
| #12 55/M      | 15                     | M                           | 27,082.4              | Vp4       | *7 → 9 (Outfield PD)        | #1 TACE         | None            | 50 Gy/10 fxs  | PR            | C   | Expire/5 mo           | G1, G3   | (–) | (–)             |

Pts. patients, HCC hepatocellular carcinoma, AFP alpha-fetoprotein, PVTT portal vein tumor thrombus, CP score Child–Pugh score, RT radiotherapy, Tx. Therapy, Fxs fractions, LC local control, FU follow-up, mo months, M male, F female, GI gastrointestinal, M multiple, S solitary, TACE trans-arterial chemoembolization, RFA radiofrequency ablation, PR partial response, SD stable disease, PD progressive disease, C control, P progression, G grade
Most of the patients in this study showed hepatic and gastrointestinal toxicity limited to grades 1–2. None of the patients had grade 3 or higher gastrointestinal symptoms. Most of grade 3 elevation of liver enzymes and bilirubin was due to disease progression. The grade 3 liver enzyme elevations that possibly related to RT were identified in two patients who underwent SBRT for PVTT through 45 Gy in 5 fxs and 50 Gy in 5 fxs, respectively. The dose-volume parameter for each patient were as follows; (Case 1: PTV 64.3 cm³, liver volume 1830.7 cm³, liver Dmean 14.3 Gy, Liver D700 cm³ 15.3 Gy, Liver V21Gy 401.1 cm³/Case 2: PTV 81.8 cm³, liver volume 1893.1 cm³, liver Dmean 11.2 Gy, Liver D700 cm³ 8.9 Gy, Liver V21Gy 277.4 cm³). Both patients satisfied the dose constrains and recovered to normal value and grade 1 after 3 months from onset, respectively. There was no case of increased CP score more than 2 points by RT without disease progression. Considering previous studies of MRI-guided RT performed on liver lesions, this is considered a reasonable result (Feldman et al. 2019; Boldrini et al. 2021). Boldrini et al. (2021) performed SBRT with BED 100 Gy₁₀ or higher for ten HCC patients, and only one patient showed a change in CP score from A to B. Feldman et al. (2019) reported that 13% of 29 unresectable liver tumor patients who received MRI-guided RT showed mild gastrointestinal symptoms of less than grade 3. MRI-guided HFRT or SBRT using real-time tumor tracking and gating is considered a feasible treatment with acceptable hepatic and gastrointestinal toxicity.

This study has several limitations. First, as this study has a small number of patients and short follow-up duration, the analysis of the effect and toxicity of RT was might be limited. Second, this study included variable patients that accompanied distant metastasis, LN metastasis or multiple lesions. It might be affected the overall prognosis of patients for RT. Third, as this study was a retrospective study, patients received heterogenous treatments, including TACE or surgery. Despite of several limitations, this study as the first analysis to MRI-guided tumor tracking RT for PVTT in unresectable HCC patients, it suggested the possibility of MRI-guided HFRT and SBRT for PVTT.

### Table 4 Previous studies of radiotherapy for PVTT in HCC patients

| Study                  | No. | PVTT extent | Combine Tx | RT target | RT dose (Gy/fxs) | Response (%) | Median survival (mo) | IHC  |
|------------------------|-----|-------------|------------|-----------|-----------------|--------------|----------------------|------|
| Li et al. (2016)       | 108 | All PVTT    | TACE       | PVTT      | 50–66 Gy/25–30  | CR, 17.6     | 10.9                 | NA   |
| IM et al. (2017)       | 985 | Main trunk  | –          | PVTT ± HCC mass | Median, 45/18 | CR, 6.1       | 10.2                 | NA   |
| Kosaka et al. (2021)   | 51  | Main trunk  | HAIC       | PVTT + HCC mass | 30–54/2–3 Gy fx size | CR, 2       | 12.1                 | NA   |
| Choi et al. (2021)     | 24  | All PVTT    | –          | PVTT ± HCC mass | 39–45/3–4       | CR, 8.3      | 20.8                 | NA   |
| Bai et al. (2021)      | 14  | Main trunk  | –          | PVTT      | 50/25           | Downstage to type II, 92.9% | NA   |
| Li et al. (2021)       | 102 | All PVTT    | –          | PVTT      | HFRT, 30–60/7–20 | NA           | HFRT, 10 SBRT, 10     | 1-yr, 45.7% SBRT, 45.8% |
| This study (2021)      | 12  | Main trunk  | TACE       | PVTT ± HCC mass | 50/10           | CR, 0        | 11.6                 | 1-yr, 48.9% |

PVTT portal vein tumor thrombus, HCC hepatocellular carcinoma, No. number, Tx. Therapy, RT radiotherapy, fxs fractions, mo months, IHC intrahepatic control, CR complete response, PR partial response, HAIC hepatic artery infusion chemotherapy, SMV superior mesenteric vein, HFRT hypofractionated radiotherapy, SBRT stereotatic body radiation therapy, TACE trans-arterial chemoembolization

The MRI-guided tumor tracking HFRT and SBRT for PVTT was a feasible and safe treatment option that showed favorable tumor response and local control in patients with unresectable HCC accompanying tumor thrombi in the main trunk or first branch of the portal vein in this study. The optimal target volume and fractionation of MRI-guided HFRT and SBRT for PVTT in these patients should be identified further studies.

**Conclusion**

The MRI-guided tumor tracking HFRT and SBRT for PVTT was a feasible and safe treatment option that showed favorable tumor response and local control in patients with unresectable HCC accompanying tumor thrombi in the main trunk or first branch of the portal vein in this study. The optimal target volume and fractionation of MRI-guided HFRT and SBRT for PVTT in these patients should be identified further studies.

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Availability of data and materials  All data generated or analyzed during this study are included in this article.

Declarations

Conflict of interest  The authors declare that they have no conflict of interest.

Ethical approval  This study was approved by the institutional review board of the Catholic Medical Center ethics committee (IRB No. OC21RASI0065).

Consent to participate  As a retrospective study using medical records that do not contain patient’s personal information, the consent process was exempted.

Consent for publication  As a retrospective study using medical records that do not contain patient’s personal information, the consent process was exempted.

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