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 tumor tracking magnetic resonance imaging (MRI)-guided 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 tumor tracking MRI-guided 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 α/β ratio of 10 was 75 Gy₁₀ (range, 68.4–100 Gy₁₀).

Results

The median follow-up duration was 5.0 months (range, 1.7–12.8 months). Ten patients (83.3%) showed an objective response of PVTT. At the time of analysis, 10 patients (83.3%) showed local control. The median survival of these patients was 11.6 months (range, 1.9–12.8 months). 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 of Child-Pugh score increased by more than 2 points after RT without disease progression.

Conclusion

Tumor tracking MRI-guided 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.

Introduction

Advanced hepatocellular carcinoma (HCC) frequently accompanies the macrovascular invasion of major vessels such as the portal vein and hepatic vein (Hou et al. 2012; Wang et al. 2021; Rodríguez-Perálvarez et al. 2013). Portal vein tumor thrombus (PVTT), which is the most common pattern of macrovascular invasion in HCC patients (Cabibbo et al. 2010; Chan et al. 2011; Cheng et al. 2016), is found clinically in 40–60% of HCC patients at the time of diagnosis (Sun et al. 2016; Cheng et al. 2020; Cerrito et al. 2019). The prognosis is very poor, the overall survival (OS) of patients without treatment is 2–4 months (Minagawa and Makuuchi 2006; Stuart, Anand, and Jenkins 1996; Fuster et al. 1996; Sun et al. 2016; Cheng et al. 2016). PVTT cause portal hypertension, deterioration of liver function, and can be a source of tumor dissemination (Sun et al. 2016; Cheng et al. 2016). In HCC with PVTT, surgical resection or TACE can be used for selective patients, so effective treatment is often limited (Sun et al. 2016; Minagawa and Makuuchi 2006; Llovet et al. 1999; Bruix and Sherman 2011). Radiation therapy (RT) has been attempted

as a local therapy for PVTT because it can be used regardless of tumor location and vascular invasion (Sugahara et al. 2009; Yamada et al. 2003; Kim et al. 2005; Han et al. 2008; Koo et al. 2010; Yoon et al. 2012; Tang et al. 2013). 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 ('2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma' 2019; Yoon et al. 2018; Im et al. 2017; Zhao et al. 2017; Katamura et al. 2009; Yoon et al. 2012; Tang et al. 2013). Several studies have suggested a dose-response relationship between RT and treatment outcomes of PVTT (Sun et al. 2016; Kim et al. 2005; Toya et al. 2007; Lee et al. 2014; Iwamoto et al. 2019). 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 (Xi et al. 2013; Shui et al. 2018; Kamiyama et al. 2007; Bujold et al. 2013; Hong et al. 2016; Kim et al. 2013b). Especially in Asian, as HCC is common in patients who had underlying liver diseases such as chronic hepatitis B or C and liver cirrhosis('2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma' 2019; Kim et al. 2013a; 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 is also a major cause of the decrease the prescription dose of RT to maintain liver tolerance. Magnetic resonance imaging (MRI)-guided RT using tumor tracking method 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. 2021a). 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). 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 classification (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. Patients who did not complete RT, received conventional fractionated RT, or 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 tesla (T) MR scan simulation using the ViewRay Linac MRIdian system (ViewRay, Cleveland, Ohio) that consisted of an MR scanner and a 6 MV flattening filter-free linear accelerator. Patients were immobilized in the supine position with the arm elevated using the Vaclock fixation system. 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 seconds 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 MR scan was not satisfactory to confirm the target lesion, it was performed again in the same way. After the initial MR scan was completed, a cine MRI scan was acquired for 10 seconds with EBH. The most appropriate sagittal plane was selected, the target for PVT was 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 minutes 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 MR simulation image to obtain the electron density data.

The gross tumor volume (GTV) for the PVT was contoured by a radiation oncologist on the MR simulation image, referring to the CT simulation image and diagnostic imaging (Primovist 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 intensity of the hepatobiliary phase or diffusion restriction of the diffusion-weighted image in Primovist dynamic liver MRI were contoured for GTV. The PTV was set at a 5-mm margin on the GTV. The PTV was compromised when 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 MRIdian treatment planning system (ViewRay Inc., Mountain View, CA, USA) (**Fig. 1**). 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 700cc 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 seconds of MRI scanning with EBH method. Adjustment of the alignment was performed compared to the plan imaging on the target lesion. After that, a cine MRI scan was performed for 10 seconds with EBH. The most appropriate sagittal plane was selected for target 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 response 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 Primovist dynamic liver MRI according to modified response evaluation criteria in solid tumors (mRECIST) version 1.1. 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, ascites, and Child-Pugh score (CP score) were evaluated. For evaluation of gastrointestinal toxicity, history taking for nausea, dyspepsia, esophagitis, or gastritis 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. 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. 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 Gy₁₀ (range, 68.4–100 Gy₁₀). The median values of GTV and PTV were 30.8 cc (range, 13.5–903.7cc) and 78.4 cc (range, 44.4–1540.4cc), respectively. The median liver volume was 1830.7cc (range, 946.7–3193cc). The median mean liver dose was 13.43 Gy (range, 5.83–21.94 Gy) (**Table 2.**).

Tumor response and survival

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 each showed stable disease (SD) and progressive disease (PD). At the time of analysis, 10 patients (83.3%) showed local control of PVTT lesions, and five patients died. The median survival time was 11.6 months (range, 1.9–12.8 months), and the 1-year overall survival (OS) was 28.1%. Two patients died due to hepatorenal syndrome, and three died of HCC progression.

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. 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 had 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 (Chent et al. 2016; Sun et al. 2016; Minagawa et al. 2006; Stuart et al. 1996; Fuster et al. 1996). Surgical treatment can be considered for types I–II PVTT; however, in the case of types III–IV PVTT is challenging, and the postoperative mortality has been reported to be up to 28% (Shi et al. 2010; Ikai et al. 2007; Chen et al. 2006; Wu et al. 2000; Ikai et al. 2006), and the recurrence rate is high (Hasegawa et al. 2013; Sun et al. 2016). In addition, TACE alone showed limited tumor response and survival benefit for HCC patients with PVTT, and it can be tried in selected patients who have preserved liver function (Luo et al. 2011; Liu et al. 2014; Jang et al. 2007). 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 (Sugahara et al. 2009; Yamada et al. 2003; Kim et al. 2005; Han et al. 2008; Koo et al. 2010; Yoon et al. 2004; Tang et al. 2013;). The RT combined with locoregional therapy such as TACE and HAIC showed encouraging results for tumor response and survival (Tang et al. 2013; Yoon et al. 2018; Zhao et al. 2017; Katamura et al. 2009). In this study, RT for PVTT in patients with unresectable HCC with tumor thrombus of the main trunk or first branch of the portal vein showed favorable results, with an objective response rate of 83.3% and local control rate of 83.3%. These results are higher than those of previous studies that analyzed the effect of RT on PVTT (**Table 3**). 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 (Kim et al. 2005; Xi et al. 2013; Shui et al. 2018; Kamiyama et al. 2007; Bujold et al. 2013; Hong et al. 2016; Kim et al. 2013; Liu et al. 2014). Kim et al. reported that RT with a BED of 58 Gy₁₀ or higher improved tumor response and overall survival (OS) in HCC patients with PVTT. Li et al. compared the treatment effect between IMRT and SBRT technique in HCC patients with PVTT; OS and progression-free survival were better when BED 100 Gy₁₀ or higher was prescribed, regardless of the technique (Li et al. 2021). 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. MRI-guided RT using real-time tumor tracking and gating techniques 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). Although this study showed a high tumor response and local control, it showed a relatively low survival rate compared to previous studies (**Table 3**). Since this study included a small number of patients and the median follow-up duration was as short as 5 months, the survival analysis was limited. Two patients out of 12 patients had distant metastasis at the start of radiotherapy. In addition, 5 patients had large HCCs with a mass size greater than 10 cm, and most patients (8 patients) had multiple HCC masses. For liver tolerance, RT was performed on PVTT lesions only, except for two patients who received RT, including adjacent HCC masses. 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 grade 3 elevation of liver enzymes and bilirubin was due to disease progression, and in other cases showing a recovery pattern. In addition, radiation-induced liver disease was not identified in this study. Considering previous studies of MR-guided RT performed on liver lesions, this is considered a reasonable result (Boldrini et al. 2021b; Feldman et al. 2019). Boldrini et al. 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 (Boldrini et al. 2021b). Feldman et al. reported that 13% of 29 unresectable liver tumor patients who received MR-guided RT showed mild gastrointestinal symptoms of less than grade 3 (Feldman et al. 2019). MR-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 included a small number of patients and a short follow-up duration, the analysis of the effect and toxicity of RT was limited. Second, as this was a retrospective study, patients received various treatments, including TACE or surgery, which might have affected the treatment outcome. However, this study as the first to analyze tumor tracking MRI-guided RT for PVTT in unresectable HCC patients, suggested the efficacy, feasibility, and safety of MRI-guided HFRT and SBRT.

Conclusion

Tumor tracking MRI-guided HFRT and SBRT 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. In the future, the optimal target volume and fractionation of MRI-guided HFRT and SBRT for PVTT in these patients should be identified through further studies.

Declarations

Funding: Not applicable

Conflict of interest

No conflict of interest.

Availability of data and material

All data generated or analyzed during this study are included in this article.

Ethics 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.

References

- '2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma'. 2019. *Korean J Radiol*, 20: 1042-113.
- Bai, S., Y. Wu, Y. Yan, R. Li, H. Kang, J. Zhang, W. Ma, Y. Gao, B. Hui, H. Ma, X. Zhang, and J. Ren. 2021. 'Evaluation of the Efficacy and Toxicity of Radiotherapy for Type III-IV Portal Vein Tumor Thrombi', *Technol Cancer Res Treat*, 20: 1533033821995286.
- Boldrini, L., A. Romano, S. Mariani, D. Cusumano, F. Catucci, L. Placidi, G. C. Mattiucci, G. Chiloiro, F. Cellini, M. A. Gambacorta, L. Indovina, and V. Valentini. 2021a. 'MRI-guided stereotactic radiation therapy for hepatocellular carcinoma: a feasible and safe innovative treatment approach', *J Cancer Res Clin Oncol*.
- . 2021b. 'MRI-guided stereotactic radiation therapy for hepatocellular carcinoma: a feasible and safe innovative treatment approach', *J Cancer Res Clin Oncol*, 147: 2057-68.
- Bruix, J., and M. Sherman. 2011. 'Management of hepatocellular carcinoma: an update', *Hepatology*, 53: 1020-2.
- Bujold, A., C. A. Massey, J. J. Kim, J. Brierley, C. Cho, R. K. Wong, R. E. Dinniwell, Z. Kassam, J. Ringash, B. Cummings, J. Sykes, M. Sherman, J. J. Knox, and L. A. Dawson. 2013. 'Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma', *J Clin Oncol*, 31: 1631-9.
- Cabibbo, G., M. Enea, M. Attanasio, J. Bruix, A. Craxì, and C. Cammà. 2010. 'A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma', *Hepatology*, 51: 1274-83.
- Cerrito, L., B. E. Annicchiarico, R. Iezzi, A. Gasbarrini, M. Pompili, and F. R. Ponziani. 2019. 'Treatment of hepatocellular carcinoma in patients with portal vein tumor thrombosis: Beyond the known frontiers', *World J Gastroenterol*, 25: 4360-82.
- Chan, S. L., F. K. Mo, P. J. Johnson, G. S. Liem, T. C. Chan, M. C. Poon, B. B. Ma, T. W. Leung, P. B. Lai, A. T. Chan, T. S. Mok, and W. Yeo. 2011. 'Prospective validation of the Chinese University Prognostic Index and comparison with other staging systems for hepatocellular carcinoma in an Asian population', *J Gastroenterol Hepatol*, 26: 340-7.
- Chen, X. P., F. Z. Qiu, Z. D. Wu, Z. W. Zhang, Z. Y. Huang, Y. F. Chen, B. X. Zhang, S. Q. He, and W. G. Zhang. 2006. 'Effects of location and extension of portal vein tumor thrombus on long-term outcomes of surgical treatment for hepatocellular carcinoma', *Ann Surg Oncol*, 13: 940-6.
- Cheng, S., M. Chen, J. Cai, J. Sun, R. Guo, X. Bi, W. Y. Lau, and M. Wu. 2020. 'Chinese Expert Consensus on Multidisciplinary Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (2018 Edition)', *Liver Cancer*, 9: 28-40.

Cheng, S., J. Yang, F. Shen, W. Zhou, Y. Wang, W. Cong, G. S. Yang, H. Cheng, H. Hu, C. Gao, J. Guo, A. Li, Y. Meng, X. Jiang, Y. Yang, G. Qian, M. Luo, B. Hu, X. Man, B. Zhang, C. Su, F. Zhou, N. Li, J. Shi, M. Wang, Y. Zheng, W. Guo, J. Sun, H. Wang, W. Y. Lau, and M. C. Wu. 2016. 'Multidisciplinary management of hepatocellular carcinoma with portal vein tumor thrombus - Eastern Hepatobiliary Surgical Hospital consensus statement', *Oncotarget*, 7: 40816-29.

Feldman, A. M., A. Modh, C. Glide-Hurst, I. J. Chetty, and B. Movsas. 2019. 'Real-time Magnetic Resonance-guided Liver Stereotactic Body Radiation Therapy: An Institutional Report Using a Magnetic Resonance-Linac System', *Cureus*, 11: e5774.

Fuster, J., J. C. García-Valdecasas, L. Grande, J. Tabet, J. Bruix, T. Anglada, P. Taurá, A. M. Lacy, X. González, R. Vilana, C. Bru, M. Solé, and J. Visa. 1996. 'Hepatocellular carcinoma and cirrhosis. Results of surgical treatment in a European series', *Ann Surg*, 223: 297-302.

Han, K. H., J. Seong, J. K. Kim, S. H. Ahn, D. Y. Lee, and C. Y. Chon. 2008. 'Pilot clinical trial of localized concurrent chemoradiation therapy for locally advanced hepatocellular carcinoma with portal vein thrombosis', *Cancer*, 113: 995-1003.

Hasegawa, K., N. Kokudo, M. Makuuchi, N. Izumi, T. Ichida, M. Kudo, Y. Ku, M. Sakamoto, O. Nakashima, O. Matsui, and Y. Matsuyama. 2013. 'Comparison of resection and ablation for hepatocellular carcinoma: a cohort study based on a Japanese nationwide survey', *J Hepatol*, 58: 724-9.

Hong, T. S., J. Y. Wo, B. Y. Yeap, E. Ben-Josef, E. I. McDonnell, L. S. Blaszkowsky, E. L. Kwak, J. N. Allen, J. W. Clark, L. Goyal, J. E. Murphy, M. M. Javle, J. A. Wolfgang, L. C. Drapek, R. S. Arellano, H. J. Mamon, J. T. Mullen, S. S. Yoon, K. K. Tanabe, C. R. Ferrone, D. P. Ryan, T. F. DeLaney, C. H. Crane, and A. X. Zhu. 2016. 'Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma', *J Clin Oncol*, 34: 460-8.

Hou, J. Z., Z. C. Zeng, J. Y. Zhang, J. Fan, J. Zhou, and M. S. Zeng. 2012. 'Influence of tumor thrombus location on the outcome of external-beam radiation therapy in advanced hepatocellular carcinoma with macrovascular invasion', *Int J Radiat Oncol Biol Phys*, 84: 362-8.

Ikai, I., S. Aii, M. Okazaki, K. Okita, M. Omata, M. Kojiro, K. Takayasu, Y. Nakanuma, M. Makuuchi, Y. Matsuyama, M. Monden, and M. Kudo. 2007. 'Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan', *Hepatol Res*, 37: 676-91.

Ikai, I., E. Hatano, S. Hasegawa, H. Fujii, K. Taura, N. Uyama, and Y. Shimahara. 2006. 'Prognostic index for patients with hepatocellular carcinoma combined with tumor thrombosis in the major portal vein', *J Am Coll Surg*, 202: 431-8.

Ikai, I., Y. Yamamoto, N. Yamamoto, H. Terajima, E. Hatano, Y. Shimahara, and Y. Yamaoka. 2003. 'Results of hepatic resection for hepatocellular carcinoma invading major portal and/or hepatic veins', *Surg Oncol*

- Im, J. H., S. M. Yoon, H. C. Park, J. H. Kim, J. I. Yu, T. H. Kim, J. W. Kim, T. K. Nam, K. Kim, H. S. Jang, J. H. Kim, M. S. Kim, W. S. Yoon, I. Jung, and J. Seong. 2017. 'Radiotherapeutic strategies for hepatocellular carcinoma with portal vein tumour thrombosis in a hepatitis B endemic area', *Liver Int*, 37: 90-100.
- Iwamoto, H., M. Nomiyama, T. Niizeki, S. Shimose, T. Shirono, M. Nakano, M. Satani, S. Okamura, Y. Noda, N. Kamachi, M. Sakai, H. Suzuki, R. Kuromatsu, E. Ogo, T. Abe, M. Tanaka, H. Koga, and T. Torimura. 2019. 'Dose and Location of Irradiation Determine Survival for Patients with Hepatocellular Carcinoma with Macrovascular Invasion in External Beam Radiation Therapy', *Oncology*, 96: 192-99.
- Jang, J. W., S. H. Bae, J. Y. Choi, H. J. Oh, M. S. Kim, S. Y. Lee, C. W. Kim, U. I. Chang, S. W. Nam, S. B. Cha, Y. J. Lee, H. J. Chun, B. G. Choi, J. Y. Byun, and S. K. Yoon. 2007. 'A combination therapy with transarterial chemo-lipiodolization and systemic chemo-infusion for large extensive hepatocellular carcinoma invading portal vein in comparison with conservative management', *Cancer Chemother Pharmacol*, 59: 9-15.
- Kamiyama, Toshiya, Kazuaki Nakanishi, Hideki Yokoo, Munenori Tahara, Takahito Nakagawa, Hirofumi Kamachi, Hiroshi Taguchi, Hiroki Shirato, Michiaki Matsushita, and Satoru Todo. 2007. 'Efficacy of preoperative radiotherapy to portal vein tumor thrombus in the main trunk or first branch in patients with hepatocellular carcinoma', *International Journal of Clinical Oncology*, 12: 363-68.
- Katamura, Y., H. Aikata, S. Takaki, T. Azakami, T. Kawaoka, K. Waki, A. Hiramatsu, Y. Kawakami, S. Takahashi, M. Kenjo, N. Toyota, K. Ito, and K. Chayama. 2009. 'Intra-arterial 5-fluorouracil/interferon combination therapy for advanced hepatocellular carcinoma with or without three-dimensional conformal radiotherapy for portal vein tumor thrombosis', *J Gastroenterol*, 44: 492-502.
- Kim, D. Y., W. Park, D. H. Lim, J. H. Lee, B. C. Yoo, S. W. Paik, K. C. Kho, T. H. Kim, Y. C. Ahn, and S. J. Huh. 2005. 'Three-dimensional conformal radiotherapy for portal vein thrombosis of hepatocellular carcinoma', *Cancer*, 103: 2419-26.
- Kim, J. Y., E. J. Yoo, J. W. Jang, J. H. Kwon, K. J. Kim, and C. S. Kay. 2013a. 'Hypofractionated radiotherapy using helical tomotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis', *Radiat Oncol*, 8: 15.
- Kim, Ji-Yoon, Eun-Jung Yoo, Jeong-Won Jang, Jung-Hyun Kwon, Ki-Jun Kim, and Chul-Seung Kay. 2013b. 'Hypofractionated radiotherapy using helical tomotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis', *Radiation Oncology*, 8: 15.
- Koo, J. E., J. H. Kim, Y. S. Lim, S. J. Park, H. J. Won, K. B. Sung, and D. J. Suh. 2010. 'Combination of transarterial chemoembolization and three-dimensional conformal radiotherapy for hepatocellular carcinoma with inferior vena cava tumor thrombus', *Int J Radiat Oncol Biol Phys*, 78: 180-7.

Lee, Ju Hye, Dong Hyun Kim, Yong Kan Ki, Ji Ho Nam, Jeong Heo, Hyun Young Woo, Dong Won Kim, and Won Taek Kim. 2014. 'Three-dimensional conformal radiotherapy for portal vein tumor thrombosis alone in advanced hepatocellular carcinoma', *Radiation oncology journal*, 32: 170-78.

Li, Li-Qing, Ying Zhou, Yong Huang, Ping Liang, Shi-Xiong Liang, and Ting-Shi Su. 2021. 'Stereotactic body radiotherapy versus intensity-modulated radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis', *Hepatology International*.

Liu, L., C. Zhang, Y. Zhao, X. Qi, H. Chen, W. Bai, C. He, W. Guo, Z. Yin, D. Fan, and G. Han. 2014. 'Transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma with portal vein tumor thrombosis: prognostic factors in a single-center study of 188 patients', *Biomed Res Int*, 2014: 194278.

Llovet, J. M., J. Bustamante, A. Castells, R. Vilana, C. Ayuso Mdel, M. Sala, C. Brú, J. Rodés, and J. Bruix. 1999. 'Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials', *Hepatology*, 29: 62-7.

Luo, J., R. P. Guo, E. C. Lai, Y. J. Zhang, W. Y. Lau, M. S. Chen, and M. Shi. 2011. 'Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study', *Ann Surg Oncol*, 18: 413-20.

Menten, M. J., M. F. Fast, S. Nill, C. P. Kamerling, F. McDonald, and U. Oelfke. 2016. 'Lung stereotactic body radiotherapy with an MR-linac - Quantifying the impact of the magnetic field and real-time tumor tracking', *Radiother Oncol*, 119: 461-6.

Minagawa, M., and M. Makuuchi. 2006. 'Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus', *World J Gastroenterol*, 12: 7561-7.

Rodríguez-Perálvarez, M., T. V. Luong, L. Andreana, T. Meyer, A. P. Dhillon, and A. K. Burroughs. 2013. 'A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability', *Ann Surg Oncol*, 20: 325-39.

Shi, J., E. C. Lai, N. Li, W. X. Guo, J. Xue, W. Y. Lau, M. C. Wu, and S. Q. Cheng. 2010. 'Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus', *Ann Surg Oncol*, 17: 2073-80.

Shui, Yongjie, Wei Yu, Xiaoqiu Ren, Yinglu Guo, Jing Xu, Tao Ma, Bicheng Zhang, Jianjun Wu, Qinghai Li, Qiongge Hu, Li Shen, Xueli Bai, Tingbo Liang, and Qichun Wei. 2018. 'Stereotactic body radiotherapy based treatment for hepatocellular carcinoma with extensive portal vein tumor thrombosis', *Radiation Oncology*, 13: 188.

Stuart, K. E., A. J. Anand, and R. L. Jenkins. 1996. 'Hepatocellular carcinoma in the United States. Prognostic features, treatment outcome, and survival', *Cancer*, 77: 2217-22.

- Sugahara, S., H. Nakayama, K. Fukuda, M. Mizumoto, M. Tokita, M. Abei, J. Shoda, Y. Matsuzaki, E. Thono, K. Tsuboi, and K. Tokuuye. 2009. 'Proton-beam therapy for hepatocellular carcinoma associated with portal vein tumor thrombosis', *Strahlenther Onkol*, 185: 782-8.
- Sun, J. X., J. Shi, N. Li, W. X. Guo, M. C. Wu, W. Y. Lau, and S. Q. Cheng. 2016. 'Portal vein tumor thrombus is a bottleneck in the treatment of hepatocellular carcinoma', *Cancer Biol Med*, 13: 452-58.
- Tang, Q. H., A. J. Li, G. M. Yang, E. C. Lai, W. P. Zhou, Z. H. Jiang, W. Y. Lau, and M. C. Wu. 2013. 'Surgical resection versus conformal radiotherapy combined with TACE for resectable hepatocellular carcinoma with portal vein tumor thrombus: a comparative study', *World J Surg*, 37: 1362-70.
- Toya, Ryo, Ryuji Murakami, Yuji Baba, Ryuichi Nishimura, Shoji Morishita, Osamu Ikeda, Koichi Kawanaka, Toru Beppu, Shinichi Sugiyama, Takashi Sakamoto, Yasuyuki Yamashita, and Natsuo Oya. 2007. 'Conformal radiation therapy for portal vein tumor thrombosis of hepatocellular carcinoma', *Radiotherapy and Oncology*, 84: 266-71.
- Wang, Wentao, Yaxun Guo, Jingtao Zhong, Qi Wang, Xin Wang, Honglong Wei, Jie Li, and Peng Xiu. 2021. 'The clinical significance of microvascular invasion in the surgical planning and postoperative sequential treatment in hepatocellular carcinoma', *Scientific Reports*, 11: 2415.
- Wu, C. C., S. R. Hsieh, J. T. Chen, W. L. Ho, M. C. Lin, D. C. Yeh, T. J. Liu, and K. P'Eng F. 2000. 'An appraisal of liver and portal vein resection for hepatocellular carcinoma with tumor thrombi extending to portal bifurcation', *Arch Surg*, 135: 1273-9.
- Xi, M., L. Zhang, L. Zhao, Q. Q. Li, S. P. Guo, Z. Z. Feng, X. W. Deng, X. Y. Huang, and M. Z. Liu. 2013. 'Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis', *PLoS One*, 8: e63864.
- Yamada, K., K. Izaki, K. Sugimoto, H. Mayahara, Y. Morita, E. Yoden, S. Matsumoto, T. Soejima, and K. Sugimura. 2003. 'Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma', *Int J Radiat Oncol Biol Phys*, 57: 113-9.
- Yoon, S. M., Y. S. Lim, H. J. Won, J. H. Kim, K. M. Kim, H. C. Lee, Y. H. Chung, Y. S. Lee, S. G. Lee, J. H. Park, and D. J. Suh. 2012. 'Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: long-term patient outcomes', *Int J Radiat Oncol Biol Phys*, 82: 2004-11.
- Yoon, S. M., B. Y. Ryoo, S. J. Lee, J. H. Kim, J. H. Shin, J. H. An, H. C. Lee, and Y. S. Lim. 2018. 'Efficacy and Safety of Transarterial Chemoembolization Plus External Beam Radiotherapy vs Sorafenib in Hepatocellular Carcinoma With Macroscopic Vascular Invasion: A Randomized Clinical Trial', *JAMA Oncol*, 4: 661-69.

Zhao, Q., K. Zhu, J. Yue, Z. Qi, S. Jiang, X. Xu, R. Feng, and R. Wang. 2017. 'Comparison of intra-arterial chemoembolization with and without radiotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: a meta-analysis', *Ther Clin Risk Manag*, 13: 21-31.

Tables

Table 1. Patient's characteristics

Factor		No. (%), total, 12
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)
ECOG_PS	0-1	9 (75)
	2	3 (25)
C-P classification	A	11 (91.7)
	B	1 (8.3)
Mass size	< 5cm	3 (25)
	5cm-10cm	4 (33.3)
	> 10cm	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; ECOG_PS, Eastern Cooperative Oncology Group performance status; C-P classification, Child-Pugh classification; PVT, portal vein tumor thrombus; LN, lymph node

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	
TACE	8 (66.7)
RFA	1 (8.3)
Sorafenib	2 (16.7)
Lenvatinib	2 (16.7)
Atezolizumab + bevacizumab	1 (8.3)
Radiotherapy	
GTV (cc)	Median, 30.8 cc (range, 13.5-903.7 cc)
PTV (cc)	Median, 78.4 cc (range, 44.4-1540.4 cc)
Liver (cc)	Median, 1830.7 cc (range, 946.7-3193 cc)
Normal liver (whole liver-GTV, cc)	Median, 1286.8 cc (range, 800.1-2017.7 cc)
Prescribed dose	
HFRT	50 Gy/10 fxs
SBRT	36-50 Gy/4-5 fxs
BED ₁₀	Median, 75 Gy ₁₀ (range, 68.4-100Gy ₁₀)
Liver Dmean	Median, 13.43 Gy (range, 5.83-21.94)
Liver V15 (cc)	Median, 476.1 cc (range, 67.5-1005.1cc)
Liver V21 (cc)	276.9 cc(range, 32.8-686.4cc)

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;

*Liver Dmean; mean irradiation dose of liver

*Liver V15 (cc); liver volume that was irradiated more than 15 Gy

*Liver V21 (cc): liver volume that was irradiated more than 15 Gy

Table 3. Previous studies of radiotherapy for PVTT in HCC patients.

Study	No.	PVTT extent	Combine Tx.	RT target	RT dose	Response	Median survival & OS
(Yamada et al.,2003)	19	First branch	TACE	PVTT	60 Gy/30 fxs	CR, 0 PR, 57.9%	7mo, 1-yr, 40.6%
(Kim et al.,2005)	59	Main trunk or first branch	-	PVTT +HCC mass	30-54 Gy/2-3 Gy fx size	CR, 6.8% PR, 39%	Responders- 10.7 mo, 1-yr, 40.7%
(Han et al., 2008)	40	Main trunk or first branch	CCRT followed by HAIC	PVTT	45 Gy/25 fxs	CR, 0% PR, 45%	13.1 mo, 1-yr, 57.6%
(Yoon et al., 2010)	412	PVTT or IVCTT	TACE	PVTT ± HCC mass	Median, 40 Gy (21-60 Gy)/2-5 fx size	CR, 6.6% PR, 33.0%	10.6 mo, 1-yr, 42.5%
(Bai et al. 2021)	14	Main trunk or extension to SMV	-	PVTT	50 Gy/25 fxs	Downstage to type II, 92.9%	NA
This study, 2021	12	Main trunk or first branch	-	PVTT ± HCC mass	50 Gy/10 fxs, 36-50 Gy/4-5 fxs	CR, 0% PR, 83.3%	11.6 mo 1-yr, 28.1%

No., number; Tx., therapy; RT, radiotherapy; OS, overall survival; PVTT, portal vein tumor thrombus; TACE, trans-arterial chemoembolization; mo, months; fxs, fractions; CR, complete response; PR, partial response; HCC, hepatocellular carcinoma; CCRT, concurrent chemoradiotherapy; IVCTT, inferior vena cava tumor thrombus; SMV, superior mesenteric vein

Figures

Figure 1

Example of plan of stereotactic body radiation therapy for portal vein tumor thrombi. The patient received stereotactic body radiation therapy of 50 Gy in 5 fractions for portal vein tumor thrombus. 95% of the prescription dose was planned to cover more than 95% of the PTV volume. The volume of normal liver that irradiated less than 15 Gy was more than 700cc. *Orange line-95% isodose line (47.5 Gy), yellow line-90% isodose line (45 Gy), green line-80% isodose line (40 Gy), cyan line-42% isodose line (21 Gy), blue line-30% isodose line (15 Gy)

Figure 2

MRI-guided tumor tracking and gating radiotherapy through CINE MRI During radiotherapy, the beam was automatically turned off if the target was out of the boundary by more than a threshold of 3%