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Original Article

Efficacy and Safety of Three-dimensional Conformal Radiotherapy for Macroscopic Vascular Invasion of Hepatocellular Carcinoma

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Chemotherapy is insufficient to treat macroscopic vascular invasion (MVI) of hepatocellular carcinoma (HCC). We retrospectively investigated the treatment outcomes of patients who underwent three-dimensional conformal radiotherapy (3D-CRT) for HCC MVI and analyzed prognostic factors by multivariate analysis using a Cox proportional hazard model. Sixty-five patients were studied. MVI sites were the portal vein (n = 48 patients), portal and hepatic veins (n = 8), and hepatic vein (n = 9). The median irradiation dose was 50 Gy. The median survival time (MST) was 7.5 months. Performance status 2 or 3, modified albumin-bilirubin grade 2b or 3, and massive/diffuse type were poor prognostic factors. Nineteen patients (29%) with a treatment effect of 3 or 4 (≥ 50% of tumor necrosis or regression) at the irradiation sites according to the Response Evaluation Criteria in Cancer of the Liver showed longer survival than those with an effect of 1 or 2 (MST 18.7 vs. 5.9 months, $p < 0.001$). No treatment-related death occurred. The hepatic function reserve was preserved in more than 70% of patients. 3D-CRT controlled HCC MVI safely and was suggested to be a good treatment option.

Key words: hepatocellular carcinoma, macroscopic vascular invasion, portal vein tumor thrombosis, hepatic vein tumor thrombosis, three-dimensional conformal radiotherapy

Macroscopic tumor invasion into the major portal and hepatic veins often develops in advanced hepatocellular carcinoma (HCC) causing various symptoms such as edema, ascites, jaundice due to decreased hepatic blood flow in the portal vein, and congestion due to hepatic vein occlusion. In this urgent condition, local treatments such as surgery, radiofrequency ablation (RFA), and transcatheter arterial chemoembolization (TACE) are often difficult to perform.

Since the advent of sorafenib, systemic drug therapies, such as multi-kinase inhibitors (regorafenib, lenvatinib, and cabozantinib), anti-VEGF/VEGFR antibodies (bevacizumab, ramucirumab), and immune checkpoint inhibitors (ICIs) have been the standard treatment for HCC patients with macroscopic vascular invasion (MVI). In the subgroup analyses of the SHARP study [1], the median survival time (MST) of MVI-positive HCC was 8.1 months in the sorafenib group (n = 108) and 4.9 months in the placebo group (n = 123). The hazard ratio (HR) was 0.68 (95% confidence interval [CI]: 0.49-0.93). In the subgroup analyses of the IMbrave150 study [2], the MST of MVI-positive HCC was 12.9 months in the atezolizumab

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(anti-PD-L1 antibody) plus bevacizumab (anti-VEGF antibody) group (n = 129) and 9.1 months in the sorafenib group (n = 71). The hazard ratio was 0.58 (95%CI: 0.38-0.89). However, the effectiveness is not sufficient, and there are many patients for whom these molecular-targeted drugs are not indicated due to poor general condition, decreased hepatic function, and complications.

The Japanese Clinical Practice Guidelines for Hepatocellular Carcinoma 2017 <https://www.jsh.or.jp/English/examination_en/guidelines_hepatocellular_carcinoma_2017.html> (accessed June 14, 2022) state that three-dimensional conformal radiotherapy (3D-CRT) is "weakly recommended" for HCC in cases in which standard treatments are not indicated for portal vein tumor thrombosis (PVTT) and in which stereotactic radiation therapy (SRT) or particle-beam radiation therapy is difficult to apply. The American Association for the Study of Liver Diseases (AASLD) practice guidance [3] does not mention radiation therapy (RT). The European Association for the Study of the Liver (EASL) guidelines [4] state the following: "External beam radiotherapy is under investigation. So far, there is no robust evidence to support this therapeutic approach in the management of HCC (evidence low; recommendation weak)."

However, many reports have shown the effectiveness of radiation therapy for HCC with vascular invasion, including 3D-CRT [5-13]. Here, we aimed to analyze our single institute data on the efficacy and safety of 3D-CRT for MVI-HCC and assessed its feasibility and applicability as a treatment option in clinical practice.

Materials and Methods

Patients. This retrospective study was approved by the Institutional Review Board of Shikoku Cancer Center (approval number 2018-61) and conducted in accordance with the Declaration of Helsinki. For informed consent, we provided information about the study on the center's website and offered patients and their families a convenient opt-out mechanism.

Medical records were surveyed regarding the patient's background, details of 3D-CRT, and patient outcomes. Sixty-five patients with unresectable HCC MVI who underwent 3D-CRT from January 2008 to March 2019 were included. The observation period was set until July 2021. All patients provided informed consent for 3D-CRT prior to treatment. MVI into the portal vein, hepatic vein, inferior vena cava, or right atrium was confirmed by contrast-enhanced CT or MRI. The gross tumor types (nodular, massive, or diffuse) per Eggel's classification were also estimated from the contrast-enhanced CT or MRI.

The therapeutic effect on the irradiated lesion was determined by CT or MRI in accordance with the Response Evaluation Criteria in Cancer of the Liver (RECICL) (2019 Revised version) [14]. In this study, only the local therapeutic effect was evaluated, and the extra-irradiation lesions were omitted. Treatment effect (TE) categories of 3 (≥ 50% tumor necrosis or reduction in tumor size) and 4 (100% tumor necrosis or reduction in tumor size) were considered to represent a treatment response, and effect predictors were analyzed by comparing cases with TE3/TE4 and TE1 (tumor enlargement of ≥ 50%)/TE2 (effect other than TE4, TE3 or TE1).

We investigated patients' performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) before and after treatment. The effect on hepatic reserve was examined by comparing the Child-Pugh class, albumin-bilirubin (ALBI) grade, and modified ALBI (mALBI) grade [15] before and immediately after treatment.

Adverse events (AEs) during radiation therapy were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0-JCOG.

The criteria for 3D-CRT in HCC MVI were ineligibility for surgery, RFA, or TACE, and PS 0-2 and Child-Pugh A or B classifications. Those with Child-Pugh C and expected prognosis of less than 1 month were excluded. Although only 2 cases with Child-Pugh C were included after obtaining of the informed consent, because 3D-CRT was considered to have some merits for them.

Radiotherapy. The primary target of 3D-CRT was the major MVI. Radiation fields included the MVI and the causative tumor. To prevent severe liver dysfunction, the radiation fields had to be limited and thus could not cover all the HCC tumors in most patients with multiple and widespread HCC. Thus, in this study, patients' gross tumor volume (GTV) was not equivalent to the treated target volume. The treated targets were determined by the radiation oncologist, considering the risks and benefits of each patient.

Treatments were planned using plain CT images with 2-mm slices. CT scan data were transferred to the treatment planning system (Eclipse; Varian Medical Systems, Palo Alto, CA, USA). The treated targets were delineated on CT images in the treatment planning system. In principle, planning target volumes were made by adding margins of 5-10 mm to the treated targets. No measures were taken against respiratory motion.

Beam angles were designed to minimize the volume of irradiated critical organs, including the liver, kidneys, gastrointestinal tract, and spinal cord. In principle, mean doses to the liver and kidneys were constrained to < 30 Gy and < 15 Gy, respectively, and maximum doses to the gastrointestinal tract and spinal cord were constrained to < 55 Gy and < 45 Gy, respectively. For dose calculation, a calculation algorithm with corrections for tissue heterogeneity was used (before September 2015, Pencil Beam Convolution [Batho Power Law]; thereafter, an analytical anisotropic algorithm). Lineac 10-MV X-rays (Clinac 21EX linear accelerator; Varian Medical Systems) were used for radiotherapy. We did not use image-guided radiotherapy (gold markers or respiratory control).

In principle, irradiation dose was 50 Gy with a daily fraction size of 2 Gy. Irradiation was performed once a day except for Saturday, Sunday, and holidays. The irradiation doses were determined at the discretion of radiation oncologists, considering the hepatic reserve, general condition, and prognosis. For patients with poor hepatic reserve and/or short expected prognosis, 30 Gy with a daily fraction size of 3 Gy was delivered. One patient with good hepatic reserve was irradiated with 60 Gy.

Because the 3D-CRT target was typically located at the hepatic hilum, dietary restrictions were not applied.

Follow up. The anti-tumor effect was judged by CT or MRI at 1, 3, and 6 months after the conclusion of 3D-CRT. The follow-up and survival periods were calculated from the initiation of radiation therapy.

Statistical analysis. Univariate and multivariate analyses were performed using a Cox proportional hazards model for survival time and a logistic model for response. In the multivariate analysis, the models were constructed using stepwise variable selection. A significance level of 0.1 was required to allow a variable into the model, and a significance level of 0.08 was required for a variable to stay in the model. The Kaplan-Meier method was used to estimate the survival curve, and a significant difference test was performed using the log-rank test. Statistical significance was set at $p < 0.05$. SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used for the analysis.

Results

Baseline patient characteristics. The background characteristics of included patients are presented in Table 1. The median age was 72 years. Thirteen patients (20%) had poor PS scores of 2 or 3; 22 (34%) were Child-Pugh class B or C; 53 (82%) had ALBI grades of 2 or 3, and 38 (58%) had mALBI grades of 2b or 3. Five patients (8%) had a single lesion. There were 18 patients (28%) with nodular type, 25 (38%) with massive type, and 22 (34%) with diffuse type. The vascular invasion sites included 48 portal veins (74%), 8 portal and hepatic veins (12%), and 9 hepatic veins (14%). Twenty-one patients (32%) had extrahepatic lesions. Five patients (8%) were treated with sorafenib before 3D-CRT.

3D-CRT. In all patients, 3D-CRT was planned so as to include the MVI in the irradiation fields. No other treatments were added during the 3D-CRT period. Fifty-two patients (80%) had additional lesions outside of an irradiation field. The median treated target volume was 69.8 cm^3 (range, 7.7-933.8). The median irradiation dose was 50 Gy (range, 26-60). The median mean liver dose was 14.8 Gy (range, 4.8-32.5). Table 2 shows the details of the irradiation dose, the number of cases, and the equivalent dose in 2-Gy fractions (EQD2).

Sixty-one patients (94%) completed the initially planned dose. Irradiation was discontinued in 4 patients. Details are shown in Table 3. The reasons for discontinuing (*i.e.*, not completing the planned irradiation dose) were as follows: worsened ascites (40 Gy) (n = 1 patient), exacerbation of extra-irradiation lesions (40 Gy) (n = 1), ECOG PS deterioration (26 Gy) (n = 1), and emphysema exacerbation (40 Gy) (n = 1).

Survival. All patients died from HCC (n = 63) or esophageal cancer (n = 2). The MST from the start of 3D-CRT was 7.5 months (95%CI: 5.2-12.6). The 1-year survival rate was 38.5% (95%CI: 26.8-50.0). Thirteen patients had good liver function and general condition before 3D-CRT and subsequently received standard sorafenib or lenvatinib treatment. In these patients, the

Table 1 Baseline patient background (n = 65)

Characteristics	Units/Classifications	
Age (years)	Median (range)	72 (41–88)
Sex	Male/Female	48/17
ECOG PS	0/1/2/3	8/44/11/2
Child-Pugh class	A/B/C	43/20/2
ALBI grade	1/2/3	12/47/6
mALBI grade	1/2a/2b/3	12/15/32/6
Etiology of liver disease	HCV/HBV/other	38/11/16
Tumor number	Single/multiple	5/60
Main tumor size (cm)	Median (range)	7.7 (3.1–20.0)
Tumor type	Nodular/massive/diffuse	18/25/22
Macroscopic vascular invasion	Portal vein	48
	Portal vein + Hepatic vein	8
	Hepatic vein	9
Vp	0/1/2/3/4	9/2/13/22/19
Vv	0/1/2/3	48/1/3/13
Extra-hepatic lesion	+/−	21/44
Extra-irradiation lesion of the liver	+/−	52/13
Treated target volume (cm^3)	Median (range)	69.8 (7.7–933.8)
Ascites	+/−	20/45
Platelet ($\times 10^4/\mu l$)	Median (range)	11.1 (4.3–29.8)
NLR	Median (range)	2.91 (0.38–9.92)
Albumin (g/dl)	Median (range)	3.5 (2.1–4.4)
Total bilirubin (mg/dl)	Median (range)	0.87 (0.32–3.65)
Prothrombin time (%)	Median (range)	77 (44–107)
AFP (ng/ml)	Median (range)	594 (4–1,029,000)
DCP (mAU/ml)	Median (range)	7030 (22–200719)

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; DCP, des-gamma-carboxyprothrombin; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; mALBI, modified albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio.

Table 2 Irradiation dose and equivalent dose in 2-Gy fractions

Total dose/fraction (Fr)	n	EQD2
60 Gy/30 Fr	1	60 Gy
50.4 Gy/28 Fr	2	49.9 Gy
50 Gy/25 Fr	43	50 Gy
48.4 Gy/23 Fr(23.4 Gy/13 Fr + 25 Gy/10 Fr)	1	49 Gy
45 Gy/25 Fr	4	44.2 Gy
40 Gy/16 Fr	3	41.6 Gy
40 Gy/20 Fr	5	40 Gy
30 Gy/10 Fr	5	30 Gy
26 Gy/13 Fr	1	26 Gy

EQD2, equivalent dose in 2-Gy fractions.

MST was 13.6 months (95%CI: 8.0-15.7) whereas in those who could not receive such standard chemotherapy after 3D-CRT the MST was 6.0 months (95%CI: 4.6-10.2) ($p = 0.41$).

Prognostic factors. In the multivariate analysis, PS 2 or 3 (HR: 2.18, 95%CI: 1.15-4.14, $p = 0.016$), mALBI 2b or 3 (HR: 2.32, 95%CI: 1.36-3.96, $p = 0.002$), and massive or diffuse type tumor (HR: 2.76, 95%CI: 1.51-5.04, $p = 0.002$) were independent poor prognostic factors (Table 4). The survival curves according to the number of poor prognostic factors are shown in Fig. 1. Statistically, there was a difference between the four groups (log-rank test, $p < 0.0001$), and those with greater numbers of poor prognostic factors showed worse prognoses, as expected.

Tumor response to 3D-CRT. A TE evaluation with the RECICL was possible in 52 patients (80%), and 19 patients (29%) showed a TE3 or TE4 response (Table 5). The response rates of 49 patients with PVTT, 6 patients with PVTT + hepatic vein tumor thrombosis (HVTT), and 10 patients with HVTT were 29% (n = 14), 33% (n = 2), and 30% (n = 3), respectively. The MST was 18.7 months (95%CI: 14.1-27.0) in the TE3/TE4 patients, which was better than 5.9 months (95%CI: 4.5-8.0) in the TE1/TE2 patients (HR: 3.83, 95%CI: 1.97-7.44, $p < 0.001$) or 2.9 months (95%CI: 2.0-6.0) in the no-evaluation (NE) patients (HR: 6.75, 95%CI: 3.01-

Table 3 Summary of patients who discontinued 3D-CRT

Case no.	Child-Pugh class, score	Ascites	ECOG PS	MVI	Irradiation dose (Gy)	Mean liver dose (Gy)	Reasons for discontinuation
1	B, 7	moderate	1	Vp4	40	12.5	worsened ascites
2	B, 8	massive	1	Vp2	40	10.4	exacerbation of extra-irradiation lesions
3	B, 9	mild	2	Vp3+Vv2	26	8.6	ECOG PS deterioration
4	A, 5	non	2	Vv2	40	19.3	emphysema exacerbation

ECOG PS, Eastern Cooperative Oncology Group performance status; MVI, macroscopic vascular invasion.

Table 4 Univariate and multivariate regression analyses of patient characteristics for overall survival using a Cox proportional hazard model (n=65)

Factor	Univariate analysis		Multivariate analysis		
	Hazard ratio	*P*-value	Hazard ratio	95% CI	*P*-value
Age (≥71 years-old)	0.81	0.41			
Sex (male)	1.19	0.55			
ECOG PS (2, 3)	1.84	0.055	2.18	1.15–4.14	0.016
Child-Pugh Class (B, C)	1.88	0.018			
ALBI grade (2, 3)	1.32	0.39			
mALBI grade (2b, 3)	1.91	0.012	2.32	1.36–3.96	0.002
Etiology of liver disease (HCV)	1.11	0.69			
Tumor size (≥7 cm)	1.60	0.082			
Tumor type (massive/diffuse)	2.11	0.009	2.76	1.51–5.04	0.002
Irradiation site (PVTT)	1.40	0.33			
Extra-hepatic lesion (+)	1.28	0.36			
Extra-irradiation lesion in the liver (+)	1.69	0.11			
Treated target volume (≥70 cm^3)	0.87	0.59			
Ascites (+)	1.45	0.19			
Platelet (<$10\times10^4/\mu l$)	0.82	0.46			
NLR (≥3)	1.35	0.23			
AFP (≥600 ng/ml)	1.66	0.046			
DCP (≥5000 mAU/ml)	1.48	0.12			

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; DCP, des-gamma-carboxyprothrombin; ECOG PS, Eastern Cooperative Oncology Group performance status; HCV, hepatitis C virus; mALBI, modified albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio; PVTT, portal vein tumor thrombosis.

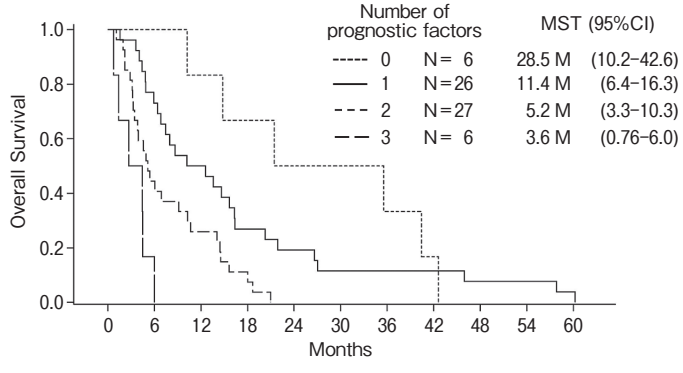

Fig. 1 Overall survival of patients by number of prognostic factors. Log-rank test $p<0.0001$.

15.17, $p<0.001$) (Fig. 2). In the univariate analysis excluding 13 patients with NE, a serum des-gamma-carboxyl prothrombin (DCP) level less than 5000 mAU/ml was the only effect predictor for TE3/TE4 (Table 6).

Safety. No treatment-related deaths occurred. The AEs causing 3D-CRT discontinuation (1 case each of worsened ascites, exacerbation of extra-irradiation lesions, PS deterioration, and emphysema exacerbation) seemed to be due to disease progression or exacerbation of comorbid diseases.

Grade 3 laboratory abnormalities were seen in 13 patients during the radiotherapy period: 6 with increased AST or ALT, 5 with thrombocytopenia, and 4 with leukopenia (with duplication). However, most of these events were due to primary disease. None of the patients discontinued treatment because of adverse events.

There were 8 cases of gastrointestinal bleeding after the end of 3D-CRT. There were no cases of bleeding during treatment. The reasons for bleeding were rupture of esophageal varices in 5 cases, portal hypertensive gastritis (PHG) in 2 cases, and unknown in 1 case. The median period from the end of 3D-CRT to bleeding was 75 days (9-379 days). The patient who suffered esophageal varices rupture on the 9th day after 3D-CRT had a Child-Pugh score of 9 and Vp4 before treatment, and the esophagus had not been irradiated. Of the 8 cases, the gastrointestinal tract was included within the irradiation field in only 1 case with PHG.

ECOG PS and hepatic reserve changes immediately after treatment are summarized in Table 7. Child-Pugh class and ALBI grade were unchanged in more than 80% of the patients. The mALBI grade was unchanged in 72% of the patients.

Post-3D-CRT treatment. Thirty-four (52%) patients received additional treatment after 3D-CRT: hepatic arterial infusion chemotherapy in 21 patients, sorafenib in 12 patients, TACE in 6 patients, lenvatinib in 2 patients, RFA in 2 patients, regorafenib in 1 patient, and ramucirumab in 1 patient. The median time from the end of 3D-CRT to the start of molecular-targeted drugs was 72 days (9-1276 days). There were two cases of gastrointestinal bleeding after the start of sorafenib. Both were ruptures of esophageal varices, but the esophagus was outside the irradiation area. The durations from the start of 3D-CRT to bleeding were 413 and 116 days, and those from the start of sorafenib to bleeding were 14 and 52 days. No gastrointestinal

Table 5 Radiological response of 3D-CRT according to Response Evaluation Criteria in Cancer of the Liver (2019 Revised version)

Treatment effect (TE)	Number of patients
TE4a	0
TE4b	1
TE3	18
TE2	30
TE1	3
no evaluation	13

TE4: Tumor necrosis of 100% or 100% reduction in tumor size
TE4a: necrotized area larger than the original tumor
TE4b: necrotized area similar in size to the original tumor
TE3: Tumor necrosis of 50–100% or 50–100% reduction in tumor size
TE2: Effect other than TE3 or TE1
TE1: Tumor enlargement ≥50% (excluding the area of necrosis after treatment)

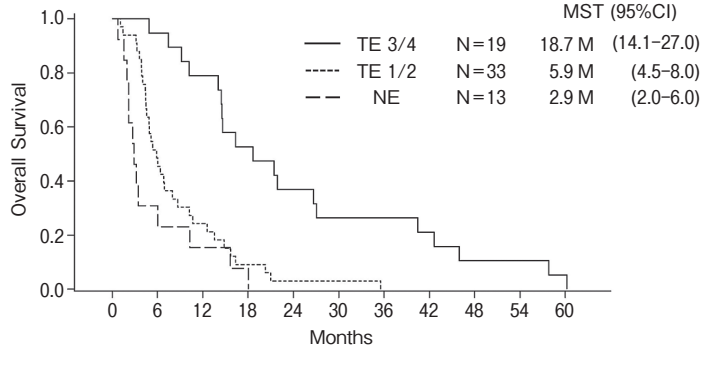

Fig. 2 Overall survival of patients with a treatment effect (TE) of 3/4, TE 1/2, or no evaluation (NE) of Response Evaluation Criteria in Cancer of the Liver (2019 Revised version). Statistically significant differences in survival were observed between the groups with TE 1/2 vs TE 3/4 (hazard ratio: 3.83; 95% confidence interval: 1.97–7.44; $p<0.001$), and between those with NE vs TE 3/4 (hazard ratio: 6.75; 95% confidence interval: 3.01–15.17; $p<0.001$).

Table 6 Logistic analyses of patient background factors for treatment effect (TE) 3/4

Factor	TE3/4 (n=19)	TE1/2 (n=33)	Univariate analysis		
	n	n	Odds ratio	95% CI	*P*-value
Age (≥71 years-old)	10	16	0.85	0.27− 2.62	0.77
Sex (male)	14	26	1.33	0.36− 4.96	0.67
ECOG PS (2, 3)	2	7	2.29	0.42−12.36	0.34
Child-Pugh Class (B, C)	3	10	2.32	0.55− 9.78	0.25
ALBI grade (2, 3)	15	26	0.99	0.25− 3.95	0.99
mALBI grade (2b, 3)	7	19	2.33	0.73− 7.42	0.15
Etiology of liver disease (HCV)	11	17	0.77	0.25− 2.41	0.66
Tumor size (≥7 cm)	10	23	2.07	0.64− 6.65	0.22
Tumor type (massive/diffuse)	12	24	1.56	0.47− 5.20	0.47
Irradiation site (PVTT)	16	27	0.84	0.19− 3.85	0.83
Extra-hepatic lesion (+)	5	13	1.82	0.53− 6.27	0.34
Extra-irradiation lesion in the liver (+)	14	27	1.61	0.42− 6.21	0.49
Treated target volume (≥70 cm^3)	8	13	1.32	0.36− 3.53	0.85
Ascites (+)	4	7	1.01	0.25− 4.03	0.99
Platelet (<$10 \times 10^4/\mu l$)	10	11	0.45	0.14− 1.43	0.18
NLR (≥3)	7	16	1.61	0.51− 5.12	0.42
AFP (≥600 ng/ml)	9	14	0.82	0.26− 2.55	0.73
DCP (≥5000 mAU/ml)	7	22	3.43	1.05−11.16	0.04
EQD2 (<45 Gy)	3	7	1.44	0.32− 6.37	0.63

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; DCP, des-gamma-carboxyprothrombin; ECOG PS, Eastern Cooperative Oncology Group performance status; EQD2, equivalent dose in 2-Gy fractions; HCV, hepatitis C virus; mALBI, modified albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio; PVTT, portal vein tumor thrombosis.

Table 7 Change of ECOG PS, Child-Pugh class, ALBI grade, and mALBI grade after 3D-CRT (n=65)

	Improvement	No change	Worsened
ECOG PS	4 (6%)	57 (88%)	4 (6%)
Child-Pugh class	2 (3%)	53 (82%)	10 (15%)
ALBI grade	2 (3%)	56 (86%)	7 (11%)
mALBI grade	3 (4%)	44 (68%)	18 (28%)

ALBI, albumin-bilirubin; ECOG PS, Eastern Cooperative Oncology Group performance status; mALBI, modified albumin-bilirubin.

perforation occurred during treatment with molecular-targeted drugs.

Good-response case. The case of a 60-year-old male with a good response is presented in Fig. 3. Pretreatment CT (Fig. 3A) showed portal vein infiltration of Vp2 (extension to the second-order branch) in the lateral hepatic segment. Multiple intrahepatic lesions and lymph node metastases were also observed. One month after starting treatment with sorafenib 800 mg, CT (Fig. 3B) showed that the portal vein infiltration had progressed to the left portal vein bifurcation and had become status Vp3 (extension to the first-order branch). Consecutive lateral hepatic tumors also markedly increased, and sorafenib was considered ineffective. At that time, regorafenib and lenvatinib were not approved for health insurance in Japan. After obtaining informed consent from the patient, 3D-CRT of 50 Gy was performed mainly in the advanced portal vein invasion area. The irradiation dose diagram is shown in Fig. 3C. Four months later (Fig. 3D), the portal vein tumor invasion had improved to status Vp2, and the main tumor had shrunk by 50% or more. This patient survived for 14.7 months from the start of 3D-CRT.

Discussion

This study revealed that the MST was 7.5 months in patients who received 3D-CRT against MVI-positive advanced HCC and that 3D-CRT yielded 50% or more tumor necrosis or regression (TE3/4) in approximately 30% of irradiated tumors. In the assessments of liver function after 3D-CRT, a status decrease was observed in 11-28% of patients with various assessment tools while status was preserved in 72-89% of the patients. In addition, we found that serum DCP level was a candidate for an effect predictor of 3D-CRT. Moreover, PS, mALBI, and tumor type were significant prognostic

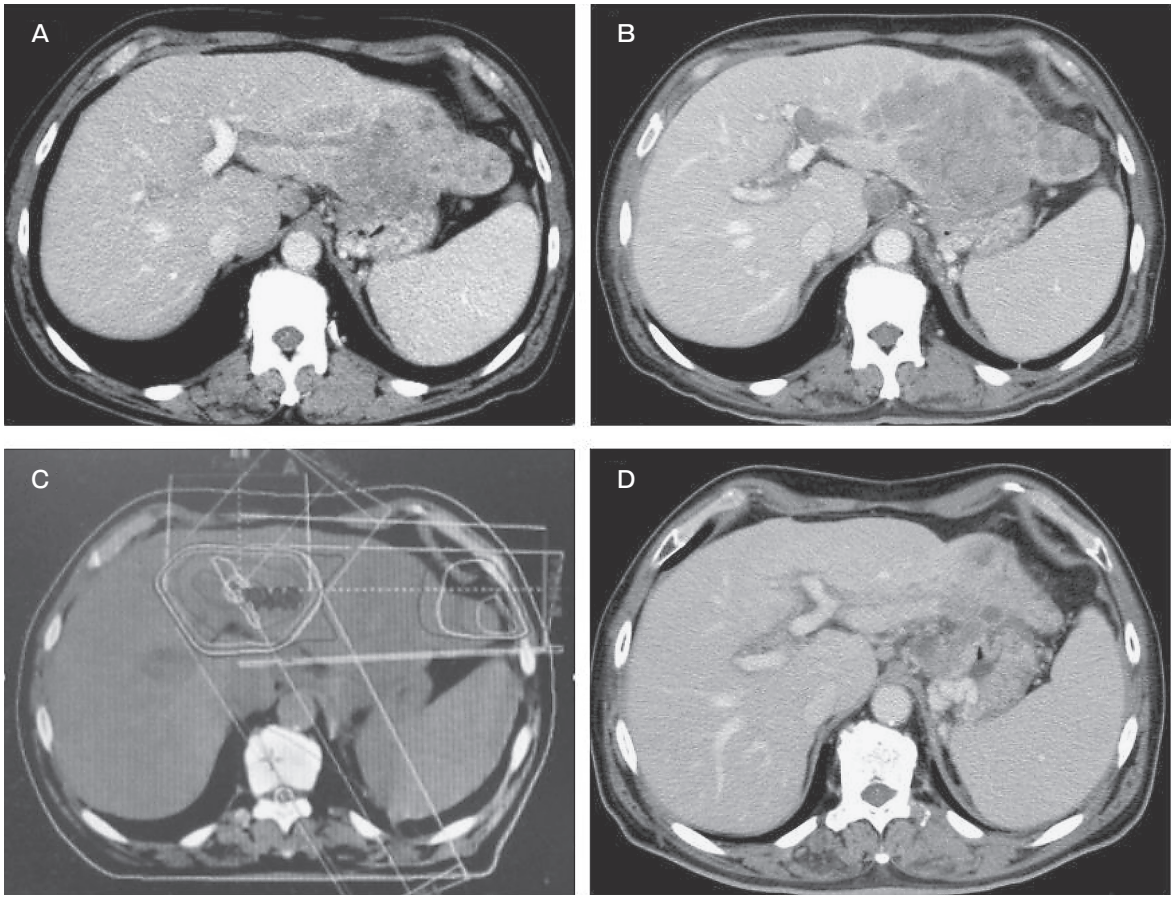

Fig. 3 Enhanced computed tomography scans of a patient with a good response. A) Portal vein invasion from the tumor of a hepatic lateral segment reaches the umbilical portion of the portal vein before sorafenib 800 mg/day treatment. B) The tumor progressed one month after sorafenib treatment. C) Three-dimensional radiation (50 Gy) map planning. D) The portal vein invasion receded, and the tumor showed shrinkage 4 months after 3D-CRT started.

factors.

Although many retrospective studies on radiation therapy for HCC with vascular invasion have been reported [8-13], the various indices of efficacy, such as tumor response and survival time on 3D-CRT, differ widely and have been difficult to interpret and discuss. A meta-analysis of radiation modalities (3D-CRT, selective internal radiation therapy, and stereotactic body radiation therapy) for HCC with PVTT showed pooled 1-year OS rates of 43.8-48.5% and response rates of 33.3-70.7% [16]. There was no intergroup difference in the efficacy results. Although our 1-year survival (36%) and response (29%) rates of HCC against PVTT appeared slightly inferior to those of this meta-analysis, our results seemed feasible in real-world practice. The reason for this efficacy difference might be due to differences in patient backgrounds.

As for the standard chemotherapy, sorafenib or lenvatinib was administered to 13 patients after 3D-CRT. These patients had relatively good disease conditions and prolonged survival. Based on our present results, we could not determine which is the better initial treatment for MVI-positive HCC: chemotherapy with molecular-targeted agents or 3D-CRT. Only one report has compared sorafenib with radiation therapy using propensity score-matched analysis [17]. The MSTs of radiation and sorafenib were reported as 10.9 months and 4.8 months, respectively ($p=0.029$). However, the number of patients in each treatment arm was small (28 patients). In our study, 52 patients (80%) had lesions outside the irradiation fields, and 22 patients (34%) were Child-Pugh class B or C. In addition, 12 patients (18%) received 3D-CRT before sorafenib was approved in Japan (May 2009). Under such adverse

conditions, the MST was 7.5 months. This seems not bad, considering that the SHARP study found MVI-positive MSTs of 8.1 months and 4.9 months in the sorafenib and placebo groups, respectively [1]. Further studies are needed to determine the clinical significance of radiation therapy in this specific HCC subgroup.

3D-CRT can be safely performed in general hospitals and is widely applicable to MVI-positive HCC. Indeed, liver function was preserved in over 70% of patients in whom 3D-CRT was performed, and PS was maintained in over 90% of patients. Additionally, this therapy could be applied to patients with Child-Pugh class B or C who were not eligible for standard chemotherapy.

In this study, there were no cases of gastrointestinal bleeding during radiation therapy, but 8 bleeding cases were recognized after 3D-CRT. Portal hypertension is expected in cases of portal vein infiltration, and sufficient caution is required for gastrointestinal bleeding. Only 5 patients had a single tumor; most had extrahepatic lesions or multiple intrahepatic lesions. The primary tumor size was large, with a median of 7.7 cm, and 16 patients had large tumors (>10 cm). In most patients, it was difficult to include the entire tumor within the irradiation range. Therefore, we prioritized suppressing the progression of vascular invasion. Despite these limitations, we experienced many effective cases of local MVI control, as shown in Fig. 3.

In the multivariate analysis, PS2 or 3, mALBI grade 2b or 3, and massive/diffuse type were poor prognostic factors. These results were identical to those previously reported in the literature for MVI-positive HCC [18-22] and seemed to be reasonable. The prognosis was particularly poor in patients with overlapping poor prognostic factors. When treating such patients, it is necessary to thoroughly consider the benefits before starting treatment. In this study, tumor necrosis or shrinkage of 50% or more was observed in 29% of patients, and the MST was good, at 18.9 months. Of the 19 responding cases, post-treatment was performed in 11 cases: 9 cases of TAI, 5 cases of TACE, 2 cases of sorafenib, and 1 case of RFA. These post-treatments might have contributed to the survival time in these patients. The response to vascular infiltration and improvement of portal and/or vena cava blood flow help to maintain hepatic reserve and PS, and might also prolong patient survival. DCP of less than 5000 mAU/ml may be an effect predictor, and this should be further investigated in a study with larger patient enrollment.

This study has some limitations. An inevitable bias exists due to the small and select number of patients available for a single-institution retrospective study, and this may have affected the results. 3D-CRT requires a long treatment period of around 1.5 months, and the dose concentration is lower than that of SRT or particle-beam radiation therapy. Many effective drugs for advanced HCC have been developed over the last 12 years. In particular, the advent of an ICI and molecular-targeted drug combination therapy (*i.e.*, atezolizumab plus bevacizumab) has significantly changed the treatment of HCC. The influence of these limitations on the survival results of our study is unclear.

In conclusion, 3D-CRT induced 50% or more tumor necrosis or regression of MVI in approximately 30% of patients with MVI-positive HCC. This therapy might provide survival benefit without serious adverse events and thereby should be considered a good treatment option in patients not indicated for other treatments. However, it should be carefully applied in patients with two or more poor prognostic factors. Further investigations including various combinations of molecular-targeted agents and ICI drugs are needed to improve the results of 3D-CRT therapy.

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