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Clinical Results of Radiotherapy That Targeted for Tumor Thrombi from Hepatocellular Carcinoma: A Multicenter Retrospective Study

Takuya Nagano[1, *], Akihiko Hoshi[2], Masayuki Kurosaki[3], Kazuma Sasamura[4], Kaoru Tsuchiya[3], Kazuma Toda[1], Hirofumi Kuwabara[2], Meika Namba[2], Daigoro Matsubara[5], Sayako Oota[5], Yasuo Yoshioka[4], Ryoichi Yoshimura[1], Namiki Izumi[3]

[1]Department of Radiation Therapeutics and Oncology, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan

[2]Department of Radiology, Musashino Red Cross Hospital, Musashino-shi, Tokyo, Japan

[3]Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Musashino-shi, Tokyo, Japan

[4]Department of Radiation Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Tokyo, Japan

[5]Department of Radiology, Asahi General Hospital, Asahi-shi, Chiba, Japan

Email address:

ngnmrad@tmd.ac.jp (T. Nagano)

[*]Corresponding author

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Abstract: Background: The aim of this multicenter study was to evaluate the outcome of radiotherapy (RT) that targeted for tumor thrombi (TT) from hepatocellular carcinoma (HCC), including the portal vein, hepatic vein, inferior vena cava, and bile duct TT. Methods: Patients who received RT for the treatment of TT between 2005 and 2020 were retrospectively reviewed. We compared patient characteristics, overall survival (OS), the combined chemotherapy regimen, and objective response rates (ORRs) between the treatment modalities and analyzed cumulative incidence formula (CIF) for the deterioration in the Child-Pugh class and the progression of intrahepatic tumors. Results: We evaluated 64 patients, 39 of whom received combined chemotherapy with RT. Multivariate analysis showed that the Child-Pugh class, primary tumor size and the response of TT were significant prognostic factors for OS and the total equivalent dose in 2 Gy fractions (EQD2) of more than 48.75 Gy significantly contributed to ORRs (p=0.04). In the multivariate analysis of CIF, only acute liver damage was the significant factor for the deterioration in the Child-Pugh class (p=0.01) and the length of TT was significant for the progression of intrahepatic tumors (p=0.03). Conclusion: High doses should be delivered to TT, but long tumor thrombi are difficult to control. Tumor thrombus length is more important in predicting intrahepatic progression than the location of the tumor thrombus.

Keywords: Combined Chemotherapy, Radiation Therapy, Hepatocellular Carcinoma, Macroscopic Vascular Invasion, Tumor Thrombosis

1. Introduction

Patients with advanced hepatocellular carcinoma (HCC) often present with the invasion of the hepatic vasculature and bile ducts. They cause extensive intrahepatic dissemination of the tumor. Moreover, portal vein tumor thrombosis (PVTT) decreases the blood supply to the normal liver, and finally causes portal hypertension, ascites, hepatic encephalopathy, and deteriorating liver function [1]. Hepatic vein tumor thrombosis (HVTT) and inferior vena cava tumor thrombosis (IVCTT) may flow into the heart and lung, leading to pulmonary embolism and lung metastasis [2]. Therefore, these conditions can be life-threatening, and their prognosis remains very poor.

Molecular targeted therapy using sorafenib continues to

increase as the standard systemic therapy for patients with advanced HCC, including HCC with macroscopic vascular invasion [3, 4]. Sorafenib was shown to significantly improve the overall survival (OS) and disease control rates when compared with placebo, but the tumor response was limited [5, 6]. Transarterial chemoembolization (TACE) is only safe for selected patients because it is associated with an increased risk of ischemic necrosis of the liver and of treatment-related death in patients with PVTT, and its efficacy has remained unsatisfactory [1, 7]. Although hepatic artery infusion chemotherapy (HAIC) has been attempted, it has not showed survival benefit [8].

Although the role of radiotherapy (RT) for HCC had been limited due to the risks of radiation-induced liver disease, recent RT techniques, including three-dimensional conformal radiotherapy (3D-RT), image-guided radiotherapy, and respiratory-gated radiotherapy, as well as information on partial volume liver tolerance, have allowed the delivery of higher radiation doses to the tumor than previously thought possible [1]. Several studies have evaluated the clinical outcomes of RT for inoperable HCC and results showed that RT can produce survival benefits compared to treatment of sorafenib or TACE alone [3, 9-13]. However, because the tumor appearance, irradiation dose, additional treatment such as TACE, and so on are different among the studies, eligible patients and tumors and the appropriate treatment strategy including RT have been unclear.

In this study, we retrospectively evaluated the clinical outcomes in HCC patients treated with RT only for tumor thrombus of hepatic vasculature and bile ducts, and extracted the tumor and treatment factors correlated with the tumor thrombosis response, survival, and cumulative incidence ratio to consider the appropriate treatment for them.

2. Materials and Methods

2.1. Patients

This multicenter retrospective study was conducted at XXX. The clinical and radiological data of patients who received RT for PVTT, HVTT, IVCTT, or bile duct tumor thrombosis (BDTT) of HCC between 2005 and 2020 were reviewed. The requirement for informed consent was waived because we reviewed anonymous data. The multicenter study approval was obtained from the institutional review board of XXX.

HCC and tumor thrombosis were diagnosed with dynamic imaging studies, using computed tomography (CT) or magnetic resonance imaging (MRI) with contrast enhancement [4]. Minor portal invasion or portal invasion at the first branch was classified as Vp2-3, and one at the main portal branch was classified as Vp4. The main hepatic vein invasion was classified as Vv2 and IVCTT as Vv3. BDTT at the first branch was classified as B3 and common hepatic duct tumor thrombosis as B4.

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

2.2. Treatment

Image-guided RT was performed in all patients. They received a single daily fraction of 2 or 3 Gy using 6–10 MV X-ray five days per week. Although the 3 Gy/fraction was often irradiated in XXX, when stereotactic radiotherapy (SRT) was performed, 9-12 Gy/fraction was irradiated. As different doses per fraction were used, the equivalent dose in 2 Gy fractions (EQD2), as the α/β ratio of 10 using a linear-quadratic model, was calculated in this study. The gross tumor volume (GTV) included only tumor thrombus in principal, and the primary tumor was partly included in the GTV if the tumor thrombus was close to it. It's not necessary for the primary tumor to be fully irradiated. The clinical target volume (CTV) equaled the GTV. The internal target volume (ITV) was delineated from contrast-enhanced four-dimensional (4D)-CTs, then the planning target volume (PTV) was extended by 5–10 mm from the ITV. The system of respiratory-gated irradiation was used, and patients received RT while holding their breath. If the tumor was assessed as having little movement due to breathing, it was irradiated at free breathing. Cone-beam CT was performed to ensure the relative position of the diaphragm. If the position was found to be not stable, cone-beam CT was performed daily.

Combined chemotherapy was administered for the tumor thrombosis within three months before the start of RT or after completing RT in this study. Combined local chemotherapy included either TACE or HAIC, and HAIC contained high-dose cisplatin (60 mg/m^2) or low-dose cisplatin (20 mg/m^2, day 1 and day 8) plus continuous infusion of 5-fluorouracil (350 mg/m^2, days 1–5, days 8–12) using a subcutaneous infusion port. Combined systemic treatment included sorafenib, regorafenib, lenvatinib or others.

2.3. Tumor Thrombosis Evaluation

Between one to six months after the completion of RT, the size of the tumor thrombus was evaluated using contrast-enhanced CT and/or MRI. On the other hand, the size of the primary tumor was not evaluated because not all the patients were irradiated to the primary tumor. The length of tumor thrombus was precisely measured using a three-dimensional image analysis system (Fujifilm, SYNAPSE VINCENT). We plotted points of the center of tumor thrombus in each axial slices and summed up the lengths between the points (Figure 1). Examples of actual patient images are shown in Figure 2. To eliminate measurement bias, in addition to being measured by radiologists at each of the divisional hospitals, the corresponding author measured again the length of the tumor thrombus in all patients. The definitions of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were based on the modified Response Evaluation Criteria in Solid Tumors according to

the previous studies [1, 2]; CR was defined as a complete disappearance of tumor thrombus; PR as at least a 50% decrease in the length of thrombus; SD as a < 50% decrease or < 25% increase in the length of thrombus; PD as > 25% increase in the length of thrombus. Patients with a tumor response of CR or PR were classified as responders, and patients with tumor response of SD or PD were classified as non-responders.

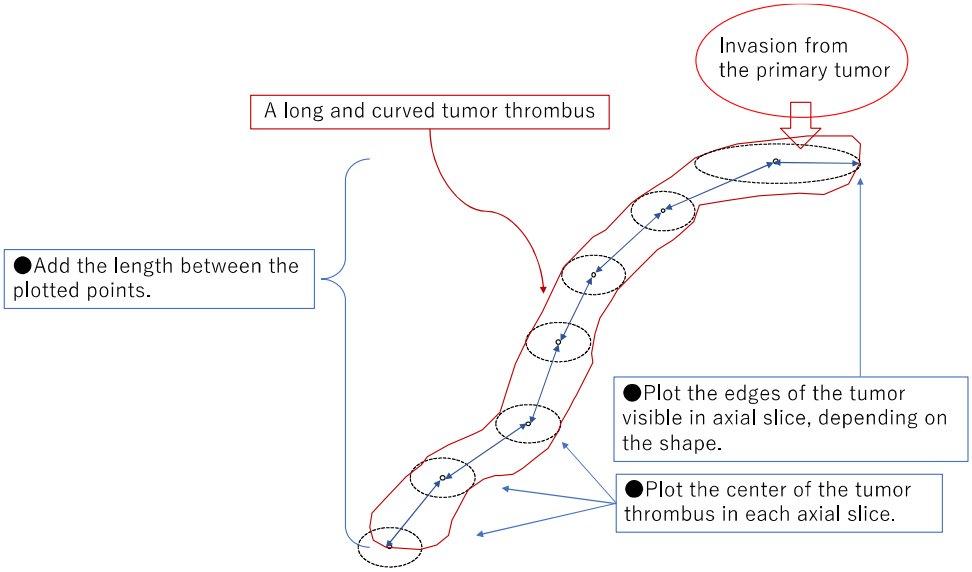

Figure 1. *The measurement of the tumor thrombi.*

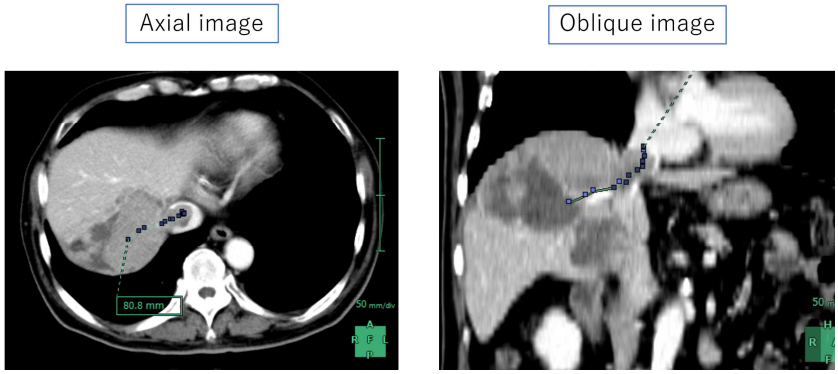

Figure 2. *Example of measurement of the tumor thrombus length using a three-dimensional image analysis system (Fujifilm, SYNAPSE VINCENT).*

The left figure is an axial slice with the center of the tumor thrombus plotted. And the right figure is an oblique slice that shows most of the plotted points. Not all points are on a single plane because long tumor thrombi are usually curved. Without this system, it would be impossible to accurately measure the length of the tumor thrombus.

2.4. Liver Toxicity

Acute adverse effects of the liver occurring within 3 months after RT were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. And acute adverse effects of the liver more than grade 3 was considered as a acute adverse event of the liver after RT. The deterioration in the CPC was also evaluated as late adverse effects after RT. And because the deterioration in the CPC was also caused by the progression of the intrahepatic tumor, cumulative incidence formula (CIF) of the deterioration in the CPC was analyzed in order to evaluate competing risks. We evaluated the irradiated relative volume of the remaining normal liver that received more than 30 Gy (V30Gy). A total irradiated dose of the liver was also calculated as a biologically effective dose 3 (BED3) and an equivalent dose in 2 Gy fractions (EQD2) using a linear-quadratic model with α/β ratios of 3, to evaluate acute and late adverse effects for the liver.

2.5. Statistics

The overall survival (OS) was estimated from the date of beginning RT to the date of death of the patient or last contact with the patient. The OS rate was calculated according to the Kaplan-Meier method, and the univariate analysis and multivariate analysis were performed using the log-rank test and a Cox regression model, respectively, to identify prognostic factors. To assess competing risk bias, all patients' causes of death were examined. The objective response rates (ORRs) were tested by using the Fisher analysis in the univariate analysis, and the multivariate analysis was performed using a logistic regression model. The cumulative incidence formulas for the deterioration in the CPC, and the progression of the

progression of the intrahepatic/extrahepatic tumor were analyzed by using the Fine and Gray regression model.

Receiver operating characteristic (ROC) curve analysis was used to calculate a threshold value for the length of tumor thrombus and size of the primary tumor in relation to objective response. This value was used in analysis of OS, ORRs, and CIF. Values with p values of < 0.05 by univariate analysis were chosen for multivariate analysis, and p values less than 0.05 were considered statistically significant.

All the statistical analyses were performed using EZR software, version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 2.13.0; The R Foundation for Statistical Computing, Vienna, Austria). All the statistical analyses were two-sided, and a p value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics

Although 97 patients received RT for PVTT, HVTT, or BDTT during this study's period, 33 patients were excluded as the response evaluation using CT and/or MRI after RT was not carried out in 32 patients, and in one patient there were no data for the clinical characteristics. The remaining 64 patients were enrolled in this study and their clinical characteristics are summarized in Table 1.

The median age of the 64 patients was 71 years (range 51–85 years), and although the viral hepatitis C caused hepatitis in half of them (n=34), non-virus infection caused hepatitis in 37% of the patients (n=23). PVTT was diagnosed in 34 patients and the main PVTT (Vp4) accounted for 47% of them (n=16). HVTT was diagnosed in 16 patients and IVCTT (Vv3) accounted for 88% of them (n=14). Two sites among PVTT, HVTT/IVCTT or BDTT were seen in four patients: both Vv3 and Vp4 in two, both Vv3 and Vp2 in one and both B3 and Vp4 in one. BDTT was diagnosed in nine patients: B3 in four and B4 in five. The median length of tumor thrombus was 3.8 cm (range 0.8–14.2 cm) and that of the primary tumor was 3.9 cm (range 0–13.1 cm). A threshold value for the length of tumor thrombus and primary tumor size in relation to tumor thrombus response were 3.2 cm and 4 cm, respectively. This value was used in the analysis of OS, ORRs and CIF. Lymph-node metastasis was seen in 16% (n=10) and distant metastasis was seen in 19% (n=12): lung metastasis in seven, dissemination in two, adrenal metastasis in two, pancreatic metastasis in one and bone metastasis in one.

The median EQD2 of the enrolled patients was 48.75 Gy (range: 32.5–88 Gy). Actually, 31 patients received 45 Gy in 15 fractions, 21 received 39 Gy in 13 fractions, 4 received 50 Gy in 25 fractions, 2 received 60 Gy in 30 fractions, 1 received 30 Gy in 10 fractions, 1 received 56 Gy in 28 fractions, and 3 received SRT of 48-54 Gy in 4-6 fractions (Table 2).

Combined chemotherapy was administered to 39 patients. Local chemotherapy was undergone by 25 patients: TACE in 13 and HAIC in 13. Systemic treatment with sorafenib was administered to 14 patients, and lenvatinib was to 3. Other systemic anticancer drugs were used in 4 patients, and one of them also received TACE.

Table 1. *Summary of clinical characteristics.*

Characteristic (n=64)	Median (range)/ no. of patients	(%)
Gender		
Male	50	78
Female	14	22
Age (years)	71 (51-85)	
ECOG PS		
0-1	54	84
2-3	9	14
4	1	2
Etiology of hepatitis		
Hepatitis B virus	7	11
Hepatitis C virus	29	45
B or C virus and Alcohol	5	8
Alcohol	10	16
NASH	5	8
Others	8	13
Child-Pugh class		
A	40	63
B	22	34
C	2	3
Tumor thrombosis invasion site		
Vp2	2	5
Vp3	16	25
Vp4	16	25
Vv2	2	3
Vv3	14	22
2 sites (Vp, Vv or Bile duct)	4	6
Bile duct	9	14
T*		
T2	11	17
T3	2	3
T4	51	80
N*		
N0	54	84
N1	10	16
M*		
M0	52	81
M1	12	19
Staging*		
Ⅱ	8	13
Ⅲa	1	2
Ⅲb	36	56
Ⅳa	7	11
Ⅳb	12	19
Length of tumor thrombus (cm)		
<3.2	43	67
≥3.2	21	33
Primary tumor size (cm)		
<4	35	55
≥4	29	45

NASH, Non-alcoholic steatohepatitis; Vv2, Presence of a tumor thrombus in a major hepatic vein; Vv3, Presence of a tumor thrombus in inferior vena cava; 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; 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 (or both).

*Staging of hepatocellular carcinoma was performed according to the 8th edition of the Union for International Cancer Control (UICC)-Tumor Node Metastasis (TNM) classification.

Table 2. *Treatment characteristics.*

Treatment Characteristic (n=64)	Median (range)/ no. of patients	(%)
Chemotherapy (Beofre RT/After RT)		
TACE/None or None/TACE	9	14
HAIC/None or None/HAIC	8	13
TACE/HAIC	1	2
Sorafenib/Sorafenib or None/Sorafenib	9	14
HAIC/Sorafenib	3	5
TACE/Sorafenib or Sorafenib/TACE	2	3
TACE/Other agents	1	2
Lenvatinib/Lenvatinib or None/Lenvatinib	2	3
Lenvatinib/HAIC	1	2
Other agents/Other agents or None/Other agents	3	5
None	25	39
EQD2 (Gy)		
32.5	1	2
41.67	1	2
42.35	21	33
48.75	31	48
50	4	6
56	1	2
60	2	3
≥83 (SRT)	3	5
Irradiated sites		
Both primary tumor and its thrombus	16	25
Only tumor thrombus	48	75

EQD2, Equivalent dose in 2-Gy fractions; RT, radiation therapy; HAIC, Hepatic arterial infusion chemotherapy; TACE, Transarterial chemoembolization.

3.2. Overall Survival

The median follow-up period for all the patients was 8 months (range 2–90 months), and the median survival time was 9 months. The one- and three-year OS rates were 44% and 17%, respectively (Figure 3). Thirty-nine patients died from the disease. Six patients died of acute causes: esophageal variceal rupture in 4, asphyxiation in 1, and a perioperative infection in 1. Ten patients were alive until the statistics were discontinued. Ten patients lost their follow-up.

In the univariate analysis the ECOG PS (p=0.01), Child-Pugh class (p=0.003), primary tumor size (p=0.009), length of tumor thrombus (p=0.01), EQD2 (p=0.001), combined chemotherapy (p=0.04), response of the tumor thrombus (p=0.005), and irradiated sites (p=0.04) were significantly related with OS (Table 3). Multivariate analyses were performed among these six important factors, and Child-Pugh class (HR 12, 95% CI [2.8, 5.8], p=0.000002), primary tumor size (HR 5.2, 95% CI [1.4, 2.7], p=0.003), and response of the tumor thrombus (HR 0.5, 95% CI [0.1, 0.3], p=0.0002) were shown as unique significant factors. Age, N stage, M stage, length of the primary tumor, or grade and site of tumor thrombosis were not related to the OS.

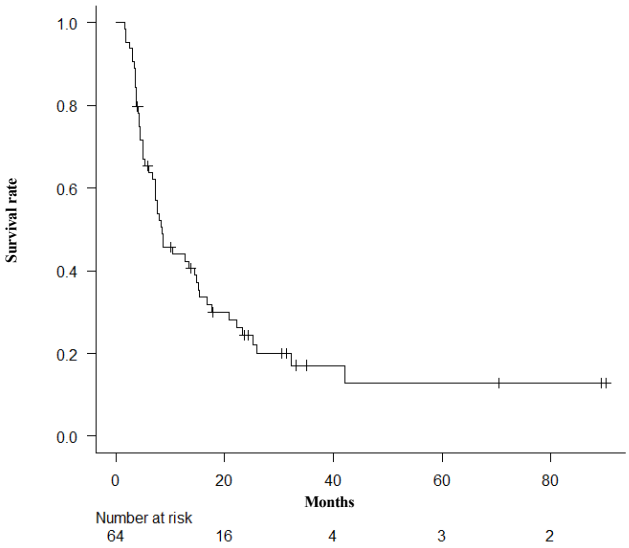

Figure 3. *Overall survival of all the patients.*

The median survival time was 9 months for all the patients. The one- and three-year OS rates were 44% and 17%, respectively.

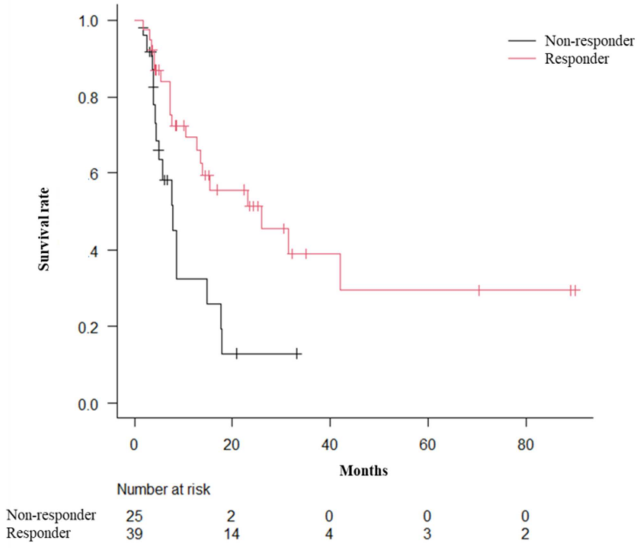

Figure 4. *Overall survival between the responders and the non-responders groups.*

The one-year survival rate of the responder and non-responder groups was 69% and 32%, respectively (p=0.005). Responders had significantly better OS than non-responders.

Table 3. *Univariate and multivariate analysis of the prognostic factors influencing the OS.*

Prognostic factor	No.	Univariate analysis		Multivariate analysis	
		1-year OS (%)	P-value	HR (95% CI)	P-value
Gender					
Male	50	60	0.7		
Female	14	5			
Age (y)					

Prognostic factor	No.	Univariate analysis		Multivariate analysis	
		1-year OS (%)	P-value	HR (95% CI)	P-value
<60	9	51	0.7		
≥60	55	57			
ECOG PS					
0–1	54	64	0.01	1.6 (0.3-0.7)	0.4
2–4	10	24			
Child-Pugh class					
A	39	65	0.003	12 (2.8-5.8)	0.000002
B-C	25	42			
Grade of tumor thorombosis					
Vv2 or Vp2-3 or BDTT	19	60	0.9		
Vv3 or Vp4	45	55			
Site of tumor thorombosis					
PVTT	34	47	0.4		
HVTT/IVCTT	17	73			
Both PVTT and HVTT/IVCTT	4	33			
BDTT	9	75			
Presense of BDTT					
Yes	9	56	0.8		
No	55	42			
T					
T2	11	100	0.05		
T3	2	NA			
T4	51	49			
N					
N0	54	54	0.9		
N1	10	69			
M					
M0	52	54	0.4		
M1	12	72			
TNM staging					
II	8	100	0.3		
IIIa	1	NA			
IIIb	36	44			
IVa	7	57			
IVb	12	72			
Primary tumor size (cm)					
<4	35	73	0.009	5.2 (1.4-2.7)	0.003
≥4	29	35			
Length of tumor thrombosis (cm)					
<3.2	43	64	0.01	1.5 (0.4-0.7)	0.4
≥3.2	21	42			
EQD2 (Gy)					
<48.75	23	37	0.001	1 (1.4-2.7)	0.06
≥48.75	41	67			
Combined CTX with RT (Local or Systemic)					
Yes	39	63	0.04		
No	25	47			
Acute adverse event					
Yes	9	54	0.5		
No	55	89			
Response					
Yes	39	69	0.005	0.5 (0.1-0.25)	0.0002
No	25	32			
Irradiated sites					
Both primary tumor and its thrombus	18	63	0.04		
Only tumor thrombus	48	38			

OS, Overall survival; HR, Hazard ratio; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BDTT, Bile duct tumor thrombosis; PVTT, Portal vein tumor thrombosis; IVCTT, Inferior vena cava tumor thrombosis; HVTT, Hepatic vein tumor thrombosis; Vv2, Presence of a tumor thrombus in a major hepatic vein; Vv3, Presence of a tumor thrombus in inferior vena cava; 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; 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 (or both); EQD2, Equivalent dose in 2-Gy fractions; CTX, Chemotherapy; RT, radiation therapy; HAIC, Hepatic arterial infusion chemotherapy; TACE, Transarterial chemoembolization.

3.3. Tumor Response

Of the 64 patients, 27 patients (42%) achieved CR, 12 patients (19%) achieved PR, 22 patients (34%) had SD, and 3 patients had PD (5%). The ORR of all the patients was 61%.

The ORRs of patients who received an EQD2 of < 48.75 Gy or >=48.75 Gy were 44% and 71% (p=0.04). In the univariate analysis, EQD2 was only significantly related to the tumor response (Table 4). In the multivariate analysis, no factors were found to be significantly different. The one-year OS rates of responders (n=39) and non-responders (n=25) were 69% and 32%, respectively, and the difference was statistically significant (p=0.005, Figure 3).

Table 4. *Response of tumor thrombosis.*

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	**P-value**	**Odds ratio (95% CI)**	**P-value**
ECOG PS				
0–1	0.59 (0.11-2.9)	0.5		
2–4				
Cause of hepatitis				
Viral hepatitis B or C	0.54 (0.17-1.7)	0.3		
others				
Child-Pugh class				
A	1.23 (0.39-4)	0.8		
B-C				
Site				
Vv2 or Vp2-3 or BD	0.87 (0.24-3)	1		
Vv3 or Vp4				
T				
T2-3	0.23 (0.02-1.19)	0.06	1.13 (0.037-0.21)	0.07
T4				
N				
N0	0.59 (0.11-2.92)	0.5		
N1				
M				
M0	0.58 (0.13-2.51)	0.5		
M1				
Primary tumor size (cm)				
<4	0.64 (0.2-1.98)	0.5	4.67 (0.4-1.4)	0.6
≥4				
Length of tumor thrombosis (cm)				
<3.2	0.44 (0.13-1.45)	0.2	1.8 (0.15-0.5)	0.3
≥3.2				
EQD2 (Gy)				
<48.75	3.1 (0.95-10.4)	0.04	8.5 (0.9-2.9)	0.08
≥48.75				
Combined CTX with RT (Local or Systemic CTX)				
Yes	1.39 (0.44-4.4)	0.6		
No				
Irradiated sites				
Both primary tumor and its thrombus	0.64 (0.15-2.4)	0.6	3.7 (0.25-0.96)	1.0
Only tumor thrombus				

CI, Confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; Vv2, Presence of a tumor thrombus in a major hepatic vein; Vv3, Presence of a tumor thrombus in inferior vena cava; 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; 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 (or both); EQD2, Equivalent dose in 2-Gy fractions; CTX, Chemotherapy; RT, radiation therapy; HAIC, Hepatic arterial infusion chemotherapy; TACE, Transarterial chemoembolization.

3.4. Liver Toxicities and Cumulative Incidence Analysis

Nine patients (14%) were observed to have elevated levels of AST/ALT of more than Grade 3. One of them suffered from rupture of esophageal varices because of liver cirrhosis and acute liver failure of Grade 4. One suffered from a pulmonary embolism and an unknown fever. Two suffered acute liver failure after treatment of TACE or HAIC. Two died of disease progression two months after the elevated level of AST/ALT. The other three patients recovered from acute liver toxicity for about 10 days without any reason or events.

Deterioration in the Child-Pugh class was observed in 21 patients (48%). On the other hand, 31 patients (33%) died or lost to follow-up and 12 patients (19%) survived without liver damage. Because it was not known whether their liver failures were due to disease progression or adverse events, we evaluated CIF for the deterioration in the Child-Pugh class and the progression of intrahepatic/extrahepatic tumors.

In the univariate analysis, an event of acute liver failure was only significantly related to the deterioration in the Child-Pugh class (HR 3.1, 95% CI [1.3, 7.6], p=0.001). In the multivariate

analysis, event of acute liver failure was either only significantly related to the deterioration in the Child-Pugh class (HR 3.3, 95% CI [1.3, 8.2], p=0.01, Table 5).

Table 5. *Cumulative incidence for the deterioration of Child-Pugh class between the factors.*

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
ECOG PS				
0–1	2.1 (0.8-5.8)	0.2		
2–4				
Cause of hepatitis				
Viral hepatitis B or C	0.6 (0.2-1.5)	0.3		
others				
Child-Pugh class			0.7 (0.3-1.98)	0.5
A	0.8 (0.3-2.1)	0.7		
B-C				
Site				
Vv2 or Vp2-3 or BD	1.4 (0.5-3.9)	0.5		
Vv3 or Vp4				
T				
T2-3	1.6 (0.4-5.7)	0.5		
T4				
N				
N0	0.9 (0.3-3.1)	0.9		
N1				
M				
M0	0.9 (0.4-2.5)	1		
M1				
Primary tumor size (cm)				
<4	1.8 (0.8-4.2)	0.2		
>4				
Length of tumor thrombosis (cm)				
<3.2	1.3 (0.6-3.1)	0.5		
≥3.2				
EQD2 (Gy)				
<48.75	1.2 (0.4-2.9)	0.7	1.2 (0.3-4)	0.8
≥48.75				
Combined CTX with RT (Local or Systemic CTX)				
Yes	1.2 (0.5-3.1)	0.7	0.96 (0.28-3.3)	1.0
No				
Acute adverse events				
Yes	3.1 (1.3-7.6)	0.001	3.3 (1.3-8.2)	0.01
No				
Response				
Yes	1.6 (0.6-4.2)	0.3	1.5 (0.54-4.1)	0.5
No				
Irradiated sites				
Both primary tumor and its thrombus	0.6 (0.2-1.8)	0.4		
Only tumor thrombus				

CI, Confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; Vv2, Presence of a tumor thrombus in a major hepatic vein; Vv3, Presence of a tumor thrombus in inferior vena cava; 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; 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 (or both); EQD2, Equivalent dose in 2-Gy fractions; CTX, Chemotherapy; RT, radiation therapy; HAIC, Hepatic arterial infusion chemotherapy; TACE, Transarterial chemoembolization.

The progression of intrahepatic tumors was observed in 39 patients (61%). On the other hand, 22 patients (34%) died or lost to follow-up and 3 patients (5%) survived without the progression of intrahepatic tumors.

In the univariate analysis, the length of TT was only significantly related to the progression of intrahepatic tumors (HR 0.4, 95% CI [0.2, 0.9], p=0.03). In the multivariate analysis, the length of TT was either only significantly related to the progression of intrahepatic tumors (HR 0.3, 95% CI [0.1, 0.9], p=0.03, Table 6).

Table 6. *Cumulative incidence for progression of the intrahepatic tumor between the factors.*

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
ECOG PS				
0–1	1 (0.4-2.6)	0.9		
2–4				
Cause of hepatitis				
Viral hepatitis B or C	1 (0.5-1.8)	1		
others				
Child-Pugh class				
A	0.5 (0.2-1.1)	0.09	0.6 (0.2-1.5)	0.3
B-C				
Site				
Vv2 or Vp2-3 or BD	0.8 (0.4-1.5)	0.4		
Vv3 or Vp4				
T				
T2-3	1.4 (0.6-3)	0.4		
T4				
N				
N0	0.5 (0.2-1.5)	0.2		
N1				
M				
M0	0.9 (0.4-1.8)	0.7		
M1				
Primary tumor size (cm)				
<4	0.7 (0.4-1.4)	0.4	1.1 (0.5-2.5)	0.8
≥4				
Length of tumor thrombosis (cm)				
<3.2	0.4 (0.2-0.9)	0.03	0.3 (0.1-0.9)	0.03
≥3.2				
EQD2 (Gy)				
<48.75Gy	0.8 (0.4-1.6)	0.6		
≥48.75				
Combined CTX with RT (Local or Systemic CTX)				
Yes	1.1 (0.6-2.1)	0.8		
No				
Acute adverse events				
Yes	0.6 (0.2-1.5)	0.3		
No				
Response				
Yes	0.7 (0.4-1.3)	0.3	0.5 (0.3-1.1)	0.08
No				
Irradiated sites				
Both primary tumor and its thrombus	1.8 (0.96-3.3)	0.07	1.6 (0.7-3.5)	0.3
Only tumor thrombus				

The progression of extrahepatic tumors was observed in 25 patients (39%). On the other hand, 8 patients (13%) died or lost to follow-up and 31 patients (48%) survived without the progression of extrahepatic tumors.

In the univariate analysis, M1 was only significantly related to the progression of extrahepatic tumors (HR 6.5, 95% CI [2.8, 15], p=0.0002). In the multivariate analysis, M1 was either only significantly related to the progression of extrahepatic tumors (HR 5.6, 95% CI [2.6, 11.9], $p < 0.00001$, Table 7).

Table 7. *Cumulative incidence for progression of the extrahepatic c tumor between the factors.*

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
ECOG PS				
0–1	0.4 (0.1-1.7)	0.2		
2–4				
Cause of hepatitis				
Viral hepatitis B or C	1.3 (0.6-2.9)	0.4		
others				
Child-Pugh class				
A	0.4 (0.1-0.98)	0.04	0.4 (0.1-1.1)	0.6
B-C				
Site				
Vv2 or Vp2-3 or BD	2.1 (0.8-5.2)	0.1		

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Vv3 or Vp4				
T				
T2-3	7.9 (1.1-58)	0.04	4.8 (0.6-37.9)	0.1
T4				
N				
N0	1.7 (0.7-4.6)	0.3		
N1				
M				
M0	6.5 (2.8-15)	<0.001	5.6 (2.6-11.9)	<0.001
M1				
Primary tumor size (cm)				
<4	1.2 (0.6-2.7)	0.6		
≥4				
Length of tumor thrombosis (cm)				
<3.2	1.1 (0.5-2.6)	0.8		
≥3.2				
EQD2 (Gy)				
<48.75Gy	1.1 (0.5-2.6)	0.8		
≥48.75				
Combined CTX with RT (Local or Systemic CTX)				
Yes	1.9 (0.8-4.4)	0.1		
No				
Acute adverse events				
Yes	1.7 (0.7-4.2)	0.3		
No				
Response				
Yes	0.6 (0.3-1.2)	0.2		
No				
Irradiated sites				
Both primary tumor and its thrombus	1.1 (0.5-2.6)	0.8		
Only tumor thrombus				

V30Gy was evaluated in 48 patients whose data was not lost. The median volume of V30Gy of the normal liver was 14% (range of 1–55%). Median EQD2 and BED irradiated to the normal liver were 9 Gy (range of 1–26) and 14 Gy (range of 1–43), respectively.

4. Discussion

We retrospectively evaluated the treatment results of RT with or without chemotherapy for 64 patients with HCC that invaded PV, HV, IVC, or BD.

Although there are various treatment modalities for advanced HCC, including sorafenib, regorafenib, lenvatinib, surgery, TACE, HAIC, and RT, no standard therapeutic options are as of yet established.

In particular, the selection of treatment for HCC with a macroscopic vascular invasion (MVI) that causes poor prognosis is still controversial. Sorafenib and regorafenib have demonstrated significant benefits for OS and safety in the analysis of randomized phase III trials [5, 6, 14, 15]. The trials showed that the median OS for patients with advanced HCC, a well-preserved liver function, and undergoing treatment with sorafenib was 7-11 months, and the ORR was only 2–3%. Although the disease control rate, that was defined as the percentage of patients with CR, PR, or SD based on radiologic review, was 43-53%. In a nationwide survey of advanced HCC in Japan it was shown that HAIC can have a significant positive impact on OS, the median OS was 14 months in patients with advanced HCC and 8.8 months longer than the control group [8]. Analysis in a non-randomized prospective study showed that TACE can be an effective treatment for PVTT, and the one-year OS rate was 18% and the ORR was 20% [7]. Although the multicenter cohort studies of surgery for PVTT showed that the five-year OS was 10–39% and median survival time was 11–21 months [16-18], surgery is generally not feasible in patients with advanced HCC due to the spreading of multiple intrahepatic tumors or insufficient function of the remaining liver. As described above, sorafenib, regorafenib, TACE and HAIC have been the standard of treatment for advanced and inoperable HCC on the basis of large trials in Japan. However, as shown in the table 8, the patient backgrounds in these studies were heterogenous and only subgroup analyses have been performed to assess patients with MVI.

On the other hand, previous studies have suggested the potential therapeutic role of RT in patients with MVI of HCC, and the OS rates in those studies were better than any other studies with other treatment modalities. A large multicenter study has already assessed the efficacy of RT [19], and the one-year OS of patients with PVTT was found to be 43% and the ORR was 52%. Moreover, the PVTT responders had a better median survival time than the non-responders (14 months versus 6 months, $p < 0.05$). A randomized clinical trial have also revealed the efficacy of the combined treatment of TACE and RT [20]. The median OS of patients with MVI was found to be 14 months and significantly longer than sorafenib

(14 months versus 11 months, p=0.04). In our study, the OS rate was similar to that of the multicenter study, and the OS rate of responders was also significantly better than that of non-responders (75% versus 35%, p=0.009). The objective response must be an important endpoint, because reducing the tumor thrombosis size can delay intravascular tumor growth and the deterioration of liver function, by preserving adequate vascular flow, as well as by facilitating subsequent treatment of the primary tumor.

Table 8. *Comparison of clinical results for advanced HCC among treatment modalities.*

	No. of all the Pts	No. of Pts with macrovascular invasion	Objective Responses rate (%)	Response of whole tumor or only tumor thrumbus	1-year OS (%)	Median OS
Regorafenib [5]	379	110	11	Whole	NA	11
Sorafenib [6]	299	108	2	Whole	44	11
Sorafenib [14]	150	54	5	Whole	NA	7
TACE [7]	84	84	20	Whole	18	5
HAIC [8]	476	NA	40	Whole	NA	14
RT [11]	985	985	52	Only tumor thrombus	43	10

HCC, Hepatocellular carcinoma; Pts, Patients; OS, Overall survival; RT, Radiation therapy; HAIC, Hepatic arterial infusion chemotherapy; TACE, Transarterial chemoembolization.

We analyzed the prognostic factors relating to the ORR, which was evaluated using dynamic imaging studies according to the modified criteria, and a prescribed dose was a unique significant factor (Odds ratio 3.1, 95% CI [0.95, 10.4], p=0.04) in the univariate analysis. This finding was consistent with the results of previous studies that recommended a prescribed dose higher than 45–50 in EQD2 [2, 19-23]. Although some studies emphasized the impact of the local response in relation to the OS, few studies have suggested factors relating to the ORR. The Child-Pugh class, T stage, cause of hepatitis, tumor size, site of tumor thrombosis (PV, HV, IVC, or BD), combined chemotherapy including sorafenib, HAIC, or TACE, none of them were found to be related with ORR in our study.

The OS of patients with EOCG PS 0-1, Child-Pugh class A, T2 stage, a primary tumor size less than 4 cm, a tumor thrombus length of less than 3.2 cm, more than 48.75 Gy of EQD2, combined chemotherapy, the response of the tumor thrombus, or both primary tumor and tumor thrombus irradiated was significantly better than that of other patients, in the univariate analysis. The Child-Pugh class A was extracted as a significant prognostic factor among all the aforementioned factors, in the multivariate analysis.

However, in the study of HCC with MVI, survival rates and prognostic factor analysis tends to be difficult to assess due to the competing risk bias and the selection bias. Many patients with HCC were originally suffering from chronic liver damage due to a virus or heavy alcohol consumption. Treatment could worsen liver damage and shorten the prognosis. Furthermore, the method of treatment before and after radiotherapy varies according to the patient's background and the primary tumor. To resolve the competing risk bias and the selection bias, CIF were used to evaluate the risk factors.

In our study, ROC curve analysis was used to calculate a threshold value for the length of tumor thrombus s in relation to response, and that was found to be 3.2 cm. To our knowledge, this study for the first time used a three-dimensional image analysis system to measure the thrombus and there has been no study that has demonstrated the significant correlation between the length of tumor thrombus and OS, ORR, or CIF. Previous studies would have bias for measurement of the tumor thrombus because it's difficult to evaluate long and curved tumor thrombus. It was interesting to note that the length of tumor thrombus was only a unique factor related with CIF for the progression of the intrahepatic tumor, in the univariate and multivariate analysis, although the local response was significantly related with OS and the significant prognostic factor of local response was the RT dose (EQD2).

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

Yoon et al. [1] treated PVTT with a combination of TACE and RT and reported that the involvement of main or bilateral PV, a higher level of α-fetoprotein (AFP), and advanced modified UICC stage were independent predictors of decreased OS. Pao et al. [2] treated IVCTT with RT and reported that the median OS was significantly longer for patients with Child-Pugh class A, without LN metastasis, and without lung metastasis. The results of these previous studies have shown that the OS was influenced by factors that affected liver functions and systemic dissemination. The size of the tumor thrombus must influence the liver function because of the blood supply, and the liver dysfunction causes portal hypertension resulting in the rupture of collateral vessels, ascites, and hepatic encephalopathy. Even if CR or PR is not achieved for a patient with a small tumor thrombus, the maintaining SD must lead to a long-term prognosis, and small

field irradiation reduces the risk of radiation-induced liver disease (RILD).

The general guideline was that the fraction of the normal liver treated with more than 50% of prescribed dose should be less than 50% of the normal liver volume (V50% < 50%), and the volume of the normal liver that was damaged by irradiation was defined as the fraction volume of normal liver that received more than 30 Gy (V30Gy), with no more than 30% of the normal liver exposed to more than 30 Gy (V30Gy < 30%) [24]. In our study, the correlation between RILD and a dose-volume histogram was not acknowledged. This might be because we used the system of respiratory-gated irradiation to reduce the volume of the liver that was irradiated.

On the other hand, CIF for the deterioration of the Child-Pugh class suggested that acute liver damage was a unique predictor of the deterioration of the Child-Pugh class. This seems logical in the sense that chronic and irreversible liver damage was triggered by the acute liver damage event.

Recently, some studies have reported the efficacy of SRT or proton beam irradiation for HCC with MVI [22, 23, 25-27]. Focal irradiation using such a high-tech RT may be able to help change the strategy for this disease with poor prognosis.

In our study, neither the N nor M factor was significantly related to OS. This might be because systemic treatment controlled those metastases and their prognosis was not different from the patients without N or M factor. Prospective studies are needed to evaluate the efficacy of combination therapy between the local treatment of RT and systemic treatment of sorafenib for the treatment of advanced HCC with N and/or M factors. At least in CIF of the deterioration of the Child-Pugh class and the progression of the intra/extrahepatic tumor, combined chemotherapy with RT was not risk-related.

Limitation of this study is inhomogeneity of patients' characteristics, as the number of patients with HCC including MVI is relatively small even in multi-center study, and we excluded the patients who didn't undergo follow-up dynamic imaging studies after completion of RT to evaluate the ORR. Furthermore, this was a multi-center retrospective study, and because the dose-volume histograms were not calculated in 16 of all the patients due to a mechanical failure and the duration of follow-up was limited, it was impossible to fully evaluate any adverse effects on the liver function. Nevertheless, we consider that the ORR and CIF could be accurately assessed in this study without bias.

5. Conclusion

RT was a useful treatment for HCC with MVI. The local response of tumor thrombosis was significantly related to OS, and the RT dose was a significant prognostic factor for ORR. On the other hand, the length of the tumor thrombi significantly impacted the CIF for the progression of the intrahepatic tumor, in the multivariate analysis. The results suggest that high doses should be delivered to the tumor thrombi, but long tumor thrombi are difficult to control locally. The length of tumor thrombus would be a predictor of intrahepatic tumor progression and accurate measurement of tumor thrombus length is important for predicting prognosis.

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