

# Clinical results of radiotherapy for hepatocellular carcinoma with tumor thrombosis.

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## Research article

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# Abstract

**Background:** The aim of this study was to evaluate the clinical outcome of radiotherapy (RT) for hepatocellular carcinoma (HCC) with the portal vein (PV), hepatic vein (HV), inferior vena cava (IVC), and bile duct (BD) tumor thrombosis (TT).

**Methods:** Patients who received RT for the treatment of a primary tumor and tumor thrombosis at Musahino Red Cross Hospital between 2011 and 2019 were retrospectively reviewed. We compared patient characteristics, radiation dose, overall survival (OS), the combined chemotherapy regimen, and objective response rates (ORRs) between the treatment modalities.

**Results:** We evaluated 43 patients who were treated with RT, 27 of whom received combined chemotherapy with RT. The total equivalent dose in 2 Gy fractions ranged from 42.25 to 72 Gy (median 48.75 Gy). The median follow-up period after RT was 13 months (range of 2–90 months). Multivariate analysis showed that the length of tumor thrombosis was a unique significant prognostic factor for OS ( $p = 0.01$ ) and the prescribed equivalent dose of more than 48.75 Gy significantly contributed to ORRs ( $p = 0.02$ ). When compared, the one-year OS rates of responders ( $n = 25$ ) and non-responders ( $n = 18$ ) were 75% and 35%, respectively ( $p = 0.009$ ). The odds ratio of ORRs between the two total dose groups (42.35 Gy versus more than 48.75 Gy) was 9.8 (95% CI [2.1, 58.9],  $p = 0.001$ ). Combined chemotherapy with RT was a prognostic factor for OS ( $p = 0.03$ ), but it was not correlated with response rate ( $p = 0.53$ ).

**Conclusion:** Local control of tumor thrombosis was found to be a significant prognostic factor for OS in patients with HCC and its tumor thrombosis. Although various drug and treatment options for tumor thrombosis exist, RT provides a better OS.

## Background

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 [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 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 for tumor thrombosis of hepatic vasculature and bile ducts, and extracted the tumor and treatment factors correlated with the tumor response and survival to consider the appropriate treatment for them.

## Methods

### Patients

The clinical and radiological data of patients who received RT for PVTT, HVTT, IVCTT, or bile duct tumor thrombosis (BDTT) of HCC at Musahino Red Cross Hospital between 2011 and 2019 were reviewed. The requirement for informed consent was waived because we reviewed anonymous data. Study approval was obtained from the institutional review board of Musahino Red Cross Hospital.

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 Vp1-3, 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. The lengths of the tumors were measured in the axial, sagittal, or coronal CT slice.

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].

### Treatment

Three-dimensional (3D)- and image-guided conformal 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, when stereotactic radiotherapy (SRT) was performed, 9 Gy/fraction was irradiated. As different doses per fraction were used, the equivalent dose in 2 Gy fractions (EQD2), as the  $\alpha/\beta$  ratio of 10 using a linear-quadratic model, was calculated in this study. The gross tumor volume (GTV) included only tumor thrombosis in principal, and the primary tumor was partly included in the GTV if the tumor thrombosis 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 all patients received RT while holding their breath. 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 ( $60 \text{ mg/m}^2$ ) or low-dose cisplatin ( $20 \text{ mg/m}^2$ , day 1 and day 8) plus continuous infusion of 5-fluorouracil ( $350 \text{ mg/m}^2$ , days 1–5, days 8–12) using a subcutaneous infusion port. Combined systemic treatment included sorafenib, regorafenib, or others.

### Tumor evaluation

Between one to six months after the completion of RT, the size of the tumor thrombosis 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 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 thrombosis; PR as at least a 50% decrease in the thrombi diameter; SD as a  $< 50\%$  decrease or  $< 25\%$  increase in the thrombi diameter; PD as  $> 25\%$  increase in the thrombi diameter. 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.

### Liver toxicity

Acute adverse effects occurring within 3 months after RT were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and the deterioration in the Child-Pugh class was also evaluated as late adverse effects within 6 months after RT. 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  $\alpha/\beta$  ratios of 3, to evaluate acute adverse effects.

### 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. 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. Receiver operating characteristic (ROC) curve analysis was used to calculate a threshold value for the length of tumor thrombosis in relation to response. This value was used in analysis of OS and ORRs. 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). More precisely, it is a modified version of R commander (version 1.6-3), designed to include statistical functions that are frequently used in biostatistics. All the statistical analyses were two-sided, and a p value < 0.05 was considered statistically significant.

## Results

### Characteristics

Although 69 patients received RT for PVTT, HVTT, or BDTT during this study's period, 26 patients were excluded as the response evaluation using CT and/or MRI after RT was not carried out in 25 patients, and in one patient there were no data for the clinical characteristics. The remaining 43 patients were enrolled in this study and their clinical characteristics are summarized in Table 1.

The median age of the 43 patients was 73 years (range 51–85 years), and although the viral hepatitis C caused hepatitis in half of them (n = 22), non-virus infection caused hepatitis in 35% of the patients (n = 15). PVTT was diagnosed in 28 patients and the main PVTT (Vp4) accounted for 50% of them (n = 14). HVTT was diagnosed in 12 patients and IVCTT (Vv3) accounted for 83% of them (n = 10). Both PVTT and HVTT/IVCTT were seen in three patients: both Vv3 and Vp4 in two and both Vv3 and Vp2 in one. BDTT was diagnosed in six patients: B3 in three and B4 in three. The median length of tumor thrombosis was 3.2 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 thrombosis in relation to tumor thrombosis response was 3.8 cm. This value was used in the analysis of OS and ORR. Lymph-node metastasis was seen in 16% (n = 7) and distant metastasis was seen in 14% (n = 7): lung metastasis in four, dissemination in two, and bone metastasis in one.

The median EQD2 of the enrolled patients was 48.75 Gy (range: 42.35–74 Gy). Actually, 25 patients received 45 Gy in 15 fractions, 16 received 39 Gy in 13 fractions, 1 received 50 Gy in 25 fractions, and 1 received SRT of 54 Gy in 6 fractions.

Combined chemotherapy was administered to 27 patients. Local chemotherapy was undergone by 12 patients: TACE in 9 and HAIC in 9. Systemic treatment with sorafenib was administered to 11 patients, and 4 of them also received combined local chemotherapy. Other systemic anticancer drugs were used in 4 patients, and one of them also received TACE.

### Overall survival

The median follow-up period for all the patients was 13 months (range 2–90 months), and the median survival time was 15 months. The one- and three-year OS rates were 60% and 36%, respectively (Fig. 1). Twenty-two patients died from the disease.

In the univariate analysis the ECOG PS (p = 0.05), Child-Pugh class (p = 0.003), length of tumor thrombosis (p = 0.00003), EQD2 (p = 0.001), and combined chemotherapy (p = 0.03) were significantly related with OS (Table 2). Multivariate analyses were performed among these five factors, and the length of tumor thrombosis was shown as a unique significant factor (HR 4.05, 95% CI [1.4, 11.7], p = 0.01). Age, N stage, M stage, length of the primary tumor, or site of tumor thrombosis were not related to the OS.

### Tumor thrombosis response

Of the 43 patients, 18 patients (42%) achieved CR, 7 patients (16%) achieved PR, 16 patients (37%) had SD, and 2 patients had PD (5%). The ORR of all the patients was 58%.

The ORRs of patients with ECOG PS 0-1 and 2-4 were 67% and 14%, respectively ( $p = 0.016$ ). The ORRs of patients with a tumor thrombosis length of  $< 3.8$  cm and  $> 3.8$  cm were 70% and 38%, respectively ( $p = 0.055$ ). The ORRs of patients who received an EQD2 of 42.35 Gy or  $> 48.75$  Gy were 25% and 78%, respectively ( $p = 0.0012$ ). In the univariate analysis the ECOG PS and EQD2 were significantly related to the tumor response, and the length of tumor thrombosis was nearly significantly related (Table 3). In the multivariate analysis of the ECOG PS and EQD2, EQD2 was a unique significant factor (Odds ratio 6.1, 95% CI [1.3, 30],  $p = 0.025$ ). The one-year OS rates of responders ( $n = 25$ ) and non-responders ( $n = 18$ ) were 75% and 35%, respectively, and the difference was statistically significant ( $p = 0.009$ , Fig. 2).

### Liver toxicities

Four patients (9%) 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 died of disease progression two months after the elevated level of AST/ALT. The other two patients recovered from acute liver toxicity for about 10 days without treatment.

Deterioration in the Child-Pugh class was observed in 10 patients. All the patients died within three months of the deterioration being observed, although it was not known whether their liver failures were due to disease progression or adverse events. The relationship between the patients' tumors and treatment factors was evaluated in these 10 patients, and the Child-Pugh score tended to deteriorate in the patients with advanced T stage, a tumor length of more than 3.8 cm, or combined chemotherapy, although this was not statistically significant.

V30Gy was evaluated in 27 patients whose data was not lost. The median dose of V30Gy of the normal liver was 10% (range of 1–31%). Median EQD2 and BED irradiated to the normal liver were 8.6 Gy (range of 0.7–25.3) and 14.3 Gy (range of 1.1–42.1), respectively.

## Discussion

We retrospectively evaluated the treatment results of RT with or without chemotherapy for 43 patients with HCC that invaded PV, HV, IVC, or BD, and the one-year OS rate for all the patients was 60% and their ORR was 58%.

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

In particular, the selection of treatment for HCC with a vascular invasion 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 trial showed that the median OS for patients with advanced HCC, a well-preserved liver function, and undergoing treatment with sorafenib was 10.7

months, and the ORR was only 2–3%. Although the disease control rate (DCR), that was defined as the percentage of patients with CR, PR, or SD based on radiologic review, was 43%. Moreover, the median OS of the patients with macroscopic vascular invasion (MVI) and treated by sorafenib was 8.1 months and the DCR was 38.9% [14]. 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 7.9 months in patients with PVTT and 4.8 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 30% and the ORR was 19% [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.

Previous studies have suggested the potential therapeutic role of RT in patients with vascular invasion 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,  $p < 0.05$ ). 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.

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 6.1, 95% CI [1.3, 30],  $p = 0.025$ ) in the multivariate analysis. This finding was consistent with the results of previous studies that recommended a prescribed dose higher than 45–50 in EQD2 [2, 19-22]. 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 ECOG PS 0-1, Child-Pugh class A, a tumor thrombosis length of less than 3.8 cm, more than 48.75 Gy of EQD2, or combined chemotherapy was significantly better than that of other patients, in the univariate analysis. The length of tumor thrombosis was extracted as a significant prognostic factor among all the aforementioned factors, in the multivariate analysis. In our study, ROC curve analysis was used to calculate a threshold value for the length of tumor thrombosis in relation to response, and that was found to be 3.8 cm. To our knowledge, there has been no study that has demonstrated the significant correlation between the length of tumor thrombosis and OS. It was interesting to note that the length of tumor thrombosis was only a unique factor related with OS, in the 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 thrombosis tended to be irradiated in 48.75 Gy of EQD2 and long tumor thrombosis 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  $\alpha$ -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 thrombosis 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 small tumor thrombosis, 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 ( $V_{50\%} < 50\%$ ), 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 ( $V_{30Gy}$ ), with no more than 30% of the normal liver exposed to more than 30 Gy ( $V_{30Gy} < 30\%$ ) [23]. 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. Recently, some studies have reported the efficacy of SRT or proton beam irradiation for HCC with vascular invasion [21, 22, 24, 25]. 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. In detail, 78% of the patients with N or M factor had received systemic treatment after RT. 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.

Limitations of this study are the small number of patients and inhomogeneity of patients' characteristics, as the number of patients with HCC involving the vascular system is relatively small in the general population and in one hospital, and we excluded the patients who didn't undergo follow-up dynamic imaging studies after completion of RT to evaluate the ORR. Even though these limitations, we have to choose an optimal treatment option case by case because there is no high-level evidence for tumor thrombosis treatment. Furthermore, this was a retrospective study, and because the dose-volume histograms were not calculated in half of the patients and the duration of follow-up was limited, it was impossible to fully evaluate any adverse effects on the liver function.

## Conclusion

RT was a useful treatment for HCC with vascular invasion. 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 thrombosis significantly impacted the OS, in the multivariate analysis. These results indicated that early detection of tumor thrombosis and local treatment with RT may lead to maintaining the liver function and then prolonging the patients' survival.

## Declarations

Ethics approval and consent to participate

The requirement for informed consent was waived because we reviewed anonymous data. Study approval was obtained from the institutional review board of Musahino Red Cross Hospital (reference number, 30002).

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Dr. Tsuchiya reports personal fees from Eisai, personal fees from Bayer, outside the submitted work.

Other authors have nothing to declare.

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Authors' contributions

TN analyzed and interpreted the patient data. TN and RY designed research. AH, MK, K Tsuchiya, K Toda, RY, NI conducted review and editing. TN was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Not applicable.

# Abbreviations

3D-RT:

Three-dimensional conformal radiotherapy

4D:

Four-dimensional

AFP:

$\alpha$ -fetoprotein

BED3:

Biologically effective dose 3

BDTT:

Bile duct tumor thrombosis

CI:

Confidence interval

CPC:

Child-Pugh class

CR:

Complete response

CT:

Computed tomography

CTV:

Clinical target volume

CTX:

Chemotherapy

CTCAE:

## Common Terminology Criteria for Adverse Events

ECOG-PS:

Eastern Cooperative Oncology Group Performance Status

EQD2 :

Equivalent dose in 2-Gy fractions

GTV:

Gross tumor volume

Gy:

Gray

HAIC:

Hepatic arterial infusion chemotherapy

HCC:

Hepatocellular carcinoma

HVTT:

Hepatic vein tumor thrombosis

IMRT:

Intensity-modulated radiotherapy

IVC:

Inferior vena cava

IVCTT:

Inferior vena cava tumor thrombosis

NASH:

Non-alcoholic steatohepatitis

MRI:

Magnetic resonance imaging

ORRs:

Objective response rates

OS:

Overall survival

PD:

Progressive disease

PR:

Partial response

PTV:

Planning target volume

PVTT:

Portal vein tumor thrombosis

RILD

:Radiation-induced liver disease

ROC:

Receiver operating characteristic

RT:

radiation therapy

SD:

Stable disease

TACE:

Transarterial chemoembolization

UICC:

Union for International Cancer Control

V30Gy:

The irradiated relative volume of the remaining normal liver that received more than 30 Gy

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)

## References

1. Yoon SM, Lim YS, Won HJ, et al. Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: long-term patient outcomes. *Int J Radiat Oncol Biol Phys* 2012; 82: 2004–11. <https://doi.org/10.1016/j.ijrobp.2011.03.019>
2. Pao TH, Hsueh WT, Chang WL, et al. Radiotherapy for inferior vena cava tumor thrombus in patients with hepatocellular carcinoma. *BMC Cancer* (2019) 19:560 <https://doi.org/10.1186/s12885-019-5654-9>
3. Nakazawa T, Shibuya A, Okuwaki Y, et al. Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis *BMC Gastroenterology* 2014, 14:84 <https://doi.org/10.1186/1471-230X-14-84>
4. Kudo M, Matsui O, Izumi N, et al. Japanese Society of Hepatology Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. *Liver Cancer* 2014;3:458–468 <https://doi.org/10.1159/000343875>

5. Bruix J, Qin S, Merie P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; 389: 56–66 [https://doi.org/10.1016/S0140-6736\(16\)32453-9](https://doi.org/10.1016/S0140-6736(16)32453-9)
6. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med* 2008; 359, 378–390. <https://doi.org/10.1056/NEJMoa0708857>
7. Luo J, Guo RP, Lai EC, et al. Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Prospective Comparative Study. *Ann Surg Oncol* (2011) 18:413–420 <https://doi.org/10.1245/s10434-010-1321-8>
8. Nouse K, Miyahara K, Uchida D, et al. Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan. *British Journal of Cancer* (2013) 109, 1904–1907. <https://doi.org/10.1038/bjc.2013.542>
9. Wang K, GuoWX, Chen MS, et al. Multimodality Treatment for Hepatocellular Carcinoma With Portal Vein Tumor Thrombus. *Medicine* Volume 95, Number 11, March 2016 1-10. <https://doi.org/10.1097/MD.0000000000003015>
10. Bai H, Gao P, Gao H, et al. Improvement of Survival Rate for Patients with Hepatocellular Carcinoma Using Transarterial Chemoembolization in Combination with Three-Dimensional Conformal Radiation Therapy: A Meta-Analysis. *Med Sci Monit*, 2016; 22: 1773-1781. <https://dx.doi.org/10.12659/MSM.895548>
11. Kondo Y, Kimura O, Kogure T, et al. Radiation Therapy Is a Reasonable Option for Improving the Prognosis in Hepatocellular Carcinoma. *Tohoku J. Exp. Med.*, 2015, 237, 249-257. <https://doi.org/10.1620/tjem.237.249>
12. Meng MB, Cui YL, Lu Y, et al. Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: A systematic review and meta-analysis. *Radiotherapy and Oncology* 92 (2009) 184–194. <https://doi.org/10.1016/j.radonc.2008.11.002>
13. Zou LQ, Zhang BL, Chang Q, et al. 3D conformal radiotherapy combined with transcatheter arterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol* 2014 December 7; 20(45): 17227-17234. <https://doi.org/10.3748/wjg.v20.i45.17227>
14. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; 10: 25–34. [https://doi.org/10.1016/S1470-2045\(08\)70285-7](https://doi.org/10.1016/S1470-2045(08)70285-7)
15. Chen AL, Finn RS, Qin S, et al. Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in firstline treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC). *J Clin Oncol* 2017;

35: abstract 4001. [https://doi.org/10.1200/JCO.2017.35.15\\_suppl.4001](https://doi.org/10.1200/JCO.2017.35.15_suppl.4001)

16. Kokudo T, Hasegawa K, Matsuyama Y, et al. Liver Resection for Hepatocellular Carcinoma Associated With Hepatic Vein Invasion: A Japanese Nationwide Survey. *HEPATOLOGY*, VOL. 66, NO. 2, 2017 510-517 <https://doi.org/10.1002/hep.29225>
17. Pawlik T, Poon R, Abdalla E, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: Results of a multicenter study. *Surgery*. 2005;137:403-10 <https://doi.org/10.1016/j.surg.2004.12.012>
18. Torzilli G, Belghiti J, Kokudo N, et al. A Snapshot of the Effective Indications and Results of Surgery for Hepatocellular Carcinoma in Tertiary Referral Centers: Is It Adherent to the EASL/AASLD Recommendations? *Annals of Surgery*. Volume 257, Number 5, May 2013 <https://doi.org/10.1097/SLA.0b013e31828329b8>
19. Im JH, Yoon SM, Park HC, et al. Radiotherapeutic strategies for hepatocellular carcinoma with portal vein tumor thrombosis in a hepatitis B endemic area. *Liver Int* 2017;37:90–100 <https://doi.org/10.1111/liv.13191>
20. Choi Y, Kim JW, Cha H, et al. Overall response of both intrahepatic tumor and portal vein tumor thrombosis is a good prognostic factor for hepatocellular carcinoma patients receiving concurrent chemoradiotherapy. *Journal of Radiation Research*, 2014, 55, 113–120 <https://doi.org/10.1093/jrr/rrt082>
21. Matsuo Y, Yoshida K, Nishimura H, et al. Efficacy of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis/inferior vena cava tumor thrombosis: evaluation by comparison with conventional three-dimensional conformal radiotherapy. *Journal of Radiation Research*, Vol. 57, No. 5, 2016, pp. 512–523 <https://doi.org/10.1093/jrr/rrw028>
22. Xi M, Zhang L, Zhao L, et al. Effectiveness of Stereotactic Body Radiotherapy for Hepatocellular Carcinoma with Portal Vein and/or Inferior Vena Cava Tumor Thrombosis. *PLoS ONE*, 2013, 8(5): e63864. <https://doi.org/10.1371/journal.pone.0063864>
23. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 76 (3 Suppl) : S10-19, 2010 <https://doi.org/10.1016/j.ijrobp.2009.07.1754>
24. Sugahara S, Nakayama H, Fukuda K, et al. Proton-Beam Therapy for Hepatocellular Carcinoma Associated with Portal Vein Tumor Thrombosis. *Strahlenther Onkol* 2009;185:782–8 <https://doi.org/10.1007/s00066-009-2020-x>
25. Lee SU, Park JW, Kim TH, et al. Effectiveness and safety of proton beam therapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. *Strahlenther Onkol*, 2014, 190, 806–814

## Tables

Table 1. Summary of patient characteristics.

Characteristic (n = 43)	Median (range)/ no. of patients	(%)
<b>Gender</b>		
Male	34	79
Female	9	21
Age (years)	73 (51-85)	
<b>ECOG PS</b>		
0-1	36	84
2-3	6	14
4	1	2
<b>Cause of hepatitis</b>		
Hepatitis B virus	5	12
Hepatitis C virus	22	51
Both B and C virus	1	2
Alcohol	7	16
NASH	4	9
Others	4	9
<b>Child-Pugh class</b>		
A	28	65
B	13	30
C	2	5
<b>Tumor thrombosis invasion site</b>		
Vp2	1	2
Vp3	12	28
Vp4	12	28
Vv2	2	5
Vv3	7	16
Both Vp and Vv	3	7
Bile duct	6	14
<b>T</b>		
T2	7	16
T3	1	2
T4	35	81
<b>N</b>		
N0	36	84
N1	7	16
<b>M</b>		
M0	36	84
M1	7	16
<b>Staging</b>		
II	5	12
III a	1	2
III b	24	56
IV a	7	16
IV b	6	14
<b>Length of tumor thrombosis (cm)</b>		
<3.8	27	63
>3.8	16	37
<b>Primary tumor size (cm)</b>		
<6.6	29	67
>6.6	14	33
<b>EQD2 (Gy)</b>		
42.35Gy	16	37
48.75Gy	25	58
50Gy	1	2
74Gy	1	2
<b>Chemotherapy (Before RT/After RT)</b>		
TACE	6	14
HAIC	5	12
TACE/HAIC	1	2
Sorafenib	7	16
HAIC/Sorafenib	3	7
TACE/Sorafenib	1	2
TACE/Other agents	1	2
Other agents	3	7
None	16	37

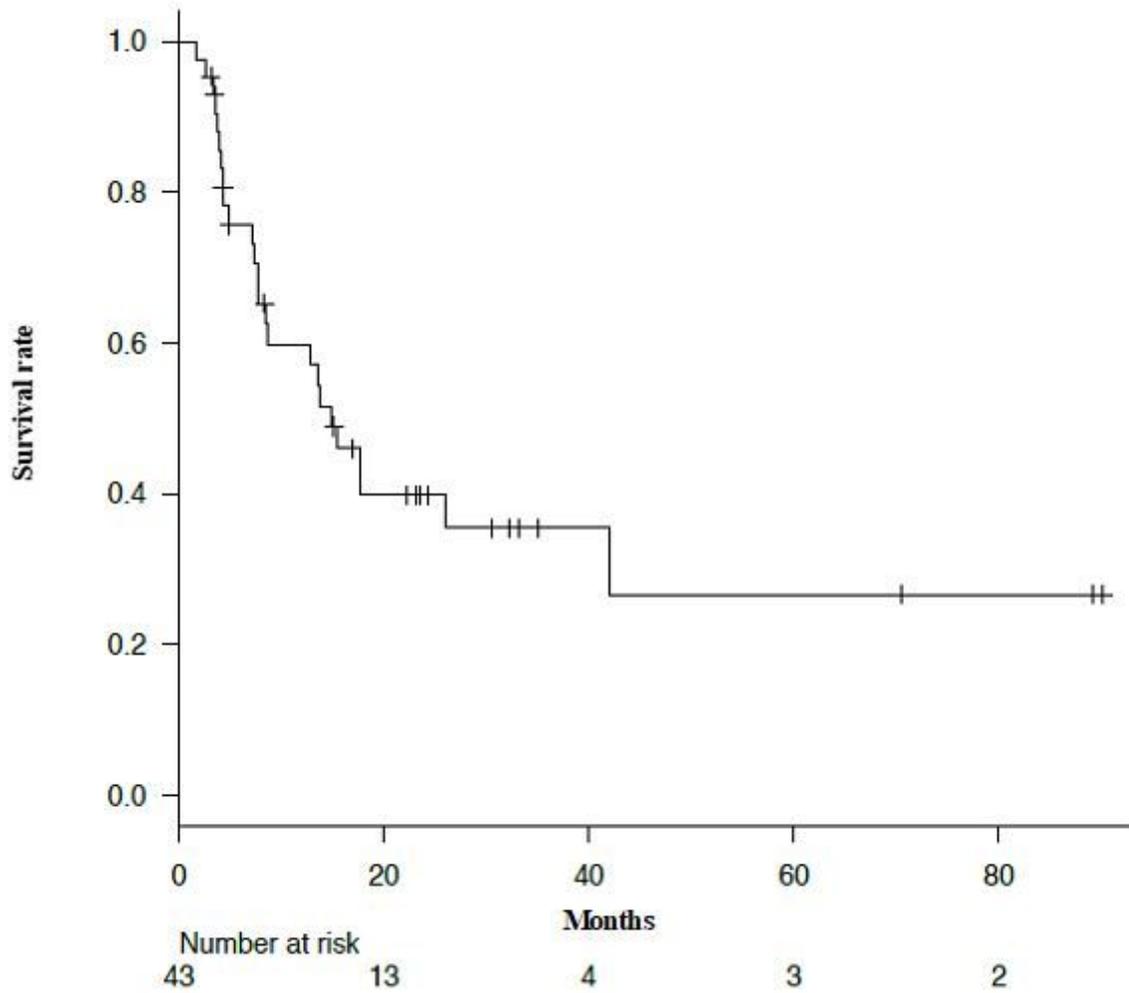
Table 2. Univariate and multivariate analysis of the prognostic factors influencing the OS.

Prognostic factor	No.	1-year OS (%)	Univariate analysis		Multivariate analysis	
				P-value	HR (95% CI)	P-value
Gender						
Male	34	57		0.87		
Female	9	71				
Age (y)						
<60	5	80		0.66		
>60	38	57				
ECOG PS						
0-1	36	67		0.05	1.2 (0.3-4.9)	0.77
2-4	7	29				
Child-Pugh class						
A	28	72		0.003	0.57 (0.68-5.7)	0.21
B	13	42				
C	2	NA				
T						
T2-3	8	88		0.09		
T4	35	53				
N						
N0	36	61		0.25		
N1	7	54				
M						
M0	36	58		0.78		
M1	7	71				
TNM staging						
II	5	NA		0.16		
IIIa-b	25	51				
IVa	6	50				
IVb	7	71				
Primary tumor size (cm)						
<6.6	29	67		0.17		
>6.6	14	40				
Length of tumor thrombosis (cm)						
<3.8	26	77		<0.001	4.96 (1.1-10)	0.03
>3.8	17	31				
Grade of tumor thrombosis						
BDTT	6	83		0.71		
Vv2 or Vp2-3	15	58				
Vv3 or Vp4	22	53				
Site of tumor thrombosis						
PVT	25	52		0.57		
HVTT/IVCT	9	67				
Both PVT and HVTT/IVCT	3	50				
BDTT	6	83				
Presense of BDTT						
Yes	6	83		0.41		
No	37	56				
EQD2 (Gy)						
42.35Gy	16	34		0.001	0.45 (0.14-1.4)	0.18
more than 48.75Gy	27	73				
Combined CTX with RT (Local or Systemic)						
Yes	27	69		0.03	0.56 (0.25-1.27)	0.166
No	16	44				
Three modalities						
Combined only local CTX (TACE, HAIC)	12	67		0.083		
Combined systemic CTX (Sorafenib, Other agents)	15	69				
RT alone	16	44				

Table 3. Response of tumor thrombosis.

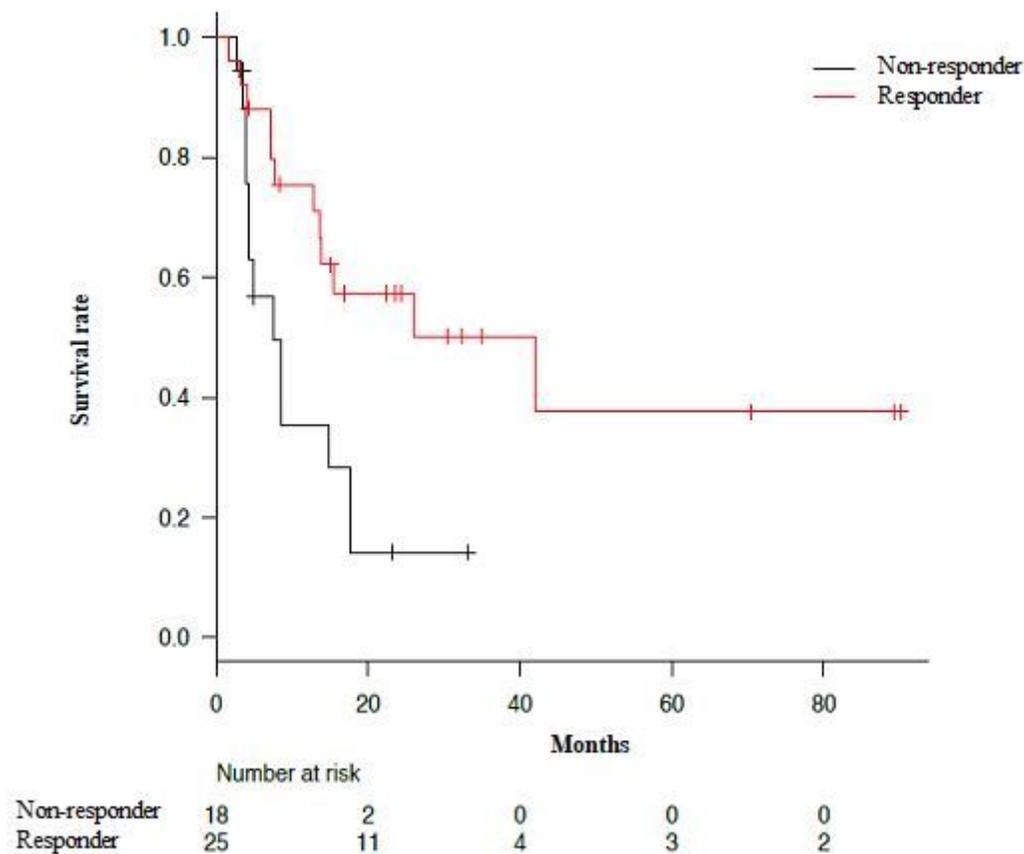
	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
ECOG PS				
0-1	0.088 (0.0017-0.85)	0.016	0.13 (0.01-1.4)	0.09
2-4				
Child-Pugh class				
A	0.89 (0.23-3.74)	1		
B-C				
T				
T2-3	0.8 (0.11-4.9)	1		
T4				
N				
N0	0.49 (0.06-3.35)	0.43		
N1				
M				
M0	4.1 (0.2-212)	0.37		
M1				
Cause of hepatitis				
Viral hepatitis B or C	0.32 (0.07-1.39)	0.11		
others				
Primary tumor size (cm)				
<6.6	0.26 (0.05-1.15)	0.054		
>6.6				
Length of tumor thrombosis (cm)				
<3.8	0.26 (0.056-1.1)	0.055		
>3.8				
Site				
Vv2 or Vp2-3 or BD	1.62 (0.37-7.16)	0.52		
Vv3 or Vp4				
EQD2 (Gy)				
42.35Gy	9.8 (2.1-58.9)	0.001	8.5 (1.9-39)	0.006
more than 48.75Gy				
Combined CTX with RT (Local or Systemic CTX)				
Yes	1.68 (0.41-7.1)	0.53		
N0				

## Figures



**Figure 1**

The OS of all the patients.



**Figure 2**

Comparison of the OS between the responder and non-responder groups. The one-year survival rate of the responder and non-responder groups was 75% (median 26 months) and 25% (median 4 months), respectively ( $p = 0.0003$ ). Responders had significantly better OS than non-responders.

## Supplementary Files

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