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ORIGINAL ARTICLE

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Efficacy of preoperative radiotherapy to portal vein tumor thrombus in the main trunk or first branch in patients with hepatocellular carcinoma

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Abstract
Background. The prognosis of hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) in the main trunk or the first branch is very poor.
Methods. Radiotherapy (RT) to PVTT was followed by hepatectomy within 2 weeks. The dose used was 30–36 Gy, in 10–12 fractions, for 15–20 days. The efficacy of preoperative RT to PVTT in the main trunk or first branch was evaluated by comparing results in patients who underwent hepatectomy (group R; $n = 15$) with preoperative RT and those without preoperative RT (group N; $n = 28$).
Results. The 1-, 3-, and 5-year survival rates in group R were 86.2%, 43.5%, and 34.8%, respectively, while these values in group N were 39.0%, 13.1%, and 13.1%, respectively. The survival curve of group R was significantly better than that of group N ($P = 0.0359$). In group R, five (83.3%) of six patients whose tumor thrombus was completely necrosed (based on pathological examination) and whose follow-up period was over 2 years survived for more than 2 years. Female sex ($P = 0.0066$), multiple tumors ($P = 0.0369$), and absence of preoperative RT ($P = 0.0359$) were ranked as significant factors for a poor prognosis by univariate analysis. Multivariate analysis revealed absence of preoperative RT and female sex to be significant factors for a poor prognosis.
Conclusion. Preoperative RT to PVTT in the main trunk or first branch improved the prognosis of patients with HCC with PVTT, and could be a promising new modality in the treatment of these patients.

Key words Hepatocellular carcinoma (HCC) Portal vein tumor thrombus (PVTT) · Preoperative radiotherapy · Hepatectomy

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Introduction

Hepatocellular carcinoma (HCC) is characterized by tumor invasion to the portal vein and tumor thrombus formation even when the tumor size is small.[1] This characteristic is a crucial factor for prognosis and recurrence in HCC.[2,3] Although transarterial chemoembolization (TACE) is not excluded from the treatment regimen for HCC with portal vein tumor thrombus (PVTT) in the main portal branch,[4] the effectiveness of TACE for HCC with PVTT remains unclear.[5,6] It has been shown that systemic chemotherapy is not sufficiently effective.[7] Recent reports suggest that hepatic arterial infusion chemotherapy is a promising approach.[8,9] Of note, the median survival period of untreated patients with portal thrombosis was reported to be only 2.7 months.[10] Hepatic resection for advanced HCC, with removal of PVTT, has been performed as an emergency procedure to avoid impending death, and this procedure may open the door to an adjuvant therapy.[11] However, even after surgical removal of the tumor with the PVTT in HCC patients, early recurrence, as intrahepatic metastasis through the portal vein thrombus, was noted in most patients.[12] Yet when liver resection was performed for a selected set of patients who had had preoperative TACE or postoperative arterial infusion therapy, long-term survival was noted.[13,14]

Because the liver shows low tolerance to whole-organ irradiation,[15] the use of radiotherapy (RT) for HCC has been restricted to palliative treatment, and it has been performed for patients in whom the condition could not be

controlled by any other mode of treatment.[16,17] However, it was reported that the tolerance dose for the liver depended significantly on the volume of liver irradiated.[18] Although the tolerance dose for whole-organ irradiation is low, a small volume of liver tissue can tolerate a high dose of RT without subsequent serious hepatic problem.[18] The outcome of RT for HCC has recently improved with a new method of irradiation to HCC that can bring about high-dose accumulation in a small area.[19,20] There have also been reports of the application of three-dimensional conformal RT in the treatment of unresectable HCC with PVTT.[21,22]

We assumed that the outcome of hepatic resection for HCC with PVTT might be improved if preoperative RT to PVTT could result in PVTT necrosis, as PVTT can cause HCC cells to be disseminated. We retrospectively reviewed and analyzed the efficacy of preoperative RT to PVTT in the main trunk or first branch in patients with HCC.

Patients and methods

Between January 1990 and October 2006, 619 consecutive patients with HCC underwent primary hepatectomy at the First Department of Surgery, Hokkaido University Hospital. Of these, 45 patients (7.3%) with PVTT in the main trunk or first branch who underwent macroscopic curative hepatectomy were selected as the subjects of this study. Two patients. ... The study patients were classified into two groups: group R, patients who underwent hepatectomy with preoperative RT to PVTT (n = 15); and group N, the patients who underwent hepatectomy without preoperative RT to PVTT (n = 28). Intrahepatic lesions were assessed by ultrasonography (US), helical computed tomography (helical CT), magnetic resonance imaging (MRI), and, if necessary, by CT during angiography. Absence of extrahepatic lesions was evaluated by imaging studies, using helical CT, MRI, and bone scintigraphy within 1 month before the operation.

Between January 1990 and March 2000, preoperative RT to PVTT was performed when decided by the patients' individual physicians. After April 2000, it was performed routinely, though it was not done in 12 patients because of their refusal. External RT targeting the PVTT, not the whole tumor, was indicated in PVTT patients prior to the surgery. The gross tumor volume (GTV) was regarded as the PVTT, ignoring the rest of the tumor; the clinical target volume (CTV) was considered as being equal to the PVTT. The planning target volume (PTV) was the GTV plus the PVTT with margins of 10 mm in the transaxial direction and 15 mm in the cranio-caudal direction, adding a 5-mm internal margin for the cranio-caudal direction. No dose volume histogram was calculated in this study. The doses used were 30 Gy in 10 fractions for 13 patients, and 36 Gy in 12 fractions for 2 patients. The dose was selected so as not to cause too much damage to the vascular components near the PVTT, which would result in postoperative complications. A wedged pair beam arrangement or anterior-posterior-opposed techniques were used for irradiation, which was performed using 6- or 10-MV X-ray beams. The treatment period was 15 to 20 days, with an average of 16 days.

Hepatectomy was performed within 2 weeks of the final delivery of the radiotherapy. When the PVTT was removed, the front of the first branch of the portal vein was exposed and subsequently incised under the occlusion of the portal trunk and proper hepatic artery. After the removal of the PVTT, blood was flushed out by backflow from the distal end by opening the proper hepatic artery and from the proximal end by opening the portal vein trunk. The wall of the portal branch was incised and sutured after flushing out the blood. When the portal trunk was completely obstructed, the PVTT was removed under portal-femoral vein passive bypass. The patients were followed at 1-month intervals by US, thoracoabdominal CT, MRI, and laboratory tests for α-fetoprotein (AFP), AFP-L3, and protein induced by vitamin K absence or antagonists-II (PIVKA-II). Bone scintigraphy was performed if indicated by clinical symptoms. In patients with intra- and/or extrahepatic recurrences, surgical removal, transcatheter arterial chemoembolization (TAE), percutaneous ethanol injection therapy (PEIT), or radiofrequency ablation (RFA) were repeatedly applied. The median follow-up period was 83 months (range, 6–197 months).

The survival rate was calculated using the Kaplan-Meier method. The prognostic factors of the subjects were analyzed by univariate and multivariate analyses.

Statistical analysis

Cumulative and disease-free survival rates were computed according to the Kaplan-Meier method and compared between the groups by the log-rank test. The Cox proportional hazards model was used for multivariate analysis. Statistical analyses using standard tests (x^2, t-test) were performed when relevant. Significance was defined as a P value of less than 0.05. The statistical analyses were performed using Stat View 5.0 for Windows (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The number of patients in group R was 15, while that in group N was 28. The level of serum albumin in group R was significantly higher than that in group N (P = 0.0211). The tumor size in group R was significantly smaller than that in group N (P = 0.0094). However, other tumor factors (serum AFP level, macroscopic type, tumor number and differentiation, and hepatic vein invasion) were almost the same in the two groups. The proportion of patients in group R with preoperative TACE was significantly higher than that in group N (P = 0.0114). The proportion of patients who had hepatitis B and/or -C virus infection, the proportion of patients with liver cirrhosis, and other factors regarding liver function reserve were not different in the

Table 1. Clinical backgrounds of patients

	Group R (n = 15)	Group N (n = 28)	P
Age (years)	53.5 ± 8.3	56.1 ± 9.6	0.3808
Sex			
Male	13	25	
Female	2	3	0.7985
Hepatitis			
HBV	7	16	
HCV	2	3	
NBNC	3	7	
BC	3	2	0.6255
Child-Pugh			
A	15	24	
B	0	4	0.1243
ICGR 15 (%)	13.1 ± 9.3	12.8 ± 4.8	0.901
Albumin (g/dl)	4.09 ± 0.39	3.74 ± 0.49	0.0211
Total bilirubin (mg/dl)	0.69 ± 0.23	0.89 ± 0.47	0.1368
Blood loss (ml)	1799.5 ± 2684.7	3350.7 ± 4735.2	0.2495
AFP (ng/ml)			
<= 200	5	10	
200<	10	18	0.8759
Macroscopic type			
Nodular	6	17	
Non-nodular	9	11	0.1943
Tumor size (cm)	6.47 ± 3.0	11.0 ± 5.9	0.0094
Tumor number			
Single	9	12	
Multiple	6	16	0.2838
Differentiation			
Well+moderately	5	18	
Poorly	10	10	0.1664
Associated liver disease			
Cirrhosis	9	11	
No cirrhosis	6	17	0.1943
Hepatic vein invasion			
+	4	12	
–	11	16	0.2952
Preoperative TACE			
+	9	6	
–	6	22	0.0114
Postoperative HAI			
+	9	16	
–	6	12	0.6267

HBV, hepatitis B virus surface antigen (HBs Ag) (+) antihepatitis C virus antibody (HCV Ab) (–); HCV, HBs Ag (–) HCV Ab (+); NBNC, HBs Ag (–) HCV Ab (–); BC, HBs Ag (+) HCV Ab (+); ICGR 15 (%), indocyanine green retention at 15 min; AFP, α-fetoprotein; TACE, transcatheter arterial chemoembolization; HAI, hepatic arterial infusion

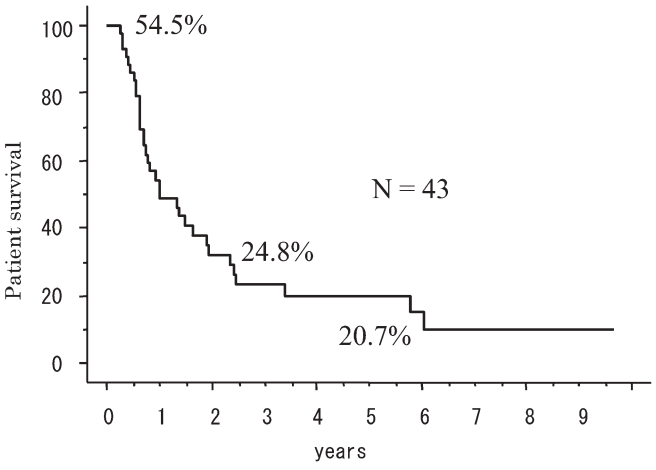

Fig. 1. The 1-, 3-, and 5-year survival rates of 43 patients with hepatocellular carcinoma with portal vein tumor thrombus (PVTT) were 54.5%, 24.8%, and 20.7%, respectively

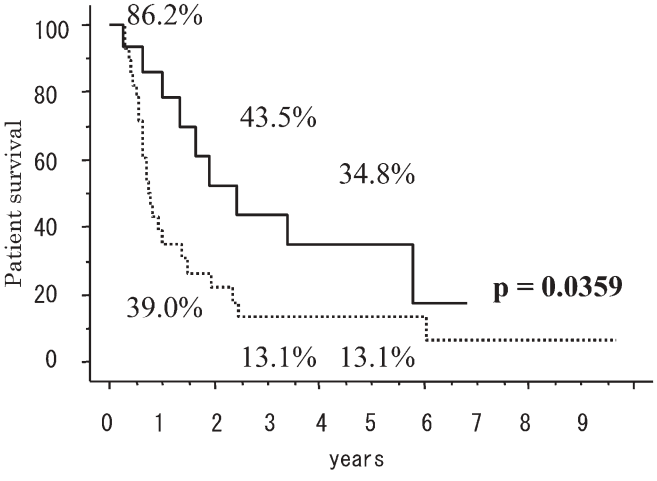

Fig. 2. The 1-, 3-, and 5-year survival rates in group R (patients who underwent hepatectomy with preoperative radiotherapy [RT] to PVTT; *continuous line*; n = 15) were 86.2%, 43.5%, and 34.8%, respectively. The 1-, 3-, and 5-year survival rates in group N (patients who underwent hepatectomy without preoperative RT to PVTT; *dashed line*; n = 28) were 39.0%, 13.1%, and 13.1%, respectively. The survival curve of group R was significantly better than that of group N (P = 0.0359)

two groups (Table 1). None of the patients had uncontrollable ascites.

Acute and late adverse effects of RT

During or shortly after RT, one patient experienced relatively severe nausea and vomiting; excluding this case, no other severe symptomatic adverse events were noted. This patient had been suffering from chronic gastritis and had a fiberscopic examination during RT; however, no new lesions were noted in or near the irradiation field. No apparent late radiation-induced complications were noted in any patients. Radiation hepatitis did not occur in any of our patients.

Survival and recurrence

Thirty-four patients died; 33 from HCC, and 1 from sepsis. The 1-, 3-, and 5-year survival rates of our 43 patients with PVTT were 54.5%, 24.8%, and 20.7%, respectively (Fig. 1); in group R, these values were 86.2%, 43.5%, and 34.8%, respectively, while in group N, they were 39.0%, 13.1%, and 13.1%, respectively. The survival curve of group R was significantly better than that of group N (P = 0.0359; Fig. 2). The median survival times of groups R and N were 1.63 and 0.76 years, respectively. Eight patients in group R showed a completely necrosed tumor thrombus (Table 2) on pathological examination, and 5 (83.3%) of 6 of these patients

Table 2. Outcome in group R patients

Sex	Age (years)	AFP (ng/ml)	Tumor size (cm)	Macroscopic type	Differentiation	vv	Tumor thrombus	Outcome	Survival period (years)
Male	57	2516	3.5	Nodular	Poor	–	Necrosis	Dead	1.63
Male	38	5004	6.5	Non nodular	Poor	–	Necrosis	Dead	3.39
Male	49	561.7	6.5	Non nodular	Complete necrosis	–	Necrosis	Dead	5.78
Male	50	5.3	5.0	Nodular	Well	–	Necrosis	Dead	2.42
Male	63	8.8	9.6	Non nodular	Moderate	+	Necrosis	Alive	6.84
Male	49	5.5	6.0	Non nodular	Moderate	–	Necrosis	Alive	5.21
Male	45	3342	6.0	Nodular	Moderate	–	Viable	Dead	1.90
Male	45	244.3	13.5	Non nodular	Poor	+	Viable	Dead	1.01
Male	49	8677	12.0	Non nodular	Poor	+	Viable	Alive	3.39
Female	56	2212	5.5	Nodular	Poor	–	Viable	Dead	0.64
Male	64	9.6	5.0	Non nodular	Poor	–	Viable	Dead	1.34
Male	51	60332	3.5	Nodular	Poor	–	Viable	Dead	0.27
Male	62	10405	6.0	Non nodular	Poor	–	Necrosis	Alive	1.32
Male	56	2010	2.4	Non nodular	Poor	–	Viable	Alive	0.65
Female	68	3.3	6.0	Nodular	Poor	+	Necrosis	Alive	0.55

vv, Hepatic vein invasion

whose follow-up period was over 2 years survived for more than 2 years after the operation.

In group R, at the end of follow up, 5 patients were alive without recurrence, and 10 showed recurrence. The sites of recurrence were the liver alone in 6 patients (60.0%) and the liver and/or distant metastasis in 4 patients (40.0%). In group N, 1 patient was alive without recurrence. The sites of recurrence were the liver alone in 7 patients (25.9%) and the liver and/or distant metastasis in 20 patients (74.1%).

Preferential factors for long-term survival after curative hepatectomy

Based on univariate analysis, female sex ($P = 0.0066$), multiple tumors ($P = 0.0369$), and absence of preoperative RT ($P = 0.0359$) were ranked as significant factors for a poor prognosis (Table 3). Preoperative TACE did not influence the prognosis of hepatectomized patients with PVTT ($P = 0.3044$). Postoperative hepatic arterial infusion therapy was performed as adjuvant therapy in 25 patients. The regimens for this therapy were: cisplatin (CDDP) + 5-fluorouracil (5-FU) in 7 patients; uracil-futrafur (UFT) + 5-FU in 10 patients; epirubicin (EPI) in 5 patients; and interferon (IFN)-alpha + 5-FU in 3 patients. The postoperative hepatic arterial infusion therapy did not influence the prognosis of hepatectomized patients with PVTT ($P = 0.7112$). However, 1 patient treated with UFT+5-FU remained alive for 36 months without recurrence, and 1 patient treated with IFN-alpha + 5-FU remained alive for 41 months, although he underwent rehepatectomy for intrahepatic recurrence 18 months after the primary operation.

Multivariate analysis of the above factors for poor prognosis revealed female sex ($P = 0.0248$; risk ratio [RR], 3.763; 95% confidence interval [CI], 1.183–11.974) and absence of preoperative RT ($P = 0.0357$; RR, 2.304; 95% CI, 1.057–5.025) as significant factors for a poor prognosis (Table 4).

Discussion

The 1-, 3-, and 5-year survival rates in our patients in group R were 86.2%, 43.5%, and 34.8%, respectively. Multivariate analysis revealed absence of preoperative RT to be a significant factor for poor prognosis ($P = 0.0357$; RR, 2.304; 95% CI, 1.057–5.025). Therefore, preoperative RT to the portal vein tumor thrombus (PVTT) in the main trunk or first branch was effective in improving the prognosis of HCC patients.

The prognosis of patients with PVTT in the main trunk or first branch is very poor; it has been reported that the median survival period of patients with portal thrombosis is only 2.7 months in the event that appropriate treatment measures are not employed.[10] Although several surgeons have reported the successful removal of PVTT with liver resection, the long-term results have not been described.[11,23] However, it has been reported recently that HCC patients with PVTT showed long-term survival when hepatectomy was combined with pre- or postoperative treatment. Minagawa et al.[13] reported that the survival rate of 18 patients, including those who underwent hepatic resection with preoperative TACE, was 42% at 5 years, although 9 patients showed portal invasion in the second-order branches. Necrosis of PVTT was detected on pathological examination in the resected patients. Ikai et al.[24] reported that approximately 10% of the patients who had tumor thrombi in the first branch and the portal trunk survived for over 5 years following hepatectomy. In that report, it was described that postoperative multidisciplinary treatments, including local and systemic adjuvant chemotherapy, were required in addition to hepatic resection because of intrahepatic metastasis.

RT for HCC has been limited to palliative treatment because of the low tolerance of the liver for RT.[15,16,18] However, the effects of a high dose of local RT have been investigated for the treatment of HCC.[19,20] Recently, it was

Table 3. Univariate analysis of factors affecting survival

	n	1-Year survival (%)	3-Year survival (%)	*P*
Age (years)				
<=55	20	55	28.1	0.9916
55<	23	53.1	17.7	
Sex				
Male	38	59.8	25.4	0.0066
Female	5	–	–	
HBs Ag				
+	28	55.4	23.8	0.5738
–	15	52.5	21	
HCV Ab				
+	10	56.3	11.3	0.8078
–	33	53.9	27.5	
Albumin (mg/dl)				
<=3.8	22	43.3	11	0.0556
3.8<	21	65.4	36	
T. Bil (mg/dl)				
<=0.8	25	52	21.7	0.6595
0.8<	18	57.8	26	
ICGR 15 (%)				
<=13	23	54.5	38.2	0.0986
13<	20	53.8	6.2	
Child-Pugh				
A	39	57.4	25.8	0.086
B	4	25	–	
AFP (ng/ml)				
<=200	15	50.6	14.4	0.8502
200<	28	56	28.8	
Macroscopic type				
Nodular	23	50.3	10.2	0.2946
Non-nodular	20	58.7	39.6	
Tumor size (cm)				
<=9.3	24	60.7	25.3	0.6565
9.3<=	19	47.4	21.3	
Tumor number				
Single	21	58.8	39	0.0369
Multiple	21	47.6	9.5	
Differentiation				
Well+moderately	23	50	22.2	0.5663
Poorly	20	57.6	19.7	
Hepatic vein invasion				
+	16	53.6	28.7	0.7206
–	27	54.9	21.1	
Cirrhosis				
+	20	57.4	23	0.8892
–	23	52.2	23.7	
Preoperative radiation therapy				
+	15	86.2	43.5	0.0359
–	28	39	13.1	
Preoperative TACE				
+	15	80	26.7	0.3044
–	28	39.1	23.2	
Postoperative HAI				
+	25	57.5	27	0.7112
–	18	50	18.8	

Table 4. Multivariate analysis of factors affecting survival

	P	Risk ratio	95% Confidence interval
Sex: female	0.0248	3.763	1.183–11.974
Preoperative radiation therapy: none	0.0357	2.304	1.057–5.025
Tumor number: multiple	0.0716	1.990	0.941–4.205

reported that partial hepatic RT was effective in treating unresectable HCC with PVTT.[25] Kim et al.[22] reported that RT induced a 45.8% objective response rate for PVTT in patients with HCC and that the responders had a significantly higher overall survival rate than the nonresponders. Lin et al.[21] reported that stereotactic or three-dimensional conformal RT (3D-CRT) could recanalize PVTT in unresectable HCC and that the response status significantly influenced the overall survival, with the responders showing better 1- and 2-year survival rates. However, because long-term surviving patients were not described in these reports, we believe that the use of RT for HCC was restricted to palliative treatment. Our purpose was to successfully treat HCC with PVTT in the main portal trunk or the first branch. Hepatectomy is the most powerful treatment modality for HCC, apart from liver transplantation, which is contraindicated in HCC patients with PVTT. Therefore, we combined preoperative RT and hepatectomy for such patients. Our method of irradiation, which minimizes irradiation in the normal liver tissue and facilitates an increase in the RT dose without significantly increasing toxicity, differs from that used in 3D-CRT. However, complete necrosis of PVTT was observed in 8 (53.3%) of 15 patients in group R, and no serious complications, including radiation hepatitis, were noted. Therefore, our method of irradiation may be effective as a neoadjuvant therapy for HCC with PVTT and may contribute to an improvement in the outcome of hepatectomy for patients with HCC with PVTT.

Prior to curative hepatectomy, the detection of HCC cells in the bone marrow by real-time reverse transcriptase polymerase chain reaction (RT-PCR) that targets AFP mRNA, which represents disseminated cancer cells, correlates with HCC recurrence and patient survival. Positive AFP mRNA levels were shown to be significantly correlated with portal vein invasion, which is a crucial factor for prognosis and recurrence in HCC.[2,3,26] Based on this viewpoint, targeting the PVTT for the prevention of cancer-cell dissemination appears to be a feasible approach. In the present study, five (83.3%) of six patients in group R with a follow-up period of over 2 years and whose tumor thrombus was completely necrosed (based on pathological examination), survived for more than 2 years. Minagawa et al.[13] reported a good survival rate in 18 HCC patients with PVTT, including those who underwent hepatic resection with preoperative TACE. Necrosis of the PVTT in these patients was detected by pathological examination. Therefore, in that study, TACE induced the PVTT necrosis, decreasing the dissemination of HCC cells to the portal system. However, in our series, the survival rates of patients with preoperative TACE were not significantly different from those of patients without preoperative TACE. It has been reported that TACE was not efficacious for all types of HCC with main portal vein thrombosis,[5,27] and preoperative TACE reduced the long-term survival rate after hepatic resection for resectable HCC;[28] thus, it seems that

the PVTT necrosis and improvement of patients' survival in our series may have been induced mainly by the preoperative RT.

The recurrence rate in our series was very high, even in patients who underwent hepatectomy with preoperative RT; therefore, it is necessary to develop a more effective technique for hepatic arterial infusion chemotherapy as an adjuvant therapy. In various regimens of hepatic arterial infusion chemotherapy, low-dose cisplatin (CDDP) and 5-FU therapy and combination therapy with interferon (IFN)-alpha/5-FU are expected to be effective.[8,9] Fukuda et al.[29] reported that 3 patients with PVTT in the portal trunk or the first branch underwent hepatectomy followed by hepatic arterial infusion chemotherapy using low-dose CDDP and 5-FU therapy, and these patients survived for over 5 years. Nagano et al.[14] reported that 15 patients with HCC with PVTT were treated with FU arterial infusion and IFN therapy (FAIT) and surgery and all these patients (100%) survived for over 1 year; of their 15 patients with surgery, but without FAIT, 10 (67%) died within 1 year.

In conclusion, preoperative RT for PVTT in the main trunk or the first branch is effective. This method could be a promising novel modality for patients with HCC with PVTT in such locations.

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