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Three-Dimensional Conformal Radiotherapy Combined Transcatheter Arterial Chemoembolization for Patients with Hepatocellular Carcinoma with Tumor Thrombus

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Abstract

The purpose of this study was to evaluate the outcomes of three-dimensional conformal radiation therapy (3D-CRT) combined with transcatheter arterial chemoembolization (TACE) for portal vein tumor thrombus (PVTT) and/or inferior vena cava tumor thrombus (IVCTT) in patients with hepatocellular carcinoma (HCC). Thirteen patients with HCC and PVTT and/or IVCTT were treated with this combined treatment modality from 2009 to 2013. TACE was performed for the intrahepatic main body of HCC, PVTT and/or IVCTT via selective feeding arteries using lipiodol, cisplatin or epirubicin hydrochloride, followed by gelatin sponge particles. 3D-CRT was performed for PVTT and/or IVCTT with a total dose of 50 Gy in 25 fractions over 5 weeks after TACE. All patients completed this combined treatment. Eight patients showed partial response (PR), four patients showed stable disease (SD), and one patient showed progressive disease (PD). Median overall survival (OS) was 17.7 months, and median cause-specific survival (CSS) was 18.3 months. All 10 patients evaluated using the enhanced computed tomography (CT) scans at 3 months after 3D-CRT showed CR or PR. Grade 3 of leukocytopenia or thrombocytopenia was observed in the acute phase in five (38.5%) patients and was observed in the late phase in three (25.0%) patients. Deterioration of Child-Pugh class occurred in two (15.4%) patients. None of the cases showed change in performance status (PS) after this combined treatment modality. We conclude that this combined treatment provides longer survival time with acceptable toxicities for patients with advanced HCC and PVTT and/or IVCTT.

Keywords: Portal Vein Tumor Thrombus; Inferior Vena Cava Tumor Thrombus; Hepatocellular Carcinoma; Radiotherapy; Combined Transcatheter Arterial Chemoembolization

Introduction

Outcomes for patients with advanced hepatocellular carcinoma (HCC) and portal vein tumor thrombus (PVTT) and/or inferior vena cava tumor thrombus (IVCTT) are very poor, with median survival rates of less than 3 months without treatment or 4 to 9 months with systemic chemotherapy [1,2]. Multidisciplinary treatment with arterial infusion chemotherapy, transcatheter arterial chemoembolization (TACE) and radiotherapy for these patients results in a median survival time (MST) of approximately 12 months [3-5]. However, the optimal combination of treatments has been not established. In this report, a new combination of radiotherapy and TACE is proposed: namely, precedent TACE performed for the intrahepatic main body of HCC, PVTT and/or IVCTT via selective feeding arteries, followed by three-dimensional conformal radiation therapy (3D-CRT) targeting PVTT or IVCTT. The present study describes our preliminary data of this combined treatment in a retrospective cohort to elucidate its feasibility and clinical utility in HCC patients with PVTT and/or IVCTT.

Materials and Methods

Patients

We retrospectively identified 13 patients who received this combined treatments between April 2009 and March 2013. HCC, PVTT and IVCTT were demonstrated by computed tomography (CT) and magnetic resonance imaging (MRI) with contrast enhancement. Patients were excluded from this combined treatment if they had Child-Pugh class C disease, they were older than 80 years, they presented with an Eastern Cooperative Oncology Group (ECOG) performance status scale of more than 3, they had undergone abdominal irradiation, they had active hepatitis or other active malignancies, or, at the time of 3D planning for radiotherapy, they had received a radiation dose of more than 30% of the 30 Gy (V_{30}) range (considered the limit of whole-liver tolerance). Written informed consent for TACE and 3D-CRT was obtained from all patients, and the study was approved by the institutional review board of Fukuoka University Hospital.

TACE

All patients underwent TACE before 3D-CRT. TACE was performed for the main body of HCC at least from the second order branches of the hepatic artery, and PVTT and/or IVCTT as well if possible, using lipiodol, cisplatin or epirubicin hydrochloride, followed by gelatin sponge particle. A mixture of 1 to 3 mL of ionized oil contrast medium (lipiodol), 50 mg of cisplatin (IA-call, Nippon Kayaku Co., Ltd.), or 30-50 mg of epirubicin hydrochloride (Farmorubicin, Pfizer, Inc.) was infused for the feeding arteries of main body of HCC, PVTT and/or IVCTT.

Radiotherapy

The treatment planning of 3D-CRT was accomplished using version 8.6 of the Eclipse treatment planning system (Varian, Palo Alto, USA). Treatment planning was performed using CT scans (slice thickness, 2.5 mm). The gross tumor volume (GTV) was defined as areas of PVTT and IVCTT, using plain CT referring to slow-attenuation intraluminal filling defects in the enhanced CT and/or MRI. The clinical target volume (CTV) was defined as the GTV plus a 0.5 cm margin. The internal margin by respiratory movement of the liver was defined using planning CT. When the respiratory movement was more than 1 cm, the internal target volume (ITV) was determined by adding the respiratory movement to the longitudinal margins of CTV. The planning target volume (PTV) contained an automated 0.5 cm expansion of the CTV/ITV to account for repositioning accuracy. The daily fraction size was 2 Gy, and a photon energy of 10 MV was used with two to four portal beams in all patients. 3D-CRT was performed 2 to 4 weeks after TACE. No main body of HCC was irradiated, and no patients received concurrent chemotherapy.

Response evaluation

PVTT and/or IVCTT was evaluated on the enhanced CT scans at 4 weeks after 3D-CRT. The volume of PVTT and/or IVCTT was calculated on plain CT for the planning and enhanced CT for the evaluation before and after this combined treatment. Complete disappearance of the PVTT and/or IVCTT was defined as a complete response (CR), more than 50% decrease in volume was defined as a partial response (PR), less than 50% decrease or no change was defined as stable disease (SD), and others were defined as progressive disease (PD). The grade of the accumulation of lipiodol of PVTT and/or IVCTT was classified into one of three groups. No accumulation was classified as group 'None', less than 30% was classified as group 'Low', and above 30% was classified as group 'High' on plain CT after TACE. The organs at risk (OAR) (i.e., liver, stomach, duodenum and right kidney) were evaluated using the device of the dose volume histogram (DVH) in the radiation therapy planning system. The adverse hematologic and gastrointestinal effects were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) ver. 4.0.

Statistical analysis

The probability of survival was calculated according to the method of Kaplan and Meier. The survival time was measured from the date of the first TACE. The relationship between the variables and survival was assessed by the log-rank test in univariate analysis. Univariate analysis of parameters was demonstrated by the Cox's proportional hazards model. Statistical significance was indicated by a p value <0.05.

Results

Patient characteristics

Clinical characteristics are summarized in Table 1. The age of the patients was 54 to 72 years (median, 64 years), and the patient population consisted of 11 males and 2 females. Performance status was score 0 in 11 patients and was score 1 in 2 patients. The Child-Pugh class was class A in 8 patients and class B in 5 patients. The location of PVTT and/or IVCTT was Vp3 (first hemiliver portal vein) in 4 patients, Vp4 (main portal vein) in 5 patients and Vv3 (inferior vena cava) in 5 patients (6). Stage of HCC was IVA in 12 patients and IVB in 1 patient.

Tumor response of PVTT and/or IVCTT

Tumor response of PVTT and/or IVCTT was CR in 0 patients, PR in 8 patients, SD in 4 patients, and PD in 1 patient. The relationship between the accumulation of lipiodol in PVTT and/or IVCTT and the response of PVTT and/or IVCTT is shown in Table 2. A statistically significant difference in PR in 8 patients and SD in 4 patients and PD in 1 patient was not observed when comparing group Low and group High (p=0.72). Ten

patients were evaluated with enhanced CT at 3 months after 3D-CRT; tumor response of PVTT and/or IVCTT was CR in 5 patients and PR in 5 patients.

Table 1. Patient Characteristics.

Patient number	13
Age	54-72 years(median, 64 years)
Gender	Male: 11, Female: 2
Performance status	0: 11, 1: 2
Child-Pugh class	A: 8, B: 5
Location of PVTT and/or IVCTT	Vp3: 4, Vp4: 5, Vv3: 5*
Stage of HCC	IVA: 12, IVB: 1
HCC	first: 8, recurrence: 5
Interval between TACE and 3D-CRT	13-48 days(median, 23 days)

*one case included simultaneous radiation therapy to two lesions
PVTT= portal vein tumor thrombus, IVCTT= inferior vena cava tumor thrombus, Vp3= first hemiliver portral vein, Vp4= main portal vein, Vv3= inferior vena cava, HCC= hepatocellular carcinoma, TACE= transcatheter arterial chemoembolization, 3D-CRT= three-dimentional conformal radiation therapy

Survival and outcome

The median follow-up time was 14.8 months (range, 2.2-56.1 months). The curves of overall survival (OS) and cause-specific survival (CSS) are shown Figure 1. Median OS and CSS were 17.7 and 18.3 months, respectively. Univariate analysis showed that the control of main body of HCC, but not Child-Pugh classes, the adjuvant treatment, response of PVTT and/or IVCTT and the accumulation of lipiodol in PVTT and/or IVCTT were prognostic factors for OS and CSS (Table 3). A representative case is shown in Figure 2.

Adjuvant and salvage therapy after combined treatment

Of the 13 patients, there was 1 cryptogenic death, and 2 patients received best supportive care. The remaining 10 patients received additional treatment. The details of the adjuvant and salvage therapy were transcatheter arterial chemoembolization (TACE) and sorafenib in 3 patients;

Table 2. Relationship between lipiodol accumulation and response of PVTT and /or IVCTT.

Lipiodol accumulation	Response of PVTT and /or IVCTT	*p* value
Low: 9	PR: 5, SD: 4	0.72
High: 4	PR: 3, PD: 1	

Low= lipiodol accumulation< 30%, High= lipiodol accumulation≧30%, PVTT= portal vein tumor thrombus, IVCTT= inferior ven cava tumor thrombus, PR= partial response, SD= stable disease, PD= progressive disease.

TACE, Fluorouracil (5-FU) and Cis-diamine dichloroplatium (CDDP) by continuous arterial infusion in 3 patients; TACE and 5-FU in 1 patient; 5-FU and CDDP by continuous arterial infusion in 1 patient; sorafenib in 1 patient; and Tegafur/Uracil (UFT) in 1 patient. The main body of HCC could be evaluated after this combined treatment in 12 patients the response was CR in 2 patients, SD in 1 patient, and PD in 9 patients.

Adverse effects

Adverse effects are summarized in Table 4. In all patients, it was possible to complete this combined treatment without interruption and without deterioration of PS. Grade 3 hematological toxicities were observed in five patients (leukocytopenia in three patients and thrombocytopenia in two patients) in the acute phase. However, all patients have been in the state of grade 2 from the pretreatment. Grade 3 hematological toxicities were observed in three patients (leukocytopenia in one patient and thrombocytopenia in two patients) in the late phase. However, these patients were also in the acute phase and progressed into the late phase. Worsening of Child-Pugh class was observed in two patients (one patient from grade A to B, and one patient from grade B to C). The mean percent volume of the total liver as a parallel organ receiving a dose exceeding 30 Gy (V_{30}) was 18.3% (range, 7.6% to 24.2%). The mean maximum dose of radiation to the gastro-duodenum as a serial organ was 35.0 Gy. The mean dose of radiation to the right kidney was 2.0 Gy. It was thought that the radiation dose of each organ was within the tolerance dose. Grade 2 acute liver functional damage was observed in two patients, and there were no adverse effects related to the gastro-duodenum or kidney.

Table 3. Univariate analyses of factors predicting overall survival.

Variable	n	Univariate *p*
Control of the main body of HCC (CR: SD•PD)	2:10 *	0.02
Child-Pugh class (A: B)	8:5	0.09
Adjuvant treatment (Yes: No)	10:3	0.88
Response of PVTT and/or IVCTT (CR: PR)	5:5**	0.26
Accumulation of lipiodol in PVTT and/or IVCTT (High: Low)	4:9	0.95

*One patient could not be evaluated because of cryptogenic death at 65 days.

** Three patients could not be evaluated because of cryptogenic death. Two patients received best supportive care over 3 months.

HCC= hepatocellular carcinoma, CR= complete response, SD= stable disease, PD= progressive disease, PVTT= portal vein tumor thrombus, IVCTT= inferior vena cava tumor.

Figure 1. Overall survival curve (A) and cause-specific survival curve (B)
MST = median survival time.

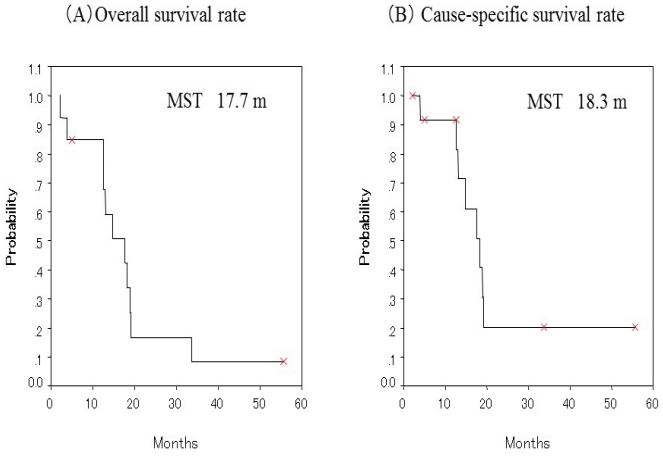
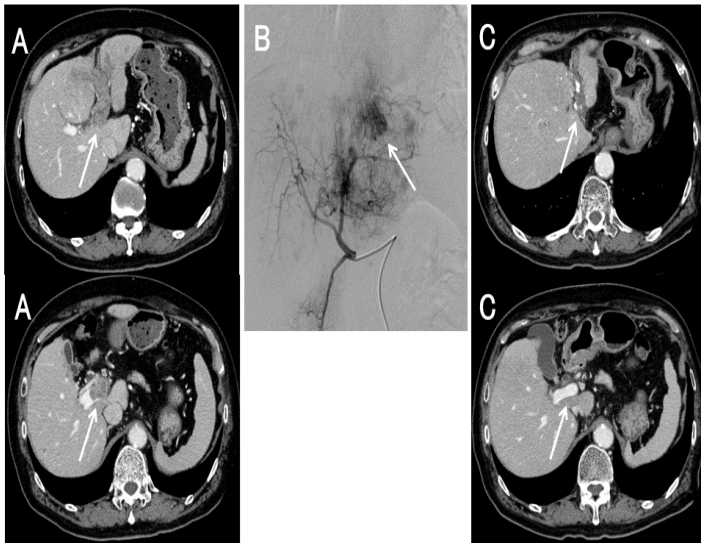


Figure 2. A representative case: enhanced CT of pre- and post-treatment and angiography of pre-treatment of CR case. This patient has survived for 4.7 years.
(A) Pre-treatment, portal vein trunk and left branches are involved. (B) "thread and streaks sign" of TACE. (C) Post-treatment, portal vein tumor thrombus are decreased in size at 1 month after the combined treatment. CT = computed tomography, CR = complete response, TACE = transcatheter arterial chemoembolization.



Discussion

The prognosis of advanced HCC with PVTT and/or IVCTT is extremely poor, and standard treatment has been not established for these patients. The presence of tumor thrombosis in the portal trunk or its first-order branches has been considered a contraindication for TACE due to the risk of ischemic liver failure [3]. However, if these tumors are left untreated, dismal outcome is likely. Indeed, PVTT may induce lethal liver dysfunction or variceal rupture due to elevated pressure in the portal venous system, and IVCTT is associated with an increased risk of sudden death due to pulmonary embolism related to dropped-out tumor thrombus.

Table 4. Side effects after combined treatment.

Variable		n
Accomplished without interruption	No	0
	Yes	13
Performance Status	Deterioration	0
	No Change	13
Acute Adverse Effects (≧Grade 3)	Leukocytopenia	3
	Thrombocytopenia	2
Late Adverse Effects (≧Grade 3)	Leukocytopenia	1
	Thrombocytopenia	2
Child-Pugh class	Worsened	2*
	No change	11

* One patient changed from A to B, and one patient changed from B to C

Some investigators have attempted to elucidate the safety and efficacy of TACE for HCC with PVTT or IVCTT [3-5, 7-10] by means of super-selective cannulation. When PVTT and/or IVCTT are hypervascular (showing so-called "thread and streaks signs" on angiography) and when super-selective cannulation is possible to the arteries supplying the PVTT or IVCTT, TACE alone may control HCC with PVTT or IVCTT. However, this approach is often impossible due to technical difficulty. In our cases, PVTT and IVCTT were all hypervascular on angiography, but super-selective cannulation to the supplying arteries was not possible in any of the cases. Further, there was no difference in the therapeutic effect of our combined therapy between those with versus without sufficient accumulation of lipiodol in PVTT or IVCTT. However, TACE may participate the good reduction rate of PVTT and/or IVCTT (PR and CR) was observed in 100% of the patients at 3 months. On the other hand, radiotherapy (3D-CRT) alone has been reported to achieve a 50 to 80% control rate for PVTT/IVCTT [7-10]. In our cases, the reduction rate of PVTT and/or IVCTT (PR and CR) was observed in 62% on CT at 1 month after this combined treatment and in 100% of the patients at 3 months. The fact that response rate of PVTT/IVCTT was better at 3 months when compared with 1 month after the treatment may be considered to be an indicator of the late effect of radiotherapy, which supports the concept of our combined treatment. Koo et al. reported that the embolization reduced blood supply in PVTT and IVCTT and that the radiosensitivity of PVTT and IVCTT decreased due to a greater percentage of hypoxic cancer cells when radiotherapy was given immediately after TACE [5]. The optimal interval between TACE and 3D-CRT is not known, but studies reported that the reoxygenation of cancer cells occurs by 2 to 3 weeks after TACE. In addition, performance status of patients and laboratory data usually improve in 2 to 3 weeks after TACE, based on our clinical experience. Thus, we performed 3D-CRT at a median 23 days after TACE [5] and obtained relatively satisfactory results. Median OS and CSS in

our study population were 17.7 and 18.3 months, respectively, which is better than those reported in previous studies (the treatment before radiotherapy with 45 to 61.2 Gy was TACE or surgery and OS was 5.3 to 13.9 months) [3,4,7-9,13]. Previous reports have suggested that Child-Pugh class, age, adjuvant therapy, and control of main body of HCC are significant prognostic factors, according to multivariate analysis [4,7,13-15]. In our study population, the control of the main body of HCC was the only prognostic factor, according to univariate analysis. The difference between findings in the present study and previous studies might be due to the small number of cases in the present study. Our study showed long term survival would result from control of the main body of HCC, enable by the additional treatment of keeping liver function and bloodstream brought by reduction of PVTT and/or IVCTT. In addition, two cases might participate in improvement of OS and CSS derived from complete response of the main body of HCC. While Yu *et al.* reported that the additional treatment after radiotherapy was associated with improved outcomes for the HCC patients with PVTT [15], standard adjuvant treatment after 3D-CRT has been not established. In our cases, various adjuvant therapies were given to 10 patients, and this small number of cases made it impossible to determine whether one therapy was superior to others. The adverse effect profile in response to combined treatment was acceptable in this study. The acute adverse effects were grade 3 leukocytopenia and thrombocytopenia. Although the incidence of these adverse events was slightly higher when compared with those reported in previous studies [4,7,8], all cases recovered with routine conservative management. Late adverse effects were grade 3 leukocytopenia and thrombocytopenia and were also reversible with conservative management. Radiation-induced liver damage (RILD) is a critical issue to consider when employing radiotherapy for HCC with PVTT and/or IVCTT, and worsening of Child-Pugh class and PS occurred in two patients (15%) in the study. This relatively low adverse effect rate is probably related to the fact that we targeted only PVTT or IVCTT with 3DCRT, and therefore, V*30* was relatively low (18.3 ± 4.6%). [7,16,17)]. Huang *et al.* reported an even lower RILD rate of 0.9% among 326 HCC patients with PVTT who were treated with radiation therapy and when V_{30} was limited to less than 30% of the normal liver [18]). Kim *et al*. reported that V_{30} should be limited to less than 60% whenever possible to minimize the risk of grade 2 or worse RILD after 3D-CRT for unresectable HCC [16]. In the present study, the maximum percent volume of V_{30} was 24.2%, and grade 2 acute liver functional damage was observed in two patients but was tolerable.

Conclusion

A new combined treatment of TACE and 3D-CRT for advanced HCC with PVTT and/or IVCTT was feasible, safe, and effective according to this preliminary study. Further investigation is needed to establish the optimal protocol for this combined treatment modality, including the possible application of intensity modulated radiotherapy (IMRT) or particle therapy and the inclusion of molecular targeted agents as adjuvant therapy [19-21].

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