THREE DIMENSIONAL CONFORMAL RADIATION THERAPY TO PORTAL VEIN THROMBOSIS AREA AS THE INITIAL TREATMENT FOR HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN THROMBOSIS: PROGNOSTIC FACTORS AND OUTCOME FOR PATIENTS COMPLETING RADIOTHERAPY BUT CONTRAINDICATED FOR OTHER TREATMENTS

Yu-Jie Huang, Stephen Wan Leung, Chong-Jong Wang, Li-Min Sun, Shyh-An Yeh, Eng-Yen Huang, Hui-Chun Chen, Fu-Min Fang, Ching-Yeh Hsiung, Hsuan-Chih Hsu

Department of Radiation Oncology, Chang Gung Memorial Hospital Kaohsiung Center

Background and Purpose : Hepatocellular carcinoma (HCC) with portal vein thrombosis (PVT) indicated poor prognosis and is the contraindication for transcatheter hepatic arterial embolization (TAE). Although the conventional method of external irradiation to HCC has been proven not effective, three-dimensional conformal radiation therapy (3D-CRT) may be an alternative choice. In this study, the prognostic factors and results of 3D-CRT to PVT area as the initial treatment for HCC with PVT patients who could not receive other treatments was investigated.

Materials and Methods : From September 1997 to August 1999, 42 patients who were initially diagnosed as HCC with PVT without any previous treatment and Eastern Cooperative Oncology Group (ECOG) performance status superior to Grade II were enrolled into the study. Radiation therapy (RT) was given via 3D-CRT technique to PVT area with 50 Gy to 61.3 Gy in daily fraction of 1.8 Gy to 2.5 Gy by individual condition. Age, sex, ECOG performance status, Child-Pugh classification, tumor location, tumor type, invaded PVT area, radiation treatment volume, alpha-fetoprotein (AFP), upper gastrointestinal (UGI) bleeding history, viral hepatitis markers for B and C, and pre-treatment liver function, on-treatment liver function, post-treatment liver function, including Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and Total Bilirubin (Bil-T), were recorded for analysis.

Results : Twenty-four patients (57%) completed the RT course and others withdrew from RT due to worsened ECOG performance status. Seven complete RT patients were lost to follow-up. Nine of 17 followed patients (53%) had positive response to RT. Seven patients (41%) underwent further TAE after RT. In the patients who could complete RT, overall survival for 3 months and 6 months were 63% and 34%. Survival rate for incomplete RT patients was 24% and 8% for 3 months and 6 months respectively. There was statistically significant difference ($p = 0.022$) in survival between patients who completed RT and their counterpart. There were no significant difference in pre-treatment, on-treatment and post-treatment AST, ALT and Bil-T level. Only 6 patients (35%) were reported to have suspicious gastric complications. Bil-T was the only significant factor for predicting whether RT could be completed or not ($p = 0.028$).

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Address reprint request to: Yu-Jie Huang, M. D., Department of Radiation Oncoloy, Chang Guny Memorial Hospital Kaohiung Center, No. 123, Ta-Pei Road. Niao Sung Hsiang, Kaohsiung Hsien 833, Taiwan.

Conclusions **:** Less than half of the patients completed the planned RT and were adequately followed, indicating the poor prognosis and selection of patients in this study. Further prospective control studies with appropriate patient enrollment, such as low bilirubin level, is required to verify the feasibility, patterns of failure, and the possible benefit of 3D-CRT as the initial treatment of HCC with PVT.
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Key words: Hepatocellular carcinoma, Portal vein thrombosis, Three-dimensional conformal radiotherapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common human malignancies and is also one of the most ominous cancers [5]. Published census from the Department of Health in Taiwan, 2000, showed that cancer death was 142.23/100,000 population. Hepatoma was the number two cause of cancer death with 27.05/100,000 population [28]. Surgical resection was the treatment of choice for HCC patients. For the majority of patients (approximately > 80%), non-surgical treatment was the only alternative [2]. Non-surgical treatment modalities, such as percutaneous ethanol injection therapy (PEIT) and transcatheter hepatic arterial embolization (TAE), had been reported to be as effective as hepatectomy for small solitary HCC, with less risk and expense [27]. The most efficacious non-surgical treatment options were TAE and transcatheter arterial chemoembolization (TACE). Systemic chemotherapy and hepatic intra-arterial chemotherapy were not very effective [16]. However, TAE is not indicated for patients with thrombosed main portal veins [26]. Its therapeutic effect is also doubtful when the tumor is infiltrative or hypovascular [15].

Radiation therapy (RT) has been applied extensively in treating malignancies, especially for local control of cancer. The conventional method of external irradiation to HCC has been proven not effective [10]. But nowadays, a new elegant technique called three-dimensional conformal radiation therapy (3D-CRT) has been available since 1990s. The treatment can be tailored to minimize the beam scatter and deliver the maximum therapeutic dose to tumors [12]. There were reports about 3D-CRT to HCC [4, 7]. They used 3D-CRT to whole tumor area and favorable results were noted. But the critical illness of these patients was not the HCC itself; Portal vein thrombosis (PVT) was a poor prognostic factor [13]. RT targeted on only PVT site with TAE had also been tried [25]. For patients who were initially diagnosed as HCC with PVT and were not candidates for TAE, this could not be practical. Therefore, these patients might be attempted to treat PVT site first. The goal was to make possible for further treatments, such as TAE, PEIT, etc. In this retrospective study, effect of 3D-CRT to PVT area as the initial treatment for HCC with PVT, especially for patients who were not candidates of other treatments but were able to complete RT courses, was investigated and presented.

MATERIALS AND METHODS

Patient population

Forty-two patients who were initially diagnosed as HCC with PVT without extrahepatic metastasis and didn't receive any previous treatment were enrolled in our study. The patients

were selected from the referrals between September 1997 and August 1999 in our department. The diagnosis was made by either liver biopsy or aspiration cytology. In cases whose pathologic report had not been available, it was diagnosed by clinical presentations, image studies and alpha-fetoprotein of more than 500 ng/ml [19, 21]. PVT was revealed by liver sonography or computed tomography (CT) and further TAE or PEIT treatment was impossible by radiologist's opinion. Referred patients were evaluated by radiation oncologist and Eastern Cooperative Oncology Group (ECOG) performance status [18] was estimated. The patients with ECOG performance status less than or equal to Grade II, that were the patients at least ambulatory and able to self-care, were planned to have the treatment. The patient's characteristics were listed in Table 1.

Radiation therapy planning

The patients were immobilized in a supine position by a thermoplastic abdomen cast and computerized treatment planning system (Pinnacle, ADAC Laboratory, U.S.A.) was used. Liver CT of each patient was performed to obtain patient contours and to define target volume. The liver CT films were read and the anatomical PVT sites were recognized by the diagnostic radiologist as gross tumor volume (GTV). The clinical target volume (CTV) was then defined consulting with GTV by the radiation oncologist (Fig. 1). It was considered to include possible thrombosed portal vein basin and its branches. Once CTV was defined, the planning target volume (PTV) was established by adding margins reflecting estimates of set-up error and respiratory motion for the individual patient (judged by fluoroscopy at the time of simulation). PTV typically extended 10-20 mm horizontally and 15-25 mm vertically beyond CTV and was documented. In our study, the PTV was from 56 cm^3 to 298 cm^3 with mean and median equal to 160 cm^3 and 152cm^3,

Table 1. Characteristics of the patients

	No. of the patients (Total patients n=42)
Gender	
Male	39 (93%)
Female	3 (7%)
Age (years)	
	Mean 53.3
	Median 56 range 32-75
Hepatitis Marker#	
HBsAg(+)	31 (74%)
Anti-HCV Ab(+)	8 (19%)
Negative for HBsAg & Anti-HCV Ab	6 (14%)
Tumor Location	
R't Lobe	26 (62%)
L't Lobe	6 (14%)
Both Lobes	10 (24%)
Tumor Type	
Solitary (<5cm)	2 (5%)
Huge (>5cm)	20 (48%)
Multiple	9 (21%)
Infiltrative	11 (26%)
Invaded PVT Area#	
R't PVT	34 (81%)
L't PVT	15 (36%)
Main PVT	29 (69%)
High AFP	13 (31%)
Liver Function	
AST*	
	Mean 3.9
	Median 4 (Range 1-10)
ALT*	
	Mean 2.3
	Median 2 (Range 1-10)
Bil-T (Grade)	
Grade I	34 (81%)
Grade II	4 (10%)
Grade III	4 (10%)
ECOG Performance Status	
Grade 0	11 (26%)
Grade 1	19 (45%)
Grade 2	12 (29%)
Child-Pugh Classification	
Class A	25 (60%)
Class B	17 (40%)
Class C	0 (0%)
Pathologic proof	11 (26%)

#Hepatitis marker and Portal vein thrombosis area were shown on episode number.

*Level of AST and ALT were the fold number of upper normal limit value of AST and ALT.

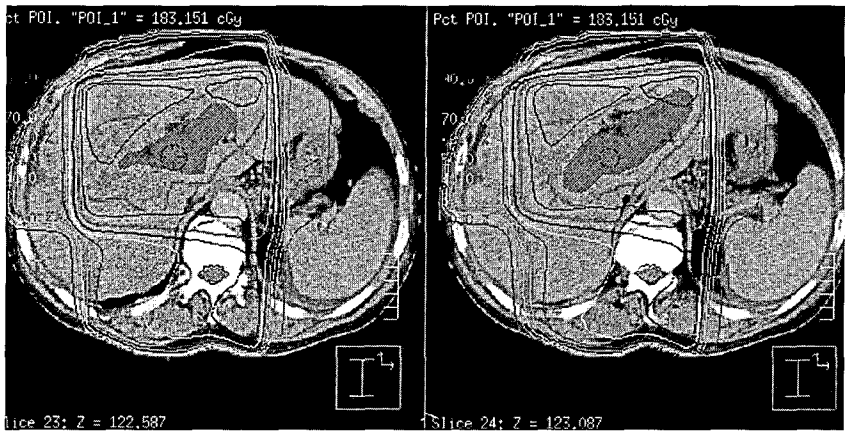

Figure 1. This was a case of hepatoma with portal vein thrombosis referred for radiation therapy. The drawn contour is portal vein thrombosis area defined by radiation oncologist as CTV for treatment planning. The circle with cross line is the radiation field isocenter.

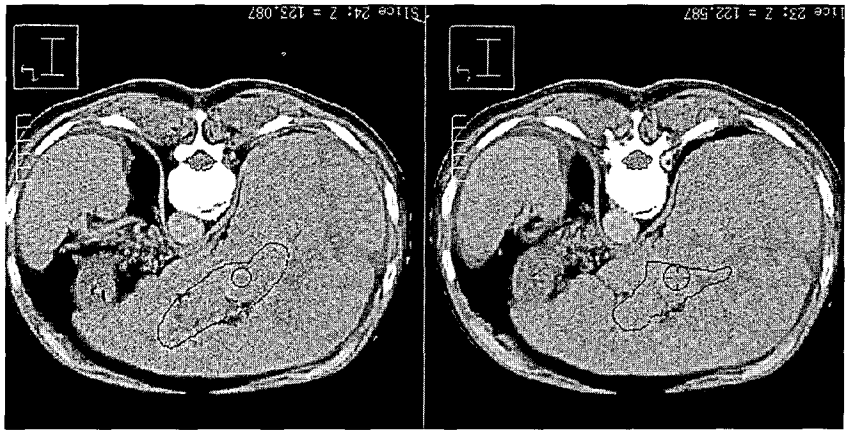

Figure 2. This was an example of isodose curves for treatment planning. The color wash area is CTV defined by radiation oncologist. The line just outside the color wash area is the contour of PTV with considering of set-up error and respiratory motion for the individual patient. The other lines showed the isodose curve. Then the radiation dose of critical organs (ex. spinal cord, stomach, kidney..etc) can be evaluated.

respectively. Once three-dimensional radiation planning was completed, isodose curve and dose-volume histogram (DVH) of organs of interest were generated and plotted [12] (Fig. 2). Field shapes and beam angles were designed to maximize tumor dose while satisfied dose constraints to normal structures, such as normal liver for 30 Gy, kidney for 23 Gy, and spinal cord for 47 Gy [6]. Typically, two to four coplanar beams were used in these patients. The treatment parameters were verified and re-simulated before radiation dose was delivered.

Treatment delivery

Patients were treated on a high-energy linear accelerator (10 MV or 15MV x-ray). In order to achieve local control benefit, 55 Gy in 22 fractions was prescribed (2.5 Gy per fraction, 1 fraction a day, 5 or 6 days per week) initially [1]. During RT courses, patients were examined

weekly by the oncologist to evaluate treatment response and toxicity. Serologic markers for liver functions, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Total Bilirubin (Bil-T) were routinely checked before RT, on the third week of irradiation, one month after RT was completed and on subsequent follow-up clinic.

Data Collection

The medical charts of the patients were reviewed. Ages of patients were divided into two groups by 55 years old as age factor. Child-Pugh classification was determined individually [23]. Hepatitis markers for B (HBsAg) and C (Anti-HCV Ab) were also recorded. Tumor location, tumor type and PVT site were documented by liver sonography and abdomen CT. The tumor location was grouped into right lobe alone, left lobe alone and both lobes. The tumor type was classified into solitary (greatest diameter $\leqq$ 5 cm), huge (greatest diameter > 5 cm), multiple (more than three separate tumors) and infiltrative (diffuse and diameter not measurable). The tumor thrombosis sites were recorded by the area of invasion, which were right portal vein, left portal vein and main portal vein individually. PTV was divided into two sizes, which were treatment volume larger than or equal to 150 cm^3 and smaller than 150 cm^3. Pre-treatment AFP was reviewed and high AFP indicated that the pre-treatment AFP was higher than 10,000 ng/ml [17]. Liver function values of AST and ALT were transformed into fold number of upper normal limit (AST 40 U/L, ALT 37 U/L in our hospital). Bil-T was classified as three grades: Grade I indicated Bil-T level was below 4 mg/dL, Grade II was equal to or greater than 4 mg/dL but below 8 mg/dL, and Grade III was equal to or above 8 mg/dL.

Medical history of upper gastrointestinal (UGI) bleeding was also reviewed. If the patient had not had any history of UGI bleeding and no previous UGI panendoscope examination, the patient was taken as negative UGI bleeding history. On following the patients after RT, if there had been still no UGI bleeding sign and no necessary UGI panendoscope done, the patient was recorded as no UGI complication for RT and otherwise the patient was recorded as positive suspicious UGI complication. Positive UGI bleeding history was determined as previous UGI bleeding symptoms recorded in chart or UGI panendoscope with positive finding before RT. After RT was completed, if there had been new finding by UGI panendoscope including gastritis or ulcer (varices were excluded), positive suspicious UGI complication was recorded and otherwise there was no UGI complication for RT.

After RT courses were completed, patients were followed monthly. The treatment response was classified into two categories, which were positive response and poor response. Positive response was defined as regressive change of the PVT, such as refilled contrast in portal vein trunk or diminished PVT sites, documented on the subsequent CT, or Doppler signal of portal vein blood flow found by abdomen sonography in previous thrombosis area, or further TAE could be able to proceed after interventional radiologist's evaluation. Otherwise, the patients were categorized as poor response.

Patients were followed until 30th April 2001. Survival rate was calculated from the date that the patient was referred to death or last follow-up date. If patients lost follow-up in our hospital and post radiotherapy image study had not been available, they were followed by telephones or letters.

Statistics

Factors predicting the completion of RT or not were tested by chi-square test and logistic regression method. Survival of the patients was calculated by Kaplan-Meier method and the difference was compared by Log-rank test. Non-parametric Friedman test was used for pre-treat-

ment, on-treatment and post-treatment liver function. We take p-value smaller than 0.05 as statistically significant.

RESULTS

Treatment outcomes

Twenty-four patients (57%) completed the planned radiation therapy course. The radiation doses were delivered as planned except in 4 patients. Two patients stopped treatment at 50Gy for worsened ECOG performance status (>Grade II). The other 2 patients were treated with 56Gy and 61.3Gy, with modified fraction sizes, 2Gy and 1.8Gy respectively, because of worsened liver functions. Among the patients who completed RT, 7 patients were lost follow-up due to the visit to other hospitals or the search for traditional herbal drug therapy. These patients were excluded for statistic analysis except survival due to unclear post RT status. There were 9 of the 17 followed patients (53%) who had positive response. Among these 9 patients, 7 patients (41%) had further TAE treatment performed after RT. Furthermore, there were 3 patients who had subsequent RT later, two for new invasion of portal vein site, one for metastatic mass at abdomen wall. Eight (47%) of the followed patients were determined as poor response and had no regressive change on PVT area objectively.

Eighteen patients (43%) did not complete RT because of progressively worse general condition with ECOG performance status more than Grade II, which made RT setup impossible. There were 6 patients who did not even start RT for the same reason. On the others, the treatment doses were from 2.5Gy to 47.5Gy. Most patients stopped RT at the dose below 22.5Gy except in 2 patients. One had treatment stopped at 37.5Gy and the other at 47.5Gy, respectively . The treatment outcomes were summarized in Table 2.

Twelve of 18 incomplete RT patients (67%) died of hepatic failure, including 4 (22%) with varices bleeding and 2 patients (11%) with hepatoma rupture. All of these patients passed away in 2 weeks after RT discontinued. In 24 patients who could complete RT, 2 patients (8%) were still alive until the end of our study. Both of them accepted subsequent TAE and live with stable diseases. One had abdominal wall metastasis and electron beam irradiation was performed so that well local control was obtained until our study was completed. There were four patients (17%) who expired at home and the actual causes of death was not available. Ten patients (42%) had hepatic failure finally, including 4 patients (17%) dying of varices bleeding and 4 (17%) patients of hepatoma rupture. Due to poor prognosis of patients enrolled in this study, further studies of patterns of failure were not available by the health insurance policy.

Predicting factors for complete RT

Main portal vein or multiple portal trunks versus single branch of portal vein invasion, and complete RT versus incomplete RT were tested by Chi-square first and it was not statistically

Table 2. Results of RT to PVT site for HCC with PVT patients

	No. of the patients (Total patients N=42)	
Complete RT	24 (57%)	
		Follow-up patients (n=17)
	Positive response for RT	9 (52%)
	Subsequent TAE performed	7 (41%)
	Poor response for RT	8 (47%)
Incomplete RT	18 (43%)	

significant (p=0.200). Furthermore, factors that predicted patients who did or did not complete RT by included age, sex, ECOG performance status, Child-Pugh Classification, tumor location, tumor type, invaded PVT site, number of portal vein invasions, hepatitis marker, history of UGI bleeding, fold number of upper limit value for normal AST and ALT, the Grades of Bil-T and PTV of 3D-CRT (Table 3). Only Bil-T was the independent factor for predicting

Table 3. The factors tested for predicting patients who completed RT or Not

		Frequency	No. of patients with RT completion	Significant
Unordered Categorical Variables				
Gender	Male	39	21	p=0.120
	Female	3	3	
Tumor Location	R't lobe	26	14	p=0.367
	R't lobe	6	5	p=0.582
	Both lobes	10	5	p=0.161
Invaded PVT Site	R't PVT	34	18	p=0.257
	R't PVT	15	10	p=0.353
	Main PVT	29	18	p=0.335
Hepatitis Marker	HBsAg(+)	31	16	p=0.224
	Anti-HCV Ab(+)	8	6	p=0.257
Ordered Variables				
Age	(≧ 55 y/o)	22	13	p=0.789
	(< 55 y/o)	20	11	
ECOG Performance Status	Grade 0	11	9	p=0.132
	Grade I	19	9	
	Grade II	12	6	
Child-Pugh Classification	A	25	17	p=0.085
	B	17	7	
Tumor Type	Solitary (< 5 cm)	2	1	p=0.407
	Huge(> 5cm)	20	10	
	Multiple	9	6	
	Infiltrative	11	7	
Number of PVT Site	1	15	7	p=0.548
	2	18	12	
	3	9	5	
PTV (Treatment Volume)	≧150 cm^3	22	12	p=0.721
	< 150 cm^3	20	12	
AFP	High	13	5	p=0.101
UGI bleeding History	Positive	11	7	p=0.612
AST Level*	= 1	5	4	p=0.243
	> 1, ≦ 3	15	10	
	> 3, ≦ 5	15	6	
	> 5	7	4	
ALT Level*	= 1	12	9	p=0.821
	> 1, ≦ 3	23	11	
	> 3, ≦ 5	5	2	
	> 5	2	2	
Bil-T Grades	Grade I	34	21	p=0.028
	Grade II	4	2	
	Grade III	4	1	

*Level of AST and ALT were the fold number of upper normal limit value of AST and ALT.

patients who completed RT or not (p=0.028). Twenty-one of 35 patients (60%) of the Grade I Bil-T and 2 of 4 patients (50%) of Grade II completed the RT course. There was only 1 of 4 patients (25%) of Grade III going through the treatment.

Survival Rates

The overall survival rates for all patients enrolled in our study were 38% at 3 months and 21% at 6 months. The median survival intervals were 65 days. In 2 patients who completed RT course, overall survival rates at 3 months and 6 months were 63% and 34%. The median survival intervals were 113 days. The survival rates for incomplete RT patients were 24% and 8% at 3 months and 6 months, respectively, with a median of 37 days. The survival difference was statistically significantly different between complete and incomplete RT patients (p=0.022) but not different in various Child-Pugh classifications (p=0.080). The survival curves were shown in Fig. 3.

Complications

There were 17 patients who completed RT and were regularly followed for analysis of their pre-treatment, on-treatment and post-treatment liver functions. There was no statistically significant difference in pre-treatment, on-treatment, and post treatment levels on AST, ALT and Bil-T level. Six patients (35%) had more than double AST level increase after RT started. No patients (0%) had more than double increase in ALT level as compared to that before RT. Six patients (35%) had worse Bil-T grade after irradiation. The distributions of liver function parameters were showed in Fig. 4. Besides, 6 patients (35%) had suspicious UGI complica-

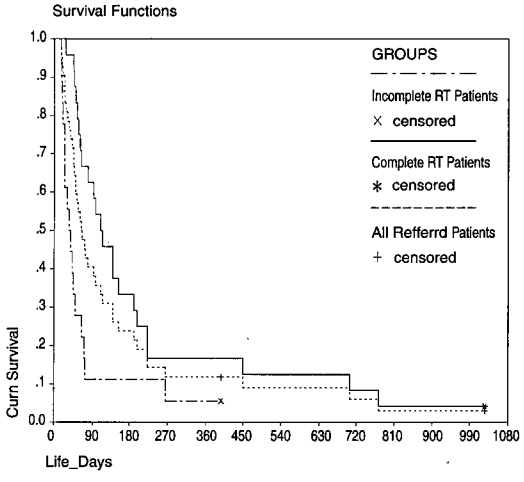

Figure 3. The survival curves were compared between all referred patients, including those who completed RT or not.

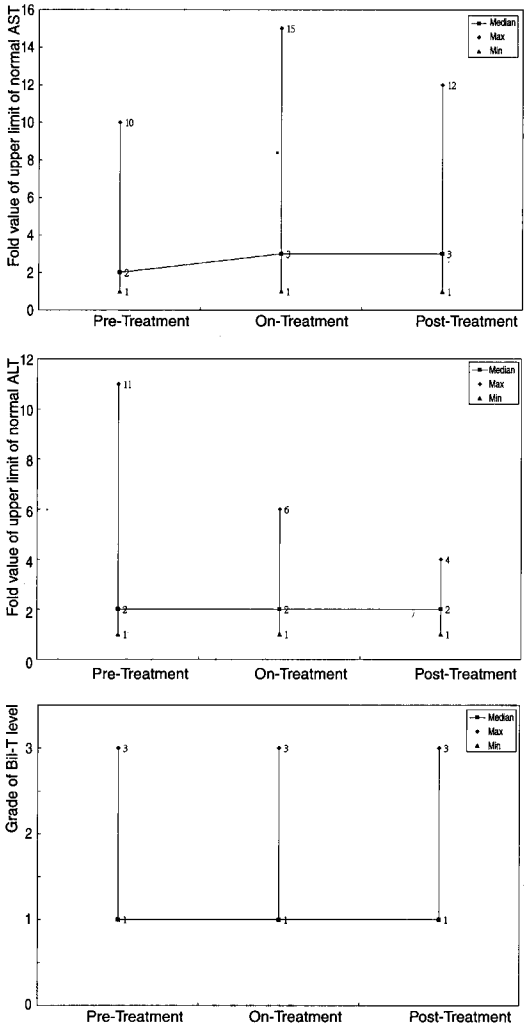

Figure 4. The liver function parameters distribution before treatment, on treatment and post treatment were graphed. No significant difference between these three stages of therapy was noted for individual tests, including AST, ALT and Bil-T.

tions but only one of them died of UGI bleeding. The patients who had elevated ALT level, worse Bil-T grade or UGI bleeding were not in the same group, though they had the same episode number.

DISCUSSION

PVT is frequently seen in patients with HCC [20]. Chen et al reported that the incidence of portal vein invasion in HCC was 60% in Taiwan and the presence of portal vein invasion was associated with a grave prognosis [3]. Intra-arterial (IA) chemotherapy, TAE, and surgery were tried for PVT patients by Kanno et al and Kumada et al [8, 9]. But the results have not been satisfactory. However, Lai et al claimed that the conventional method of external irradiation to HCC was not effective [10]. Kumada et al suggested that conformal high dose external beam radiation therapy (EBRT) (48-72.6 Gy) could be used for intra-hepatic cancers to potentially increase local control and survival over what would be expected with lower dose EBRT [9]. Cheng et al reported 58% response rate in treating of HCC with 3D-CRT [4]. For PVT, one third of the patients with objective response to 3D-CRT and combined TAE was noted by Yamada et al [25]. In this study, for patients who could not undergo TAE, we used 3D-CRT technique to treat only PVT site and increased the effective dose up to 55Gy. The intention was to dredge portal veins, and made subsequent treatment feasible. Patients who completed RT treatment course had 53% positive response rate. Furthermore, 41% of patients with complete RT received further treatment for their diseases. RT with conformal technique to only PVT area provided an alternative way to resolve the contraindication of traditional TAE for patients with HCC and PVT in 7 of 42 patients in this study.

Pirisi et al. reported an autopsy study and the survivals of patients with HCC and PVT were about 60% and 40% for 3 month and 6 month, respectively. The median survival interval was 129 days [22]. Yen et al. also revealed significant difference in survival between TAE and non-TAE groups for patients with HCC and PVT. The 6-month, 1-year and 2-year survival rates were 91.4% versus 62.3%, 51.4% versus 26.2% and 17.1% versus 4.9%. The median survival intervals of TAE and non-TAE groups were 10.3 and 3.7 months, respectively [26]. There was difference in survival between that in our study and in these reports. Patients enrolled in our study failed to undergo any conventional treatment. Basically, these patients not only had advanced HCC with PVT but were also deemed contraindicated for current treatment modalities. Therefore, the patients' basis of our study was poorer than those in the others. According to American Joint Committee for Cancer (AJCC) Staging system or Okuda staging for hepatoma, our patients were all in terminal stage, that were stage III and stage IV. However, 6-month survival rate of the patients in our study who completed RT was 34% and the counterpart was 8%, with 113 and 37 days of median survival intervals, respectively. There was statistically significant difference between these two groups.

Classically, Child-Pugh classification was used as the symbol of liver functions, but patients in our study were selected only by performance status. It was because the patients needed to be treated daily and cooperate to set up. At the same time, the selection by ECOG performance status limited the Child-Pugh classification of our patients in A and B. In the results of this study, whether the patients who got through with RT course or not appeared to be an important factor for survival. The patients who completed RT may indicate better general condition at the time when they were referred. But it seemed that Child-Pugh classification was not significantly associated with survival. This might be because Child-Pugh classification of patients in this study was only classified in 2

grades and limited the interpretation ability of liver functions. Therefore, more variables should be examined although it might reduce the significance of statistic. We tested main portal vein or multiple portal trunks versus single branch of portal vein invasion, and it was not statistically significantly difference. It was attributed to the basis of liver circulation. Main portal vein or multiple portal trunks thrombosis may deprive the greater part of portal flow that made the condition lethal, but it appeared not as critical as we thought. Bil-T was the only independent factor for predicting RT completion or not. In other words, the anatomy and the characteristics of the tumor itself may not influence the outcome. AFP is a tumor marker for HCC and indicates the normal or abnormal liver cell regeneration. It still did not affect the treatment results in this study. AST, ALT and Bil-T are the similar items for exact liver functions. AST and ALT are stored in liver cell and increase in serum level when liver cells are damaged. They cannot actually reflect the quantity of liver functions. Bil-T can show the ability of liver metabolism and excretion. So, Bil-T may be the reasonable item for evaluating the general liver condition and can be a useful factor for predicting patients who could tolerate RT course or not. In our results, higher Bil-T level was the poor prognostic factor for patients with HCC and PVT who were referred for RT.

Leung et al published a case report of conformal RT for a patient with HCC and PVT [14]. A 43-year-old male patient was diagnosed as HCC with PVT and arterioportal shunts. 3D-CRT with high focal dose was given to the left portal venous area. Shrinkage of the tumor and thrombus, disappearance of the arterioportal shunts and restoration of the hepatopedal flow of the portal vein were noted 3 months after treatment. The patient received further TAE and achieved successful tumor control. No serious complications were encountered. The effect of RT in treatment of PVT in HCC was also evaluated by Gunderson et al [7]. There were ten patients who had only unilateral portal vein involvement and the PVT area was irradiated with a dose of 30-50Gy using a linear accelerator under localization by real-time ultrasound. All ten patients responded to the external irradiation, with complete disappearance of the portal vein invasion in 5, and partial shrinkage in the other 5 patients. However, the HCC extended to the contralateral portal vein in 2 patients, though the irradiated lesion had shrunk. Six patients died after 3, 6, 7, 7, 8, and 10 months, respectively, due to the advanced HCC, rupture, liver failure, and respiratory failure. The others survived for longer than 6 months and remained follow-up when the study was completed. No post irradiation hepatitis or other complication was observed. In our study, the liver functions, which were taken as AST, ALT and Bil-T, were evaluated before RT, on 3rd week of RT and one month after RT. All of them had no statistically significant difference. The radiation-induced liver disease may develop in 4 month after RT [11]. But we had only 1-month follow-up interval after RT because of short survival. There were less than half of patients survived at 4 months after RT, and most of them died of liver failure. It could not be differentiated well between the natures of radiation hepatitis and natural disease course in our patients. So we just took 1-month interval after RT to count for post RT status. Child-Pugh classification was not included for complication analysis for the same limitation of this study. Besides, suspicious complication of stomach was about 35% with new panendoscope finding, but fortunately, only one patient with suspicious gastric complication died of UGI bleeding. There were just few complications about liver functions and stomach for patients treated by 3D-CRT to PVT site in this study. Three-dimensional radiotherapy technique to limited field not only increases the dose in order to promote local control, but may also reduce the complications. Conformal radia-

tion therapy indeed extends the accuracy and safety of RT especially in the small area. However, the follow-up interval in this study was too short to accurately evaluated the long-term side effects of RT.

There were two reported studies with combination of TAE and RT as treatment for patients with HCC and PVT. Yamada et al reported a pilot study of local RT to PVT in Japanese HCC patients [25]. Eight patients with unresectable HCC accompanied by PVT were enrolled into the study from February 1998 to December 1999. TAE was performed first and RT started 10-14 days following TAE. A total delivered dose of 60 Gy was given in a daily 2-Gy fraction, with the clinical target volume defined as PVT area only. An objective response was observed in 3 of the 8 patients. However, on follow-up angiograms the protrusion of PVT into the main portal trunk decreased in all cases. Deterioration of liver function was observed in all patients with 30% of normal liver tissue volume received more than 40% doses by DVH. There was another study of RT in combination with TAE for patients with HCC and extensive portal vein involvement by Tazawa [24]. The combined therapy was performed in 24 HCC patients with extensive PVT. External radiation targeting on PVT (50 Gy in 2-Gy fraction) was performed in combination with repetitive TAE for intralobar lesions every 3 months. The local response of PVT included complete response (CR) in 4 patients, partial response (PR) in 8 patients, no change (NC) in 8 patients, and progressive disease (PD) in 4 patients. The survival rates after 1 and 2 years were 73% and 21% in Child's A, 10% and 0% in Child B or C, and 61% and 21% in patients with the local response of CR or PR, and 19% and 9% in those with the local response of NC or PD, respectively. Child's classification was the only factor associated with the local response. As compared to the results in our study, the survival of the patients who completed RT was about 34% at 6 months, and the Bil-T was the only factor to predict patients who could complete RT or not. Bil-T was also a component of Child's criteria of the liver functions. The role of TAE was to treat the primary tumor but TAE was not effective for thrombus in portal vein. RT may be powerful in HCC but it can also destroy the normal cells and cause complications. Under these natural characteristics of the treatments, the use of combined modalities may be a better way to offset the weakness of the other. However, there are still selected patients with PVT initially contraindicated for TAE. It is our hope that 3D-CRT to PVT site may offer the further chance for the well selected patients to reverse the contraindication of TAE.

CONCLUSION

In our study, we used 3D-CRT in patients with HCC and PVT who were not candidates for other treatments. We found Bil-T was the only statistically significant factor for complete RT. This could help radiation oncologist to select potential patients for further treatment. Prospective controlled studies and more precise post treatment follow-up protocols will be needed to investigate the feasibility, patterns of failure, and the true treatment effect of this new technique.

REFERENCES

1. Aoki K, Okazaki N, Okada S, et al.: Radiotherapy for hepatocellular carcinoma: clinicopathological study of seven autopsy cases. Hepatogastroenterology 1994 Oct; 41(5): 427-431.
2. Chen MF, Hwang TL, Jeng LB, et al.: Hepatic resection in 120 patients with hepatocellular carcinoma. Arch Surg 1989; 124: 1025-1028.
3. Chen SC, Chang WY, Wang LY, Tsai JF,

Hsieh MY, Chuang WL: Influence of portal vein thrombosis in survival of patients with hepatocellular carcinoma in Taiwan. Sung JL (ed) Viral hepatitis and hepatocellular carcinoma. Excerpta Medica Hong Kong 1990; 657.

4. Cheng SH, Lin YM, Chuang VP, et al.: A pilot study of three-dimensional conformal radiotherapy in unresectable hepatocellular carcinoma. J Gastroenterol Hepatol. 1999 Oct; 14(10): 941-945.
5. Cook GC, Moosa B: Hepatocellular carcinoma: One of the world's most common malignancies. Am J Med 1985; 233: 705-708.
6. Emami B, Lyman J, Brown A, et al.: Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991; 21: 109-122.
7. Gunderson LL, Haddock MG, Foo ML, Todoroki T, Nagorney D: Conformal irradiation for hepatobiliary malignancies. Ann Oncol 1999; 10 Suppl 4: 221-225.
8. Kanno T, Kim K, Kurioka N, et al.: Study of 45 patients with hepatocellular carcinoma complicating occlusion of the main portal vein. Jpn J Gastroenterol 1985; 82: 1360-1368.
9. Kumada K, Ozawa K, Okamoto R, et al.: Hepatic resection for advanced hepatocellular carcinoma with removal of portal vein tumor thrombi. Surgery 1990; 108: 821-827.
10. Lai ECS, Choi TK, Tong SW, Ong GB, Wong J: Treatment of unresectable hepatocellular carcinoma: Results of a randomized controlled trial. World J Surg 1986; 10: 501-509.
11. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF: Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 1995 Mar 30; 31(5): 1237-1248.
12. Lawrence TS, Tesser RJ, Ten Haken RK: An application of dose volume histograms to the treatment of interahepatic malignancies with radiation therapy. Int J Radiat Oncol Biol Phys 1990; 19: 1041-1047.
13. Lerose R, Molinari R, Rocchi E, Manenti F, Villa E: Prognostic features and survival of hepatocellular carcinoma in Italy: impact of stage of disease. European Journal of Cancer 2001 Jan: 37(2): 239-245.
14. Leung SW, Huang EY, Cheng YF, Lu SN: Conformal radiation therapy for hepatoma with portal vein thrombosis. Br J Radiol 2000 May; 73(869): 550-552.
15. Lin DY, Lin SM, Liaw YF: Non-surgical treatment of hepatocellular carcinoma. J Gastroenterol Hepatol 1997 Oct; 12(9-10): S319-S328.
16. Malaguarnera M, Trovato G, Restuccia S, et al.: Treatment of nonresectable hepatocellular carcinoma: review of the literature and meta-analysis. Advances in Therapy 1994 Nov-Dec; 11(6): 303-319.
17. Nomura F, Ohnishi K, Tanabe Y: Clinical features and prognosis of hepatocellular carcinoma with reference to serum alpha-fetoprotein levels. Analysis of 606 patients. Cancer 1989 Oct 15; 64(8): 1700-1707.
18. Oken MM, Creech RH, Tormey DC, et al: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group Am J Clin Oncol 1982; 5: 649-655.
19. Okuda K: Radiological diagnosis of hepatocellular carcinoma. Annals of the Academy of Medicine, Singapore 1980 Apr; 9(2): 222-227.
20. Patton RB, Horn RC: Primary liver carcinoma. Autopsy of 60 cases. Cancer 1964; 17: 757-768.
21. Phillips PJ, Rowland R, Reid DP, Coles ME: Alpha1-fetoprotein in the diagnosis of hepatoma: statistical and cost benefit aspects. Journal of Clinical Pathology 1977 Dec; 30(12): 1129-1133.
22. Pirisi M, Avellini C, Fabris C, et al.: Portal vein thrombosis in hepatocellular carcinoma: age and sex distribution in an autopsy

study. J Cancer Res Clin Oncol 1998; 124(7): 397-400.
23. Pugh RNH, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-649.
24. Tazawa J, Maeda M, Sakai Y, et al.: Radiation therapy in combination with transcatheter arterial chemoembolization for hepatocellular carcinoma with extensive portal vein involvement. J Gastroenterol Hepatol 2001 Jun; 16(6): 660-665.
25. Yamada K, Soejima T, Sugimoto K, et al.: Pilot study of local radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. Jpn J Clin Oncol 2001 Apr; 31(4): 147-152.
26. Yen FS, Wu JC, Kuo BIT, Chiang JH, Chen TZ, Lee SD: Transcatheter arterial embolization for hepatocellular carcinoma with portal vein thrombosis. J Gastroenterol Hepatol 1995; 10: 237-240.
27. Yoshimi F, Nagao T, Inque S, et al.: Comparison of hepatectomy and transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma: Necessity for prospective randomized trial. Hepatology 1992; 16: 702-706.
28. 中華民國行政院衛生署: 衛生統計(一)公務統計 2001; p52, p73.

以三度空間順形放射治療門靜脈栓塞為肝癌合併門靜脈栓塞之初始治療方法：對於無法接受其他治療但完成放射治療病人之預後因子與結果

黃郁傑　梁　雲　王重榮　孫立民　葉世安
黃英彥　陳惠君　方富民　熊啟業　許軒之

長庚紀念醫院高雄分院　放射腫瘤科

研究背景及目的：肝癌合併門靜脈栓塞之預後不佳，並且是做經皮肝動脈血管栓塞治療（TAE）的禁忌症。雖然過去已經證實傳統的肝癌放射治療方法效果不彰，三度空間順形放射治療卻可能是另一個可選擇的替代方案。在這個研究當中，我們將分析以三度空間順形放射治療治療門靜脈栓塞為肝癌合併門靜脈栓塞為初始療法之預後因子與結果。

材料與方法：從 1997 年九月到 1999 年八月，共有 42 位病人被轉介至本科其初始診斷為肝癌合併門靜脈栓塞並且沒有接受過任何治療以及西方癌病聯合組織（ECOG）功能狀態優於二級，這些病人即為我們研究的對象。他們依照個人不同的情形針對門靜脈栓塞區域以三度空間順形放射治療給予 50 到 61.3 格雷的劑量，每日分次劑量為 1.8 至 2.5 格雷。年齡、性別、 ECOG 功能狀態、 Child-Pugh 分級、腫瘤位置、腫瘤型態、門靜脈栓塞位置、放射治療照射體積、甲型胎兒蛋白、上消化道出血病史、 B 型及 C 型肝炎標記以及接受放射治療前、治療中、治療後的肝功能指數，包括了麩草醋酸氨基轉移酶（AST）、氨基丙酸轉氨酶（ALT）及總黃疸指數（Bil-T），皆被紀錄下來以供分析。

結果：共有 24 位（57%）病患完成了放射治療療程，其他則是因為 ECOG 功能狀態惡化停止治療，其中有 7 個病人在治療後失去追蹤。在追蹤的 17 位病患當中有 9 位（53%）對放射治療有反應，其中又有 7 位（41%）病患在治療後可繼續接受 TAE 治療。完成放射治療療程的病患其 3 個月及 6 個月存活率為 63%及 34%。而未完成放射治療療程的病患則為 24%及 8%。在完成及未完成放射治療療程的病人之間，其存活率有明顯統計上的差異（p = 0.022）。病患治療前、中、後的 AST ， ALT 及 Bil-T 無明顯統計上的差異，只有 6 位病患（35%）有疑似胃部併發症之報告。 Bil-T 是在統計學上唯一對預測病患可否完成放射治療有意義之因子（p = 0.028）。

結論：此研究的病患選擇與預後不佳，只有少於一半的病人可以完成放射治療與完整的病程追蹤。因此，進一步前瞻性控制且選擇病患良好的研究是必須的，例如選擇低 Bil-T 之病人，來評估此種治療的可行性，治療失敗復發的型態，以及採用三度空間順形放射治療作為肝癌合併門靜脈栓塞之初始療法的真正效益。

[放射治療與腫瘤學 2001; 8(1): 1-14]

關鍵詞：肝癌、門靜脈栓塞、三度空間順形放射治療