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Research Article

Analysis of Prognostic and Related Factors in Hepatocellular Carcinoma Patients with Portal Vein Thrombosis after Radiotherapy

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Abstract

Aim: Patients with hepatocellular carcinoma (HCC) with portal vein or inferior vena cava tumor thrombosis (PVT or IVCT) are deemed to have poorer treatment outcomes than those without. Radiotherapy (RT) is the main treatment for HCC patients with PVT or IVCT. This study aimed to clarify the prognostic factors, safety, and quality of RT in these patients for improved therapeutic design.

Materials and Methods: Patients with HCC who had PVT or IVCT and received RT were enrolled in this study. Demographic variables, laboratory values, tumor characteristics, and RT modalities were determined before and after RT. The primary endpoint was overall survival. Predicted factors of survival were identified by univariate and multivariate analyses. The planning target volume was used to evaluate the safety margin. The imaging records of Tomo Therapy in the treatment of abdomen or pelvic tumors were used to evaluate daily different motions of the liver.

Results: Ten patients with HCC with PVT or IVCT received RT were enrolled. Pretreatment unfavorable predictors included advanced stage, positive HBsAg, higher aspartate aminotransferase (AST), and poor Child-Pugh classification. Post-treatment unfavorable predictors were higher total bilirubin, lower albumin, and higher AST ($p<0.05$). Gross tumor volume safety maximal margin at the different directions of X (right/left), Y (up/down), and Z (in/out) were 4, 8, and 8 mm, respectively.

Conclusion: These results provided the potential factors that influenced the survival of patients with HCC after RT. RT was effective for PVT or IVCT, and careful addition of adequate margin could safely overcome daily motions.

Keywords: Hepatocellular carcinoma; Portal vein thrombosis; Radiotherapy; Prognostic factors; Gross tumor volume

Introduction

Cancer is the top cause of death in Taiwan in the last 34 years. According to information from the Taiwan Department of Health and the Health Promotion Administration, Ministry of Health and Welfare, hepatocellular carcinoma (HCC) is the second most common malignancy. In 2012, the number of newly diagnosed HCC reached more than 11 000, and more than 8000 died because of HCC [1]. HCC male patient ratio is about 2.35 times higher than women (male = 7920; female = 3372). Liver cancer is often diagnosed at its terminal stage, and the 5-year survival rate remains <12% in patients with additional complications [2].

According to the data from the Surveillance, Epidemiology, and End Results (SEER) of the American Cancer Society, of the treatment of liver cancer, the five-year relative survival of local invasion tumor, regional invasion and distant metastases were 21%, 6%, and 2%, respectively. Chung-Shan Medical University Hospital's annual report of the treatment of cancer from 2004 to 2011 show that the five-year survival rate of patients with AJCC stage I, II, IIIA, IIIB, and IV were 46.4%, 26.9%, 8.9%, 6.6%, and 5.8%, respectively [3].

The status of stage III HCC invasions to the surrounding blood vessels resulting in hepatic portal vein thrombosis (PVT or IVCT), normal liver cells without oxygen, and nutrient supply are considered as poorer treatment outcomes. Patient could receive external beam radiation therapy (RT) to irradiate blocking portal vein tumor, and subsequent embolization. [4-9]. Radiotherapy (RT) using high-energy X-ray can be used to irradiate tumor lesions, kill cancer cells or stop proliferation. Due to normal liver cells also being sensitive to high-dose external beam radiation, we need to assess the tumor size, lymph node, violations of organs and position, and liver function of the patients before RT.

In cancer RT planning, a safety margin should be added around gross tumor volume (GTV) to overcome uncertainties in planning or treatment delivery. The aim of this study is to clarify prognostic factors, safety, and quality of RT in these patients and use this for further therapeutic design.

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Table 1: The characteristicsof HCC Patients with clinical AJCC-TNM Stage and Age.

Patient Numbers	cT	cN	cM	Age
1	3	0	0	55
2	2	0	0	79
3	4	0	0	70
4	3	0	0	83
5	3	0	0	55
6	3	0	0	60
8	3	0	0	72
7	3	0	0	52
9	3	0	0	36
10	3	0	0	57

Materials and Methods

Enrolled patients

Patients met the following criteria in Chung-Shan Medical University Hospital Cancer Registry database from 2009 to 2012 were enrolled:

A. Clinician diagnosed with liver cancer by puncture biopsies proved or tumors larger than 1 cm with two classical image enhancements (3-phase CT or MRI showed typical vascular characteristics) [10-13].

B. The clinical diagnosis with portal vein invasion, PVT or IVCT.

C. Receiving RT, and the radiation field must contain the portal vein tumor Patients' characteristics with clinical AJCC-TNM Stage and Age were shown in Table 1.

Prognostic factors evaluation

The following parameters of patients with re- and post-RT were recorded: Age, HBsAg, Total Bilirubin, Albumin, AST, ALT, Child-Pugh classification Radiation dose (Gy), Target Tumor volume, Tumor with whole liver volume ratio (T-L Ratio), Response and Overall survival. The date of diagnosis was used as a reference to calculate the date of death or last contact date (depending on database records), which was defined as the interval between the survival time Patients' characteristics with Pre-RT and Post-RT were shown in Table 2 and Table 3.

Table 3: Lab data, Response and Survival time of enrolled patient's post-RT.

Patient	Bilirubin (mg/dL)	Albumin (g/dL)	ALT (U/L)	AST (U/L)	Response*	Survival time (months)
1	1.13	3.5	53	53	CR	15
2	0.76	3.7	25	28	>PR	24
3	1.74	2.9	67	111	>PR	7
4	0.7	3.4	42	93	>PR	8
5	1.57	2	16	34	>PR	17
6	0.59	3.9	39	44	>PR	20
8	1.85	2.5	20	32	>PR	8
7	2.23	2.3	87	123	<PR	4
9	7.9	2.2	20	114	DP	4
10	4.28	2.4	34	110	DP	5

*CR: Complete Response; PR: Partial Response; DP: Disease Progress

RT-Planning evaluation

We further analyzed radiotherapy planning, design different clinical treatment volume (PTV), to assess the doses received by normal liver tissue. The radiotherapy PTV enclosed the Gross Tumor Volume (GTV) with anisotropic margins to account for possible uncertainties in beam alignment, patient positioning, organ motion, and organ deformation. In the RT-Plan, GTV of liver and portal vein. The addition of variable margin of GTV at different directions of X (Right/Left), Y (Up/Down), Z (In/Out), respectively was shown in Table 4. Radiotherapy planning must consider critical normal tissue structures; include bilateral Lung, Kidney, Spinal Cord, Small Intestine and Normal Liver, known as organs at risk (ORs) [14-16]. This study used Intensity Modulation Radiation Therapy (IMRT) technicality, given five angular direction 10MV energy beams, 0, 35, 240, 280, 320 degrees, respectively. The dose prescribed to V55Gy>99% in 22 fractions. RT-Planning was determined by Pinnacle3 Planning System. Dose-Volume-Histogram (DVH) was used to evaluate the RT-Planning quality by senior radiation oncologist. Tolerance of normal tissues and organs to the radiation

Table 2: Lab data, RT dose and tumor volume of enrolled patients before RT.

Patient No.	HBsAg	Bilirubin (mg/dL)	Albumin (g/dL)	ALT (U/L)	AST (U/L)	C-P Class*	Dose (Gy)	GTV (cc)	Liver Volume (cc)	T-L Ratio#
1	+	2.43	4.1	63	48	A	55	22.5	357.8	6.3%
2	-	0.49	3.2	31	55	A	57.2	379.1	986.7	38.4%
3	+	2.92	3.1	52	59	B	57.2	386.4	1825.9	21.2%
4	+	0.77	4.4	32	56	A	57.2	106.1	830.7	12.8%
5	+	2.21	2.7	22	55	B	55	286.8	1217.6	23.6%
6	+	0.69	3.9	55	68	A	57.5	304.3	1092.3	27.9%
8	+	1.95	2.9	55	72	B	52	1004.1	1704.3	58.9%
7	+	0.9	2.8	40	45	B	55	201.3	1636.9	12.3%
9	+	1.35	3.7	248	182	B	46.2	146.5	1654.3	8.9%
10	+	2.99	2.4	30	100	B	55	224.7	775.6	29.0%

*C-P class: Child-Pugh classification
#T-L Ratio: Tumor with whole liver volume ratio

Table 4: The PTV planning with addition of variable margin (mm) of GTV.

	X*	Y*	Z*
PTV-1	2	2	2
PTV-2	3	3	3
PTV-3	3	5	5
PTV-4	5	10	10
PTV-5	5	15	15

* X (Right/Left), Y (Up/Down), Z (In/Out)

Table 5: Normal liver dose-volume percentage and the average dose received.

	V5 (%)	V10 (%)	V15 (%)	V20 (%)	V25 (%)	V30 (%)	V35 (%)	Mean (cGy)
PTV-1	49.1	43.9	35.6	32.7	25.2	17.9	13.1	1424.7
PTV-2	53.5	47.6	42.2	36.4	28.8	20.9	15.5	1582.6
PTV-3	53.9	48.7	43.7	38.5	30.7	22.8	16.5	1649.4
PTV-4	59.3	53.7	49.6	44.8	36.9	27.7	19.9	1896.2
PTV-5	63.2	58.0	53.4	48.5	40.7	32.1	23.7	2090.1
Normal Tissue Tolerance Dose	86%	68%	59%	49%	35%	28%	25%	2300

dose was assessed by the criteria of Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer (RTOG/ EORTC) Late Radiation Morbidity Scoring Schema (2007). Patients receiving radiation therapy of the abdominal or pelvic tumor were enrolled for such analysis. The normal liver dose-volume percentage (V5, V10, V15, V20, V25, V26, V30, V35, V40, %) and the average dose received (Mean dose, Gy) was shown in Table 5. The kilovolt computer tomography images including KVCT Images for positioning and MVCT Images before treatment were obtained and used for calculation of daily changes. The variables of daily changes at different directions of X (Right/Left), Y (Up/Down), Z (In/Out) were analyzed according to a report from Kristy, et al. [17].

Statistical analysis

Kaplan-Meier curves were generated for survival. For univariate and multivariate analysis were used for analyzing factors correlated with the survival time, including pre- and post-RT. $P<0.05$ was considered statistically significant. All calculations were performed with SPSS 19.0 for Windows (SPSS, Chicago, IL, USA).

Results

Evaluating the prognostic factors of HCC patients with PVT or IVCT received RT

Among 42 patients with HCC who had received RT between April 2009 and October 2012, only 10 patients had PVT or IVCT received RT and were enrolled in this study. The number of complete response (CR) was 1 (10%); 6 (60%) patients had more than partial response status (>PR) and 3(30%) patients had less than partial response status (<PR). Overall median survival in partial response group was 14.1 months versus 4.3 months in stable or progress group (p =0.001) (Figure 1).

In univariate analysis, only higher post-RT AST (GOT) was considered as a significant predictor of poor survival (95% confidence interval, p =0.04). The median survival times in patients with normal AST level (<37 U/L) or not more than twice of the normal value

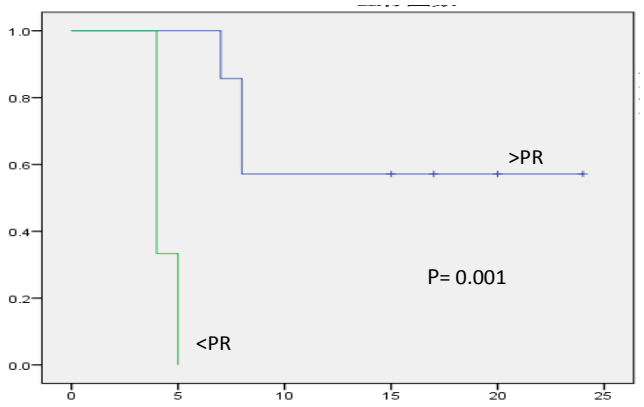

Figure 1: Overall median survival of enrolled patients. The overall median survival period of partial response (>PR) group was 14.1 months versus 4.3 months in stable or progress group (<PR).

(<76 U/L) post-RT were 16.3 ± 6.5 months and 17.5 ± 2.5 months, respectively. The average survival of patients with AST more than twice of the normal value (>76 U/L) was only 5.60 ± 1.6 months (Table 6).

From multivariate analysis, the pretreatment unfavorable predictors were advanced stage, old age, positive HBsAg, higher AST, and poorer Child-Pugh classification (Table 6). Post-treatment unfavorable predictors were higher post-RT total bilirubin, lower albumin, and higher AST (95% confidence interval, $p<0.05$) (Table 6). The average survival of patients with normal total bilirubin level (<1.2 mg/dL) after treatment was significantly higher than those with abnormal level (>1.2 mg/dL) (16.8 ± 6. 0 months versus 7.50 ± 4.3 months, $p<0.05$).

Evaluating the RT-Planning among HCC patients

Statistical analysis results of the normal liver dose-volume percentage (V5, V10, V15, V20, V25, V26, V30, V35, V40, %) and the average dose received are shown in Table 5. We compared the RTOG/EORTC criteria (V5<86%, V10<68%, V15<59%, V20<49%, V25<35%, V30<28%, V35<25%, V40<20%, Mean<23Gy) of tolerance radiation dose of normal liver, PTV1 (X+2 mm; Y+2 mm; Z+2 mm), PTV2 (X+3 mm; Y+3 mm; Z+3 mm) and PTV3 (X+3 mm; Y+5 mm; Z+5 mm) versus the dose-volume percentage and mean dose much lower than criteria. The PTV4 (X+5 mm; Y+10 mm; Z+10 mm) plan V25=36.9% is slightly higher by 1.9%, while in the V25 and V30, the PTV5 (X+5 mm; Y+15 mm; Z+15 mm) plan V25 and V30 were 40.7% and 32.1%, higher by 5.7% and 4.1%, respectively. Therefore, when patient received PTV4 and PTV5, plan shall carefully assess the potential the side effects.

We next evaluated the daily changes of liver volume among 1442 fractions from patients receiving abdominal or pelvic radiation therapy. The mean, median, and maximum motion changes in X directions were 3.01, 2.52, and 14.00 mm, respectively. The mean, median, and maximum motion changes in Y directions were 2.80, 1.71, and 24.46 mm, respectively. The mean, median, and maximum motion changes in Z directions were 3.14, 2.31, and 30.07 mm, respectively (Table 7). The mean, median, and maximum motion changes in directions of roll angle were 0.41°, 0.20°, and 3.60°, respectively (Table 7).

Table 6: Univariate or multivariate analysis of factors related to radiation therapy in enrolledpatients.

Variables		n	Survial status	*P*-values	
			Averge ± SD	Univariate	Multivariate
Stage	II	1	24.0 ± 0.0	0.185	<0.001*
	III	8	10.1 ± 5.9		
	IV	1	7.00 ± 0.0		
Age	≤60	6	10.8 ± 6.7	0.486	0.016*
	>60	4	11.8 ± 7.1		
HBsAg	Negative	1	24.0 ± 0.0	0.242	0.002*
	Postive	9	9.80 ± 5.7		
Total Biliribum	≤1.2	4	14.0 ± 8.2	0.645	0.111
	>1.2	6	9.30 ± 4.9		
Albumin	≥3.5	4	11.8 ± 6.2	0.645	0.111
	<3.5	6	10.8 ± 7.2		
ALT	≤38	4	13.5 ± 7.5	0.645	0.111
	>38	6	9.70 ± 5.9		
AST	38-76	7	13.6 ± 6.9	0.111	0.001*
	>76	3	5.70 ± 1.7		
Child-pugh classification	A	4	16.8 ± 6.0	0.07	0.037*
	B	6	7.50 ± 4.5		
Tumor size (cm)	≤5	4	14.0 ± 6.0	0.067	0.068
	>10	4	10.8 ± 7.8		
	≥15 or Multiple	2	6.50 ± 1.5		
POST-RT	≤1.2	4	16.8 ± 6.0	0.07	0.037*
Total Biliribum	>1.2	6	7.50 ± 4.5		
POST-RT	≥3.5	2	22.0 ± 2.0	0.06	0.002*
Albumin	<3.5	8	8.50 ± 4.6		
POST-RT	≤38	5	11.6 ± 7.7	1	0.179
ALT	>38	5	10.8 ± 5.8		
POST-RT AST	≤38	3	16.3 ± 6.5	0.04*	0.012*
	38-76	2	17.5 ± 2.5		
	>76	5	5.60 ± 1.6		
EBRT Dose (Gy)	≤55	6	8.80 ± 5.3	0.645	0.111
	>55	4	14.8 ± 7.4		
EBRT Volume (cc)	≤200	3	9.00 ± 4.5	0.629	0.09
	200-400	5	14.0 ± 8.1		
	>400	2	7.50 ± 0.5		
Tumor/Liver Volume ratio (%)	≤20	4	7.80 ± 4.5	0.861	0.081
	20-40	5	14.6 ± 7.4		
	>40	1	8.00 ± 0.0		
Response to EBRT	CR or PR	7	14.1 ± 6.2	0.111	
	<PR or PD	3	4.30 ± 0.5		

Discussion

The overall median survival in partial response group and in stable or progress group of our study was 14.1 months versus 4.3 months (p=0.001) (Figure 1). A previous study also observed that the survival time of 59 liver cancer patients with invasive hepatic portal vein, or PVT, received radiation therapy was different according to the response status [18]. The average survival was better in >PR group than relatively poor response (<PR or PD) (10.7 months versus 5. 3 months) [18]. Both studies got similar results.

Table 7: The daily changes of liver volume among patients receiving abdominal or pelvic radiation therapy.

	X (mm)	Y (mm)	Z (mm)	Roll (degree)
Mean	3.01	2.8	3.14	0.41
Median	2.52	1.71	2.31	0.2
SD	2.33	3.1	3	0.53
Minimum	0	0	0	0
Max	14	26.46	30.07	3.6

Table 8: The RT-Planning quality of newly planned PTV.

	V5 (%)	V10 (%)	V15 (%)	V20 (%)	V25 (%)	V30 (%)	V35 (%)	V40 (%)	Mean (cGy)
PTV-6*	58.6	53	47.9	42.3	34.3	25.1	18.8	14.1	1810
Normal Tissue Tolerance Dose	86%	68%	59%	49%	35%	28%	25%	2300Gy	2300

*PTV6: Directions X, Y and Z were added 4 mm, 8 mm and 8 mm, respectively.

With univariate or multivariate analysis, several correlation factors related to radiotherapy, such as radiation dose, target tumor volume or T-L Ratio, were found to have no significant influence to the survival time in our study ($p > 0.05$). Given that this was only a retrospective study and not a Phase I-II study, radiation oncology physicians determined how much radiation dose and irradiated volume administered. In fact, the dose and volume administered was determined according to clinical experience and the overall condition of patients with liver cancer, including the severity of liver damage and residual normal liver tissue tolerance dose, as an adjustment to the RT planning. Results showed no significant differences in the final analysis of survival time. Another conclusion was that these 10 patients that received complete RT were safe and showed no evidence of variation factors in RT plans.

Patients treated using a mold fixed, although the average and median motion value were small, still had a large maximum error and it affected the accuracy of cancer treatment. Therefore, this study confirmed the benefits of using daily image-guided technology to find and correct daily random motions. We also considered the GTV and added maximal safe margin by calculation via interpolation optimized to obtain a better plan target volume (called PTV6, Table 8). The directions of X, Y, and Z axis were not more than 4, 8, and 8 mm, respectively. In this PTV6 plan, the total irradiation volume was 263.7 cm^3, normal liver dose-volume percentage of V5, V10, V15, V20, V25, V26, V30, V35, V40 was 58.6% (<86%), 53.0% (<68%), 47.9% (59.0%), 42.3% (<49%), 34.3% (<35%) , 25.1% (<28%) , 18.8% (<25%), and 14.1% (<20.0%), respectively; the mean dose was 18.1Gy (<23Gy) (Table 8). All the calculated parameters were lower than RTOG/EORTC Normal Tissue Tolerance dose criteria. It would be expected to obtain better therapeutic outcome and less side effect if patients received RT according this PTV6 plan.

Conclusion

Radiotherapy is effective for PVT or IVCT. Overall median survival in partial response group was 14.1 months more than 4.3 months in stable or progress group. Pretreatment unfavorable predictors were advanced stage, old age, positive of HBsAg, higher AST and poorer Child-Pugh classification. Post treatment unfavorable predictors were higher total bilirubin, lower albumin, higher AST.

Careful addition of adequate margin could safely overcome the side effect of RT caused by daily motions of liver. If there is no image-guided technology to correct daily random motions (Directions of X, Y and Z mean value were 3.01 mm, 2.8 mm and 3.14 mm respectively), the GTV safety maximal margin at different directions of X (Right/Left), Y (Up/Down), Z (In/Out) should not more than 4 mm, 8 mm and 8 mm, respectively.

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