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Original Article

Prognosticators of hepatocellular carcinoma with intrahepatic vascular invasion

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Abstract

Objective: The prognosis of intrahepatic vascular invasion, including unilateral or main portal vein tumor thrombosis (PVTT) and hepatic vein thrombosis, is still poor. Many patients with intrahepatic vascular invasions never receive radiotherapy (RT). In recent years, more conformal RT techniques such as intensity-modulated RT (IMRT) have been developed and applied to treat other cancers and have significantly improved treatment results and decreased side effects. The purpose of this study is to evaluate the treatment results in patients with intrahepatic vascular invasion and explore the role of IMRT in these treatments. **Materials and Methods:** There were a total of 73 patients with newly diagnosed AJCC stage IIIB hepatocellular carcinoma (HCC), with either PVTT or hepatic vein tumor thrombosis between 2007 and 2015 in our hospital. IMRT was used for all patients who received RT. Prognostic factors, including treatment modalities, liver function, and comorbidities, were analyzed using univariate and multivariate analysis with the Cox model. Survival time was analyzed using the Kaplan–Meier method. **Results:** The longest follow-up time was 45.3 months. The median age was 67 years. Univariate analyses indicated that IMRT, transarterial chemoembolization (TACE), target therapy (sorafenib), tumor size, Child-Pugh class, and ascites were significantly associated with overall survival (OS). In multivariate analysis, IMRT (hazard ratio [HR], 0.495; $P = 0.019$), sorafenib (HR, 0.340; $P = 0.013$), tumor size (HR, 2.085; $P = 0.020$), and Child-Pugh class ($P = 0.004$), were independent prognostic predictors for patients with intrahepatic vessel invasion, but TACE and ascites were not. The outcomes of patients who had different treatment modalities were significantly different ($P < 0.001$). Patients who received IMRT with TACE had the best outcomes. Patients who received an RT dose above 5400 cGy had better outcomes than those who with a dose below 5400 cGy, although the results were not significantly different ($P = 0.248$). **Conclusion:** IMRT is an important treatment component for patients with intrahepatic vascular invasion. Combined treatment modalities, such as IMRT with TACE, could improve the outcomes of HCC patients with intrahepatic vessel invasion.

Keywords: *Hepatic vein thrombosis, Hepatocellular carcinoma, Portal vein thrombosis, Prognosticators, Radiotherapy, Transarterial chemoembolization*

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequently diagnosed cancer in the world and the third most common cause of cancer-related deaths in men [1]. Partial hepatectomy, liver transplantation, and local ablative treatments provide potentially curative therapy for HCC. However, only a minority (20%–25%) of HCC patients can be managed with curative treatment [2]. The prognosis of HCC is extremely poor in patients with advanced disease. Although several factors contribute to this poor prognosis, major vascular invasion, i.e., portal vein tumor thrombosis (PVTT) or hepatic vein tumor thrombosis (HVTT), is one of the most important factors [3].

About 8%–26% of HCC patients have main portal vein obstruction [4,5]. PVTT can lead to serious complications,

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such as portal vein hypertension, rupture of esophageal and rectal varices, ascites, and ischemic liver damage. Patients with advanced HCC with PVTT have a particularly grave prognosis [6]. The previous study showed that the median survival time of patients who have HCC with PVTT is 2–3 months if no treatment is received [7].

The incidence of HVTT ranges from 1.4% to 4.9% [8,9]. Compared with PVTT, little is known about HVTT due to its relatively low incidence [9]. Patients with both HVTT and PVTT have a worse prognosis than those with HVTT alone, due to the high risk of intrahepatic metastasis and portal hypertension complications [10].

In locally advanced HCCs, radiaotherapy (RT) has been used to relieve obstruction and improve portal blood flow if the tumor invades the biliary tree or portal vein [11]. RT techniques for the treatment of HCC have evolved substantially over the past decades. Delivery of radiation has become more precise, which has enabled higher doses of radiation to tumors while saving the normal liver parenchyma [12]. RT has also been used in combination with transarterial chemoembolization (TACE) for intermediate stage tumors.

In this study, we retrospectively analyzed the prognostic factors of stage IIIB HCC patients with either PVTT or HVTT. We also examined the outcomes of patients who were treated with combined intensity-modulated RT (IMRT) and TACE compared with TACE alone, IMRT alone, and supportive care alone.

Materials and methods

Ethics statement

This study was reviewed and approved by the Institutional Review Board of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan (B10404010). The procedures we followed were in accordance with both the ethical standards of the Institutional Review Board of our institution and with the Helsinki Declaration. Informed written consent was waived because the study was a retrospective data analysis.

Patients

Between January 1, 2007, and December 31, 2015, a total of 73 patients with newly diagnosed AJCC stage IIIB HCC who had an initial diagnosis of either PVTT or HVTT were retrospectively enrolled into the study. All patients were evaluated with a baseline history and physical examination, serum laboratory tests, including baseline liver function tests, and computed tomography or magnetic resonance imaging scan of the abdomen and pelvis.

Treatment modality

The treatment strategies adopted by physicians, patients, and their families were recorded, which included TACE alone, RT alone, both RT and TACE, and supportive care alone.

IMRT was carried out using an inverse planning system in all patients who received RT. The prescribed doses delivered by external beam RT were at least 45 Gy, ranging from 45 to 70 Gy. Conventional RT fractionation was given, namely, 3–4.5 Gy per day, 5 days per week for 2–4 weeks, with a total of 11–20 fractions. The biologically effective dose (BED) ranged from 58.5 Gy_{10} to 84.5 Gy_{10}.

Measurements of endpoint and covariates

The primary dependent variable in the study was overall survival (OS), which was calculated from the date of diagnosis to the past follow-up or death. Factors which could possibly affect OS were adjusted accordingly. These independent variables included gender, age, cancer treatment modalities received, Barcelona clinic liver cancer (BCLC) stage, initial Child-Pugh score, largest tumor size, PVTT status, HVTT status, hepatitis serological condition, liver cirrhosis, ascites, and comorbidities including diabetes mellitus (DM), hypertension (HTN), stroke, and chronic kidney disease (CKD) [Table 1]. Cancer treatment modalities for these stage IIIB patients included RT alone, TACE alone, TACE and RT, and best supportive care only.

Statistical analysis

We used commercial statistical software (SPSS version 17.0; SPSS Inc., Chicago, IL, USA) to conduct statistical analyses. The Kaplan–Meier method was used for survival analysis. The difference between survival curves was determined using the log-rank test. The Cox regression model was used in the univariate analysis to identify significant prognostic factors. Only those statistically significant variables in univariate analysis were included in multivariate analysis using the Cox regression model. All tests were two-tailed and considered to be statistically significant when $P < 0.05$.

Results

The longest follow-up time was 45.3 months. The first, median, and third quartile follow-up times were 1, 4, and 8.23 months, respectively. The relatively short follow-up time was mainly due to the poor prognosis and short survival time of these stage AJCC stage IIIB patients. The cumulative 6-month, 1-year, 2-year, and 3-year OS rates were 35.6%, 17.8%, 8.9%, and 8.9%, respectively and the median survival for all patients was 4 months.

The first, median, and third quartile ages of all these HCC patients in our hospital were 56.5, 67, and 75.5 years old, respectively; the oldest patient was 92 years old. This was a relatively older age distribution for HCC patients, compared with the rest of Taiwan, which may be due to population aging problems in Chiayi county. A total of 76.7% of patients were male. Most patients (39 patients, 53.4%) received only the best supportive care without TACE or RT. A total of 16, 11, and 7 patients received RT alone, TACE alone, and both TACE and RT, respectively. A total of 40 (54.8%) cases were Child-Pugh class B, followed by 21 (28.8%) cases with Child-Pugh class A. Only 12 (16.4%) cases were classified class C based on initial clinical and laboratory evaluation. In 54 patients (74%), the tumors were larger than 5 cm.

Intrahepatic vein invasion was classified according to the criteria of the liver cancer study group of Japan as portal tumor invasion involving first-order branches or the main trunk of the portal vein, or as tumor invasion involving first-order branches of the hepatic vein. Seventy patients had PVTT (95.9%), and eleven patients had HVTT (15.1%). Forty of the PVTT patients

Table 1: Patient characteristics (*n*=73)

Variable	Without RT (*n*=50), *n*%		With RT (*n*=23), *n*%		*P*
Gender					
Male	36	72.0%	20	87.0%	0.16
Female	14	28.0%	3	13.0%	
Age					
<65	15	30.0%	13	56.5%	0.07
≥65~<75	19	38.0%	7	30.4%	
≥75	16	32.0%	3	13.0%	
BCLC stage					
C	40	80.0%	22	95.7%	0.08
D	10	20.0%	1	4.3%	
Child Pugh Score					
Class A	12	24.0%	9	39.1%	0.28
Class B	28	56.0%	12	52.2%	
Class C	10	20.0%	2	8.7%	
Tumor Size					
<5cm	11	22.0%	8	34.8%	0.25
≥5cm	39	78.0%	15	65.2%	
Portal Vein Thrombosis					
(-)	1	2.0%	2	8.7%	0.18
(+)	49	98.0%	21	91.3%	
Main	23	46.9%	7	33.3%	0.29
Right or Left Branch	26	53.1%	14	66.7%	
Hepatic Vein Thrombosis					
(-)	45	90.0%	17	73.9%	0.07
(+)	5	10.0%	6	26.1%	
TACE					
(-)	39	78.0%	16	69.6%	0.44
(+)	11	22.0%	7	30.4%	
Sorafenib					
(-)	46	92.0%	16	69.6%	0.01
(+)	4	8.0%	7	30.4%	
Hepatitis					
(-)	14	28.0%	8	34.8%	0.09
HBV	15	30.0%	12	52.2%	
HCV	17	34.0%	2	8.7%	
HBV and HCV	4	8.0%	1	4.3%	
Liver Cirrhosis					
(-)	13	26.0%	5	21.7%	0.69
(+)	37	74.0%	18	78.3%	
Ascites					
(-)	12	24.0%	11	47.8%	0.04
(+)	38	76.0%	12	52.2%	
Diabetes Mellitus					
(-)	29	58.0%	17	73.9%	0.19
(+)	21	42.0%	6	26.1%	
Hypertension					
(-)	22	44.0%	15	65.2%	0.09
(+)	28	56.0%	8	34.8%	
Stroke					
(-)	49	98.0%	22	95.7%	0.57
(+)	1	2.0%	1	4.3%	
Chronic Kidney Disease					
(-)	48	96.0%	21	91.3%	0.41
(+)	2	4.0%	2	8.7%	

IMRT: Intensity-modulated radiation therapy; HCC: hepatocellular carcinoma; RT: radiotherapy; TACE: transcatheter arterial chemoembolization; BCLC: Barcelona Clinic Liver Cancer staging system; HBV: hepatitis B virus; HCV: hepatitis C virus; IMRT was used in all patients

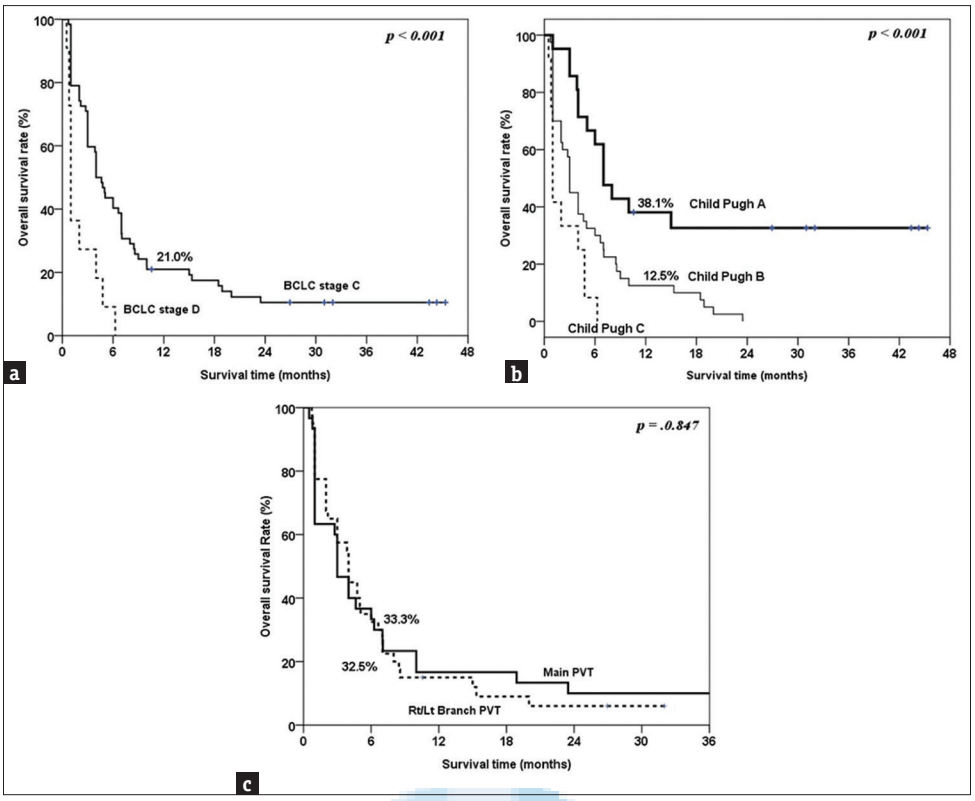

Figure 1: (a) The cumulative 6-month, 1-year, 2-year, and 3-year overall survival rates were 40.3%, 21%, 10.5%, and 10.5%, and the median survival for BCLC stage C patients was 4.32 months. For Barcelona clinic liver cancer stage D patients these rates were 9.1%, 0%, 0%, and 0%, and median survival was 1 month. (b) The cumulative 6-month, 1-year, 2-year, and 3-year overall survival rates and median survival for patients with Child-Pugh class A were 61.9%, 38.1%, 32.7%, and 32.7%, and 7 months, for Child-Pugh class B were 30.0%, 12.5%, 0%, and 0%, and 3 months, and for Child-Pugh class C were 8.3%, 0%, 0%, and 0%, and 1 month. (c) The cumulative 6-month, 1-year, 2-year, and 3-year overall survival rates and median survival for patients with right or left branch portal vein invasion were 32.5%, 15.0%, 6.0%, and censored, and 4 months, and for those with main trunk portal vein invasion, were 33.3%, 16.7%, 10%, and 10%, and 3 months

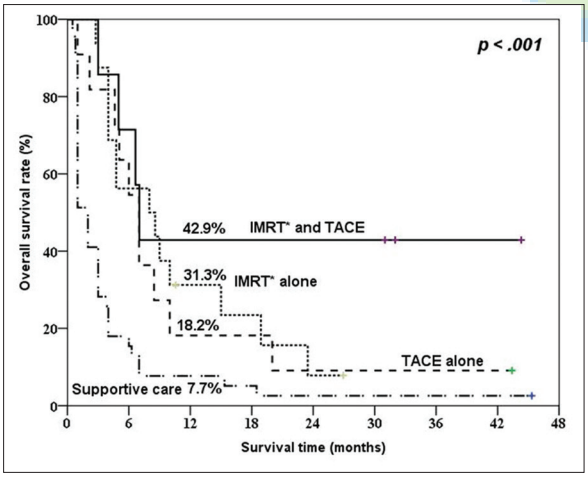

Figure 2: The cumulative 6-month, 1-year, 2-year, and 3-year overall survival rates and median survival for intensity-modulated radiotherapy with transarterial chemoembolization, were 71.4%, 42.9%, 42.9%, and 42.9%, and 7.03 months, for intensity-modulated radiotherapy alone were 56.3%, 31.3%, 7.8%, and censored, and 8.28 months, for transarterial chemoembolization alone were 54.5%, 18.2%, 9.1%, and 9.1%, and 7 months, and for supportive care, were 15.4%, 7.7%, 2.6%, and 2.6%, and 2 months

had an invasion of the first-order branch of the portal vein, and 30 patients had main trunk invasion. A total of 51 patients had hepatitis. Among them, 27, 19, and 5 patients had hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and concurrent HBV/HCV hepatitis, respectively. A total of 55 patients had liver cirrhosis (75.3%), and 50 patients had ascites. No patients received resection surgery. Eleven patients received sorafenib.

A comparison of patient characteristics (including age groups, liver functional reserve status, tumor factors, treatment modalities, and comorbidity) between patients with and without IMRT is shown in Table 1. These two groups were not significantly different except for sorafenib use and ascites which were then incorporated into univariate and multivariate analysis for adjustment and exploration of effects on prognosis [Tables 2 and 3].

Patients who were in BCLC stage C had significantly better outcomes than those in stage D [Figure 1a, $P < 0.001$]. Patients who had better liver function reserves had significantly better outcomes [Figure 1b, $P < 0.001$]. The outcomes of patients with only first-order branch portal vein invasion were not significantly different than those with main trunk invasion [Figure 1c, $P = 0.847$].

The outcomes of patients with different treatment modalities were significantly different [Figure 2, $P < 0.001$]. Patients who received IMRT combined with TACE had the best outcomes. Patients who received IMRT with TACE had nonsignificantly better outcomes than those with IMRT alone or TACE alone with one year OS rate being 42.9%, 31.3%, 18.2%,

Table 2: Univariate analysis of patient-, treatment-, and dosimetry-related variables

Variable	Univariate Analysis		
	HR	95%CI	*P*
Gender (Male, ref.)	0.732	0.405-1.323	0.732
Age			0.840
<65 (ref.)	1	-	-
≥65~<75	0.908	0.516-1.599	0.739
≥75	1.099	0.597-2.021	0.762
IMRT (no IMRT, ref.)	0.405	0.233-0.704	0.001*
TACE (no TACE, ref.)	0.472	0.260-0.858	0.014*
Sorafenib (no sorafenib, ref.)	0.270	0.120-0.608	0.002*
Tumor Size (<5 cm, ref.)	2.285	1.266-4.123	0.006*
Hepatic Vein Tumor Thrombosis (without, ref.)	0.629	0.310-1.275	0.198
Portal Vein Tumor Thrombosis (without, ref.)	3.057	0.743-12.572	0.121
Child Pugh Class			0.001*
Class A (ref.)	1	-	-
Class B	2.767	1.485-5.155	0.001*
Class C	5.902	2.589-13.455	0.000*
HBV (without, ref.)	0.875	0.538-1.423	0.237
HCV (without, ref.)	1.093	0.655-1.826	0.733
Liver Cirrhosis (without, ref.)	0.863	0.496-1.501	0.601
Ascites (without, ref.)	2.266	1.276-4.025	0.005*
Diabetes Mellitus (without, ref.)	0.99	0.597-1.641	0.969
Hypertension (without, ref.)	0.988	0.609-1.604	0.961
Stroke (without, ref.)	1.871	0.451-7.762	0.388
Chronic Kidney Disease (without, ref.)	0.639	0.231-1.763	0.135

*P<0.05; HR, hazard ratio; CI: confidence interval; ref: reference; IMRT: intensity-modulated radiotherapy; TACE: transcatheter arterial chemoembolization; HBV: hepatitis B virus; HCV: hepatitis C virus

Table 3: Multivariate analysis of patient-, treatment-, and dosimetry-related variables

Variable	Multivariate Analysis		
	HR	95%CI	*P*
IMRT (no IMRT, ref.)	0.495	0.276-0.889	0.019*
TACE (no TACE, ref.)	0.556	0.290-1.068	0.078
Sorafenib (no sorafenib, ref.)	0.340	0.145-0.800	0.013*
Tumor Size (<5 cm, ref.)	2.085	1.125-3.865	0.020*
Child Pugh Class			0.004*
Class A (ref.)	1	-	-
Class B	2.137	1.116-4.089	0.022*
Class C	4.360	1.821-10.440	0.001*
Ascites (without, ref.)	1.396	0.768-2.539	0.274

*P<0.05; HR, hazard ratio; CI: Confidence interval; ref: reference; IMRT: intensity-modulated radiotherapy; TACE: transcatheter arterial chemoembolization

respectively [Figure 2, P = 0.242 and 0.240]. The outcomes of patients who received IMRT alone were not significantly different than those with TACE alone (P = 0.714). Patients who received IMRT with TACE, IMRT alone, or TACE alone, all had better outcomes than those with supportive care only, with significant results (P = 0.002, 0.001, and 0.010, respectively).

For patients who received IMRT, the first, median, and third quartile survival times were 4, 8, and 18.9 months, respectively. Patients who received IMRT doses above 5400 cGy had better outcomes than those with doses below 5400 cGy, but the results were not significantly different [Figure 3, P = 0.248].

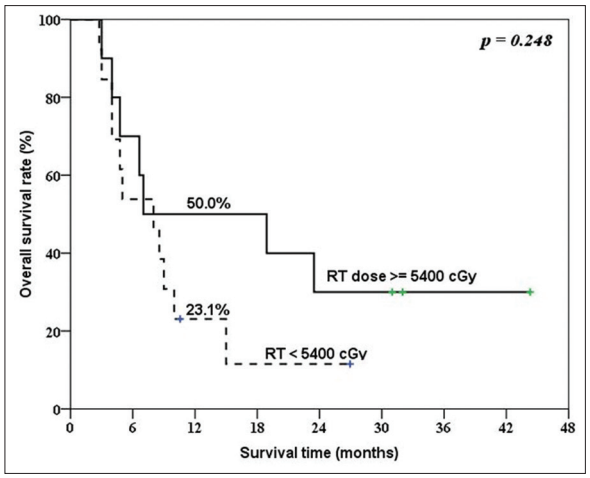

Figure 3: The cumulative 6-month, 1-year, 2-year, and 3-year overall survival rates and median survival for intensity-modulated radiotherapy doses above 5400 cGy were 70%, 50%, 30%, and 30%, and 6.83 months, and for doses below 5400 cGy, were 53.8%, 23.1%, 11.5%, and censored, and 8.57 months

Univariate analyses indicated that IMRT, TACE, sorafenib, tumor size, Child-Pugh class, and the presence of ascites were significantly associated with OS [Table 2]. On multivariate analysis [Table 3], IMRT (hazard ratio [HR], 0.495; 95% CI, 0.276–0.889; P = 0.019), sorafenib (HR, 0.340; 95% CI, 0.145–0.800; p, 0.013), tumor Size (HR, 2.085; 95% CI, 1.125–3.865; P = 0.020), and Child-Pugh class (p, 0.004), were independent prognostic predictors. TACE and ascites were not.

Gender, age, tumor size, HVTT, viral hepatitis, liver cirrhosis, ascites, comorbidities, including DM, HTN, stroke, and CKD were all found not to affect OS after multivariate analysis.

Discussion

In this study, we reviewed the preliminary treatment results of patients with clinical AJCC stage III B HCC, who were treated with different modalities at our hospital. The survival rate of our stage IIIB patients was relatively low because most of them did not receive any active treatment but only best supportive care. The reasons for this included long distances from care facilities, poor family support (many patients lived alone), and relatively old age (77.6% of patients were over 60 years old).

All treatment strategy decisions were made by a multidisciplinary cancer team of gastroenterologists, pathologists, radiologists, hepatobiliary surgeons, radiation oncologists, medical oncologists, and registered dietitians. However, patients and families may refuse suggested strategies such as RT or TACE due to the above reasons. In addition, oncologists can tailor treatment for patients living alone or with poor family support to avoid harmful side effects [13]. Relatives also play an important role in the care of cancer patients and their presence may even prolong survival [14]. In this retrospective study, 63.3% stage IIIB patients did not receive definite treatment but only best supportive are.

The study results showed that the outcomes of different treatment modalities for patients with intrahepatic vessel invasion were significantly different ($P < 0.001$). Previous limitation for RT treatment of HCC was that the radiation tolerance of the liver was far less than the therapeutic radiation dose, i.e., low therapeutic ratio [15]. However, recent RT technological developments have enabled more successful treatment of HCC by delivering a substantial dose of radiation to the tumor and avoiding peripheral normal liver tissue. Now, the improved efficacy of RT is more widely understood and increasing numbers of institutions have adopted local RT for advanced HCC [16]. In this study, patients who received RT alone had significantly better outcomes than those with best supportive care only ($P = 0.01$).

Culleton *et al*. reported a median survival of 7.9 months for HCC patients with PVTT and Child-Pugh class B to C, treated by stereotactic body RT with median dose 30 Gy in 6 fractions [17]. In this study, patients with daily dose of 3–4.5 Gy had a median survival of 8 months.

RT has also been used to treat PVTT with good outcomes [18,19]. Lee *et al*. performed RT with a BED of 39 Gy_{10} TO 70.2 Gy_{10}. Their study showed a dose-response relation with response rates for a BED <58 Gy_{10} and ≥58 Gy_{10} of 20% and 54.6%, respectively ($P = 0.034$) [18]. The study results showed that a BED ≥63.7 Gy_{10} (54 Gy) resulted in nonsignificantly better outcomes than a BED <63.7 Gy_{10}, with 1 year OS rate of 50% and 23.1%, respectively ($P = 0.248$).

Higher doses of RT could result in a higher response rate for large tumors. In our treatment experience, the prescribed doses can be increased from 45 to 70 cGy without significant radiation-induced liver disease. In this study, all patients received RT using the IMRT technique. A previous study showed that IMRT significantly reduced the probability of complications in normal tissue, compared with three-dimensional conformal RT (3DCRT) [20]. Simultaneous integrated boost-intensity modulated RT has also been shown effective for advanced HCC [21].

Advances in 3D conformal techniques for treatment planning have allowed RT to be a complement to incomplete TACE [22-24]. Conversely, Lu *et al*. compared 3DCRT followed by 2–3 series of TACE to TACE alone and found that combined treatment significantly improved clinical outcomes in patients with HCC and PVTT (mean survival time 13.0 vs. 9.0 months) [25]. A literature review showed that most combined therapy studies were 3DCRT/IMRT with TACE. Our study showed results of purely IMRT with TACE and found that clinical outcomes combining IMRT and TACE were the best, followed by IMRT alone, and TACE alone, with supportive care alone being the worst. Consistent with a previous 3DCRT study, our study reported that patients who received IMRT with TACE, and TACE alone had mean survivals of 17.8 and 8.5 months, respectively.

The prognosis of untreated HCC is grave despite improved supportive treatment. Yeung *et al*. reported on 106 Chinese patients with HCC who were not amenable to curative treatment and were managed symptomatically [6]. The overall median survival was 3 months, with Okuda stages I, II, and III of 5.1, 2.7, and 1.0 months, respectively ($P < 0.05$). In our study, patients who received best supportive care only had a mean survival of 2.3 months. Previous studies have shown that individuals in rural areas have trouble accessing palliative care due to shortages of health care professionals as well as transportation issues imposed by geography [26].

Study strengths

This study had several strengths. First, image examination results were available, including hepatic vein invasion status, and first-degree or main trunk PVTT. This study incorporated this image information into univariate and multivariate analysis to find significant prognosticators. Second, this study focused on AJCC clinical stage IIIB patients who all had intrahepatic vessel invasion. This study design could decrease the bias of cancer stage diversity.

Study limitations

Our study also had several limitations. First, the number of patients with AJCC stage IIIB was small, although the results still reached statistical significance. With respect to future work, a larger sample size would be helpful, as would a longer longitudinal study. Second, this was a retrospective review study rather than a prospective randomized controlled trial, although many variates had been adjusted. Further investigation is warranted. Third, this study lacked information on sociodemographic characteristics, such as socioeconomic status.

Conclusion

IMRT is an important treatment component in intrahepatic vascular invasion patients. Combined treatment modalities, such as IMRT with TACE, could improve the outcomes of HCC patients with intrahepatic vessel invasion. Action is needed to improve family support with social support networks and improve access to medical services, to encourage patients and their families to receive active treatment.

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Nil.

Conflicts of interest

There is no conflict of interest.

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