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ORIGINAL ARTICLE

Advanced hepatocellular carcinoma with major portal vein invasion: Therapeutic outcomes of hepatic arterial infusion chemotherapy vs concurrent radiotherapy

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Abstract

Background: Hepatocellular carcinoma (HCC) with major portal vein invasion (MPVI) presents very poor outcomes. Hepatic artery infusion chemotherapy (HAIC) and radiation therapy (RT) have both been found to be effective for advanced HCC. In this retrospective study, we compared the therapeutic outcomes of our "new" HAIC regimen with and without concurrent RT, before and after propensity score matching (PSM) in treating HCC patients with MPVI.

Methods: One hundred forty patients with MPVI received HAIC alone and 35 patients underwent concurrent HAIC and RT during a 16-year period. The left subclavian artery was adopted as the entry site for a temporary catheter placement for a 5-day chemoinfusion. The Modified Response Evaluation Criteria in Solid Tumors (mRECIST) was adopted to assess the objective response rate (ORR). The Kaplan-Meier curve was used to calculate progression-free survival (PFS) and overall survival (OS) between the two groups. Univariate and multivariate analyses by Cox regression model were used to assess hazard ratios.

Results: Of the 140 patients with Child-Pugh A liver function, the median OS was 17.0 months. In the initial cohort, higher ORR and PFS were found in the concurrent RT group than in the HAIC alone group (80% vs 66.4% and 9 vs 8 months, respectively) but shorter OS (10.5 vs 14.5 months, $p = 0.039$) was observed. After PSM, the OS was 10 and 15 months ($p = 0.012$), respectively. Multivariable Cox regression analysis revealed that the significant factors for adjusting hazard ratios for OS were Child-Pugh classification, alpha fetal protein (AFP) level, and hepatic vein invasion.

Conclusion: HAIC is an effective treatment for advanced HCC patients with MPVI. Concurrent HAIC and full-dose RT were associated with worse clinical outcomes.

Keywords: Hepatic artery; Hepatocellular carcinoma; Portal vein; Radiotherapy; Retrospective study

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common solid tumor and the third leading cause of cancer-related death globally.[1] Portal vein invasion occurs in 35% to 50% of patients at the time of diagnosis.[1,2] Studies show that even under the best supportive care, HCC patients with major portal vein invasion (MPVI) have overall survival (OS) of <4 months.[2–4] Combined immuno-target therapy (atezolizumab and bevacizumab)[5] has been recently recommended as the first-line therapy for advanced HCC (aHCC), with a median OS of 7.6 months in patients with main portal vein invasion.[6] In the event that there is no response to immuno-target combination therapy, hepatic artery infusion chemotherapy (HAIC) could be administered as the second-line therapy.[7] The median OS of traditional HAIC has been reported to be 5.7 to 10 months,[8–16] vs 10.5 months for oxoliplatin, fluorouracil, leucovorin (FOLFOX) HAIC,[16] 12 months for new-FP regimen (fine-powder cisplatin suspended in Lipiodol and 5-fluorouracil),[17] and 13.3 months for Yittrium-90 (Y90) radioembolization,[18] 8.7 months for radiotherapy (RT) alone,[19] 12.9 months for FOLFOX HAIC plus sorafenib,[16] 7.5 to 12.1 months for concurrent HAIC and RT,[20,21] and 13.2 months for transarterial chemoembolization plus RT.[22] To enhance the survival benefit, we developed a "new" HAIC regimen by combining a low dose of chemoinfusion and lipiodol embolization, hypothesizing that there was a synergistic effect of chemoinfusion and embolization. In the present retrospective study, we report the clinical outcomes of 175 HCC patients with MPVI treated by our "new" HAIC regimen, of which 35 patients also had received concurrent radiation therapy. The clinical results of the 175 patients with and without concurrent RT before and after propensity score matching (PSM) are analyzed and reported.

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2. METHODS

This retrospective study enrolled consecutive aHCC patients treated by HAIC in Kaohsiung Veterans General Hospital between January 2002 and December 2018. HCC was diagnosed by either pathologic proof or elevation of the alpha fetal protein (AFP) ≥400 ng/mL, along with triphasic contrast enhanced computed tomography (CT) and/or dynamic magnetic resonance images (MRIs). The inclusion criteria in this study were (a) ages of 18 to 85 years old; (b) Child-Pugh liver function class of A (CP-A) or B (CP-B); (c) Eastern Cooperative Oncology Group (ECOG) performance statuses ≤2; (d) aHCC (stage C as per the Barcelona Clinic Liver Cancer [BCLC] criteria) with MPVI (including lobar portal vein [Vp3] and main portal vein [Vp4] invasion); (e) platelet counts ≥50 000/cumm and white cell counts ≥2500/cumm; (f) prothrombin time international normalized ratio (INR) ≤1.5. Patients had received less than two courses of HAIC, or without radiological follow-up images were excluded from this study. Patients with extrahepatic spread (EHS) were not excluded if their life expectancy was ≥3 months. BCLC stage C patients with Child A liver function had also received tyrosine kinase inhibitor (sorafenib 400 mg bid) therapy after 2013 as the target agent was not available in our hospital before that time. See Fig. 1 for the enrolled patient flow chart.

2.1. Hepatic arterial infusion chemotherapy

Instead of a routine femoral artery puncture, we adopted the left subclavian (axillary) artery as the entry site under ultrasonographic guidance. This approach provided comfortability for patients during a 5-day chemoinfusion. Under fluoroscopic guidance, we inserted a 65 cm, 4-F catheter (J-curve, Terumo, Tokyo, Japan) into the common/proper hepatic artery or replaced right hepatic artery.[23] To prevent gastrointestinal upset due to the infusion of anticancer drugs, the proximal gastroduodenal artery (GDA) was usually embolized by metallic coils. If necessary, the right gastric artery was also occluded via a microcatheter with metallic microcoils.

Our HAIC regimen consisted of a daily pump-infusion of 10 mg/m^2 cisplatin, 2 mg/m^2 mitomycin-C, and 15 mg/m^2 leucovorin, each administered for 20 to 30 minutes, plus a slow infusion (22 hours) of 100 mg/m^2 5-fluorouracil (5-FU) for 5 days. After completion of the 5-day chemoinfusion, we injected 10 mL lipiodol (Guerbet, Aulnay sous Bois, France) into the hepatic artery via the existing 4-F angio-catheter. Because of the high affinity between HCC and ethiodized oil, most of the injected lipiodol flowed into and was retained in the HCC lesions, sparing the non-tumorous parenchyma. Gelfoam or other embolizing particles were not injected to prevent potential liver damages. The angio-catheter was then removed after the lipiodol injection on the fifth treatment day. The scheduled interval between any two treatments was 6 weeks. After every two courses of HAIC treatment, dynamic CT or MRI of the liver was followed. The upper limit of treatment courses was set at six to eight courses (usually six), because we had observed no extra-therapeutic benefit from our early clinical experience. The treatment was terminated if there was either radiological progress or significant deterioration of patients' liver function.

2.2. Radiation therapy

For the group of patients who received concurrent HAIC and RT, RT commenced within 3 weeks after the first course of HAIC. To provide optimum setup accuracy for these patients, abdominal compression during free-breathing CT simulation (GE Discovery CT 590 RT) was applied. In patients with large or infiltrative HCC, the clinical target volume (CTV) was set to encompass the MPVI with a 1 cm extension into the intrahepatic lesions. In cases, where the HCC was small and abutting, the CTV comprised both the intrahepatic lesions and the PVTT. The planning target volume (PTV) was determined by adding a 1.5 cm margin to the CTV. An Eclipse planning system (Varian Medical Systems, version 13, Palo Alto, CA) was used to determine dose prescriptions. The dose (2-4.5 Gy, five fractions per week) was delivered by a Varian Medical Systems linear accelerator to the PTV using 10 MX-rays. According to the QUANTEC

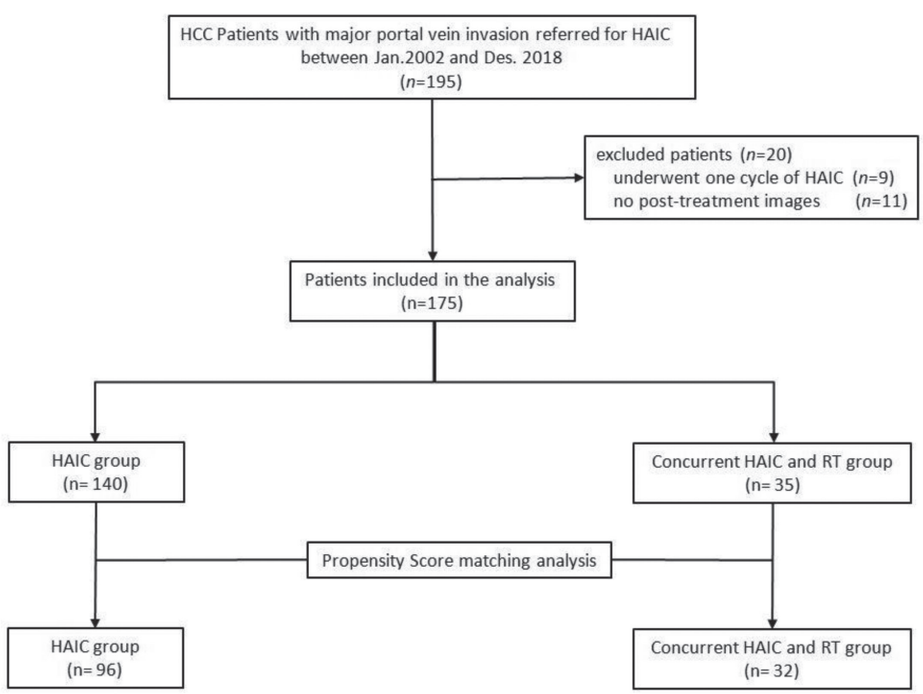

Fig. 1 Flowchart of patient enrollment. HAIC = hepatic artery infusion chemotherapy; HCC = hepatocellular carcinoma; RT = radiation therapy.

guidelines,[24] normal liver volume and baseline hepatic function were used to determine the total radiation dose.

2.3. Assessment of response

To assess the radiologic response, the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[25] was adopted in this study, which was defined as follows: complete response (CR)—no evidence of residual viable neoplastic lesions; partial response (PR)—enhanced viable target lesions with at least a 30% decrease in the sum of their diameters, using the baseline sum of the diameters of target lesions as reference; progressive disease (PD)—viable target lesions with an increase of at least 20% in the sum of their diameters; and stable disease (SD)—cases that were neither PR nor PD. Objective response (OR) or responders were defined as the sum of CR and PR. Non-responders were defined as the patients of SD and PD. The treatment response was usually determined after completion of the treatment courses (six courses). But in patients who received less than six courses, the final follow-up images (after at least two HAIC courses) were used to determine the treatment response.

2.4. Progression-free survival and OS

Progression-free survival (PFS) and OS were defined as the time period between initiation of HAIC treatment and tumor progression and death from any cause.[25] In this study, we reported the intrahepatic PFS (IH-PFS) instead of the whole disease progression, as metastatic lesions in these aHCC patients were not excluded. The OS and prognostic factors were analyzed between the 140 HAIC alone and 35 concurrent RT patients both before and after PSM.

2.5. Ethics statement

Our hospital's ethical committee had approved the HAIC regimen therapy to treat aHCC patients (VGHKS89-55). Every patient had signed the written informed consent before the treatment. This retrospective review of patients' radiological images and medical records was also approved by the hospital's Institutional Review Board (VGHKS22-CT7-03).

2.6. Statistical analysis

Continuous variables were expressed as mean ± SD and compared by the Mann-Whitney test. Categorical variables were compared using the chi-squared test or Fisher exact test, when appropriate. The Kaplan-Meier survival curve and the log-rank test were used to analyze and compare the median IH-PFS and OS. Univariate and multivariate analyses were performed using Cox regression model with hazard ratio (HR) of the variables. All statistical analyses were performed using the SPSS version 22.0 software (SPSS Inc., Chicago, IL). To minimize the effect of potential confounders and selection bias, we used SAS 9.4 software (SAS Institute Inc., Cary, NC) to perform PSM (three-to-one matching) by using the nearest-neighbor model of width 0.2.9. After adjustment, OS rate was recalculated for both groups. A $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Patients

One hundred seventy-five HCC patients with MPVI in our hospital received the new regiment of HAIC, either alone (group A, n = 140) or with concurrent RT (group B, n = 35) during this study period. The basic demographic data of the 175 patients are summarized in Table 1. There were 98 (70.0%) and 26 (74.3%) treatment-naïve patients with transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and surgical resection of 15.0%, 9.3%, and 5.7% vs 17.2%, 5.7%, and 2.8% in each group, respectively. There was a higher percentage of patients with chronic hepatitis B infections in group A than in group B (65.7% vs 51.4%, p = 0.018). The number of tumors, combined hepatic vein invasion, or tumor involvement were similar between the two groups, as well as maximal tumor size (10.08 ± 4.08 vs 10.44 ± 3.82 cm, p = 0.638). The concurrent RT group showed a higher percentage of EHS (34.3% vs 22.9%), but the difference was not statistically significant. Baseline characteristics were more balanced after PSM (Table 1). In group B which received concurrent RT, the range of radiation dose was 12.5 to 56 Gy (median 40 Gy), divided into doses of 2 to 4.5 Gy per fraction.

3.2. Radiologic response after treatment

The OR rate (ORR) was 66.4% (93 patients) with CR in 15.0% (Fig. 2) and PR in 51.4% in the group A patients, and an ORR of 80.0% (28 patients), CR of 8.6% and PR of 71.4% in the group B patients (p = 0.12). After PSM, in groups A and B, respectively, five (7.1%) and three (8.6%) patients showed CR and 37 (52.9%) and 25 (71.4%) patients showed PR (p = 0.598).

3.3. Progression-free and OS analyses after treatment

The mean follow-up time was 24.6 ± 2.5 months (range: 3-156 months). The median PFS was 8 vs 9 months in each group (p = 0.065). The median OS and 1-, 2- and 3-year survival rates were, respectively, 14.5 months, 58.4%, 28.9%, and 20.7% in group A, and 10.5 months, 41.2%, 16.3%, and 6.5% in group B (p = 0.025) (Fig. 3). After PSM, the median OS, 1-, 2- and 3-year survival rates were, respectively, 15 months, 59.1%, 31.3%, and 24.6% in the group A patients, and 10 months, 35.5%, 18.8%, and 7.5% in the group B patients (p = 0.012) (Fig. 4).

As for liver function, the 140 group A patients had a median OS of 17.0 and 7.8 months for Child-Pugh A and B patients (p = 0.009), vs 10.5 and 10.0 months for the 35 group B patients (p = 0.488).

3.4. Uni- and multi-variable analyses

Univariate survival analyses revealed a significantly longer survival in the group A with the prognostic factors of Child-Pugh A liver function; an AFP level <400 ng/mL; a tumor size ≤10 cm, and unilobar liver involvement (Table 2). After PSM, multivariate analysis of the prognostic factors with adjusted HR for OS was HAIC treatment (HR = 1.789, 95% CI, 1.163-2.415, p = 0.011), Child-Pugh classification (HR = 1.307, 95% CI, 0.896-1.906, p = 0.040), AFP levels (HR = 1.583, 95% CI, 0.547-1.182, p = 0.027), and hepatic vein invasion (HR = 1.278, 95% CI, 1.124-1.432, p = 0.032) (Table 2). In a subgroup analysis of the 140 HAIC alone patients, there was a statistically significant poorer survival in patients with Child-Pugh B liver function (HR = 1.67, 95% CI, 1.068-2.611, p = 0.025), maximal tumor size >10 cm (HR = 2.003, 95% CI, 1.344-2.983, p = 0.001), bilateral lobe involvement (HR = 1.586, 95% CI, 1.097-2.291, p = 0.014) and HAIC treatment courses less than three (HR = 1.253, 95% CI, 1.088-1.418, p = <0.001) (Table 3).

3.5. Major complications

None of the patients died directly related to the complications of HAIC procedures. One patient complicated with subclavian artery pseudoaneurysm at the needle entry site, which was successfully managed by deployment of a stentgraft (8 × 50 mm Viabahn; Gore, Newark, DE). Another one patient had a subcutaneous hematoma over the puncture site with spontaneous resorption, requiring no further management. Three patients had grade III thrombocytopenia during or after the HAIC treatment period. No vascular complications of occlusion or vasculitis in the hepatic artery were found.

Table 1

Basic demographic data of all 175 patients with MPVI treated with HAIC or concurrent radiotherapy

	Before PSM					After PSM				
	HAIC n = 140		HAIC + RT n = 35		*p*	HAIC n = 96		HAIC + RT n = 32		*p*
Age					0.45					0.49
≤60	70	50%	15	42.9%		45	46.9%	14	43.8%	
>60	70	50%	20	57.1%		51	53.1%	18	56.2%	
Sex					0.133					0.06
Male	119	85.0%	26	74.3%		80	83.3%	24	75.0%	
Female	21	14.0%	9	25.7%		16	16.7%	8	25.0%	
Pathogenesis					0.018					0.07
HBV	92	65.7%	18	51.4%		63	65.7%	17	53.1%	
HCV	36	25.7%	6	17.1%		22	22.9%	7	21.9%	
Non B/C	12	8.6%	11	31.4%		11	11.4%	8	25.0%	
Child Pugh					0.653					1.00
A	109	77.9%	31	88.6%		84	87.5%	28	87.5%	
B	31	22.1%	4	11.4%		12	12.5%	4	12.5%	
AFP					0.362					0.61
<400	60	42.9%	18	51.4%		42	43.7%	15	46.9%	
≥400	80	57.1%	17	48.6%		54	56.3%	17	53.1%	
Tumor size	10.08 ± 4.08 cm		10.44 ± 3.82		0.82	9.87 ± 3.73		11.14 ± 3.52		0.26
<10 cm	67	47.9%	16	45.7%		47	49.0%	14	43.8%	
≥10 cm	73	52.1%	19	54.3%		49	51.0%	18	56.2%	
Number					0.761					0.35
<5	76	54.3%	20	57.1%		50	52.1%	18	56.2%	
≥5	64	45.7%	15	42.9%		46	47.9%	14	43.8%	
Location					0.597					0.15
Unilobe	71	50.7%	16	45.7%		45	46.9%	14	43.8%	
Bilobe	69	49.3%	19	54.3%		51	53.1%	18	56.2%	
EH					0.163					0.28
No	108	77.1%	23	65.7%		73	76.0%	21	65.7%	
Yes	32	22.9%	12	34.3%		23	24.%	11	34.3%	
HVI					0.771					0.12
No	122	87.1%	32	91.4%		82	85.4%	29	90.6%	
Yes	18	12.9%	3	8.6%		14	14.6%	3	9.4%	
Course	3.81 ± 1.73		3.37 ± 1.61		0.172	4.28 ± 1.78		3.38 ± 1.68		0.36

AFP = alpha fetal protein; EH = extrahepatic metastasis; HAIC = hepatic artery infusion chemotherapy; HBV = hepatitis B virus; HCV = hepatitis C virus; HVI = hepatic vein invasion; MPVI = major portal vein invasion; PSM = propensity score matching; RT = radiation therapy.

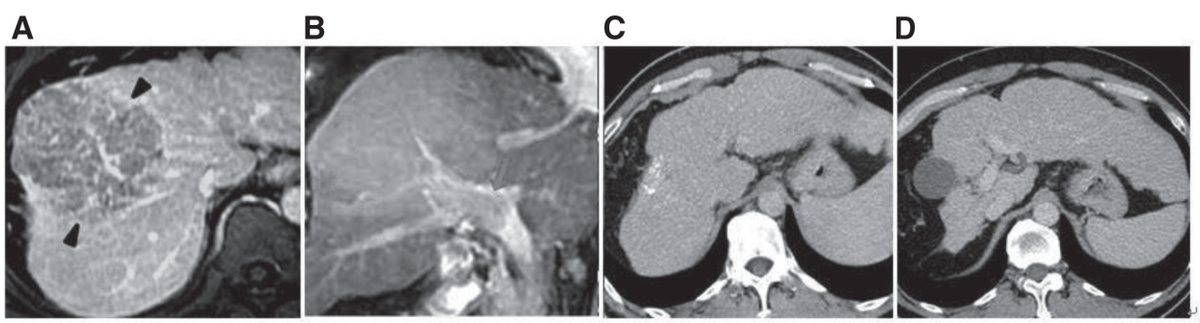

Fig. 2 A, 40 y/o, Child A male patient had a 10 cm HCC in the right lobe liver with MPVI. A and B, Liver MRI showed a 10 cm HCC (arrowheads) in the right lobe liver with main PV invasion (arrow). C and D, Liver CT showed complete remission of the intrahepatic lesions with recanalization of the major PVs (curved arrow). At the time of this writing, this patient has had a disease-free and overall survival of >15 y. CT = computed tomography; HCC = hepatocellular carcinoma; MPVI = major portal vein invasion; MRI = magnetic resonance image; PV = portal vein.

4. DISCUSSION

The SHARP trial reported that, in patients with aHCC, sorafenib prolonged the median OS from 7.9 to 10.7 months when compared with the placebo control,[26] whereas the Asia-Pacific trial reported an increase from 4.2 to 6.5 months.[27] In the subgroup analysis of the SHARP trial, the reported median OS was 8.1 months in patients with portal vein invasion,[28] and the effectiveness was even lower in hepatitis B virus (HBV) related HCC populations.[26,29] In a recent global study, Cheng et al[30] reported that immuno-target combination therapy (atezolizumab and bevacizumab) resulted in a better OS than that of sorafenib alone (19.2 vs 13.4 months, $p < 0.001$) in

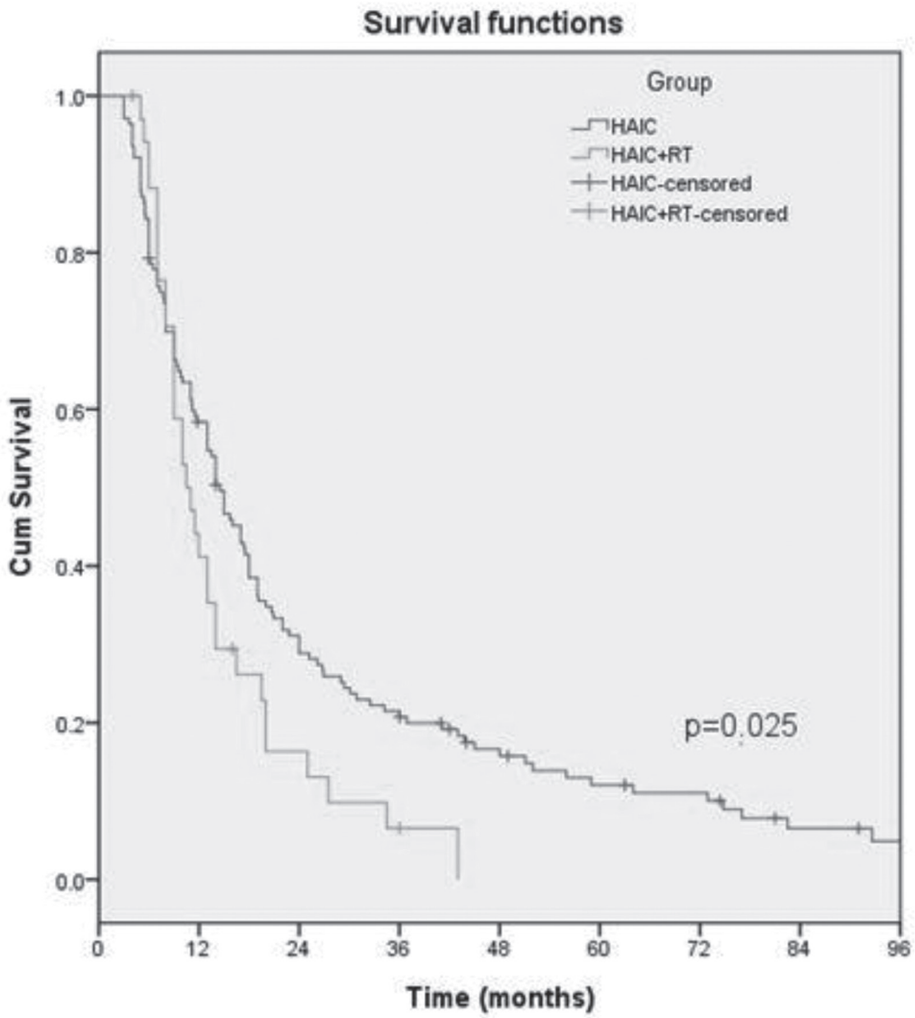

Fig. 3 The OS with vs without radiotherapy of all 175 HCC patients with MPVI. HAIC = hepatic artery infusion chemotherapy; HCC = hepatocellular carcinoma; MPVI = major portal vein invasion; OS = overall survival; RT = radiation therapy.

unresectable Child A HCC patients and also in their subgroup analysis of HCC patients with main portal vein tumor thrombus (7.6 vs 5.5 months).[6] When compared with Cheng et al's[27] prior Asian study (OS of sorafenib: 6.5 months), the additional 6.9 months of the sorafenib group in the more recent study may be attributed to differences in the statuses of the enrolled patients. Moreover, a recent randomized, double-blind, placebo-controlled, multicenter, phase 3 study[7] reported a median OS of 32.3 months using TACE alone in treating unresectable HCC patients. Thereafter, it is not scientifically accurate to report a study with the term of "unresectable HCC" as inclusion criteria and the conclusion of a 19.2-month OS resulting from immunotarget combination therapy may not be applicable to all aHCC patients. Besides, the high medical cost of the combination therapy may restrict its wide clinical application. Searching for alternative-yet-effective therapies is still warranted.

In the reported literature, the median OS of HAIC for aHCC patients was between 5.7 and 10.5 months.[8–16] Two previous studies that compared the clinical outcomes of HAIC alone and with sorafenib revealed that patients' median OS was significantly increased from 4.9 to 7.3 months[10] and from 120 to 309 days,[31] respectively. Liang et al[16] reported a better OS in patients treated by FOLFOX HAIC plus sorafenib than those were treated by HAIC alone (12.9 vs 10.5 months). In the present study of 140 MPVI patients treated by our HAIC regimen, the median OS was 14.5 months, with 17.0 months for Child-Pugh A patients group.

Iwamoto et al[17] conducted a multicenter study of a new FP HAIC regimen (cisplatin mixed with lipiodol combined with 5-FU) to treat aHCC. They also reported that the HAIC group had a better median OS than the sorafenib group (12 vs 7.9 months, $p < 0.001$).[17] In contrast with their HAIC regimen, we injected lipiodol after chemoinfusion to obtain a synergistic effect between the chemoinfusion and the embolization. The ORR was 66.4% in the present study, which was much higher than that of our early HAIC alone study.[23] It is of interest that the reversed sequence of lipiodol injection and chemoinfusion between Iwamoto et al's[17] and our regimens resulted in quite similar clinical outcomes.

RT is another effective treatment modality for aHCC. In a multicenter study in Korea, Im et al[19] reported a better median OS for HCC patients with MPVI who received concurrent RT with other treatment modalities than those who received RT alone (10.4 vs 8.7 months, $p = 0.023$). In a recent report, Kosaka et al[21] also reported a promising median OS of 12.1

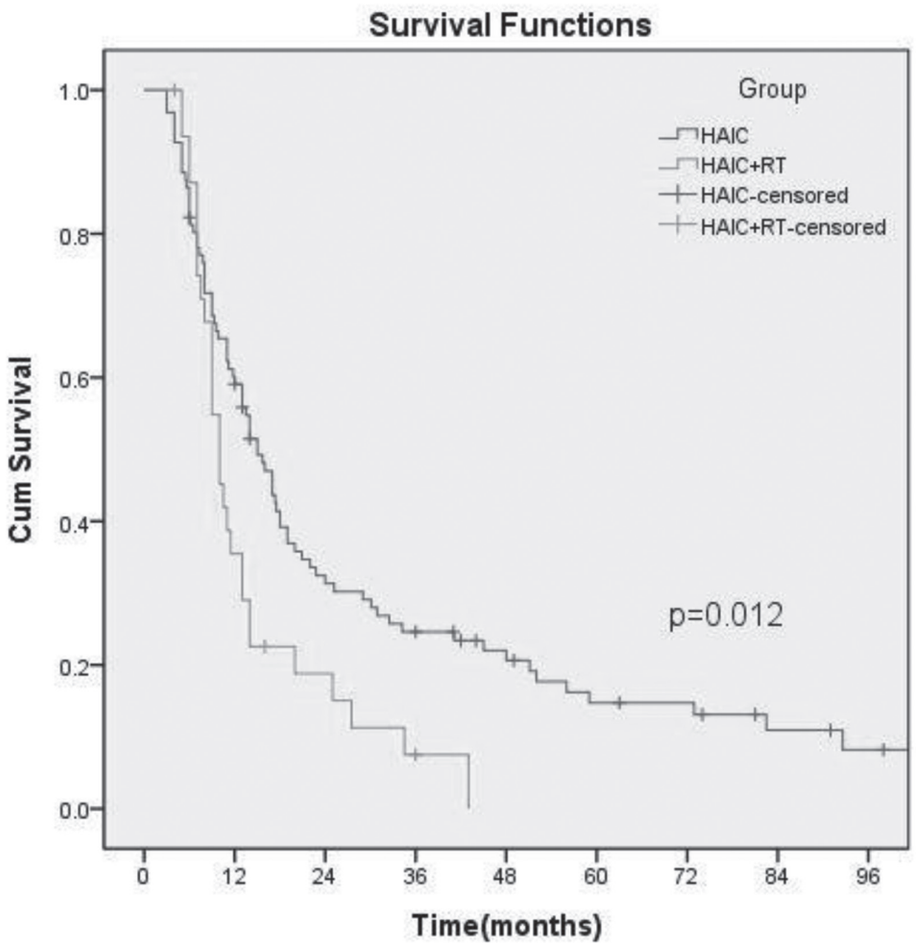

Fig. 4 After propensity score matching, the OS of HAIC alone patients (n = 70) and concurrent radiotherapy patients (n = 35) with MPVI. HAIC = hepatic artery infusion chemotherapy; MPVI = major portal vein invasion; OS = overall survival; RT = radiation therapy.

Table 2

Univariate and multivariate analysis of the HR on OS of all 175 HCC patients with major portal vein invasion

	HAIC along vs HAIC plus RT before PSM				HAIC along vs HAIC plus RT after PSM			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Group (HAIC)	1.506 (1.012-2.241)	0.043	1.289 (0.854-1.945)	0.226	1.669 (1.093-2.547)	0.018	1.789 (1.163-2.415)	0.011
Age (≤60)	1.289 (0.938-1.77)	0.117			1.375 (0.936-2.022)	0.105		
Sex (M)	1.048 (0.69-1.591)	0.826			1.181 (0.731-1.907)	0.498		
Pathogenesis (HBV)	0.883 (0.565-1.380)	0.585			0.849 (0.559-1.291)	0.570		
Child Pugh (A)	2.125 (1.47-3.071)	<0.01	2.127 (1.46-3.101)	<0.01	1.476 (0.840-2.593)	0.043	1.307 (0.896-1.906)	0.040
AFP (<400)	1.268 (0.925-1.739)	0.001	1.26 (0.912-1.741)	0.161	1.225 (0.838-1.790)	0.032	1.583 (0.547-1.182)	0.027
Tumor size (<10)	1.585 (1.15-2.185)	0.005	1.461 (1.049-2.036)	0.025	1.377 (0.938-2.021)	0.102		
Number (<5)	1.292 (0.942-1.773)	0.112			1.166 (0.798-1.705)	0.428		
Location (uni)	1.387 (1.013-1.9)	0.041	1.421 (1.032-1.957)	0.031	1.203 (0.983-1.473)	0.073		
E-H metastasis (no)	1.154 (0.8-1.667)	0.443			1.223 (0.797-1.876)	0.356		
HVI (no)	1.152 (0.704-1.886)	0.573			2.166 (1.04-4.51)	0.039	1.278 (1.124-1.432)	0.032

AFP = alpha fetal protein; E-H = extrahepatic; HAIC = hepatic artery infusion chemotherapy; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HR = hazard ratio; HVI = hepatic vein invasion; OS = overall survival; PSM = propensity score matching; RT = radiation therapy.

months in Vp4 patients treated with concurrent HAIC and RT therapy; however, in a report by Katamura et al,[20] the median OS of HCC patients with MPVI was 7.5 vs 7.9 months between groups that received combined HAIC and RT and those who were treated with HAIC alone. As for concurrent RT plus TACE or plus sorafenib, Chu et al[22] reported a median OS of 13.2 vs 12 months (p = 0.299) after PSM between the two groups. In our present study of 35 patients receiving concurrent HAIC and

Table 3

Univariate and multivariate analysis of the HR on OS of the 140 MPVI HCC patients treated by HAIC alone

	Univariate		Multivariate	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Sex (M)	1.213 (0.7-2.102)	0.889		
Age (≤60)	1.315 (0.920-1.879)	0.133		
Pathogenesis (HBV)	1	0.323		
Pathogenesis (HCV)	0.851 (0.561-1.291)	0.448		
Pathogenesis (non-B/C)	1.425 (0.771-2.636)	0.259		
Child-Pugh score (A)	1.48 (0.942-2.325)	0.089	1.67 (1.068-2.611)	0.025
AFP (<400)	1.521 (1.053-2.199)	0.026	1.3 (0.888-1.904)	0.178
Maximal tumor size (<10)	1.693 (1.171-2.45)	0.005	2.003 (1.344-2.983)	0.001
Tumor number (<5)	1.327 (0.929-1.897)	0.12		
Tumor involvement (uni)	1.426 (0.998-2.037)	0.051	1.586 (1.097-2.291)	0.014
Portal invasion (Vp3)	1.095 (0.766-1.567)	0.618		
Extrahepatic metastasis (no)	1.072 (0.701-1.638)	0.748		
Hepatic vein invasion (no)	1.303 (0.752-2.258)	0.36		
Treatment courses (≥3)	1.182 (1.039-1.325)	0.004	1.253 (1.088-1.418)	<0.001

AFP = alpha fetal protein; HAIC = hepatic artery infusion chemotherapy; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HR = hazard ratio; MPVI = major portal vein invasion; OS = overall survival; Vp3=lobar portal vein invasion.

RT, the intrahepatic ORR and median OS were 77.8% and 10.5 months, respectively, which were similar to those reported in the literature.[20–22]

Although the ORR of the concurrent RT group was high in our present study, its OS was inferior to that of the HAIC alone group (10.5 vs 14.5 months, $p = 0.039$) due to hepatic decompensation. The possibility of radiation-induced liver disease (RILD) should be cautioned against if concurrent chemotherapy with a full radiation dose (>40 Gy) is given to a cirrhotic liver. Tailored radiation doses may avoid RILD in concurrent RT combination therapy, or proton beam therapy (PBT) may be an alternative for HCC patients with macroscopic vascular invasion. The reported median OS of PBT for large HCC was 15 months.[32] Selective internal Yttrium-90 radioembolization (SIR) may also alleviate RILD in patients with unilobar, solitary HCC. Abouchaleh et al[18] reported a median OS of 13.3 months for Child A aHCC patients with PVI. Again, the high medical cost of PBT or SIR, neither of which is reimbursed in Taiwan, may limit their extensive application in aHCC patients.

In the current study, the median OS for the responders and non-responders was 20.9 and 6 months ($p < 0.01$) in group A and 11.5 and 9 months ($p = 0.086$) in group B, respectively. This indicated that treatment response was a prognostic factor in the HAIC alone group but not in the concurrent RT group, of which the initial- or after-RT liver function status may have been the key risk factor of OS. The median OS of the 140 HAIC alone patients in our study was 17 months for CP-A and 7.8 months for CP-B patients ($p < 0.001$); considering these results together with Nagai et al's[33] series of patients treated with HAIC plus sorafenib (10.3 vs 7.7 months) and Abouchaleh et al's[18] series of patients treated with SIR (13.3 vs 6.9 months)[18] indicates that aggressive treatments of any sort should be cautioned against for Child-Pugh B HCC patients.

This study contained some limitations. First, this was a retrospective study. It was affected by baseline confounding factors. Second, the fact that we excluded patients without posttreatment imaging follow-up may have affected the OS in a favorable way. Third, the time span of patients was long, with RT group enrolled later. This inevitably led to the heterogeneity of patients included in this study, especially in an era when there was a rapid development of immuno-target systemic therapy. However, as the two patient groups were treated equally in this aspect along the study timeline, and PSM was adopted for comparison, we considered the effect of patient heterogeneity on our results to be minimal, yet the factor of early termination of target therapy after liver function deterioration in group B patient still existed. Finally, a retrospective study via medical chart review could have theoretically missed some data regarding adverse effects of mild treatment.

In conclusion, our HAIC regimen of combining intrahepatic arterial chemoinfusion and lipiodol embolization is effective and safe in treating aHCC patients with MPVI.

Concurrent HAIC and full dose RT were associated with worse clinical outcomes. Our HAIC regimen may be adopted as either the first-line therapy or as a second-line therapy after the failure of atezolizumab and bevacizumab immuno-target combination therapy for aHCC patients.

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