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CLINICAL INVESTIGATION

Transcatheter Arterial Chemoembolization for Advanced Hepatocellular Carcinoma with Inferior Vena Cava and Right Atrial Tumors

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Abstract Advanced hepatocelluar carcinoma (HCC) with invasion of venous systems usually indicates not only a poor prognosis but also a contraindication for transcatheter arterial chemoembolization (TACE). This study evaluated the feasibility of TACE for advanced HCC with inferior vena cava (IVC) and right atrium (RA) tumors and, also, to search for the ideal embolization particle size. Twenty-six patients who had HCC invasion into the IVC included five patients with coexistent RA tumors that were treated with TACE. The chemoembolization method was cisplatin, doxorubicin, and mitomycin C mixed with Lipiodol and Ivalon. The selection of Ivalon particles was divided into two groups based on their size: (A) >180 μm, $N = 9$; and (B) 47–180 μm, $N = 17$. The overall response rate was 53.8% (14/26). Based on the response to TACE, the median survival period of the entire group was 4.2 months (range, 1.5 to 76.7 months). The median survival period of the 14 responders was 13.5 months (1.5–76.7 months), and that of the 12 nonresponders, 3.3 months (2.1 to 24.3 months) ($p < 0.002$). Comparing the two Ivalon particle sizes, the response rate was 12.5% (1/9 patients) for group A and 76.5% for group B (13/17 patients) ($p < 0.02$). No serious complication was observed post-chemoembolization. In conclusion, TACE is a safe and effective treatment for advanced HCC with IVC and RA tumors, and small Ivalon particles (47–180 μm) are superior to large ones (>180 μm).

Keywords Transcatheter arterial chemoembolization · Hepatocellular carcinoma · Inferior vena cava · Right atrium

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Introduction

Advanced hepatocellular carcinoma (HCC) with tumor thrombi in portal veins (PVs), the inferior vena cava (IVC), or the right atrium (RA) has an extremely poor prognosis. Without treatment, the survival duration is <3 months [1]. HCC invasion of PV results in liver failure or esophageal varices bleeding and has been considered to be the terminal stage. HCC invasion into the IVC and RA may be complicated by lung metastasis, pulmonary infarction, secondary Budd-Chiari syndrome, ball-valve thrombus syndrome, and intractable heart failure and carries the threat of sudden death.

Several methods are available to treat HCC invasion to IVC and RA, including surgery, radiotherapy, systemic chemotherapy, and TACE [2]. Surgical resection combined with chemotherapy is efficacious but is still limited by the patient's hepatic reserve [3]. Conventional radiotherapies for advanced HCC have shown disappointing results accompanied by severe complications [4–6]. The response rates of systemic chemotherapy for HCC are only <20% [7]. TACE for HCC is considered to be an effective and safe therapy in many serial reports [8]. Until now, TACE for advanced HCC with invasion of PV, IVC, and RA is still considered a contraindication at many institutions.

Katsumori et al. reported the safety and efficacy of TACE for HCC with PV tumors [9]. However, there have been only limited case reports of TACE for HCC with IVC and RA tumors [10–12]. Furthermore, there has been no study concerning the sizes of embolized particles in TACE for advanced HCC.

Our study evaluates whether TACE can be performed safely and effectively in advanced HCC patients with IVC and RA tumors and searches for the ideal particle size to target the venous tumors.

Materials and Methods

From August 1997 to December 2005, 26 patients underwent TACE for advanced HCC with IVC tumors and 5 of them had coexisting RA tumors at our institution. Thirteen patients had PV tumors simultaneously. The age range was from 34 to 74 years. The sex distribution was 20 males and 6 females. The other baseline characteristics of patients are summarized in Table 1. All patients had three-phase spiral computed tomography (CT) of the abdomen in axial images at 7-mm slice thickness to demonstrate the extent of liver tumors into the IVC and/or RA. Additionally, 13 of 26 patients had PV thrombosis. Eleven patients had thrombosis of the right PV and two had thrombosis of the left PV. Two patients had concomitant main PV thrombosis. The histological or cytological diagnosis of HCC was confirmed by either fine-needle aspiration or core biopsy in all patients. Serum bilirubin level >3 mg/dl and Child C liver disease are the exclusion criteria. Visceral angiograms including celiac, superior mesenteric, and hepatic arteriograms were routinely performed prior to chemoembolization. All patients had constant monitoring of blood pressure, heart rate, and blood oxygen saturation throughout the procedure.

Definitions of Venous Tumor Response

Two parameters on CT images were used to evaluate the response of IVC and RA tumors: the diameter and the length of the tumor. Partial response was defined as a reduction in tumor diameter of >20% or in tumor length of more than one CT slice (>7 mm). Complete response was defined as total clearance of tumors in the IVC or RA. Others including stable condition were considered to be nonresponse.

Chemoembolization

Preprocedure, patients were hydrated with 1000 ml normal saline solution and medicated with 5 mg tropisetron, 5 mg dexamethasone, and 10 mg metoclopramide.

Celiac and superior mesentery arteriograms were routinely performed to show hepatic arterial anatomy and portal venous system and to ensure either patent portal veins or periportal collaterals with hepatopedal flow. Selective

Table 1 Baseline characteristics of the patients

	All (N = 26)	Responders (N = 14)	Nonresponders (N = 12)
Age, yr (range)	57 (34–74)	55 (40–74)	56 (34–73)
Gender, M/F	20/6	8/6	12/0
Hepatitis B virus	17	8	9
Hepatitis C virus	4	2	2
Hepatitis B & C virus	4	3	1
Serum total bilirubin, μmol/L (range)	20 (10–46)	19 (10–31)	20 (12–46)
Serum albumin, g/L (range)	37 (29–47)	37 (29–47)	37 (31–43)
Prothrombin time, s (range)	13.9 (10.9–16.1)	13.8 (11.9–15.3)	13.9 (10.9–16.1)
Serum α-fetoprotein, ng/ml			
(<20/20–400/ > 400)	(8/6/12)	(4/3/7)	(4/3/5)
Tumor mass			
(uninodular/multinodular /diffuse)	(3/14/9)	(2/6/6)	(1/8/3)
Diameter of the largest tumor, cm	10.9 (6–19)	11.6 (6–19)	10.2 (6.5–14)
Tumor volume ≥50% of liver volume, no.	13 (50%)	6 (23%)	7 (27%)
Right atrium tumor	5	5	0
Hepatic vein invasion			
(right/middle/left)	(15/6/2)	(6/3/2)	(8/4/0)
Portal vein obstruction			
(right/left/main)	(11/2/2)	(6/2/1)	(5/0/1)
Okuda stage (I/II/III)	(8/17/1)	(5/8/1)	(3/9/0)

hepatic and/or extrahepatic arteriogram, especially inferior phrenic arteries, were performed to demonstrate tumor vascularity, blood supplies, and arteriovenous shuntings.

The standard dosage of our chemoembolization protocol consists of three drugs, 100 mg cisplatin, 50 mg doxorubicin, and 10 mg mitomycin C, dissolved in 10 ml normal saline, then mixed with Lipiodol (Lipiodol Ultrafluide; Laboratoire Guerbet, Aul-nay-sous-Bois, France) at a 1:1.1 volume ratio. Lipiodol volume is 10% larger than the drug mixture and rinsing continuously between two syringes to assure emulsion formation.

Particulate materials are added to the above drug-Lipiodol emulsion to improve drug retention inside the tumor. Polyvinyl alcohol (PVA or Ivalon; Cook Inc., Bloomington, IN, USA) particles >180 μm were used as embolization agents until 1999, then smaller PVA particles (two sizes, 47–90 and 90–180 μm). There is no difference in the embolization technique before versus after 1999, except PVA size. Based on PVA size, the patients were divided into two groups. In group A ($N = 9$), the PVA particles were >180 μm. In group B ($N = 17$), they were 47–180 μm.

The catheter was placed as close as to the tumor as possible. The PVA particles were mixed with the drug-Lipiodol emulsion. Embolization proceeded with slow injection of the above mixture till the tumor was well opacified by the Lipiodol. When arterial flow started to slow down, we stopped the procedure. This was to avoid reflux of drugs and also to prevent excessive embolization of the peribiliary plexus and the segmental hepatic artery itself. Attention was paid not to reach total stasis of arterial flow, especially in patients with PV thrombosis.

If arteriovenous or arterioportal shuntings were present, a small bolus of 1–2 ml drug-Lipiodol emulsion was injected first to observe the flow pattern and the tumor uptakes. If shunting was prominent, larger PVA particles were used. When shunting was decreased, smaller PVA particles were added for the remaining tumor.

The total amount of chemotherapeutic agents administrated was dependent on the total vascular spaces of the tumor, but not the size of the tumor itself. Nineteen patients received the full dosage of drugs, and the others received >60% of the standard dosage.

Follow-up Study

Immediate nonenhanced CT was obtained within 30 min after TACE to assess the completeness of tumor embolization, especially the venous component of the tumor. One month after TACE, all patients underwent triphasic CT studies. Patients with residual tumors received repeat TACE 6 to 8 weeks after the previous TACE. Patients were followed up until death or to the end of the study period (January 31, 2006).

Statistical Analysis

Statistical analyses were performed with chi-square analysis and Fisher's exact test where appropriate, with statistical significance achieved at a p value <0.05. Survival rates were analyzed by the Kaplan-Meier actuarial method, with statistical significance determined by the log-rank statistic with SAS 8.02 statistical software (SAS Institute Inc., Cary, NC, USA). Univariate and multivariate survival analyses were performed on selected variables, including AFP, albumin, total bilirubin, Child-Pugh score, Okuda stage, PV thrombosis, tumor type, tumor volume (>50%), and age (Table 2). A value of $p < 0.05$ was considered statistically significant.

Results

Survival and Response

All 26 patients tolerated sequential TACE over the course of the study without treatment-related major complications. Twenty-two patients expired during the course of the study. The survival period of the entire group was from 1.5 to 76.7 months (median, 4.2 months) (Fig. 1). The 12-, 24-, and 36-month survival rates were 41%, 25%, and 7%, respectively.

Based on tumor response to TACE by image study, the 26 patients were divided into two groups, 14 responders (53.8%) and 12 nonresponders (46.2%). The two groups were balanced in their main characteristics, especially in the size and distribution of tumors and PV invasion (Table 1). The median survival of responders was 13.5 months (range, 1.5 to 76.7 months), while that of nonresponders was 3.3 months (2.1 to 24.3 months). The difference in the survival period of the two groups was statistically significant ($p < 0.002$; Fig. 2).

When the coexisting PV tumor was added to the survival analysis, the survival of 13 patients without PV tumor was 10.9 months and that of the other 13 patients with PV tumor was 14.3 months. The survival rate by coexisting PV tumor was not statistically significant ($p = 0.98$) (Fig. 3). Additionally, comparison of patients with coexisting PV tumor in responders (8/14 patients) versus nonresponders (5/12 patients) also showed no statistically significant difference ($p = 0.43$). Of five patients who had RA tumors, three showed complete response (60%) and one partial response (20%). The last patient showed tumor progression. Tumor response by particle size showed only 1 of 8 patients (12.5%) in group A and 13 of 18 patients (72.2%) in group B. The difference in response rate was statistically significant ($p < 0.01$). Four of five patients (80%) with regression of RA tumors were all in group B.

Table 2 Univariate and multivariate analysis in patients with advanced HCC with IVC/RA tumors

	Univariate analysis			Multivariate analysis		
	RR	95% CI	*p*	RR	95% CI	*p*
AFP						
<20	1			1		
20–400	0.66	(0.19–2.26)	0.51	0.61	(0.06–5.95)	0.67
>400	1.87	(0.70–4.97)	0.21	1.60	(0.22–11.5)	0.64
Albumin	0.81	(0.36–1.83)	0.62	1.45	(0.42–5.04)	0.56
Total bilirubin	2.31	(0.73–7.30)	0.15	1.27	(0.21–7.58)	0.79
Child-Pugh score	1.64	(0.94–2.85)	0.08*	2.76	(0.99–7.72)	0.05*
Okuda stage						
I	1			1		
II	2.00	(0.76–5.27)	0.16	0.18	(0.01–2.78)	0.22
III	1.93	(0.22–16.79)	0.55	0.04	(0.00–4.83)	0.18
PV thrombosis	0.98	(0.42–2.33)	0.97	1.29	(0.41–4.00)	0.67
Tumor type						
(infiltrated/mass)	1.24	(0.53–2.93)	0.62	1.30	(0.34–4.92)	0.70
Tumor volume (>50%)	0.14	(0.04–0.50)	0.003*	0.04	(0.003–0.57)	0.02*
Age	0.99	(0.95–1.03)	0.53	1.03	(0.95–1.12)	0.46

Note: RR, relative risk; CI, confidence interval; AFP, α-fetoprotein; PV, portal vein

* Statistically significant correlation

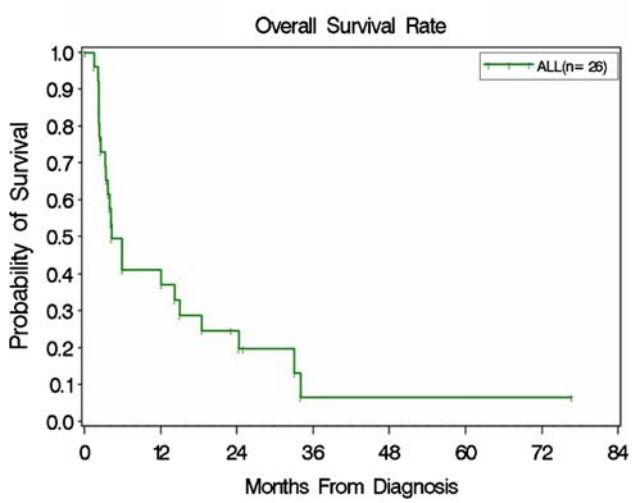

Fig. 1 Overall survival rate of the entire group

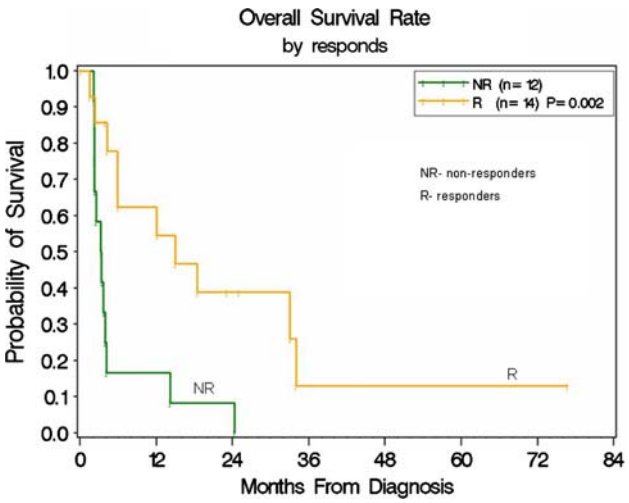

Fig. 2 Survival rate by response after TACE

Prognostic Factors

Prognostic factors included in univariate and multivariate survival analysis were AFP, albumin, total bilirubin, Child-Pugh score, Okuda stage, PV thrombosis, tumor type, tumor volume (>50%), and age. Both univariate and multivariate survival analysis showed statistically significant correlation with Child-Pugh score and tumor volume (>50%) (Table 2).

Complications

Immediate CT after TACE showed only a trace of Lipiodol retention in both lower lungs of all patients, but without symptoms of dyspnea, chest pain, or a decline in blood oxygen saturation. There was no TACE-related liver failure, 30-day mortality, or encephalopathy. Especially, pulmonary embolism was not observed after embolization in the entire group. Other minor complications were fever (80.7%), abdominal pain (70.9%), vomiting (61.5%), and transient deterioration of liver function (100%).

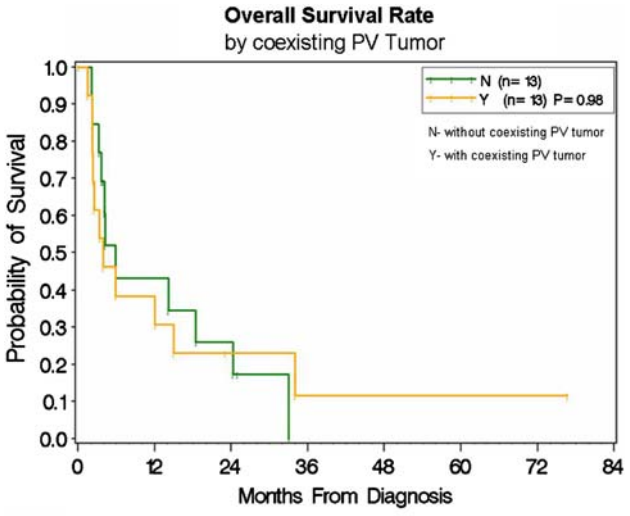

Fig. 3 Survival rate by coexisting PV tumor

Illustrative Cases

Case 1. Complete response of IVC/RA tumor, with 6 year 4 month survival

A 70-year-old man had a history of hepatitis B and C. He was referred to our hospital after CT scan diagnosis of hepatic tumors with IVC and RA invasion. Pertinent laboratory tests were as follows: AST (GOT), 91 U/L; ALT (GPT), 94 U/L; total bilirubin, 0.7 mg/day; albumin, 3.8 g/dl; HBsAg, positive; HCV antibody, positive; and AFP, 30 ng/ml.

CT scan of the abdomen showed hepatic tumors with IVC and RA tumors (Fig. 4A). Proper hepatic arteriogram showed a prominent hypervascular tumor extending into the IVC an RA with delineation of multiple fine vessels (thread and streaks sign) (Fig. 4B). TACE was performed at the right and middle hepatic arteries with 50% standard drug dosage and 100 mg PVA (47–180 μm). CT scan 1 month after TACE showed shrinkage and necrosis of IVC and RA tumors (Fig. 4C) and excellent Lipiodol retention in these tumors (Fig. 4D). CT scan 2 months after TACE showed clearance of IVC and RA tumors (Fig. 4E and F). The patient had been treated with six courses of TACE and was still alive after 6 years 4 months.

Case 2. Complete response of IVC/RA and PV tumor with 2 year 7 month survival

In February 2002, a 69-year-old woman was referred to our hospital because of upper abdominal pain and a palpable hepatic mass. She was diagnosed as having cirrhosis of the liver and HCC.

Pertinent laboratory tests were as follows: AST (GOT), 90 U/L; ALT (GPT), 42 U/L; albumin, 3.0 g/dl; total bilirubin, 1.2 mg/dl; HBsAg, negative; HCV antibody, positive; and AFP, 6.2 ng/ml.

CT scan of the abdomen showed a 12-cm tumor in the left lobe of the liver, with invasion of the IVC and RA (Fig. 5A) and tumor thrombus in the left PV (Fig. 5B). Common hepatic arteriogram showed a huge hypervascular left hepatic tumor extending via the IVC into the RA (thread and streaks sign) (Fig. 5C) accompanied by marked arterioportal and arteriovenous shunting (Fig. 5D). TACE was performed at the left hepatic artery with the standard dosage and 75 mg PVA (47–180 μm). CT scan 1 month post TACE showed shrinkage of the RA and hepatic tumors with excellent Lipiodol retention in tumors (Fig. 5E and F) and an opacified left PV (Fig. 5F). CT after 2 months showed clearance of the RA tumor and marked reduction of the left hepatic tumors (Fig. 5G and H).

Until July 2004, the paient's hepatic tumors were controlled well by three courses of TACE. However, tumor recurrence in the right lobe with invasion into the main PV resulted in progressive hepatic failure. She expired in September 2004, for a total survival of 2 years 7 months.

Case 3. HCC with HV, IVC/RA, and PV tumor, and lung metastasis, with 2 year 9 month survival

A 55-year-old man had been suffering from persistent dry cough for 2 to 3 months. Chest x-ray showed multiple lung nodules with elevation of the right hemidiaphragm. He was referred to our hospital under the diagnosis of liver tumors with lung metastasis.

Pertinent laboratory tests were as follows: AST (GOT), 53 U/L; ALT(GPT), 43 U/L; albumin, 3.9 g/dl; total bilirubin, 1.0 mg/dl; HBsAg, positive; HCV antibody, negative; and AFP, 47,978 ng/ml.

CT scan showed multiple liver tumors with IVC, RA, and right PV tumor invasion (Fig. 6A and B). Right hepatic arteriogram showed hypervascular hepatic tumors and IVC (Fig. 6C) and PV tumors (thread and streaks sign) (Fig. 6C). TACE of the right hepatic artery with 50% of the standard drug dosage and 75 mg PVA (47–180 μm). The immediate CT scan showed Lipiodol retention in the RA (Fig. 6D) and PV (Fig. 6E) tumors, but a Lipiodol pooling defect in the main tumor near the dome (Fig. 6D). CT scan after two sessions of TACE including extrahepatic arterial embolization (right inferior phrenic artery) showed shrinkage and necrosis of RA/IVC tumors (Fig. 6F and G) and reopening of the right PV (Fig. 6H).

The patient received four courses of TACE and expired 2 years 9 months later due to progressive recurrent tumors in the liver parenchyma, but none in the venous systems.

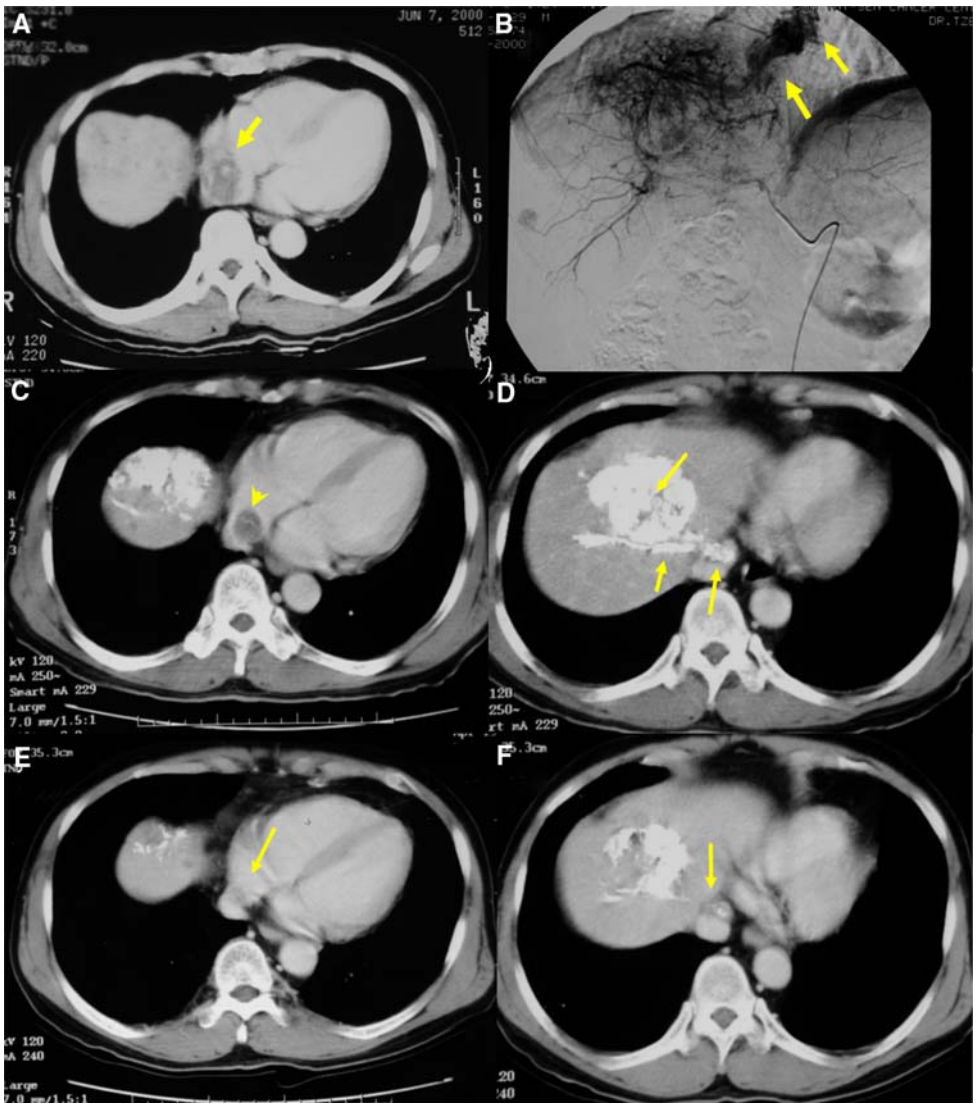

Fig. 4 HCC with invasion into IVC/ RA. (**A**) CT scan shows hepatic tumors with IVC and RA tumors (arrow). (**B**) Proper hepatic arteriogram shows an 8- to 10-cm hypervascular tumor extending into IVC an RA (thread and streaks sign) (arrows). (**C**, **D**) CT scan 1 month after TACE shows shrinkage and necrosis of IVC and RA tumors (arrowhead) with excellent Lipiodol retention in right lobe and right hepatic vein tumors (arrows). (**E**, **F**) CT scan 2 months after TACE shows clearance of IVC and RA tumors (arrows)

Discussion

The natural course of HCC with tumor thrombus in the PV, IVC, or RA is dismal. Until now, greatly advanced HCC with tumor extension into the IVC and RA has had an extremely poor prognosis. The median survival of patients with IVC tumor thrombus was only 2–3 months without effective treatment [13]. For HCC with a tumor thrombus extending into the IVC, no effective treatment has yet been reported. Previous studies on conventional radiotherapies for HCC have shown disappointing results accompanied by severe complications [4–6]. The outcome of surgery for HCC with IVC tumor thrombi has also been disappointing, with a mean postoperative survival time ranging from 7.3 to 8.4 months [14, 15].

TACE has become an acceptable treatment for most unresectable HCCs. Recent randomized controlled trials confirmed a distinct survival advantage for TACE in patients with unresectable HCC [16–18]. Greatly advanced HCC including PV or IVC thrombosis is still considered an absolute contraindication for TACE at most institutions because of the potentially increased risk of liver failure after the procedure. However, recent articles have demonstrated the safety and efficacy of TACE in those patients with advanced HCC. Georgiades et al. showed that TACE was not a contraindication in patients with PV thrombosis and had a survival benefit [19]. Additionally, Kiely et al. suggested that TACE can be performed safely in patients with advanced disease and decreased hepatic reserve [20]. However, there is still a lack of large series in the literature showing the efficacy and safety in patients with advanced HCC with IVC and RA tumors treated by TACE. A search of the literature revealed only some case report studies about TACE in treatment of HCC with IVC and RA tumors [10–12].

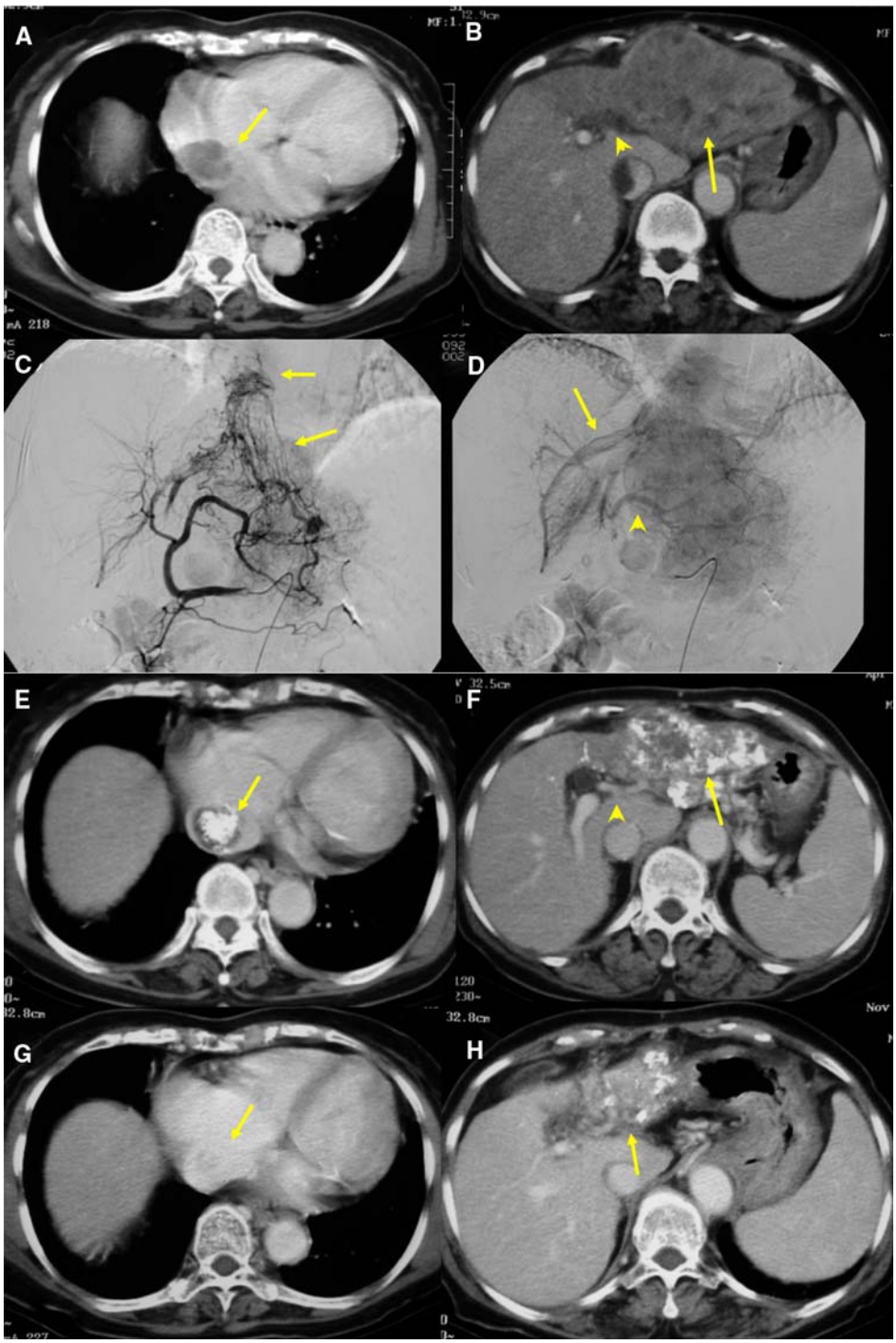

Fig. 5 HCC of left hepatic lobe with invasion into IVC/RA and left portal vein. (**A**) CT shows hepatic tumor invasion of the IVC and RA (arrows). (**B**) A 12-cm tumor in the left hepatic lobe (arrow) and nonopacified left portal vein (arrowhead). (**C**) Common hepatic arteriogram, early phase, shows a huge hypervascular left hepatic tumor extending via the IVC into the RA (arrows). (**D**) Late phase, marked arterioportal (arrowhead) and arteriovenous shuntings (arrows). (**E**, **F**) CT scan 1 month after TACE shows shrinkage RA and hepatic tumors with excellent Lipiodol retention in tumor (arrows) and opacified left portal vein (arrowhead). (**G**, **H**) CT after 2 months shows clearance of the RA tumor and marked left lobe tumor reduction

Our study indicates that TACE not only is not contraindicated in patients with advanced HCC with invasion into the IVC and RA, but also is beneficial to their survival. The effectiveness of TACE in our study is clear when survival durations of responder versus nonresponder patients are compared (Fig. 2). In our study, the median survival of responders was 13.5 months, whereas nonresponders had a median survival of 3.3 months, a significant difference ($p = 0.002$).

In the literature, HCC patients with invasion into the IVC and RA without treatment have an extremely poor prognosis, i.e., <3 months, similar to that of patients with PV tumor thrombi. Zeng et al. [13] also showed the same results. In the study published by Georgiades [19], the 1-,

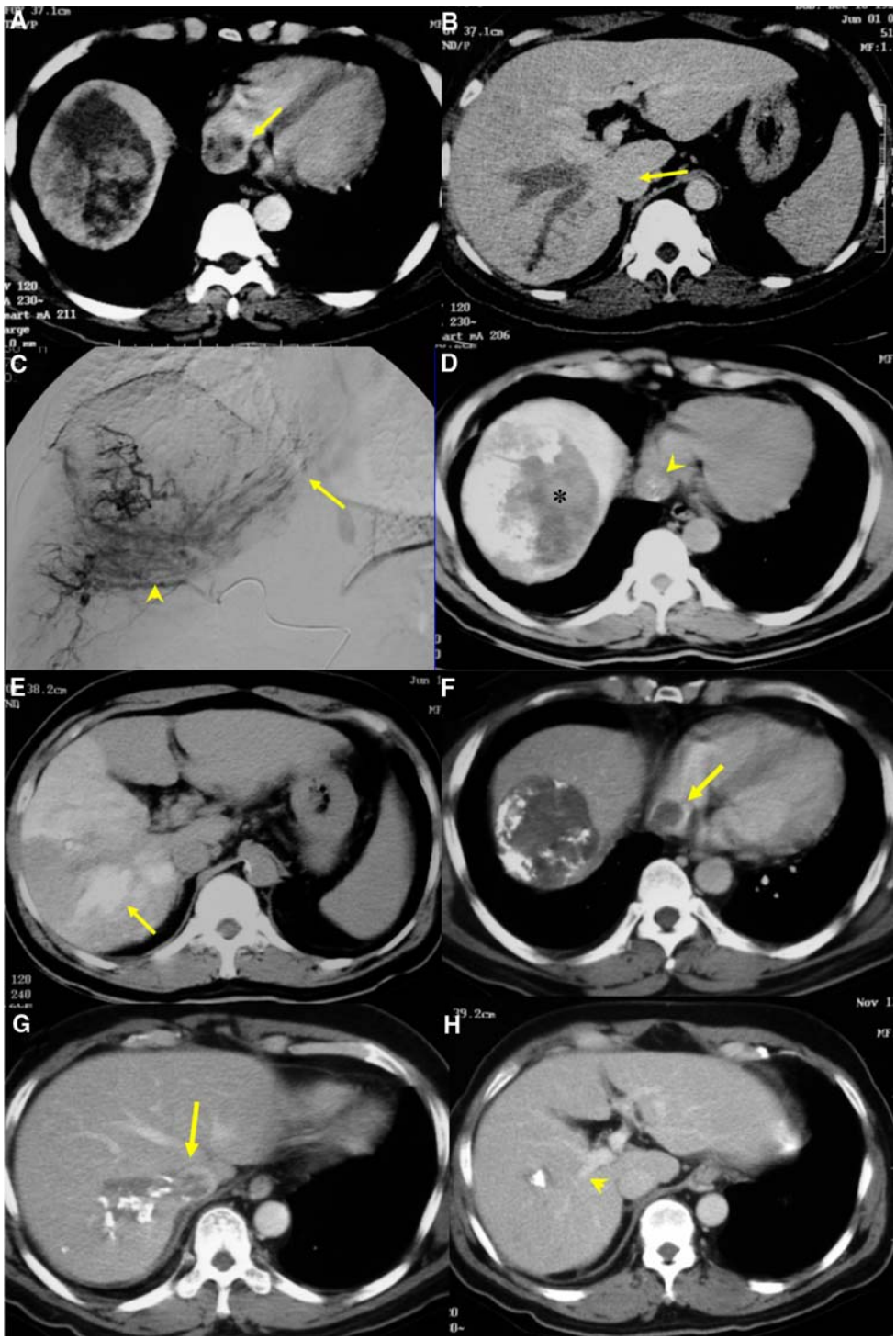

Fig. 6 HCC with invasion into the IVC/RA and right portal veins. (**A**, **B**) CT scan shows multiple liver tumors and IVC, RA, and right portal vein tumor invasion. (**C**) Right hepatic arteriogram shows hypervascular hepatic tumors and IVC (arrow) and portal vein tumors (arrow head): "thread and streaks sign." (**D**) Immediate CT scan after TACE shows Lipiodol retention in liver and IVC-RA tumors (arrowhead) but a pooling defect around the liver dome (*). (**E**) Immediate CT also shows Lipiodol retention in one branch of right portal vein. (**F**, **G**, **H**) CT scan after two sessions of TACE including right inferior phrenic arterial embolization shows shrinkage and necrosis of RA/IVC tumors (arrow) and reopening of right portal vein (arrowhead)

2-, and 3-year survival rates of patients with HCC and PV thrombosis have been reported to be 17%, 8%, and 0%, respectively. Nevertheless, the 1-, 2-, and 3-year survival rates of patients with HCC and IVC/RA thrombosis in our study were 41%, 25%, and 7%. According to our results treatment with TACE effected a survival benefit in some patients.

We observed that TACE using different particle sizes showed different response rates. The response rate (72.2%) of group B (PVA < 180 μm) was significantly higher than that of group A (PVA > 180 μm) ($p < 0.01$). It is suggested that smaller embolized particles more effectively blocked the arterial flow not only closer to but also directly into the tumors and, thus, prolonged the retention time of

chemotherapeutic agents in tumors. This can also explain why the patients showed a higher response rate (80%) of RA tumors treated with smaller PVA particles. The resolution of RA tumors should decrease the risk of sudden death and intractable heart failure in these patients.

Our past experience using Gelfoam pledgets (1 to 2 mm) and larger Ivalon particles (250 to 420 μm) frequently resulted in a reduction of parenchymal tumors but seldom showed improvement of tumors within the PV, IVC, and RA. We believe that these agents blocked tumor vessels well proximal to the tumor mass. We systematically studied and downsized the particles so they would reach and stay within the tumors to provide the maximal effect. It is widely believed that tumor vessels are larger than arterioles supplying the normal sinusoids. Thus, it is possible to find a proper particle size which targets the tumor but spares the normal parenchyma. Our study suggested that a size of 47–180 μm meets this goal. Our future study will further compare two subgroups of particles, 47–90 and 90–180 μm.

Immediate nonenhanced CT after TACE was used to evaluate the distribution of Lipiodol within the tumors and to predict the effectiveness of the treatment in our patients (Fig. 6D). We observed in two nonresponding patients that Lipiodol only pooled in some parts of the IVC and RA tumors on CT scan after TACE. That is because their tumor blood supplies were from more than one artery including both hepatic and extrahepatic sources. In this series, the right inferior phrenic artery was the most common extrahepatic feeder of IVC/RA tumors. We suggest that all feeding arteries of IVC/RA tumors be completely embolized in the first session of TACE, if technically feasible, to achieve a good response.

The presence of the "thread and streaks sign" in the venous tumors in all 26 patients indicated that the enlarged vasa vasorum of the venous wall is a vital element of tumoral growth within the vein. To treat them effectively, the embolization particles should be smaller than these vessels. Considering the marked difference in response rate (12.5% vs 72.2%) between the large (180-μm) and the small (47- to 180-μm) PVA particle sizes, we postulated that 47–180 μm is closer to the true diameter of tumor-feeding arteries. CT scan immediately following TACE was very useful in the demonstration of how well the venous tumor was embolized (Figs. 4D, 5E, 6D and E).

When a stage IV patient has a large tumor bulk, PV, IVC, and RA tumor, and lung metastasis, as in case 3, traditionally it is usually treated with only palliative chemotherapy or symptomatic treatment. Because of the reasonable hepatic function reserve (total bilirubin, <1.0 mg/dl), we decided to proceed with aggressive TACE. The marked response of the liver tumor (Figs. 6G and H) and survival of 2 years 9 months in this patient support the concept of aggressive primary tumor treatment in the presence of distant metastasis.

PV tumor thrombus seems not to be a major factor in influencing the response to TACE in these patients with IVC/RA tumor because its presence showed no difference in responders versus nonresponders (Fig. 3). Accordingly, it should not be a contraindication to TACE in patients who have IVC/RA tumors, even coexistent with PV tumors, if the hepatic reserve is adequate. Although the survival rate also showed no difference in the presence of PV tumors, the survival of nonresponders with coexisting PV tumors was still the worst (Fig. 7). According to the univariate and multivariate survival analyses of our series, tumor volume >50% and Child-Pugh score were the only two main prognostic factors with statistic significance in these patients (Table 2).

The theoretical concern of complications from TACE for IVC /RA tumors is pulmonary embolism induced by embolized particles because the angiography of IVC and RA tumors demonstrate the "thread and streaks" sign of the tumors accompanying with marked arteriovenous shuntings into the heart [21]. Besides, the mechanism of diminution of IVC and RA tumors is thought to be tumor necrosis followed by breaking-down to form emboli. However, no pulmonary embolic event was detected clinically throughout the courses of our patients. This study suggests that PVA particles (47–180 μm) were trapped by tumors and not passed through into the lungs. Another reason for the safety of TACE of IVC/RA tumors might be because the surfaces of IVC and RA tumors were smooth and mostly covered with endothelia as demonstrated in autopsy cases by Kojiro et al. [22]. This endothelial barrier might prevent the necrotic tumor from disrupting into the IVC. After TACE, the necrotic venous tumor thrombus might shrink and retract backward instead of fragmenting

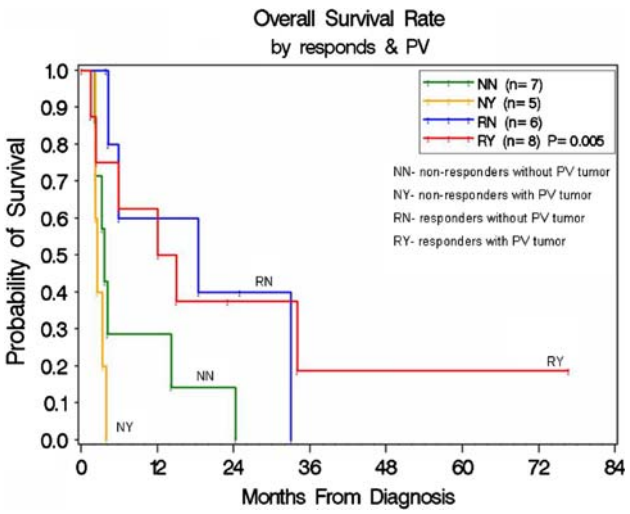

Fig. 7 Survival rate by response and PV tumor

into the IVC or pulmonary artery because of the intact endothelial barrier.

In conclusion, our study suggests that TACE is an effective and safe treatment method in patients with advanced HCC invading the IVC and RA. Smaller embolized particles (47–180 μm) are more effective. Overall, these patients showed a high response rate of IVC/RA tumors to TACE, without major complications, and some of them gained survival benefit.

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