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Original Article

Transcatheter Arterial Chemoembolization in Patient with Hepatocellular Carcinoma in Srinagarind Hospital; Complications and Results

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Abstract

Background: Transcatheter arterial chemoembolization (TACE) is known to be one of the best palliative treatment for unresectable HCC. However, its severe complications make its use controversial.

Purpose: To evaluate the complications and results of TACE in our treated cases.

Materials and Methods: Forty-seven patients underwent 88 TACE sessions during January 1, 2003 to December 31, 2004 at Srinagarind Hospital. Their clinical records, complications of TACE, tumor response, and survival outcomes, were reviewed retrospectively.

Results: Forty-seven patients (40 males [85%], 7 females [15%], mean age 51 years, underwent 88 chemoembolizations. Forty-two patients (89%) had documented cirrhosis, 28 (59%) had hepatitis B and 39 (83%) were chronic alcohol drinkers. Thirty-eight patients (81%), and 9 patients (19%) were categorized in Child's A and B classes, respectively. The common complications of TACE included fever (83%), abdominal pain (37%) and transient nausea/emesis (20%). Two patients with right portal vein (RPV) thrombosis developed acute liver failure within few days after TACE. One of them had sepsis syndrome. Partial and minimal tumor response was observed (33%). Overall survival rate was 61%, 48%, 27%, and 9% of patients at up to 6 months, 1, 2, and 3 years, respectively. The mean survival time was 13.1 months.

Conclusion: Most complications in our study can be corrected except for serious complication (acute liver failure) in 2 cases with RPV invasion. Very careful pretreatment planning should help reduce the problem. The response of treatment was found in 33%. The 2- and 3-years survival rate was 27% and 9%, respectively. We believe that we can do better in the future if the patients come to us in earlier stage.

Keywords: hepatocellular carcinoma (HCC), Transcatheter arterial chemoembolization (TACE), complications

Introduction

Hepatocellular carcinoma (HCC) is a highly malignant tumor with a high morbidity and mortality rate. It represents the 5th most common cause of death from cancer worldwide. In Thailand, liver cancer had been found to be a leading cancer in men, and the 3rd in women.[1] Improvement of imaging technology has enabled to diagnosis of HCC at an early stage, making possible to treat tumors locally. Liver resection remains a curative treatment, particularly in the patient with TMN stage I which have 5 year survival rate about 70-75%.[2] Despite the availability of screening procedures for detection of early HCC (i.e. ultrasonography and serum α-fetoprotein [AFP] levels), the majority of patients are still not considered suitable for curative resection. Transcatheter arterial chemoembolization (TACE) had been recommended for treatment of unresectable HCC patients for reducing the mortality or morbidity, and prolong quality of life.[2]

The rationale for arterial embolization is progression of HCC, closely link to neo-angiogenic activity. At very early stage, the tumor is not highly vascularized. Its blood supply is from both the portal vein and the hepatic artery. When the tumor grows larger than 2 cm, the blood supply is mostly dependent on the hepatic artery. Large HCC receives blood supply almost entirely through the hepatic artery. Therefore arterial obstruction is the basis for an effective therapy. A mixture of chemotherapeutic agent and Lipiodol followed by absorbable gelatin sponge particles are generally used for embolization.[3-5]

TACE-related complications reported previously such as tumor rupture with hemoperitoneum, cerebral or pulmonary embolism, acute hepatic failure, liver abscess, severe septic complications, and bile duct injury[6-11] make its use controversial. We started to perform TACE in our institution since 1990, but before 2000 the medical records and film storage were incomplete. The aim of this study was to evaluate TACE-related complications, and the results after treatment by retrospective review of our clinical experience during January 1, 2003 to December 31 2004.

Materials and Methods

This was a single-center retrospective study of unresectable HCC who required TACE between January 1, 2004 and December 31, 2005. The medical records of 64 patients were reviewed. Seventeen cases were excluded due to inability to perform chemoembolization after hepatic angiogram or evidence of contraindication for TACE (e.g. complete portal vein thrombosis, Child-Pugh class C, and severe hepatic or renal insufficiency). We recruited 47 cases (88 sessions of successful TACE treatment) to search for evidence of complications in each session, response of treatment, and the survival rate at up to 6 months, 1, 2, and 3 years.

The diagnosis of HCC was made either histological (n= 8), or by hepatic arteriogram and computed tomography (CT) scan combined with serum AFP level (n=39). The American Joint Committee on Cancer (AJCC) and Okuda staging system were used, for tumor staging.

Our inclusion criteria for TACE were Child's A or B class, bilirubin level < 3 mg/dL, prothrombin time ≤ 3 seconds above the control value, a serum creatinine concentration < 2 mg/dL, no total portal vein thrombosis, and no extensive arterio-venous shunting.

TACE procedures were performed by experienced radiologists in a standard fashion. Informed

consent was obtained from every patient for each procedure. After conventional hepatic angiography, a vascular catheter was inserted superselectively into the branch of the hepatic artery that supplied the tumor. The catheter uses were 5 Fr catheter and microcatheters (2.7 Fr or 3 Fr in diameter). Chemoembolization was initiated by infusion of a mixture of iodized oil (Lipiodol; Guerbet, France) and doxorubicin hydrochloride (Adriamycin; Kyowa Hakko Kogyo, Tokyo, Japan) to occlude tumor feeding arteries, followed by administration of absorbable gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, Mich) 1-2 mm in diameter soaked with 5-10 ml of nonionic contrast medium.

The doses of doxorubicin hydrochloride and iodized oil were 8-40 mg and 3-10 ml, respectively. The doses were given depended on the tumor size, the position of the catheter, the patient's liver function, and the response to previous treatment.

Re-chemoembolization was performed in 23 patients with 4-8 weeks interval between treatment sessions. Just before the next TACE, the liver function and CT of the liver or other imaging studies were checked to assess the response of the tumor and to evaluate the functional reserve of liver using the same criteria mentioned previously. The procedure was not re-performed in the patients who have poor liver function or no obvious tumor vessels. After the treatment, liver function test was periodically checked in patient with severe post-embolization syndrome or signs of hepatic failure. Blood culture was performed in patients with high and sustained fever. Appropriate imaging modalities such as chest radiography, ultrasonography, and CT scan were used for detection of TACE-related complications.

Additional treatments such as Percutaneous Ethanol Injection (PEI) (n=9) and open surgical injection (n=1), were performed after the last TACE. One case underwent right hepatectomy after 2 sessions of TACE. Additional systemic chemotherapy was administered in 2 patients.

Tumor response was assessed objectively by the change in tumor size on US, CT or MR imagings. The reduction in tumor size was measured at the same image level, representing the maximum dimension.[12] The response was determined on follow-up CT scan at 4-6 weeks after last chemoembolization. Tumor response has to be maintained for at least one month. Response criteria, based on the reduction of perpendicular diameter in the tumor are as follows: 1.) A complete response (CR) was total disappearance of tumor; 2.) A partial response (PR) was a reduction in tumor size of more than 50%; 3.) A minimal response (MR) was a reduction of 25-50%; 4.) No change (ND) was a change in tumor size less than ± 25%; 5.) Progressive disease (PD) was an enlargement of more than 25%.[13]

Results

There were 47 HCC patients (40 males [85%], 7 females [15%], mean age 51 years [range 14-79 years old]), underwent successful TACE. The patient characteristics are shown in Table 1. Forty-two patients (89%) had documented cirrhosis. Thirty-eight patients (81%), and nine patients (19%) had Child A and B cirrhosis, respectively. Twenty-eight patients (59%) were hepatitis B carriers, 8 patients (17%) were hepatitis C carriers, and 39 patients (83%) were chronic alcohol drinkers. Four patients had HCC without documented cirrhosis, hepatitis B or C. Two cases of Child's A class presented with ruptured HCC. Segmentectomy of the liver was

required to stop bleeding prior to TACE. The detail of serum AFP levels, tumor staging, and tumor size is shown in Table 1.

The total number of TACE sessions was 88. The average number of TACE sessions per patient was 1.8, ranged from 1 to 6 sessions. The duration

Table 1 Baseline characteristics of the patient with hepatocellular carcinoma

Characteristics		N=47
Demography:		
- Age, mean (range)		51 (14-79)
- Sex, M:F		40 (85%) : 7(15%)
Cirrhosis		42 (89%)
Chronic alcohol drinkers		39 (83%)
Hepatitis: B		28 (59%)
C		8 (17%)
Biochemistry (mean, range)		
- Serum bilirubin (mg/dL)		0.96 (0.2-2.6)
- Prothrombin time (second)		13.2 (10.2-17.6)
- Serum albumin (mg/dL)		3.4 (2.9-4.7)
- Alkaline phosphatase (IU/L)		160.5 (70-368)
Distribution of serum AFP level (IU/ml)		
< 10		6 (13%)
10 - 100		9 (20%)
101 - 500		5 (10%)
500 - 1000		5 (10%)
> 1000		22 (47%)
Disease characteristics		
- Tumor size (cm):	< 5	7 (15%)
	5 - 10	25 (53%)
	> 10	15 (32%)
- AJCC stage:	I	0 (0%)
	II	3 (6%)
	IIIa	22 (47%)
	IIIb	2 (4%)
	IVa	17 (37%)
	IVb	3 (6%)
- Okuda stage:	I	26 (55%)
	II	20 (44%)
	III	1 (1%)
- Child-Pugh class:	A	38 (81%)
	B	9 (19%)

of hospitalization was 2 to 21 days. The majority of cases (60 sessions) were discharged from the hospital within 3 days after each procedure. In the patients who were hospitalized longer than 7 days (20 sessions) with long period of fever and suspicious for sepsis syndrome, the final cause of fever was found to be tumor necrosis. Three patients were admitted longer because of deterioration of hepatic function. The other 5 patients can be discharged on the following day after chemoembolization.

The complications are listed in Table 2.

Thrombocytopenia were identified in 10/88 sessions of TACE (11%) and associated with cirrhotic patients whose imaging demonstrated splenomegaly and portal hypertension in alls cases. This could be explained by hypersplenism. None of the cases had severe coagulopathic complication or other rare complications (e.g. bleeding hematoma at punctured site, variceal bleeding, gastrointestinal bleeding from peptic ulcer/gastritis, tumor ruptured, liver abscess, bile duct injury, pulmonary or cerebral embolism, or bile duct injury).

Table 2 Complications related TACE procedure (n=88)

Complications	Incidence number (%)
Post-TACE syndromes	
- Fever	73 (83%)
- Abdominal pain	33 (37%)
- Nausea/Vomiting	18 (20%)
Deterioration of liver function	3 (3%)
- Reversible	1/3 (1%)
- Irreversible with acute hepatic failure	2/3 (2%)
Acute calculous cholecystitis	1 (1%)
Thrombocytopenia	10 (11%)

Post-TACE syndrome

The most frequent complications were fever, abdominal pain, and nausea/vomiting. The mean duration of fever was 2 days (range, 0-17 days). The long duration of fever associated with the initial tumor size, high dosage of Adriamycin, and development of severe hepatic deterioration and hepatic encephalopathy. Nausea/vomiting and abdominal pain were self-limiting in the majority of cases. The remaining could be controlled by the administration of anti-emetics and analgesic drugs. Mean duration time of abdominal pain was 0.8 day (range 0-6 days). Long duration of abdominal pain was 4, 5, and 6 days, associated with the tumor larger than 10 cm accompanying using 5 Fr catheter.

Deterioration of liver function

Three patients had deterioration of liver function defined as an increased in serum bilirubin concentration (2 mg/dL or higher), newly developed ascites or hepatic encephalopathy. All of them were identified in the first session of TACE. One patient developed within 3 days and spontaneously recovered in 1 week after treatment. Irreversible deterioration with acute liver failure occurred in 2 patients who had pre-existing tumor invasion nearly total occluded the right portal vein. One of them also had acute calculous cholecystitis as a precipitating cause (Table 3).

Response of treatment

Thirty six patients (76%) were evaluated for responses. Other 11 patients were not analyzed because follow-up CT scan was not available. Six patients (16%) had partial response, 6 (16%) had minimal response, no change in 8 cases (22%).

Table 3 Characteristics of the patients who had hepatic deterioration.

Characteristics	Reversible (n=1)	Irreversible (n=2)	
		1st patient	2nd patient
Gender : Age	Male : 52	Male : 50	Male : 50
Child-Pugh class	A	A	A
AJCC staging	4	4	4
Tumor location	Segment 2/3	Segment 8/5	Segment 6/7
Tumor Size	15	10	13
Catheter size	5 Fr	3 Fr	5 Fr
Vascular supply	Lt. hepatic a.	Rt. hepatic a.	Rt. hepatic a.
Drugs use			
- Adriamycin	16 mg	16 mg	40 mg
- Lipiodol	6 ml	6 ml	10 ml
Vascular invasion	None	RPV*	RPV*
Precipitating cause	None	None	Acute calculous cholecystitis
Survival time	3 years	24 days	23 days of admission without survival record

* RPV: Right portal vein

Table 4 Response to TACE (n=36)*

Tumor size (cm)	CR	PR	MR	NC	PD	Total
< 5	0	1	2	2	1	6
5-10	0	5	2	4	7	18
> 10	0	0	2	2	8	12
Response	0	6	6	8	16	36
Percentage (%)	0	16	16	22	44	100

* Follow-up CT scan in 11 patients were not available
* CR = complete response, PR = partial response, MR = minimal response, NC = no change, PD = progression of disease

Progressive disease was observed in 16 (44%) cases (Table 4). One patient in PR group is still alive after 3 years and received only 3 sessions of TACE (Fig. 1). One patient in MR group received 3 courses of TACE had a right hepatectomy within 3 months after the last TACE session. The histologic examination demonstrated fibrosis of tumor tissue without residual tumor cells.

Survival time

The record of survival time was not available in 3 of 47 cases. Survival time of the remaining 44 patients ranged from 24 days to 3 years. The survival outcome related with clinical staging and Child classes is shown in Table 5. The overall survival rate was 61%, 48%, 27%, and 9% of patients after 6 months, 1, 2, and 3 years with mean survival time 13.1 months. Two patients with right main portal vein involvement had survival time approximately 1 month.

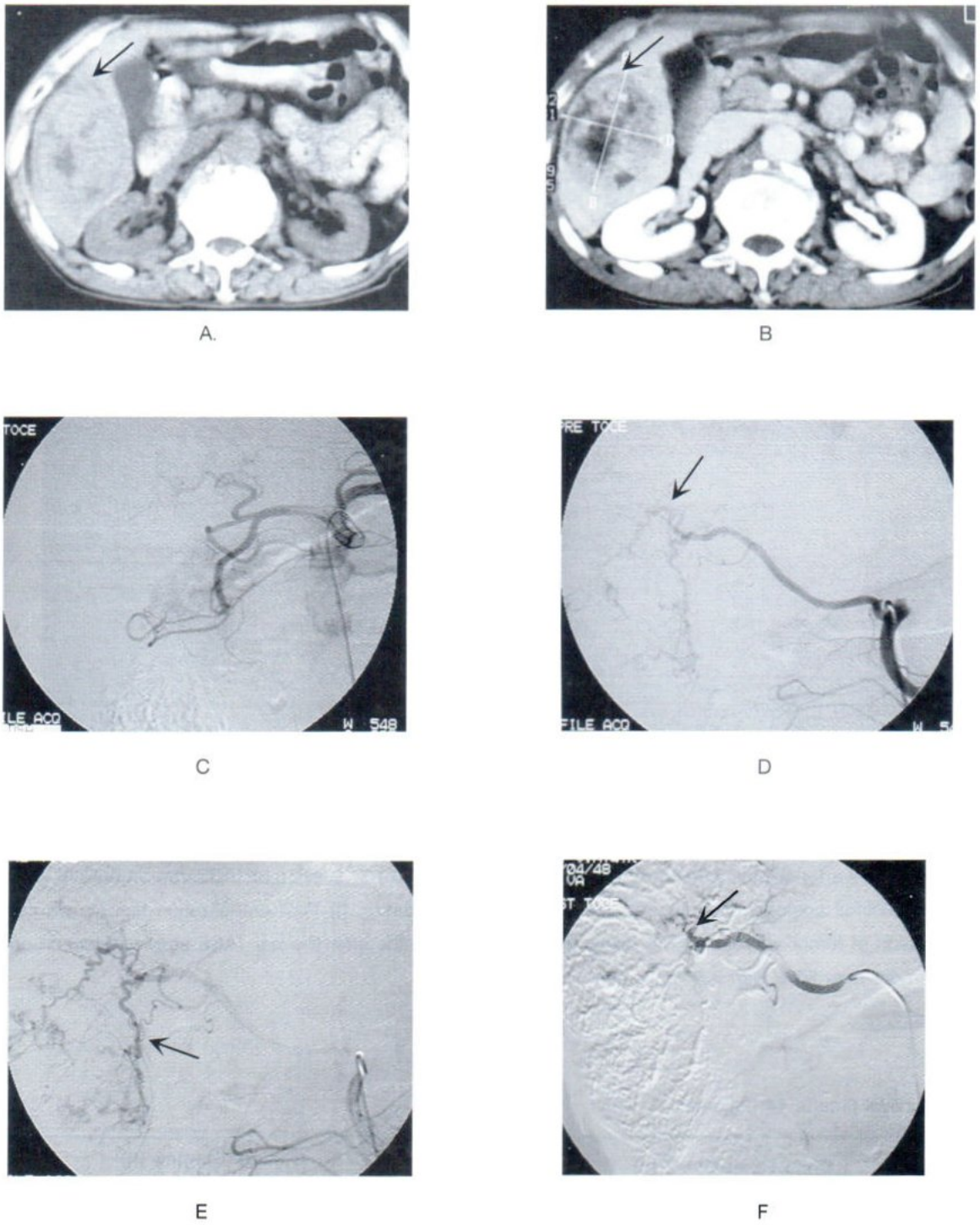

Fig.1 74-years-old man with HCC stage III underwent 3 courses of TACE. 1st session of TACE, **(a through f)**. **(a,b)** Initial CT scan shows a 7-cm mixed iso- to hypodense heterogeneously enhancing mass at segment 6 of right lobe liver. **(c,d,e)**. Angiogram shows hypervascularized tumor at right lobe liver (thick arrow) supplied by replaced right hepatic artery from SMA (thin arrow). **(f)**. Post-TACE film shows complete occlusion of tumor vessels (arrow).

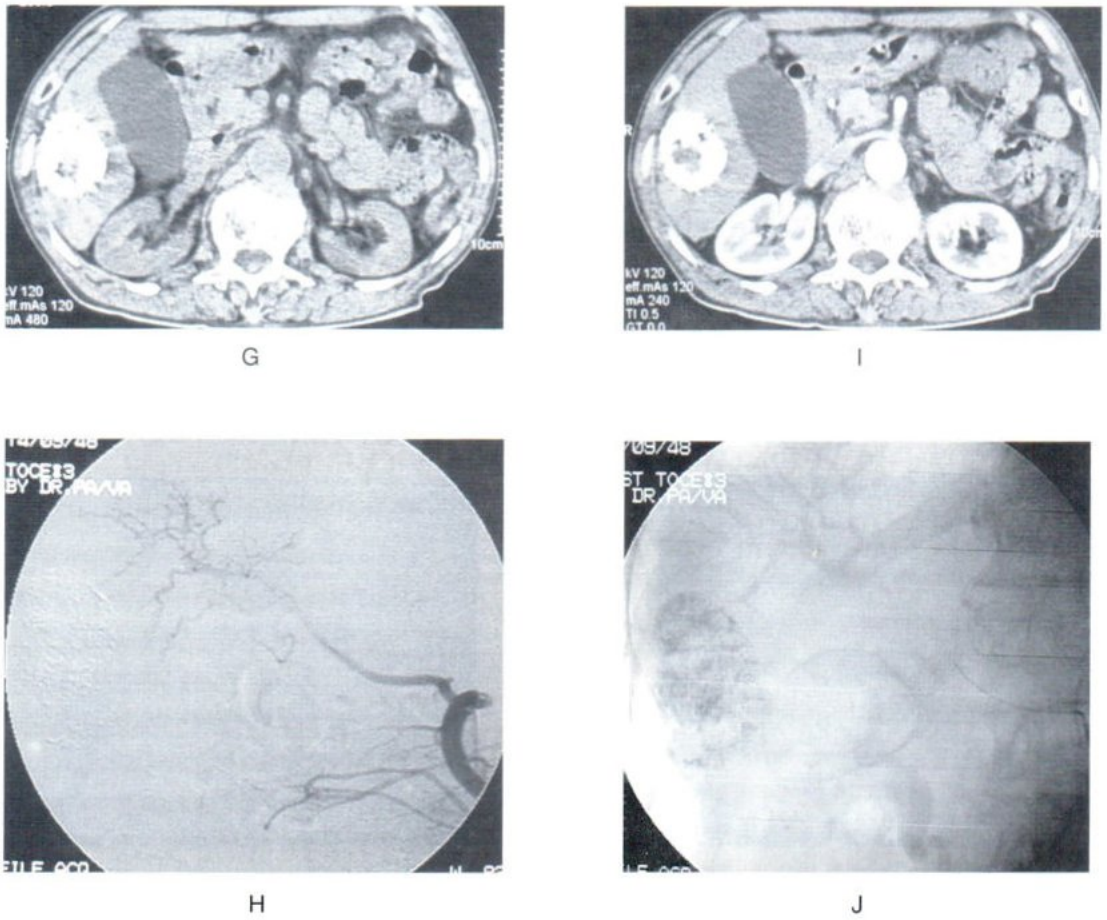

Fig.1 (continued). **(g)** Follow-up CT scan after 2nd TACE, pre and post contrast-enhanced CT show lipiodol staining with minimal arterial enhancement of the HCC at segment 5. **(h)** 3rd session of TACE, pre-embolized angiogram show minimal angiogenic activity at medial aspect of the tumor. **(j)** Post embolization film shows complete occlusion of tumor vessels. **(i)** The follow up CT scan 5-months after the last TACE shows reduction of tumor size more than 50% with > 90% lipiodol staining.

Table 5 Survival time in 44 patients*

Survive (years)	Child-Pugh Class (n)		Cases (%)	Clinical Staging (n)				
	A (36)	B (8)		II (3)	IIIa (20)	IIIb (2)	IVa (16)	IVb (3)
0.5	23	4	27 (61%)	3	14	1	9	0
1	18	3	21 (48%)	3	12	1	5	0
2	10	3	12 (27%)	3	6	0	3	0
3	3	1	4 (9%)	2	1	0	1	0

* Survival record not available in 3 patients

Discussion

Over the past 20 years, TACE has become the treatment of choice for patients with inoperable HCC. TACE has been shown to improve survival.[1,16] However, this survival benefit may be offset by the worsening of liver function. In this study, the serious complication of TACE was hepatic insufficiency. Portal vein obstruction is a well-known risk factor for hepatic failure and infarction after hepatic artery embolization.[14,15] In our series, 2 patients with nearly total RPV obstruction (Figure 1) had acute hepatic failure after TACE. Therefore, TACE should be cautiously performed with a reduced amount of chemoembolic agents and selective administration of them into tumor feeding arteries. In patients with either right or left major branch of main portal vein obstruction, if there are other predisposing factors to hepatic insufficiency, TACE may be contraindicated because of the risk of irreversible deterioration of the hepatic function. The liver with HCC is frequently compromised by cirrhosis and chronic hepatitis. A safe dose of iodized oil to the compromised liver has not been determined as yet. The total dosage of Lipiodol should be less than 20 ml (0.25-0.3 mL/kg) in order to prevent pulmonary oil embolism.[16] On the basis of our clinical experience, the amount of the iodized oil used is limited to less than 10 ml in all patients of our study.

Most common TACE-related complication in this study was post-embolization syndrome (fever [83%], abdominal pain [38%], and N/V [20%]), similar to those reported in the literature reviews[13,17,19]. Although, it is self-limited or can be managed, it can be considered a major complication of TACE because it prolonged hospitalization and impairs patient compliance with additional repeated treatments. Fever after TACE is mainly due to tumor necrosis. In the clinical setting, it is difficult to differentiate between fever due to tumor necrosis and fever due to secondary infection. In our study, post-embolization syndrome can be predicted on the basis of the size of the tumor to a certain degree. Therefore, unexpectedly high and prolonged fever after TACE in patients with a small tumor size developed sudden onset of high fever with chills, septic complications should be considered. In this study, most of the cases that had longer duration of fever with suspected septic complication had negative aerobic hemoculture and the final diagnosis was fever due to tumor necrosis. Sepsis was documented in only one patient with predisposing factor (acute calculous cholecystitis). Fatal sepsis insults were not found because we used strict sterile technique like other operative procedures. The cause of abdominal pain after TACE is unclear.

Liver function deterioration was found in 3% of total 88 TACE procedures, slightly lower incidence when compared to FAN J, et al.[13] (5%, 4 of 80 patients) and Chung JW, et al.[18] (15%, 54 of 351 cases). Chan OA, et al.[19] reported that 3% of their cases, developed hepatic encephalopathy or hepatic failure. This is close to our study (2%, 2 of 88 TACE sessions). We identified the factors that appear to predispose our patients to developed irreversible acute hepatic failure after TACE, to be a high dosage of Adriamycin 40 mg with evidence of RPV invasion (n=2).

Regarding response to treatment, Fan J, et al.[13] and Chan OA et al.[19] reported that the majority of their patients had partial response (reduction in tumor size more than 50%). In our study, we discovered that the majority of cases had progressive disease which should be due to initial tumor size larger than 10 cm in greatest dimension associated

with advanced tumor staging at the time of presentation.

Survival outcome of patients treated with TACE in this study were 48%, 27%, and 9% of patients at up to 1, 2, and 3 years with mean survival time 13.1 months, shorter time when compared to Llovet et al[2] (survival rates, 82% at 1 year and 63% at 2 years), and Fan J, et al[13] (87%, 46%, and 28% at 1-, 2-, and 3-years respectively). The reason should be due to different study design, patient characteristics, and treatment regimens. Our result was closed to that reported by Huang YH et al.[20] which had survival rates in TACE group at 1 year (42%), 3 years (13%), and median survival 9.2 ± 3 months. Our patient selection may be quite similar.

One of our patients with stage IV HCC caused by hepatitis B virus without evidence of cirrhosis survived more than 3 years. She underwent 2 sessions of TACE. After the 2nd procedure, CT imaging showed reduction in size of tumor from 12 to 9 cm and decreased serum AFP level from 1.8 to 1.11 IU/ml. Then surgical resection (right hepatectomy) was considered and the pathological report revealed no residual tumor with free surgical margin. The long survival time may reflect pre-operative down sizing and down staging by TACE. Another patient, AJCC stage III, the tumor size reduced from 7 to 3 cm after 3 sessions of TACE, survived longer than 3 years (Fig. 1).

The low complications of our procedure should alert the involved clinicians (hepatologists, hepatobiliary surgeons, oncologists, and interventionists) to chose TACE as an alternative treatment modality. The awareness of TACE-related complications should help in better management. However, this study is a retrospective review. There is limitation such as incomplete data collection and small number of patients. Nowadays many other palliative treatments with or without added neo-adjuvant therapy for inoperable HCC patients such as PEI, radiofrequency ablation, or transcatheter arterial embolization with radionuclide labeled iodized oil were used as alternative procedures. Comparative study with each treatment modalities and further prospective randomized trials of sufficient number of patients remain necessary.

Conclusion

Most complications in our study can be managed. Serious complications, acute liver failure occurred in 2 patients with RPV invasion. Very careful pre-treatment planning should help to solving/reducing the problem. As for the result of treatment, 32% in our patients had partial and minimal tumor response, and the 2- and 3-years survival rate was 27% and 9%, respectively. We believe that we can improve it if the patients come to us in earlier stage.

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