Table 2 Drug-related adverse events

	Any	Grade 3/4
Overall incidence	53 (98)	36 (68)
Hematological		
Hemoglobin	1 (2)	0
Leukocytes	4 (8)	0
Platelets	14 (26)	3 (6)
Dermatologic events		
Hand–foot skin reaction	39 (72)	14 (26)
Rash	27 (50)	7 (13)
Alopecia	9 (17)	
Gastrointestinal events		
Anorexia	12 (22)	4 (7)
Diarrhea	17 (32)	0
Vomiting	3 (6)	1 (2)
Fatigue	22 (41)	0
Voice changes	2 (4)	0
Hypertension	14 (26)	0
Abdominal pain not otherwise specified	5 (9)	0
Bleeding	4 (8)	2 (4)
Laboratory		
AST	30 (55)	13 (24)
ALT	28 (52)	8 (15)
Bilirubin	15 (28)	6 (11)
Amylase	15 (28)	3 (6)
Liver failure	10 (19)	

Liver failure is defined as encephalopathy, massive ascites, or jaundice

Table 3 Adverse events causing dose reduction

	Number of patients (%)
Patients requiring dose reduction	45 (83)
Hand–foot skin reaction	21 (38)
AST/ALT	8 (15)
Rash	7 (13)
Liver failure	4 (7)
Anorexia	2 (4)
Bleeding	2 (4)
Vomiting	1 (2)
Time to dose reduction	
<2 weeks	24 (44)
≥2 weeks to <4 weeks	12 (22)
≥4 weeks	9 (17)

treatment discontinuation were liver failure ($n = 4$, 7%), HFSR ($n = 4$, 6%), fatigue ($n = 3$, 6%), and abdominal pain not otherwise specified ($n = 3$, 6%). The median time to treatment failure (TTF; defined as the period from first treatment to discontinuation of sorafenib treatment, progression, or death) was 2 months (Fig. 1).

Table 4 Adverse events leading to treatment discontinuation

	Number of patients (%)
Any adverse events	17 (31)
Liver failure	4 (7)
Hand–foot skin reaction	3 (6)
Fatigue	3 (6)
Abdominal pain not otherwise specified	3 (6)
Anorexia	2 (4)
Rash	2 (4)

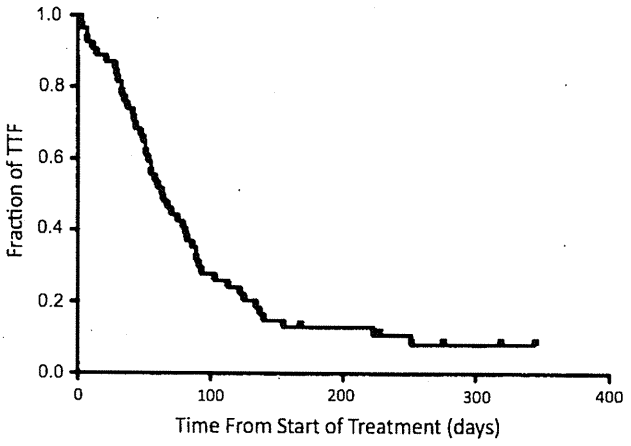

Fig. 1 Kaplan–Meier analysis of time to treatment failure (TTF). The median TTF was 2 months

Efficacy

According to RECIST version 1.1, one patient (2%) had a partial response, 25 patients had stable disease (57%), and the disease control rate (DCR; defined as no disease progression for ≥4 weeks) was 34% (Table 5).

At the time of analysis, with a median follow-up of 5.7 months (range 0.5–13.3), 49 patients had discontinued treatment (92%) and 28 patients were dead (52%). The overall median survival was 6.9 months (Fig. 2)

Discussion

The SHARP and Asia-Pacific studies, large, multicentre, phase III, randomized, double-blind, placebo-controlled trials of sorafenib, revealed a survival benefit and the tolerability of sorafenib in advanced HCC patients. However, considering the varying etiologies and treatment strategies for HCC in different regions [4], it is unclear whether these results apply to Japanese HCC patients. In Japan, high-risk groups for HCC, such as cirrhosis or hepatitis patients, undergo ultrasonography every 3–4 months and CT or MRI every 6–12 months for the early detection of HCC. Because we find HCC when it is earlier, Japanese HCC

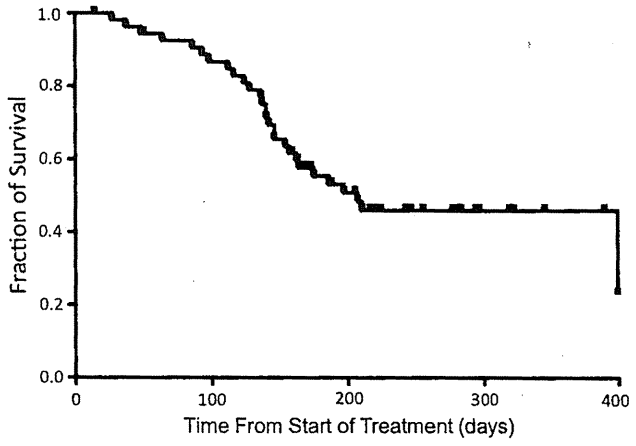

Fig. 2 Kaplan-Meier analysis of overall survival (OS). The median OS was 6.9 months

Table 5 Response rates using the response evaluation criteria in solid tumors

Response ($n = 44$)	Number of patients (%)
Complete response	0
Partial response	1 (2)
Stable disease	25 (57)
Progressive disease	18 (41)
DCR	15 (34)

DCR is the disease control rate, defined as the proportion of patients who had a best response rating of a complete response, partial response, or stable disease that was maintained for ≥4 weeks from the first manifestation of the rating

patients are often able to undergo surgery, local ablation, and TACE. Despite the efficacy of these procedures, patients frequently develop recurrence or disease progression after these treatments. In contrast, in much of the rest of Asia, the majority of patients are present with advanced disease, with large tumors, multiple tumors, and portal tumor thrombosis. These patients are less likely to receive curative treatment [18]. Furthermore, the liver function of HBV-related HCC patients tends to be better than that of HCV-related HCC patients. Shiratori et al. [2] reported that 38.6, 39.3, and 22.1% of cases presented as Child-Pugh A, B, and C when the severity of cirrhosis was classified in Japanese HCV-related HCC patients. By contrast, among the HBV-related HCC patients, 65.2, 26.1, and 8.7% cases presented as Child-Pugh A, B, and C. Additionally, liver function might worsen with the repetition of local therapies because sorafenib was only given to Child-Pugh A patients. Fewer HCV-related HCC patients (52%) were included in the present analysis compared with the general HCC prevalence in Japan (71–75%) [2, 6].

In the SHARP study, common drug-related adverse events were diarrhea (39%), fatigue (22%), HFSR (21%), rash (16%), alopecia (14%), anorexia (14%), and nausea (11%) [14]. Dose reduction due to adverse events was needed in 26% of subjects. The most common adverse events leading to dose reduction were diarrhea (8%), HFSR (5%), and rash (3%) [14]. Treatment was discontinued because of adverse events in 38%. The most frequent adverse events leading to sorafenib discontinuation were gastrointestinal events (6%), fatigue (5%), and liver dysfunction (5%) [14]. In comparison, in the Asia-Pacific study, the common drug-related adverse events were HFSR (45.0%), diarrhea (25.5%), alopecia (24.8%), fatigue (20.1%), rash (18.8%), hypertension (18.8%), and anorexia (12.8%) [15]. Dose reduction due to adverse events was needed in 30.9%, and treatment was discontinued due to adverse events in 19.5% [15]. The most common drug-related adverse events resulting in dose reduction were HFSR (11.4%) and diarrhea (7.4%) [15]. Compared with these studies, we observed a higher incidence of adverse events, especially HFSR, rash, hypertension, and liver failure.

The incidence of HFSR and rash in the Asia-Pacific study was higher than in the SHARP study [14, 15]. In a phase I study of a small population of Japanese patients with HCC, five of the six patients experienced HFSR and four experienced rash; these patients were Child-Pugh A receiving 400 mg twice daily [16]. In a phase II study of Japanese patients with advanced renal cell carcinoma [19], HFSR occurred in 55% and rash occurred in 37.4%. Asian patients, particularly Japanese, frequently develop HFSR. Although it is possible that the physiological difference is partly associated with race, prevention and management of HFSR are required in Japanese patients.

Regarding hypertension, Wu et al. [20] reported a 23.4% (95% CI 16.0–32.9%) overall incidence from a systemic review and meta-analysis of nine studies of renal cell cancer or other solid tumor. Hypertension was experienced by 14 patients (26%) in our study; no case was grade 3/4. Varying rates of hypertension have been reported, with a 5% incidence in the SHARP study and an 18.8% incidence in the Asia-Pacific study. In our study, the incidence of hypertension was comparable with that reported by Wu et al., although it was slightly higher compared with that reported in the SHARP and Asia-Pacific studies.

Liver failure occurred in ten patients (19%), while it was uncommon in the SHARP and Asia-Pacific studies. Nevertheless, Ozenne et al. [21] reported that seven (21%) French patients with Child-Pugh A experienced liver failure. The SHARP and Asia-Pacific studies showed the efficacy of sorafenib in carefully selected patients with advanced HCC. Liver failure may occur with the use of sorafenib in an unselected cirrhotic population. In our study, the median time to experience liver failure was 33 days (range 7–115); liver failure can happen in the

early days of treatment. Furthermore, a common adverse event leading to treatment discontinuation was liver failure (7%).

In our study, 43 patients required dose reduction due to adverse events (83%). This was more frequent than in either the SHARP or Asia-Pacific studies. The most common adverse event leading to dose reduction was HFSR (43%) [12, 13]. Our patients suffered more HFSR than those in the SHARP and Asia-Pacific studies [12, 13]. The cause may be differences, such as age or race. Nevertheless, treatment discontinuation due to HFSR was required in only 6% of the patients; in the majority of the patients, it could be controlled by dose reduction. This concurred with the finding that two of seven patients with Child-Pugh A experienced HFSR when they took 400 mg daily in the Japanese phase I study [16].

In our series, 44% of the patients required dose reduction within 2 weeks and the median daily dose was 450 mg (range 182–800), demonstrating that it is difficult for Japanese patients to continue sorafenib treatment at 400 mg twice daily. Treatment was discontinued because of adverse events in 31% of our patients, which was similar to the rate in the SHARP study, but higher than in the Asia-Pacific study. Adverse events could be managed by dose reduction in the majority of patients. Therefore, careful follow-up is recommended.

The median overall survival was 10.7 months in the SHARP trial and 6.5 months in the Asia-Pacific trial. The differences in survival time might have been caused by differences in patient background. Patients in the Asia-Pacific study displayed more extrahepatic spread, more hepatic tumors, a worse ECOG-PS, and increased concentrations of AFP compared with patients in the SHARP study [14, 15]. The median survival time was 9.2 months in a phase II study [17] and 15.6 months in a Japanese phase I study [16], although Child-Pugh B patients were included in both of these studies. More recently, two retrospective studies from Europe showed that the median survival times for Child-Pugh A patients were 8.9 [21] and 8.3 months [22]. The median overall survival in our series was 6.9 months, although the survival benefits cannot be directly compared, as this was a retrospective study. Our study included many patients with higher serum AFP levels, suggesting the inclusion of highly advanced cases in the present study.

In summary, the present study demonstrated that sorafenib was generally tolerated in Japanese HCC patients because the probability of treatment discontinuation due to adverse events was acceptable, although most patients needed dose reduction. The overall safety profile of sorafenib was similar to that seen in previous studies in patients with HCC, except for the higher rates of HFSR, rash, and liver failure.

Acknowledgements We want to thank Yu Yoshida, Kazuyoshi Nakamura, and Takao Nishikawa for their contributions.

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Hepatology Research

Hepatology Research 2011; 41: 853–866 doi: 10.1111/j.1872-034X.2011.00836.x

Original Article

Portal blood supply to locally progressed hepatocellular carcinoma after transcatheter arterial chemoembolization: Observation on CT during arterial portography

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Aim: To analyze the clinical features of locally progressed hepatocellular carcinoma (HCC) supplied by portal blood (PB) after transcatheter arterial chemoembolization (TACE).

Methods: This cohort included 12 tumors (mean diameter ± SD, 1.8 ± 0.8 cm) in 10 patients. PB supply to tumors was judged by CT during arterial portography (CTAP). Imaging data and the clinical course were retrospectively evaluated.

Results: Six tumors initially had a small tumor portion supplied by PB. In four tumors, TACE was incomplete because of technical problems. PB supply to recurrent tumors was demonstrated 7.3 ± 3.7 months after TACE. On follow-up arteriography, all embolized branches were occluded or severely attenuated. Four tumors showing a partial stain were treated by additional TACE ($n = 3$) or TACE plus radiofrequency (RF) ablation ($n = 1$), one without staining was treated by RF ablation, and seven were followed-up. All tumors progressed except for one treated by RF ablation. On serial CTAP images, relatively large-diameter portal veins directly entered 11 tumors (91.7%) and connected with intratumoral vessels in nine (75%). During follow-up, partial arterial supply was demonstrated in two tumors and additional TACE was performed. Nine patients died after 31.4 ± 16.2 months due to tumor progression ($n = 8$), or hepatic failure ($n = 1$). One patient has survived for 53 months despite multiple tumors.

Conclusions: PB supply to locally progressed tumor after TACE became apparent on CTAP. Arterial damage by TACE, incomplete TACE, and preexisting tumor tissues supplied by PB may be the main causes.

Key words: CT during arterioportography, hepatocellular carcinoma, portal blood supply, transcatheter arterial chemoembolization, tumor progression

INTRODUCTION

TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION (TACE) is one of the effective therapeutic options for inoperable hepatocellular carcinoma (HCC).[1–3] Because moderately to poorly-differentiated HCC (classical HCC) is exclusively supplied by arterial blood, embolization of the hepatic artery can be theoretically expected to result in selective ischemic necrosis of the tumor tissue.[1]

However, HCC frequently shows local progression after TACE. Portal blood supply to HCC lesions is considered as one of the important causes of tumor survival after TACE.[4–6] To our knowledge, there are no reports concerning imaging findings of portal blood supply to locally progressed HCC after TACE except for a case report by Choi *et al.*[6]

We evaluated the portal blood supply to locally progressed HCC lesions using serial computed tomography (CT) during arterial portography (CTAP) performed just prior to each repeated TACE. Thus, the purpose of this study was to retrospectively analyze the imaging data and clinical course of locally progressed HCC lesions supplied by portal blood after TACE.

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Received 14 March 2011; revision 24 April 2011; accepted 11 May 2011.

METHODS

Patient

THIS WAS A retrospective study in which existing imaging data were used with no effect on patient care; Institutional Review Board approval is not required at our institution for this type of study. Written informed consent was obtained from each patient before all TACE procedures.

Between September 2001 and December 2007, 277 patients were clinically diagnosed as having local progression of HCC after TACE. Imaging findings and clinical data of all patients were retrospectively analyzed. The diagnosis of local tumor progression was established when a viable tumor developed in or adjacent to the treated tumor with or without disappearance of iodized oil or when a tumor portion without iodized oil accumulation was enlarged on dynamic CT and/or magnetic resonance (MR) imaging. Portal blood supply to progressed HCC was judged as positive when all or the majority of the viable tumor showed isoattenuation or hyperattenuation compared to the background liver parenchyma on follow-up CTAP. We found 12 HCC lesions in 10 patients fed by portal blood during the same period. There were six men and four women, ranging in age from 49 to 82 years (mean values ± standard deviation, 68.8 ± 9.8 years). All patients had liver cirrhosis related to hepatitis C virus. One to 13 TACE procedures (mean, 4.4 ± 3.5 times) had been performed during follow-up periods ranging from 5 to 100 months (mean, 41.3 ± 25.8 months) before disclosure of the portal blood supply to locally progressed HCC. One patient had undergone 4 TACE sessions on the right inferior phrenic artery (IPA) and another patient had undergone 5 TACE sessions on the right IPA and 2 sessions on the right renal capsular artery (RCA). Two patients had also undergone a single radiofrequency (RF) ablation therapy in addition to TACE at another site.

The diagnosis of local tumor progression was clinically established in seven tumors. Histopathological confirmation was obtained in five tumors (autopsy [$n = 3$], needle biopsy [$n = 2$]). Serum alpha-fetoprotein level (AFP) was elevated in eight patients (normal range < 20 ng/mL, range 132–16748, 132–400 [$n = 4$], 401–1000 [$n = 2$], >1001 [$n = 2$]) and normal in one patient. Serum levels of AFP were not measured in one patient. Serum protein induced in vitamin K absence II (PIVKA-II) level was elevated in four patients (normal range < 40 mAU/mL [μg/L], range, 52–313, 52–200 [$n = 1$], 201–400 [$n = 3$]) and normal in five patients. Serum levels of PIVKA-II were not measured in one patient. All patients showed elevated serum levels of either AFP or PIVKA-II.

CTAP protocol

During the TACE procedure, CTAP was routinely performed using a multidetector-row (MD) helical CT scanner (Aquilion-4, Aquilion-16, and Aquilion-64; Toshiba, Tokyo, Japan). Scanning in a craniocaudal direction (3-collimation, 3-mm-thick sections, 3-mm-reconstruction intervals, 135 kVp, and 200 mAs) was performed to cover the entire liver during a single breath hold. Seventy ml of diluted contrast material (35 mL of contrast material, 350 mg I/mL of iomeprol; Iomeron 350 [Ezai; Toyo, Japan] or 370 mg I/mL of iopamidol; Iopamiron 370 [Bayer, Osaka, Japan] in 35 mL of sterile saline) was injected using a power injector at a rate of 2.5 mL/s through a catheter placed in the superior mesenteric artery after administration of 2.5 μg of prostagrandin E1 (Liple; Tanabe Mitsubishi, Osaka, Japan). When replaced hepatic branches or arterial flow from the superior mesenteric artery toward the liver and tumor was demonstrated, the catheter tip was deeply advanced until these branches were avoided. Scanning was initiated 35 s after the injection of contrast material. The scan durations of a 4-, 16-, and 64-MDCT scanner for a scanned length of 20 cm were 7.3, 7.4, and 4.7 s, respectively.

Staring May 2006, CTAP studies were also performed using a cone-beam CT technique (XperCT; Philips Medical Systems; Best, The Netherlands) in three patients. Three-hundred and twelve projection images with X-ray parameters of 120 kV and 50–325 mAs were obtained with a 10.4-second acquisition and a 207-degree rotation of a 30 × 38 cm flat panel detector on the angiographic C-arm (Allula Xper FD20; Philips Medical Systems) around the patient. Forty mL of 370 mg I/mL of iopamidol was injected at a rate of 3 mL/s after administration of 2.5 μg of prostagrandin E1. Scanning was initiated 25 s after the injection of contrast material. Three-mm thickness images at optimal cross section were reconstructed using a workstation (Philips Medical Systems).

TACE procedure

All TACE procedures were performed by injecting either a mixture of 2–5 ml of iodized oil (Lipiodol; Andre Guerbet, Aulnaysous-Bois, France) and anticancer drugs (10–30 mg of epirubicin [Farmorbicin; Pfizer, Tokyo, Japan] and 2–6 mg of mitomycin C [Mitomycin; Kyowa Hakko Kirin, Tokyo, Japan]) followed by gelatin sponge

particles (Gelfoam; Upjohn, Kalamazoo, MI, USA, or Gelpart; Nippon Kayaku, Tokyo, Japan). After confirmation of tumor stain on arteriogram, TACE was performed through a 1.8-F tip (Carnelian PIXIE; Tokai Medical Products, Kasugai, Japan), 2-F tip (Progreat α; Terumo, Tokyo, Japan), or 2.4-F tip (Microferret; Cook, Bloomington, IN, USA) microcatheter navigated into the target vessel as distally as possible through a 4-F catheter. TACE through an extrahepatic collateral was also performed in the same fashion, if necessary. TACE procedures were ended when the tumor stain disappeared on arteriogram.

We named TACE performed just before disclosure of the portal blood supply to locally progressed tumors as "triggered TACE."

Follow-up

In all patients, unenhanced CT was obtained 1 week after the TACE procedure in order to check for iodized oil accumulation in the target tumor. All patients were followed by dynamic CT or MR imaging every 2–4 months after triggered TACE. Angiography and CTAP were performed when tumor progression was suspected on follow-up images. When a locally progressed or newly developed tumor fed by arterial blood was demonstrated on angiography, additional TACE procedure, either through the hepatic artery and extrahepatic collaterals, was also performed. The locally progressed tumor without a tumor stain on angiography was either followed or treated by RF ablation, if possible.

RESULTS

CTAP and angiographic findings just before triggered TACE

THE FINDINGS ARE summarized in Table 1. The maximal tumor diameter ranged from 1–4 cm (mean, 1.8 ± 0.8 cm). Six tumors (50%) showed portal perfusion defect in the entire tumor (Figs 1,2). Six tumors (50%) showed a small tumor portion with decreased or preserved portal perfusion mainly at the periphery of the tumor (Fig. 3).

All tumors showed a tumor stain on arteriogram (Figs 1,2). TACE was performed at the subsubsegmental artery ($n = 3$), subsegmental artery ($n = 6$), segmental artery ($n = 2$) of the hepatic artery. In the remaining tumor, TACE was performed at the right hepatic artery because of the presence of multicentric tumors and attenuation of the hepatic artery by previous TACE.

Table 1 Summary of each tumor and triggered TACE

Patient no./Age (year)/Sex	Tumor size (cm)	Tumor location†	Portal blood supply on CTAP	TACE level	Iodized oil accumulation
1/69/F	1.9	S8/4	None	Subsubsegmental	Dense, entire
2/61/M	2.6	S3	None	Subsegmental	Dense, entire
	2	S8	Periphery	Segmental	Dense, hypervascular portion
3/68/M	1.7	S8	None	Subsubsegmental	Sparse‡
	1.6	S3	Periphery	Subsubsegmental	Dense, hypervascular portion
4/82/F	4	S7	Periphery	Segmental, RRCA	Dense, hypervascular portion
5/49/M	1.7	S3	None	Subsegmental	Dense, partial defect‡
6/75/M	1.4	S8	Periphery	Subsegmental	Dense, hypervascular portion
7/65/M	2.1	S3	None	Subsegmental	Sparse‡
8/73/F	1	S3	None	Subsegmental	Dense, entire
9/81/M	1	S7	Periphery	Lober	Sparse‡
10/65/F	1.3	S8	Periphery	Subsegmental	Dense, hypervascular portion

†Liver segment according to Couinaud classification.
‡Technical trouble during TACE was suspected.
CTAP, CT during arterial portography; RRCA, right renal capsular artery; TACE, trancatheter arterial chemoembolization.

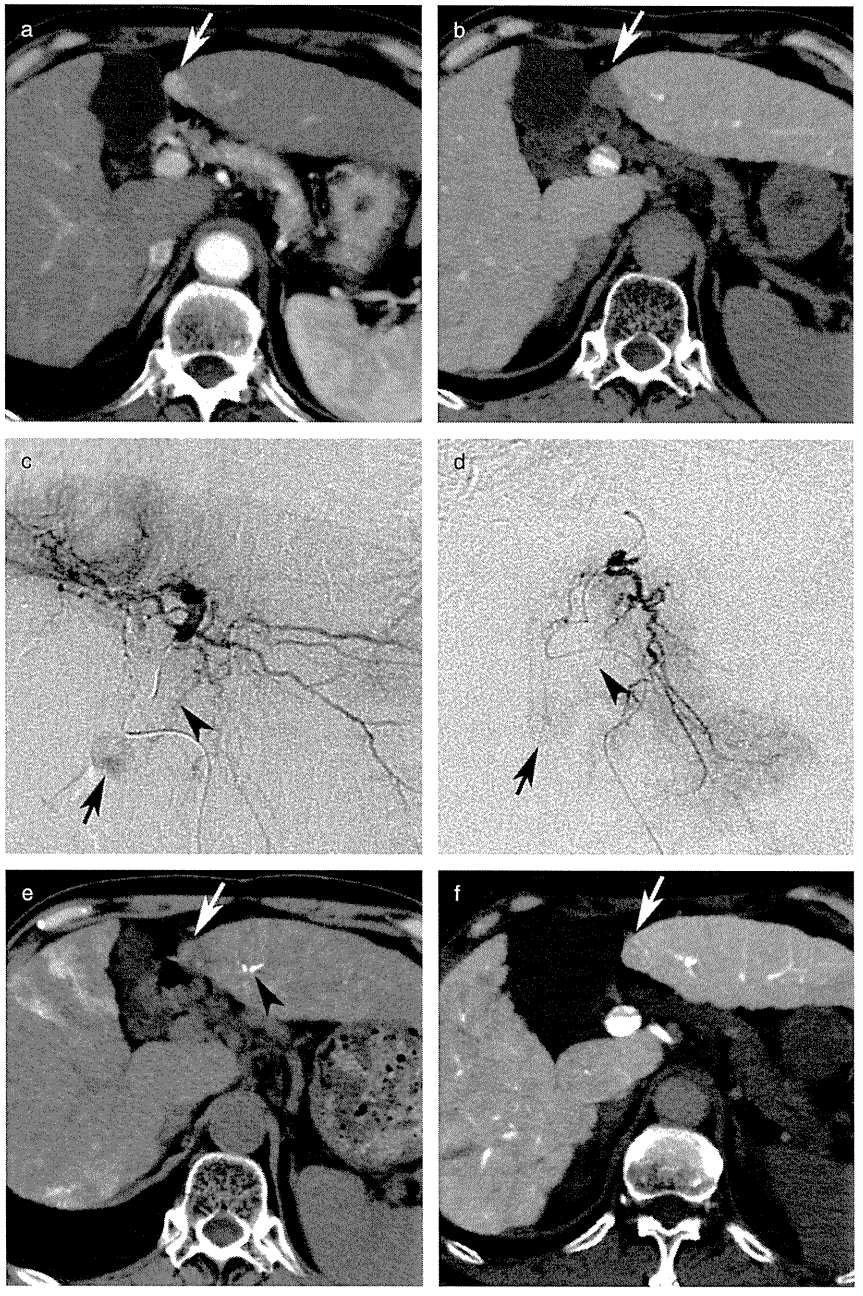

Figure 1 Images in a 65-year-old man with a tumor fed by portal blood. (a) Arterial phase CT shows a hypervascular tumor in segment 3 of the liver (arrow). (b) CTAP shows portal perfusion defect in the tumor (arrow). (c) Arteriogram of the lateral segmental artery of the left hepatic artery shows a tumor stain (arrow) supplied by the ventral lateral segmental artery (A3) (arrowhead). (d) Selective arteriogram of A3 shows stasis of the tumor-feeding branch (arrow) and the tumor stain becomes faint (arrowhead). TACE was performed at this point. (e) CT obtained 1 week after TACE shows that iodized oil is sparsely accumulated in the tumor (arrow), although it is densely retained in A3 (arrowhead). Iodized oil in the tumor had washed out on follow-up CT obtained 6 months after TACE (not shown). (f) On CTAP obtained 7 months after TACE, the tumor has changed to isoattenuating and hyperattenuating. (g) On CTAP obtained 26 months after TACE, the tumor is enlarged and relatively large portal veins directly enter the tumor and connect with intratumoral vessels (arrows). In addition, the branch of the left hepatic vein runs adjacent to the tumor (arrowheads). On CT obtained 30 seconds after CTAP, the tumor appears as hypoattenuating. Iodized oil is still retained in A3 (arrow) suggesting complete occlusion of A3.

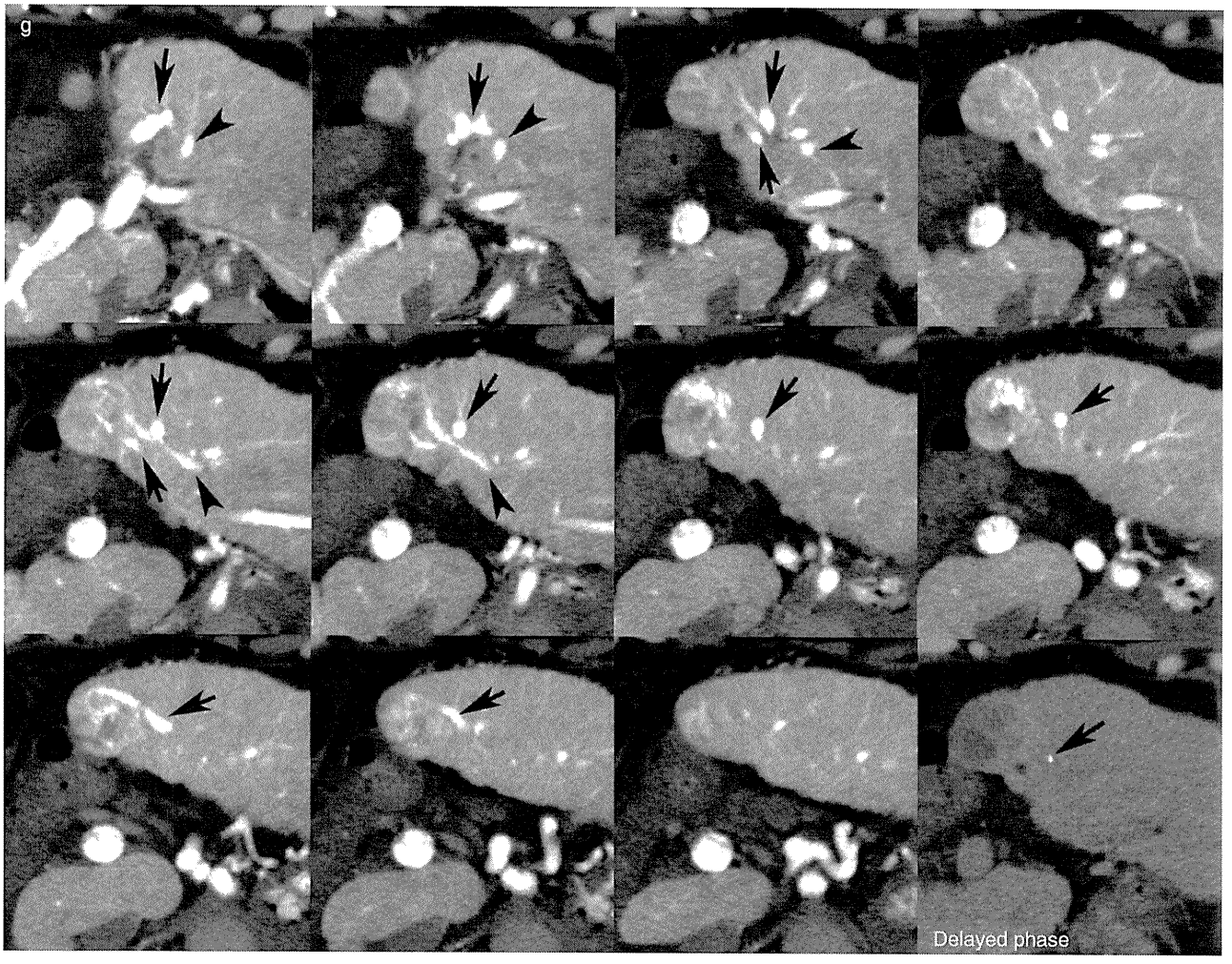

Figure 1 *Continued.*

The tumor-feeding right RCA was also embolized in one tumor. During catheter manipulation, the tumor stain became unclear in two tumors, probably because of a spasm or air embolism in the tumor-feeding branch (Fig. 1). TACE was performed in both tumors injecting a small amount of a mixture of iodized oil and anticancer drugs and gelatin sponge particles.

Outcomes of triggered TACE

Of six tumors with portal perfusion defect on CTAP, three tumors showed dense iodized oil accumulation in the entire tumor on CT obtained 1 week after TACE. Two tumors in which the stain was weakened during the catheter manipulation showed sparse iodized oil accumulation (Fig. 1). In the remaining tumor, iodized oil was densely accumulated in most of the tumor except for a small part (Fig. 2).

Of six tumors showing a small portion with decreased or preserved portal perfusion on CTAP, five tumors showed dense iodized accumulation only in the tumor portion with portal perfusion defect on CT obtained 1 week after TACE (Fig. 3). In the remaining tumor, iodized oil was sparsely accumulated even in the tumor portion with portal perfusion defect.

In eight tumors, iodized oil was washed out and viable tumor was detected ($n = 2$) or gradually enlarged ($n = 6$) on follow-up CT obtained 1–10 months (mean, 5.5 ± 3.3 months) after TACE. In four tumors, viable tumor was demonstrated adjacent to densely accumulated iodized oil on follow-up CT obtained after 5–12 months (mean, 7.8 ± 3.4 months), including one

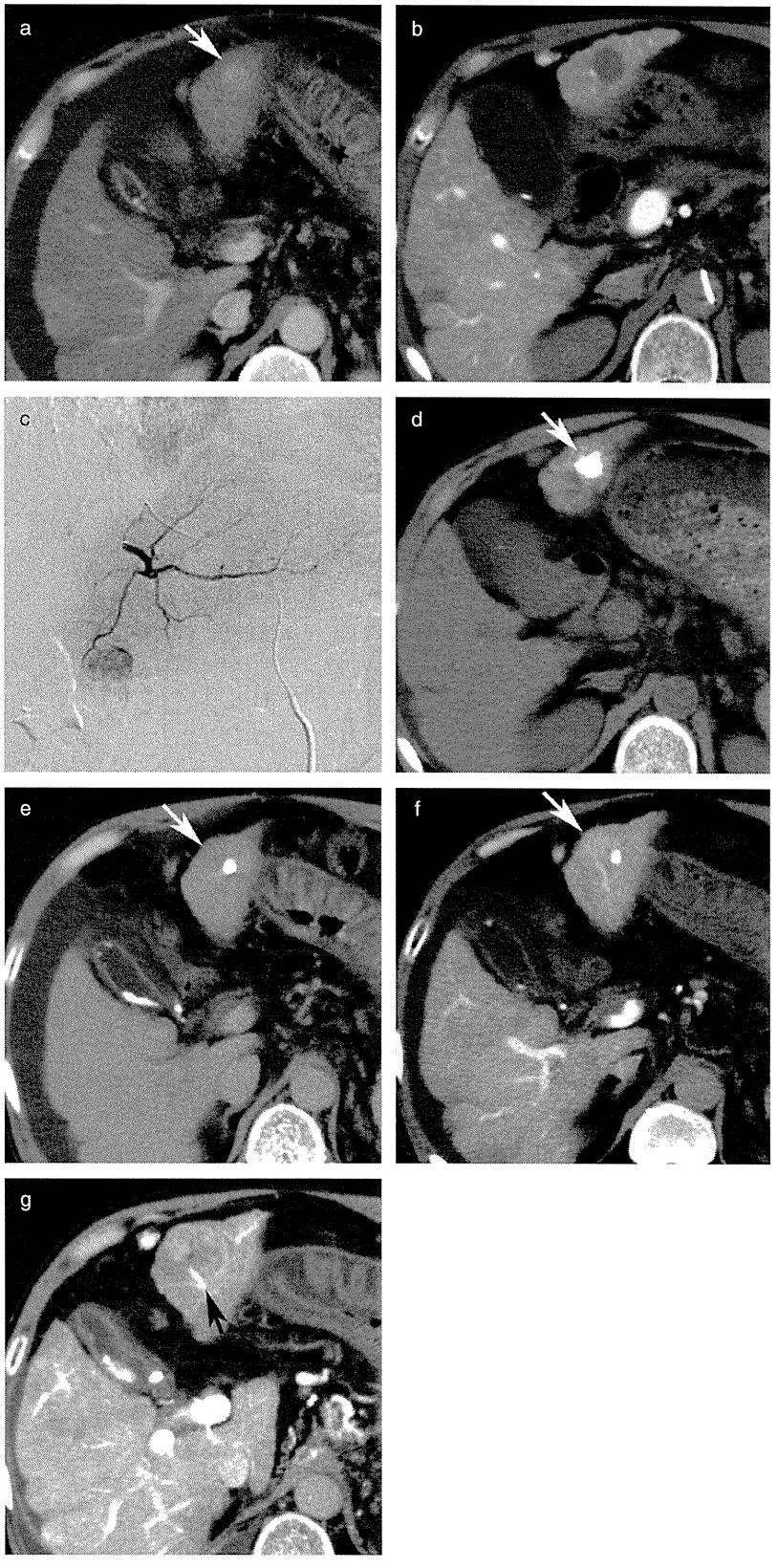

Figure 2 Images in a 49-year-old man with a tumor fed by portal blood. (a) Arterial phase CT shows a hypervascular tumor in segment 3 of the liver. (b) CTAP shows portal perfusion defect in the tumor. (c) Selective arteriogram of A3 shows a tumor stain. TACE was performed at this point. (d) CT obtained 1 week after TACE shows that iodized oil is not accumulated in the ventral portion of the tumor (arrow). (e) Delayed phase CT obtained 11 months after TACE shows a hypoattenuating tumor adjacent to the densely retained iodized oil (arrow). (f) CTAP obtained 12 months after TACE shows that the tumor is supplied by portal blood (arrow). (g) CTAP obtained 33 months after TACE shows that the tumor is enlarged and the portal vein directly enters the tumor.

tumor with incomplete iodized oil accumulation in a small hypervascular tumor portion (Figs 2,4).

CTAP findings at demonstration of the portal blood supply to locally progressed HCC

The findings are summarized in Table 2. Follow-up CTAP was performed 1–13 months (mean, 7.3 ± 3.7 months) after triggered TACE. The maximal tumor diameter supplied by portal blood ranged from 1.5–5.3 cm (mean, 2.5 ± 1.1 cm). In comparison with tumor diameter before triggered TACE, 10 tumors (83.3%) were enlarged and two (16.7%) were reduced in size.

One tumor (8.3%) showed hyperattenuation of the entire tumor (Fig. 2). Eleven tumors (91.7%) showed inhomogenous attenuation. Among these, five tumors (41.7%) showed hyperattemuation and isoattenuation (Figs 1,3), four (33.3%) showed hyperattenuation including a nodular hypoattenuating area, one (8.3%) showed a nodular hyperattenuation within the hypoattenuating area (Fig. 4), and one (8.3%) showed a rim-like and septum-like hyperattenuation around the hypoattenuating area.

Angiographic findings at demonstration of the portal blood supply to locally progressed HCC

Damage to the hepatic arterial branches by triggered TACE was observed in all 12 tumors. Of 11 tumors treated by TACE at a level more distal than the segmental artery, the embolized feeding branches were occluded ($n = 8$) or severely attenuated ($n = 3$) (Figs 4,5). Occlusion of tumor-feeding branches arising from the right RCA was also demonstrated in one tumor. In the remaining tumor treated by TACE of the right hepatic artery, severe attenuation of the right hepatic artery was observed.

In eight tumors without hypoattenuating areas ($n = 6$) or with a small hypoattenuating area ($n = 2$) on CTAP, there were no tumor stains demonstrated via the arterial side either through the hepatic and extrahepatic arteries. CT during hepatic arteriograhy (CTHA) was performed in one of these tumors, and showed hepatic arterial perfusion defect not only in the locally progressed tumor but also in the surrounding liver parenchyma (Fig. 4). Four tumors with hypoattenuating areas on CTAP showed a partial tumor stain through the neighboring hepatic subsegmental artery.

Four tumors showing a partial tumor stain were treated by additional TACE. In one of these tumors, RF ablation for tumor portions supplied by portal blood was added after tumor biopsy using an 18 G needle (Monopty; Bard, Tempe, AZ, USA). In another tumor without obvious tumor stains, tumor biopsy and RF ablation were performed. The remaining seven tumors that did not show any tumor stains were followed without further treatment because of multiple other tumors ($n = 5$) or difficulty that prevented RF ablation ($n = 2$).

Outcomes and serial CTAP findings of each tumor

All patients were followed-up for 10–56 months (mean, 32.9 ± 16.0 months) after triggered TACE. One to 9 (mean, 4.9 ± 3.0) additional CTAP studies were performed in nine tumors, mainly to evaluate other tumors in the same patient. In all tumors but one, the tumor portion fed by portal blood was gradually enlarged. Only one tumor treated by RF ablation was well controlled during the 56-months follow-up. Serial CTAP images showed that relatively large-diameter portal veins directly entered 11 tumors (91.7%) and these connected with intranodular vessels in nine tumors (75%) (Figs 1,2,4,5).

In two tumors located in the lateral segment of the left lobe, CTAP obtained 26 months after triggered TACE showed that a branch of the left hepatic vein ran adjacent to the locally progressed tumor and was suspected being a tumor drainage vein (Figs 1,5). In two other tumors without tumor stains on arteriogram at disclosure of portal blood supply, partial arterial supply was demonstrated on follow-up arteriogram obtained after 33 and 44 months, respectively. Large vessels (probably

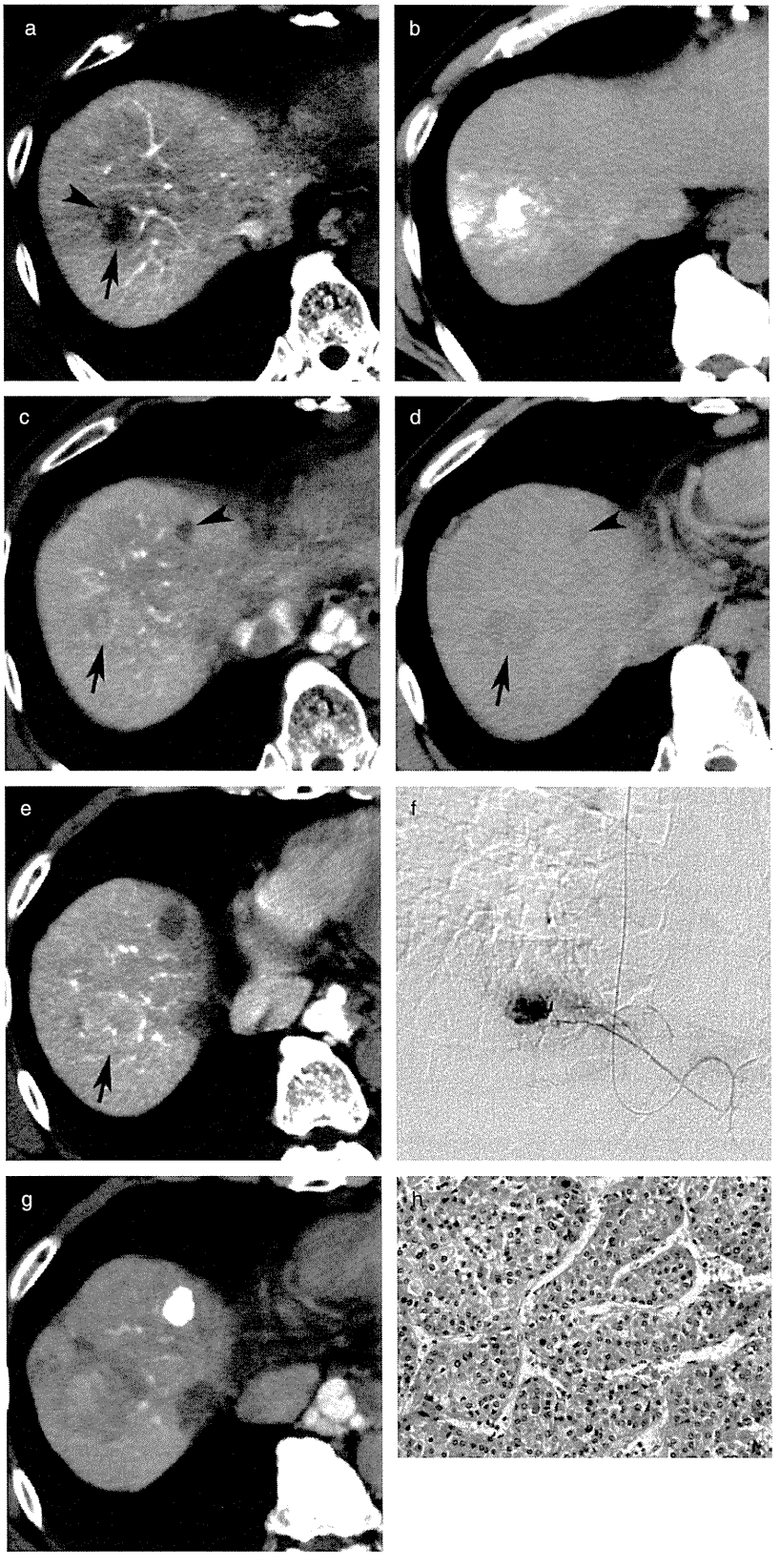

Figure 3 Images in a 61-year-old man with a tumor fed by portal blood. (a) CTAP shows a tumor with portal perfusion defect in segment 8 of the liver (arrow). A small tumor portion with preserved portal blood is also seen at the periphery of the tumor (arrowhead). TACE was performed at the anterior segmental artery of the right hepatic artery (not shown). (b) CT obtained 1 week after TACE shows dense iodized oil accumulation in almost all tumor portions with portal perfusion defect. However, the tumor progressed 7 months later (not shown). (c) On CTAP obtained 10 months after TACE, the tumor is enlarged and shows isoattenuation and hyperattenuation (arrow). Another tumor has also developed at another site (arrowhead). (d) CT obtained 30 seconds after CTAP shows that both tumors are demonstrated as hypoattenuating. (e) CTAP obtained 15 months after TACE shows that both tumors are enlarged. (f) On arteriography, the recurrent tumor does not show any tumor stains (not shown). The newly developed tumor is supplied by the phrenic branch of the right internal mammary artery. TACE was performed through the branch. (g) CTAP obtained 23 months after TACE shows that the tumor is enlarged and the embolized tumor is well controlled. (h) The patient died of tumor progression including cervical and mediastinal lymph node metastases 31 month after triggered TACE. The majority of the autopsy specimen of the tumor supplied by portal blood is diagnosed as moderately-differentiated HCC (hematoxylin and eosin staining, × 200).

portal veins) were demonstrated within the tumor via the arterial side in both tumors and iodized oil flowed into these vessels during the additional TACE procedure (Fig. 5).

Nine patients died 5–26 months (mean, 31.4 ± 16.2 months) after triggered TACE. Eight of these patients died of tumor progression, including three with distant metastases [lung ($n = 1$), brain ($n = 1$), neck and mediastinal lymph nodes ($n = 1$)]. The remaining patient died of hepatic failure despite good tumor control by RF ablation. One patient has survived 53 months after triggered TACE with multiple viable tumors fed by arterial blood and portal blood in the liver.

Histopathological findings

Autopsy was performed in two patients 10 and 31 months after triggered TACE, respectively. Three tumors supplied by portal blood were confirmed in addition to several tumors supplied by arterial blood. Histologically, all three tumors were diagnosed as moderately-differentiated HCC including a small component of well-differentiated HCC (Fig. 3). Two other tumors in other two patients were also diagnosed as moderately-differentiated HCC by needle biopsy (Fig. 4). However, the origin of the intratumoral vessels could not be determined even in autopsy cases.

DISCUSSION

HCC FREQUENTLY ARISES by multistep sequential development from a dysplastic nodule, a dysplastic nodule with malignant foci, a well-differentiated HCC nodule to definite classical HCC in cirrhotic liver.[7,8] During the multistep process of hepatocarcinogenesis, the source of vascular supply in a hepatic nodule switches from the portal vein to the hepatic artery. Intranodular portal blood flow tends to decrease as the grade of malignancy increases, and classic HCC is mainly supplied by arterial blood.[7–10] Early-stage HCC usually has well-differentiated tumor portions fed by portal blood,[8,9] and tumor cells of capsular invasion are also supplied by both arterial and portal blood even in classical HCC.[11]

Portal blood supply to HCC after TACE is thought to be one of the causes of tumor survival.[4–6] Ekelund *et al.* investigated the blood supply in rats with experimental liver tumors after arterial embolization with gelatin sponge powder or ethanol.[4] They found that portal blood supply to tumors clearly increased after arterial embolization. Using an immunohistochemical method, Goseki *et al.* reported the increase of residual tumor cells supplied by portal blood after TACE.[5] Choi *et al.* reported that the nourishing vessels of tumors treated by repeated TACE changed from the hepatic artery to the portal vein.[6] Sufficient therapeutic effects of combined arterial and portal embolization compared to those of conventional arterial side TACE as well as excellent local control effects in tumors with marked portal vein visualization by iodized oil during TACE may supports these hypotheses.[11–16] Clinically, however, portal blood supply to locally progressed HCCs has not received much attention.

When the tumor-feeding branch is occluded by TACE, a survived tumor may receive arterial blood from two other possible pathways; intact neighboring hepatic arterial branches and extrahepatic collaterals.[17,18] When the neighboring hepatic branches are occluded and extrahepatic arteries cannot reach the tumor because of tumor location or interruption of collaterals by previous TACE, the survived tumor may not be able to receive arterial blood. Under such circumstances, the pro-

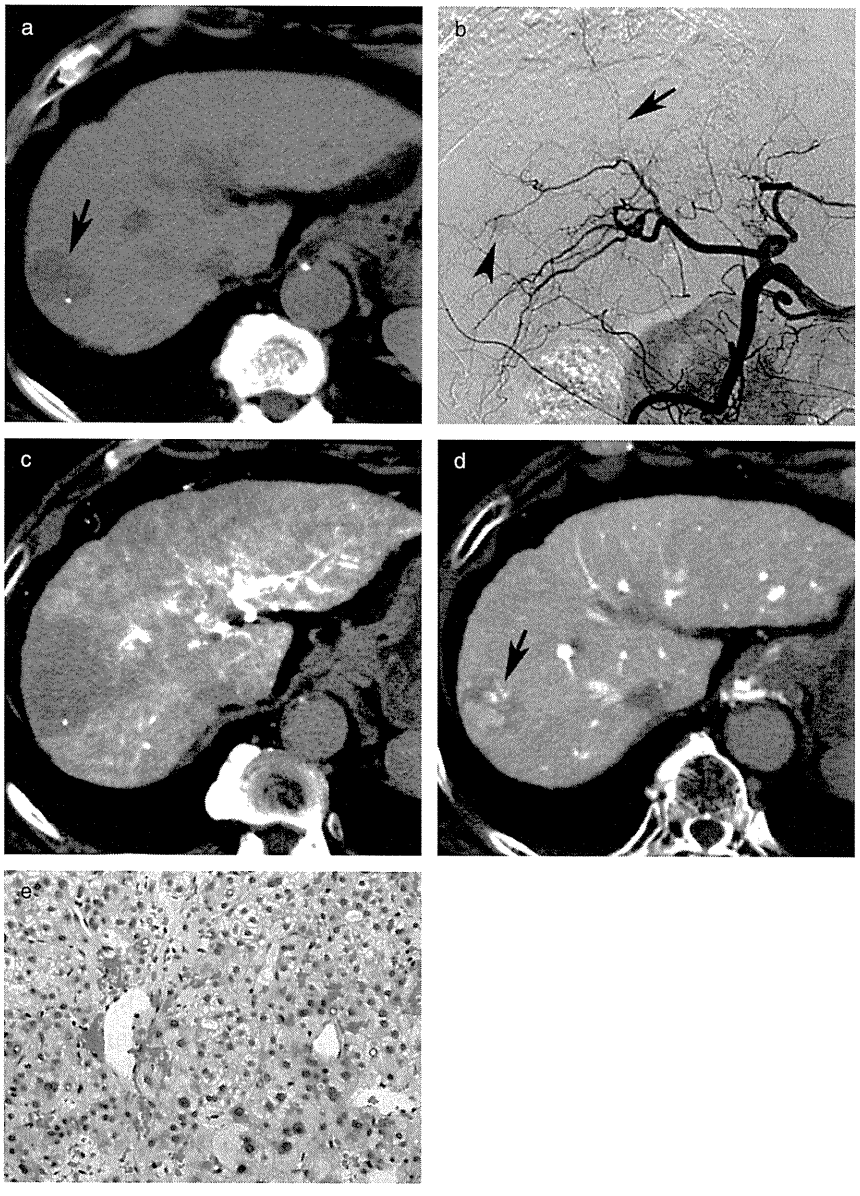

Figure 4 Images in a 75-year-old man with a tumor fed by portal blood. (a) Unenhanced CT obtained 13 months after TACE shows a hypoattenuating mass near the iodized oil accumulated tumor in segment 8 of the liver (arrow). (b) Celiac arteriogram shows that the anterior superior subsegmental artery of the liver is severely attenuated by the previous TACE procedure. There are no tumor stains corresponding to the recurrent tumor. A newly developed tumor is seen at another site (arrowhead), and TACE was subsequently performed for this tumor (not shown). (c) CTHA shows arterial perfusion defect including the tumor. (d) On CTAP, the tumor shows hyoattenuation and hyperattenuation (mosaic-like enhancement). The portal veins directly enter the tumor (arrow). (e) Diagnosis of moderately-differentiated HCC is established by needle biopsy specimen (hematoxylin and eosin staining, x 200). RF ablation was performed for this tumor.

gressed tumor may mainly be nourished by portal blood and the hemodynamics may become apparent on imaging.

The present study included two different types of tumors. According to CTAP and angiographic findings, 50% of tumors were supplied by arterial blood alone before TACE. In such tumors, tumor blood usually enters via the hepatic artery and drains into the portal venules connecting with tumor sinusoids near the tumor capsule.[9,19] Tochio *et al.* discovered patent portal

Table 2 Outcomes of each tumor

Patient no./Age (y)/Sex	Size of recurrent tumor (cm)	Duration between TACE and tumor recurrence (mo)	CTAP findings	Damage of embolized arteries	Angiographic findings	Histological findings	Additional treatment	Outcomes
1/69/F	1.6	5	Hypo and hyper	Occluded	Stain, partial	Mod	TACE + RFA	Dead, 47 mo (T)
2/61/M	2.8	10	Iso and hyper	Occluded	No stains	Mod > Well	Follow-up	Dead, 31 mo (T)
	2.6	9	Hypo and hyper	Occluded	Stain, partial	Mod > Well	TACE	
3/68/M	1.8	1	Hypo and hyper	Attenuated	Spain, partial	None	TACE	Dead, 14 mo (T)
	1.9	2	Iso and hyper	Occluded	No stains	None	Follow-up	
4/82/F	5.3	8	Hypo and hyper	Occluded	Stain, partial	None	TACE	Dead, 21 mo (T)
5/49/M	2.3	9	Hyper	Occluded	No stains	None	Follow-up†	Dead, 38 mo (T)
6/75/M	3.2	12	Hypo and hyper	Attenuated	No stains	Mod	RFA	Dead, 56 mo (H)
7/65/M	1.5	6	Iso and hyper	Occluded	No stains	None	Follow-up	Dead, 46 mo (T)
8/73/F	1.6	10	Iso and hyper	Occluded	No stains	None	Follow-up‡	Alive, 53 mo
9/81/M	2.1	4	Hypo and hyper	Attenuated	No stains	Mod	Follow-up	Dead, 10 mo (T)
10/65/F	2.8	5	Iso and hyper	Attenuated	No stains	None	Follow-up	Dead, 20 mo (T)

†Additional TACE was performed 44 months after disclosure of the portal blood supply to the recurrent tumor.
‡Additional TACE was performed 33 months after disclosure of the portal blood supply to the recurrent tumor.
CTAP, CT during arterial portography; (H), hepatic failure; Hyper, hyperattenuation; Hypo, hypoattenuation; Iso, isoattenuation; Mod, moderately differentiated; RFA, radiofrequency ablation; (T), tumor progression; TACE, transcatheter arterial chemoembolization; Well, well-differentiated.

branches at the periphery or septum of classical HCC nodules.[20] It is speculated that blood flow in such remnant portal veins within HCC changes to regurgitating draining flow as a result of markedly increased arterial flow induced by intranodular neovascularization. When the increased arterial flow is blocked by TACE, flow in the remnant portal veins may reverse directions. If the afferent arteries are completely occluded while tumor sinusoids persist due to incomplete TACE, these portal veins may switch to feeding vessels of the surviving HCC tissues. Entirely or partially incomplete iodized oil accumulation despite hypervascularity was found in four tumors (33%) in the present series, which might support this hypothesis. On the other hand, 50% of the tumors in this study initially showed a small tumor portion supplied by portal blood. In such tumors, the tumor tissues originally supplied by portal blood might also survive after TACE.[21] However, the combination of CTAP and angiography might not be sensitive to the detection of a small portion of tumor tissue supplied by portal blood at the periphery of the tumor. In the present study, two tumors supplied by portal blood developed adjacent to the tumor showing dense iodized oil accumulation. This suggested that both tumors initially had a small tumor portion supplied by portal blood. It might be occasionally difficult to demonstrate such a tumor tissue without CTHA study.

Ultraselective TACE has strong therapeutic effects on small HCC lesions,[14,15] even on some early-stage tumors with hypovascular tumor portions.[22] However, far advancement of a microcatheter carries the risks of incomplete TACE due to vascular spasm, air embolism, or vessel injury, in addition to missing small feeders.[14] Technical problems, such as complete occlusion of tumor-feeding artery and incomplete occlusion of tumor sinusoids, may exaggerate the portal blood supply to survived tumors. Occlusion or severe attenuation of the embolized arterial branches on follow-up angiograms might support this hypothesis. In two tumors, partial tumor stain was demonstrated again via the arterial side on follow-up arteriograms, obtained 33 and 44 months later, respectively. In both tumors, arteriogram showed large vessels, probably portal veins, in the tumor. We speculate that some tumors supplied by portal blood may eventually be partially supplied by arterial blood when the hepatic or extrahepatic arteries are sufficiently restored to feed a progressed tumor. In addition, the large vessels demonstrated on arteriograms may correspond to intratumoral vessels on CTAP, and these may be demonstrated through arterioportal

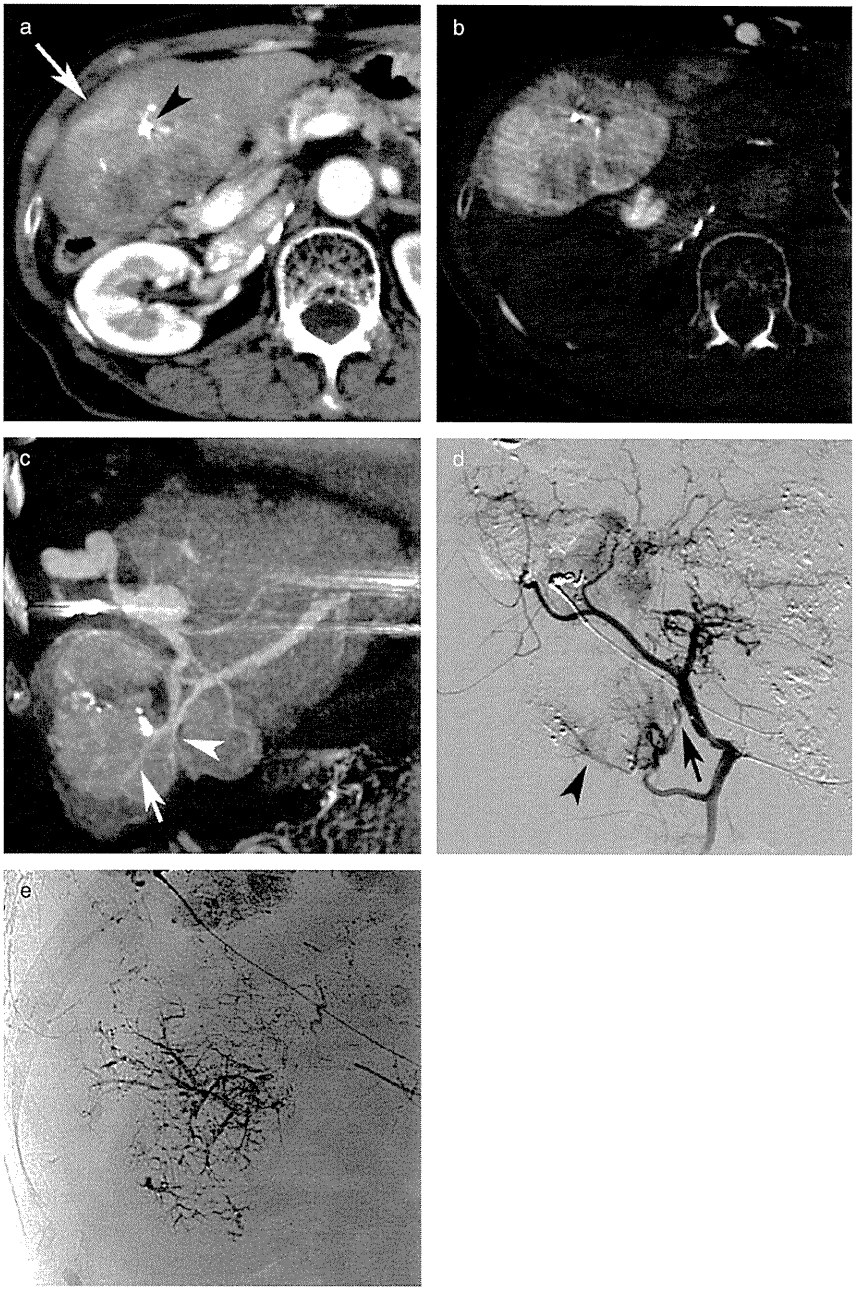

Figure 5 Images in a 73-year-old woman with a tumor fed by portal blood. (a) Arterial phase CT obtained 44 months after triggered TACE shows a large tumor in the left lobe of the liver. Iodized oil in the tumor is also seen (arrow). (b) CTAP obtained 44 months after triggered TACE using cone-beam CT technique shows that the tumor is mainly supplied by portal blood. (c) On maximum intensity projection image of oblique coronal view of CTAP using cone-beam CT technique, a large portal vein is observed directly entering the tumor (arrow). The branch of the left hepatic vein also runs adjacent to the tumor (arrowhead). Artifacts from metallic coils are also seen. (d) Left hepatic arteriogram shows a partial tumor stain supplied by a branch directly arising from the proximal portion. The large vessel (probably the portal vein) is seen in the tumor (arrow). The lateral segmental artery of the left hepatic artery is severely attenuated by previous TACE sessions. (e) During TACE, large vessels are demonstrated in the tumor via the arterial side. To date, the tumor has gradually enlarged despite additional TACE (not shown).

connections via the arterial side, that was confirmed by experimental hepatic metastatic nodules.[23]

In approximately 92% of our tumors, CTAP clearly demonstrated large-diameter portal veins directly entering into the tumor, these were suspected of being remnant portal veins. Although dilated intratumoral vessels were also seen in 75% of tumors, it was uncertain whether these intratumoral vessels were dilated original tumor sinusoids or remnant portal veins, even on autopsy specimens. There is another question of where tumor blood entering via the portal vein drains. In two tumors, it was suggested that the hepatic veins provided as tumor drainage. We speculate that the drainage vessels may also change from peritumoral portal veins to peritumoral hepatic veins when the nourishing vessels switch from the arteries to portal veins, although intratumoral hepatic veins are usually occluded early during hepatocarcinogenesis.[24] Intact intratumoral or peritumoral hepatic veins may be necessary so that the tumor would maintain the portal blood supply. Thus, we speculate that the survived tumor can progress while continuously receiving portal blood when the afferent artery is completely interrupted at the early step of carcinogenesis.

Kudo and Hirano *et al.* reported an atypical large well-differentiated HCC mainly supplied by portal blood.[25,26] There are several differences between the tumors in their series and these in ours. First, the entire or the major areas of our tumors were fed by arterial blood before TACE. Second, most our tumors showed inhomogenous enhancement by portal blood, whereas atypical large well-differentiated HCCs usually show almost uniform enhancement on CTAP.[25,26] Finally, all our tumors were histologically proven to be moderately-differentiated HCC.

There are several limitations in the present study. First, histological confirmation of HCC was not obtained in any tumors before TACE. However, we consider that advances in imaging modalities can facilitate establishment of the diagnosis of HCC without biopsy. Second, histopathologic confirmation of HCC was only obtained in 42% of locally progressed tumors supplied by portal blood. However, elevation of serum tumor marker levels and tumor progression during the follow-up period might establish the diagnosis of locally progressed HCC. Third, CTHA was not performed in any patient before TACE. This might be a significant limitation to detect a hypovascular tumor portion supplied by portal blood mainly located at the periphery of the tumor. Therefore, the actual incidence of tumor portions being supplied by portal blood might have been underestimated in our cases. Finally, locally progressed tumors that were obviously fed by portal blood were selected in the present study. Faint portal blood supply at the periphery of a survived tumor may not be rare but cannot be detected even by a combination of CTAP and CTHA.

In conclusion, portal blood supply to HCC lesions after TACE may cause local tumor progression. CTAP can clearly depict relatively large-diameter portal veins entering the tumor and connecting with intranodular vessels. Incomplete TACE and/or the presence of tumor tissues initially supplied by portal blood are thought to be the main causes of the portal blood supply to locally progressed HCC. For such tumors, TACE may have limited therapeutic effects and RF ablation may be effective. Interventional radiologists and physicians should become well aware of such unusual tumors.

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Jpn J Radiol (2011) 29:286–290
DOI 10.1007/s11604-010-0540-z

TECHNICAL NOTE

Microcoil embolization during abdominal vascular interventions through microcatheters with a tip of 2 French or less

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Received: September 5, 2010 / Accepted: November 1, 2010

Abstract
Purpose. The aim of this study was to evaluate the technical aspects of embolization using microcoils through a microcatheter with a tip of 2F or smaller during abdominal vascular interventions.
Materials and methods. Coil embolization through a microcatheter with a tip of 2F or smaller was attempted in 73 procedures. Two types of microcoil—Liquid Coil (Boston Scientific, Watertown, MA, USA) and Tornado Coil (Cook, Bloomington, IN, USA)—were deployed through four types of thinner microcatheter [2F tip (n = 49) and 1.8F tip (n = 24)]. Coil jams in the microcatheter and coil migration were evaluated.
Results. In total, 286 microcoils were placed (mean ± SD, 3.9 ± 4.3 coils per procedure, range 1–32 coils). In 19 procedures (26.9%), Liquid Coils were used alone. In 44 (60.3%), Tornado Coils were used alone. In 10 (13.7%), Liquid Coils and Tornado Coils were combined. There were no coil jams in the microcatheter in this series. One Tornado Coil (0.3%) delivered into the gastroduodenal artery migrated to the right hepatic artery.
Conclusion. Liquid Coils and Tornado Coils can be placed through a thinner microcatheter without difficulty. However, there is a risk of coil migration in large vessels or at the proximal site because the catheter tip is not stabilized.

Key words Microcoil · Embolotherapy · Thinner microcatheter

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Introduction

Coil embolization is frequently necessary during abdominal vascular interventions, such as for hemostasis of peritoneal or gastrointestinal bleeding[1] and prevention of nontarget embolization accompanied by transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC).[2] With advances in microcatheter technologies, superselective catheterization even into small branches has become possible.[3] A thinner microcatheter can only be accessed when the target vessel is small and tortuous; therefore, coil deployment through a thinner microcatheter is required in some circumstances. However, coil deployment through a microcatheter with a tip of 2F or smaller cannot be ensured because of the narrow inner lumen. In addition, there is a risk of misplacement of the microcoil due to sagging of the catheter tip because the tip of a thinner microcatheter is highly flexible.

We attempted coil embolization during abdominal vascular interventions using microcatheters with a tip of 2F or smaller. We describe our experience here.

Materials and methods

We performed a retrospective study to analyze the technical aspects of microcoil embolization through a thinner

microcatheter during abdominal vascular interventional procedures. Institutional review board approval is not required for this type of study at our institution. Written informed consent was obtained from each patient before the interventional procedure.

Between January 2003 and May 2010, coil embolization through a microcatheter with a tip of 2F or less was attempted in 73 abdominal vascular interventional procedures in 61 patients. We attempted microcoil embolization through thinner microcatheters in two types of case: (1) cases in which TACE for HCC was simultaneously attempted ($n = 49$); and (2) cases in which catheterization into the target branch seemed difficult because it was small and tortuous ($n = 12$).

There were 35 men and 26 women with a mean ± SD age of 68.4 ± 10.2 years (range 33–84 years). In all, 12 procedures were performed for hemostasis of gastrointestinal bleeding ($n = 10$) or intraperitoneal bleeding ($n = 2$), and gastric or colonic branches were mainly embolized. A total of 41 procedures were attempted to occlude small branches that did not supply the liver, such as the falciform artery or gastric branches, during TACE for HCC to prevent nontarget embolization. Another 20 procedures were attempted to occlude arterioportal shunts of the liver. Among them, 19 procedures were performed before TACE for HCC to prevent massive inflow of embolic materials into the portal veins through preexisting arterioportal shunts. The remaining procedure was performed to occlude a high-flow arterioportal shunt that developed after percutaneous transhepatic obliteration of rectal varices. Hepatic arterial branches were embolized by microcoils during the procedures.

Four types of microcatheter with a tip of 2F or less were used. Among 73 procedures, Progreat α (Terumo, Tokyo, Japan) with a 2F tip was used in 48 procedures, Carnelian Pixie (Tokai Medical Products, Kasugai, Japan) with a 1.8F tip was used in 19, Carry Win (UTM, Nagoya, Japan) with a 1.8F tip was used in 5, and Masters Parkway (Asahi Intecc, Seto, Japan) with a 2F tip was used in 1.

Two types of microcoil were used: Berenstein Liquid Coils (Boston Scientific, Watertown, MA, USA) and Tornado Embolization Microcoils (Cook, Bloomington, IN, USA). The Liquid Coils were delivered by saline infusion using a 2.5-ml syringe. The Tornado Coils were delivered by a pusher wire. A 0.016-inch guidewire (GT-wire; Terumo) was used as the pusher wire in all but six procedures. In the remaining six procedures, a 0.017-inch pusher wire (C-Stopper; Piolax, Kanagawa, Japan) was used. Coil type and size were determined according to the configuration of the target branch and its arterial flow. The Liquid Coils were mainly used for tortuous branches. With the Tornado Coils, the coils were slightly larger than the diameter of the target branch, in particular when the blood flow of the target branch was fast. Coil jams in the microcatheter and coil migration were evaluated.

Results

In all, 88 arterial branches were embolized during 73 procedures (Table 1). A total of 286 microcoils (79 Liquid Coils and 207 Tornado Coils; mean 3.9 ± 4.3 coils per procedure, range 1–32 coils) were delivered through thinner microcatheters. In 19 procedures (26.9%), 1–8 (mean 2.5 ± 1.5) Liquid Coils were used alone. In 44 procedures (60.3%), 1–32 (mean 4.2 ± 1.5) Tornado Coils were used alone. In 10 procedures (13.7%), 1–8 (mean 3.1 ± 2.3) Liquid Coils and 1–6 (mean 2.4 ± 1.8) Tornado Coils were combined. The 5–20 cm long Liquid Coils were deployed through a thinner microcatheter. For Tornado Coils, 2 × 3 mm to 2 × 5 mm diameter coils were used.

There were no coil jams in the microcatheter during any procedure in this series. All but one of the target branches were successfully embolized by microcoils through thinner microcatheters (Fig. 1). Of 286 microcoils, one 2 × 3 mm diameter Tornado Coil (0.3%) delivered into the gastroduodenal artery through the Masters Parkway catheter migrated to the right hepatic artery during coil deployment. In this case, microcoil embolization of the gastroduodenal artery had already been performed in another hospital to stop bleeding from pancreatic carcinoma (one microcoil had already

Table 1. Embolized arterial branches

Embolized branch	No.
Hepatic artery (distal to the subsubsegmental artery)	21
Left gastric artery	11
Falciform artery	8
Right gastric artery	7
Accessory left gastric artery	7
Right inferior phrenic artery	7
Right colic artery	6
Gastroduodenal artery	4
Posterosuperior pancreaticoduodenal artery	3
Ileal artery	3
Anterosuperior pancreaticoduodenal artery	2
Omental artery	2
Posterior intercostal artery	2
Cystic artery	1
Dorsal pancreatic artery	1
Left internal mammary artery	1
Transverse pancreatic artery	1
Right renal artery (arcuate artery)	1
Total	88