Iodized oil accumulation in the hypovascular tumor portion of early-stage hepatocellular carcinoma after ultraselective transcatheter arterial chemoembolization

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Abstract

Purpose We evaluated iodized oil accumulation in the hypovascular portion of early-stage hepatocellular carcinoma (HCC) after ultraselective transcatheter arterial embolization (TACE).

Materials and methods Forty-seven HCC lesions with hypovascular portions were treated by TACE at the distal level of the sub-subsegmental artery of the liver. Portal blood in the hypovascular portion was classed in two grades by computed tomography (CT) during arterial portography: decreased and preserved. Iodized oil accumulation was classed into three grades on CT obtained 1 week after TACE: (1) dense accumulation in the almost entire tumor, including the hypovascular portion (grade 2); (2) dense accumulation in hypervascular portions but sparse accumulation in hypovascular portion (grade 1); and (3) sparse accumulation or no accumulation (grade 0). Findings on serial follow-up CT images were also analyzed.

Results Portal blood in the hypovascular portion was decreased in 32 lesions, and preserved in 15 lesions. On CT 1 week after TACE, 32 tumors (68.1%)—23 with decreased portal blood and 9 with preserved portal blood—were classed as grade 2. Twelve tumors (25.5%), six with decreased portal blood and six with preserved portal blood,

were classed as grade 1. Three tumors (6.4%) with decreased portal blood were classed into grade 0. In total, 25 tumors (53.2%), 22 in grade 2 and 3 in grade 1, were well controlled by ultraselective TACE during the mean follow-up of 15.8 months.

Conclusions Iodized oil accumulation and retention in the hypovascular portion of early-stage HCC was frequently observed after ultraselective TACE, mainly in the hypovascular portion with decreased portal blood.

Keywords Hepatocellular carcinoma · Hypovascular tumor portion · Iodized oil accumulation · Transcatheter arterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) frequently arises by multistep sequential development from a dysplastic nodule, a dysplastic nodule with malignant foci, a well-differentiated HCC nodule to definite classic HCC in the cirrhotic livers [1–6]. 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 [2–6].

Early-stage HCC, including a dysplastic nodule with malignant foci and well-differentiated HCC, is generally supplied by both arterial and portal blood [2–7]. In a few reports about the efficacy of TACE for dysplastic nodule and early-stage HCC, TACE is only effective for hypervascular malignant foci that are supplied by arterial blood [7, 8]. We have introduced a 2-F tip microcatheter into ultraselective catheterization of the tumor-feeding artery at

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the most distal level of the sub-subsegmental artery of the liver [9]. We have frequently observed dense iodized oil accumulation not only in the hypervascular portions but also hypovascular portions of early-stage HCC on computed tomography (CT) obtained after ultraselective TACE.

In this report, we describe the outcomes of ultraselective TACE for early-stage HCC with hypovascular tumor portions, focusing on the relationship between iodized oil accumulation and the degree of portal blood flow.

Materials and methods

We retrospectively analyzed iodized oil accumulation and retention after ultraselective TACE in early-stage HCC lesions with hypervascular foci and obvious hypovascular tumor portions comprising more than 50% of the area on the maximal axial tumor section on dynamic CT. Institutional review board approval is not required at our institution for this type of study. Written informed consent was obtained from each patient before the TACE procedure. The hypovascular tumor portion was defined, as an area within the tumor that did not show early enhancement on dynamic CT. Ultraselective TACE was defined as TACE performed at the most distal level of the sub-subsegmental artery of the liver.

All CT images were obtained using a multidetector-row helical CT scanner (Aquilion-4, Aquilion-16, or Aquilion-64; Toshiba, Tokyo, Japan) with a 3-mm collimation, 5-mm-thick sections, and 5-mm reconstruction intervals. First, unenhanced scanning was performed during a single breath-hold. Two arterial phase images with a 6-s interval were obtained 35 s after intravenous (IV) administration of 100 ml of iohexol (Omnipaque 300; Daiichi, Tokyo, Japan) at a rate of 3 ml/s during a single breath-hold. Finally, equilibrium-phase images were obtained 120 s after injection of contrast material during a single breath-hold. Magnetic resonance (MR) images and/or CT during hepatic arteriography (CTHA) were also performed in several lesions to confirm the presence of the hypovascular tumor area. CTHA images with a 2-mm collimation, 3-mm-thick sections, and 3-mm reconstruction intervals were obtained 7 s after injection of 30 ml of diluted contrast material (15 ml of iopamidol [Iopamiron 370; Schering, Osaka, Japan], or iomeprol [Iomeron 350; Ezai, Tokyo, Japan] in 15 ml of saline) at a rate of 2 ml/s through the 4-F catheter advanced into the common or right hepatic artery.

We excluded an entirely hypovascular lesion and a tumor with necrosis that did not show any enhancement on dynamic CT, MR images, or CTHA. In addition, we also excluded a lesion that showed early enhancement or tumor

stain in an area comprising more than 50% of tumor area on MR images, CTHA or angiography, although dynamic CT showed early staining in the area comprising less than 50% of tumor.

Patients

Between January 2003 and December 2006, 47 early-HCC lesions with hypovascular portion in 33 patients (21 men and 12 women, mean age $68.3 \text{ years} \pm 8.7$, range 53–84 years) met the aforementioned criteria. The mean tumor diameter was $2.0 \text{ cm} \pm 0.8$ (range 0.9–4 cm). The diagnosis of early-stage HCC was made by imaging findings. The hypovascular tumor portion was also confirmed by MR images ($n = 16$) and CTHA ($n = 22$) in addition to dynamic CT. Eight patients had two tumors and three had three tumors. In addition, 6 patients simultaneously had 1 or 2 overt HCCs besides the early-stage HCC nodule. All patients had chronic hepatitis or liver cirrhosis. Twenty-three patients had hepatitis C virus, 4 patients had hepatitis B virus, and 1 patient had both hepatitis B and C viruses. One patient had a history of alcohol abuse. The etiology of liver cirrhosis was unknown in 4 patients. Fifteen patients had previously undergone TACE for other overt HCCs. Serum levels of α -fetoprotein were more than 20 ng/ml ($\mu\text{g/l}$) in 14 patients. Serum levels of protein induced in vitamin K absence II (PIVKA-II) were more than 40 mAU/ml ($\mu\text{g/l}$) in 12 patients. In 12 patients (36.3%), serum levels of both tumor markers were normal. None of the tumors were candidates for radiofrequency (RF) ablation because of the difficulty in detecting the tumor on sonography, presence of ascites, tumor location near vulnerable strictures, or patient refusal to undergo RF ablation.

Portal blood in the hypovascular tumor portion

The portal blood in the hypovascular portion was evaluated by CT during arterial portography (CTAP) before TACE. All CTAP images were obtained 35 s after injection of 70 ml of diluted contrast material (iopamidol or iomeprol; 35 ml of contrast material in 35 ml of saline) at a rate of 3 ml/s through a 4-F catheter placed in the superior mesenteric artery with a 2-mm collimation, 3-mm-thick sections, and 3-mm reconstruction intervals during a single breath hold. Before injection of contrast material, 2.5 μg of prostaglandin E1 (Lipile; Mitsubishi Pharma Corporation, Osaka, Japan) was administered through the catheter in all patients. Portal blood in the hypovascular portion was classed in two grades by CTAP findings: decreased (less attenuating than the surrounding liver parenchyma); preserved (isoattenuating to the surrounding liver

parenchyma or more attenuating than the surrounding liver parenchyma). When the different attenuated areas were mixed in a single tumor, the tumor was classed according to the dominant attenuating area.

TACE procedure

A 2-F tip microcatheter (Progreat α ; Terumo, Tokyo, Japan) was inserted into the most distal portion of the tumor-feeding sub-subsegmental artery through a 4-F catheter placed in the celiac artery, superior mesenteric artery, or common hepatic artery. To navigate the microcatheter, a 0.016-inch guide wire (GT-wire; Terumo) was routinely used in all patients. When selection of the feeding branch by the 0.016-inch guide wire was difficult, a 0.012-inch guide wire (GT-wire; Terumo) was also used. When the tumor stain was unclear, the microcatheter was inserted into the arterial branch corresponding to the portal branch running near the tumor on CTAP. The tumor-feeding branch was also identified by CTHA images when these images were obtained.

After the microcatheter was inserted into the target branch, 0.5 ml of 2% lidocaine (Xylocaine; Fujisawa, Osaka, Japan) was intra-arterially injected to prevent pain and vasospasm. First, a mixture of 0.5–5 ml of iodized oil (Lipiodol; Andre Guerbet, Aulnay-sous-Bois, France), 10–30 mg of epirubicin (Farmorbicin; Kyowa Hakko, Tokyo, Japan), and 2–6 mg of mitomycin C (Mitomycin; Kyowa Hakko) was slowly injected through the catheter. Injection of the mixture of iodized oil and anticancer drugs was stopped when the tumor-feeding branch was near stasis or when the portal vein extending to the embolized area appeared. Gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, MI) that had been cut into small cubes, and crushed into approximately 0.2-mm particles by pumping 50 times using a 3-way stopcock valve and two 2.5 ml syringes, were injected until the tumor-feeding branch was completely blocked. If the tumor has multiple feeders, these additional vessels were sequentially embolized in the same fashion. In patients with multiple tumors (less than three tumors), each tumor was treated by a separate ultra-selective TACE during a single TACE session. The TACE procedure was ended when the tumor-feeding branch was completely blocked on angiography.

Definition of iodized oil accumulation in the hypovascular tumor portion

Unenhanced CT with a 3-mm collimation, 5-mm-thick sections, and 5-mm reconstruction intervals was obtained 1 week after TACE to check iodized oil accumulation in

the tumor. Iodized oil accumulation was classified into three grades: (1) iodized oil had accumulated in almost the entire tumor including the hypovascular portion (grade 2); (2) iodized oil was densely accumulated in the hypervascular portion but sparsely accumulated in the hypovascular portion (grade 1); (3) iodized oil was sparsely accumulated in the hypervascular portion or had not accumulated in the tumor at all (grade 0).

Follow-up

All patients were followed by dynamic CT every 2–3 months after TACE procedures. The tumor size and retention of iodized oil within the tumor was evaluated. Development of hypovascular or hypervascular portions within or near the tumor was also evaluated.

A statistical comparison of local control rates in two different types of intratumoral portal blood dynamics was performed with the χ^2 test. *P* values of <0.05 were considered indicative of a statistically significant difference. Statistical calculations were performed by using software (StatView version 5.0; SAS, Cary, NC).

Results

On CTAP, portal blood flow of the hypovascular tumor portion was decreased in 32 lesions (Fig. 1) and preserved in 15 lesions (Figs. 2 and 3) (Table 1). One arterial branch was embolized in 38 tumors, two branches were embolized in eight tumors, and three branches were embolized in one tumor.

Grades of iodized oil accumulation in the hypovascular tumor portion (grade 1)

On the basis of the CT findings obtained 1 week after TACE, 32 tumors (68.1%)—23 with decreased portal blood and nine with preserved portal blood in the hypovascular portion—were classed as grade 2 (Figs. 1–3). Twelve tumors (25.5%), six with decreased portal blood and six with preserved portal blood in the hypovascular portion, were classed as grade 1. Three tumors (6.4%) with decreased portal blood in the hypovascular portion were classed as grade 0.

Outcomes of early-stage HCC after ultraselective TACE

In 22 of 32 tumors showing grade 2, 18 with decreased portal blood and four with preserved portal blood in the

Fig. 1 Images in a 74-year-old man with early-stage HCC 2.2 cm in diameter showing a hypovascular tumor portion. **(a)** Arterial phase CT image shows a ring-like enhanced tumor (arrow) (area of 24% of the tumor). **(b)** CTHA image also shows a ring-like enhancement. **(c)** CTAP image shows that portal blood is decreased in the entire hypovascular tumor portion. **(d)** Arteriogram of the common hepatic artery does not show any tumor stains. **(e)** Arteriogram of the branch of the anterior superior subsegmental artery does not show any tumor stains either. TACE was performed through the vessel. **(f)** Unenhanced CT obtained 1 week after TACE shows dense iodized oil accumulation in area of 85% of the tumor. **(g)** Unenhanced CT obtained 4 months after TACE shows that the size of the tumor has decreased with dense iodized oil accumulation

Fig. 2 Images in a 72-year-old woman with early-stage HCC 3 cm in diameter showing a hypovascular tumor portion with preserved portal blood flow. **(a)** Arterial phase CT image shows a hypervascular focus (area of 19% of the tumor) (arrow) enclosed in the hypovascular portion (arrowheads). **(b)** CTAP image shows a hypoattenuating area corresponding to hypervascular focus (area of 43% of the tumor) (arrow). The portal blood in the surrounding hypovascular tumor portion (arrowheads) is preserved. **(c)** Arteriogram of the right hepatic artery shows a small tumor stain (arrow). **(d)** The feeding branch was selected and TACE was performed. Portal veins diffusely appeared in the embolized area during the TACE procedure. **(e)** Iodized oil is densely accumulated in almost the entire tumor (area of 89% of the tumor) on unenhanced CT obtained 1 week after TACE. **(f)** Enhanced CT obtained 3 months after TACE shows that the size of the tumor has decreased with dense iodized oil accumulation

hypovascular portion, iodized oil was densely retained in the tumor and tumor size was reduced during $15.8 \text{ months} \pm 11.8$ (range 2–40 months) after TACE (Figs. 1–3) (Table 2). In the remaining 10 tumors, five with decreased portal blood and five with preserved portal blood in the hypovascular portion, hypervascular tumor portions were developed adjacent to the tumor portion that densely

retained iodized oil in nine (Fig. 3), and defect of iodized oil in the tumor developed in one over $11.8 \text{ months} \pm 10.6$ (range 3–37 months) after TACE.

Three of 12 tumors in grade 1, one with decreased portal blood and two with preserved portal blood, showed a reduction in size, including the hypovascular portions, over $6.7 \text{ months} \pm 1.5$ (range 5–8 months) after TACE.

Fig. 3 Images in a 74-year-old woman with early-stage HCC 1.8 cm in diameter showing a hypovascular tumor portion with increased portal flow. **(a)** Arterial phase CT image shows a hypervascular focus enclosed in the hypovascular portion (arrow). **(b)** CTHA image also shows small hypervascular foci (area of 42% of the tumor) in the hypovascular tumor portion. **(c)** CTAP image shows a central hyperattenuating area (area of 55% of the tumor) and ring-like hypoattenuation (area of 45% of the tumor) corresponding to the central hypovascular portion. **(d)** Arteriogram of the right hepatic artery shows a small tumor stain (arrow). **(e)** Spot radiograph obtained during TACE through the branch of the superior anterior subsegmental artery shows dense iodized oil accumulation in the tumor larger than the tumor stain on angiography. **(f)** Unenhanced CT image obtained 1 week after TACE shows dense iodized oil accumulation, including the hypovascular portion (area of 88% of the tumor). **(g)** Arterial phase CT image obtained 11 months after TACE shows that the tumor size is decreased, but there is early enhancement at the dorsal portion of the tumor (arrow). **(h)** Arteriogram of the right hepatic artery shows that the previously embolized branch is occluded, but tumor is supplied by the posterior superior subsegmental artery (arrow). The feeding artery was selected and additional TACE was performed

Table 1 Relationship between portal blood and iodized oil accumulation in the hypovascular tumor portion

	Decreased PV	Preserved PV	Total
Grade 2	23	9	32
Grade 1	6	6	12
Grade 0	3	0	3
Total	32	15	47

PV, portal vein flow

Table 2 Relationship between portal blood, grades of iodized oil accumulation in the hypovascular portion and tumor progression

	Controlled		Progressed		Total
	Decreased PV (Duration)	Preserved PV	Decreased PV (Duration)	Preserved PV	
Grade 2	18 (15.8 m $\pm$ 11.8)	4	5 (11.8 m $\pm$ 10.6)	5	32
Grade 1	1 (6.7 m $\pm$ 1.5)	2	5 (9.8 m $\pm$ 7.1)	4	12
Grade 0	0	0	3 (10.7 m $\pm$ 5.9)	0	3
Total	19	6	13	9	47

PV, portal vein flow

In nine of 12 tumors in grade 1, five with decreased portal blood and four with preserved portal blood in the hypovascular portion, iodized oil was washed out in two, the hypovascular portion was enlarged in two, and a hypervascular portion developed within or near the tumor in five over 9.8 months $\pm$ 7.1 (range 2–24 months) after TACE.

All three tumors in grade 0, with decreased portal blood in the hypovascular portion, were enlarged and hypervascular portions developed 10.7 months $\pm$ 5.9 (range 4–15 months) after TACE.

In total, 25 tumors (53.2%), 22 in grade 2 and three in grade 1, were considered well-controlled by ultraselective TACE during the mean follow-up of 15.8 months. Concerning the degree of portal blood in the hypovascular portion, 59.4% of tumors with decreased portal blood were considered well controlled, while only 40% of tumors with preserved portal blood showed the same outcomes. There was no statistically significant difference between local control rates of two different types of intratumoral portal blood dynamics ($P = 0.2146$).

Discussion

It is widely accepted that TACE is an effective therapy for inoperable HCC [9–12]. Moderately to poorly

differentiated HCC (classic HCC) is only supplied by arterial blood [2–6, 10]. For this reason, embolization of the hepatic artery can be theoretically expected to result in selective ischemic necrosis of the tumor tissue [10]. With advances in microcatheter guide wire technologies and TACE techniques, the therapeutic effects on classic HCC have been improved and the adverse effects on hepatic function reserve have been minimized [9, 11–13]. However, it is generally considered that the therapeutic effect of TACE for early-stage HCC is limited because it receives both arterial and portal blood [7, 8].

Takayasu et al. [7] reported that the difference in response to TACE among lesions ranging from the dysplastic nodule to classic HCC seems to depend mainly on the development of tumor vessels; namely, whether the mass appears hypervascular or hypovascular on angiogram. The frequency of tumor staining on angiogram or retention of iodized oil within the tumor correlated with the necrosis rate. Ueda et al. [8] also reported that malignant lesions within the dysplastic nodule were necrotic, whereas non-malignant areas of dysplastic nodule remained viable after TACE.

Dense accumulation of iodized oil within almost the entire tumor, including the hypovascular tumor portion, was observed in 68.1% of our tumors treated by ultraselective TACE. This suggests that iodized oil injected at the distal level of the hepatic artery simply does not reach the tumor sinusoids according to the arterial tumor vascularity observed on dynamic CT, angiography, and CTHA. In ultraselective TACE, iodized oil can be injected forcefully through the thinner microcatheter inserted into the tiny feeding artery, and therefore, it may be more widely distributed through arterioarterial, arteriportal communications via the peribiliary vascular plexus [9, 14–16] and/or the drainage route from the hypervascular tumor portion [16]. On the other hand, excessive catheterization may cause the arterial flow to decrease as a result of catheter wedging or air embolism. In fact, iodized oil was not accumulated in three tumors with decreased portal blood in the present study. It should be noted that excessive advancement of the catheter may lead to incomplete TACE [9].

In the present study, hypovascular tumor portions included two different types of intratumoral portal blood dynamics: decreased portal blood and preserved portal blood. We speculate that the hypovascular tumor portion with decreased portal blood may be dominantly supplied by arterial blood, even when neither dynamic CT nor even CTHA can demonstrate obviously increased arterial vascularity compared to the surrounding liver parenchyma. Iodized oil may reach the tumor sinusoids via the artery, and injection with slight force at the distal arterial level may also increase inflow of iodized oil into the tumor

sinusoids. In classical HCC, Terayama et al. [16] reported that some of the injected iodized oil might flow into the adjacent liver parenchyma through the drainage route of HCC. We speculate that, even in early-stage HCC, iodized oil may distribute into the hypovascular tumor portion through the drainage route of the hypervascular foci. This mechanism may also contribute iodized oil accumulation in the hypovascular tumor portion with preserved portal blood. In addition, in the hypovascular portion with preserved portal blood, some of the injected iodized oil may reach the tumor sinusoids via the portal vein through the preexisting arteriportal communications due to liver cirrhosis [9, 15].

Long-term iodized oil retention in almost the entire tumor including the hypovascular tumor portion was frequently observed in the present study. This suggested that ultraselective TACE has stronger therapeutic effects on early-stage HCC than those previously reported [7, 8]. Concerning the degree of portal blood in the hypovascular portion, 59.4% of tumors with decreased portal blood showed dense iodized oil retention and reduction after ultraselective TACE, while only 40% of tumors with preserved portal blood showed the same outcomes. These suggested that the degree of portal blood in the hypovascular tumor portion mainly influenced the therapeutic effect of TACE for early-stage HCC, although there was no statistically significant difference between local control rates of the two types of intratumoral portal blood dynamics.

There are several limitations in the present study. First, all tumors were diagnosed based on imaging findings without being histologically proven. In our experience, however, the precise diagnosis of early-stage HCC with percutaneous needle biopsy is not always easy because of the existence of various types of hepatocytic component in these lesions. In addition, serum levels of tumor markers were not elevated in approximately 40% of tumors because of the small tumor size or early stage of HCC. Second, it is difficult to judge whether the hypovascular portion without iodized oil accumulation has been controlled by TACE because such an area generally shows slow growth. Third, it is frequently difficult to recognize the feeding branch of a tumor that does not show a stain on angiography. We determined the tumor-feeding branch by referencing CTAP and CHTA images. Finally, it is also difficult to confirm that the embolized area may include the entire nodule with a safety margin. A unified helical CT and angiography system or cone-beam CT technique using a flat-panel detector angiography system may be useful to perform successful TACE for early-stage HCC [13, 17].

Radiofrequency ablation can establish complete necrosis of an HCC lesion regardless vascularity; therefore, it is suitable for treatment of early-stage HCC. However, it is

sometimes contraindicated because of excessive tumor diameter, multicentric tumor development, difficult anatomical location, or uncorrectable coagulopathies [18, 19]. We consider that ultraselective TACE may also play an important part in the treatment of early-stage HCC, especially in cases contraindicated for RF ablation, although the indication and timing of treatment may be controversial.

In conclusion, ultraselective TACE frequently achieves dense iodized oil accumulation in early-stage HCC lesion with hypovascular tumor portions and reduction in size. Injection of embolic material at the far distal portion of the hepatic artery with slight force and drainage of the hypervascular tumor foci may somewhat contribute to dense iodized oil accumulation in the hypovascular tumor portion.

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