Applying Superselective Conventional TACE

Optimal settings and technical tips for this embolization option.

BY SHIRO MIYAYAMA, MD, AND OSAMU MATSUI, MD

Transarterial chemoembolization (TACE) is the most commonly performed therapy for inoperable hepatocellular carcinoma (HCC), and a complete response after the initial TACE or during the treatment course is the most robust predictor of a favorable outcome.[1] TACE loads hypoxic and chemotherapeutic stress on HCC, and surviving tumors frequently change to a sarcomatous appearance[2] or show a mixed hepatocholangiocellular phenotype[3] and are usually more aggressive and TACE resistant. Hypoxia induced by TACE also stimulates vascular endothelial growth factor production by the residual tumor cells, which may be a potential cause of recurrent disease.[4] Furthermore, some surviving tumors are fed by portal blood if the arterial branches, including extrahepatic collaterals, are severely damaged.[5] This suggests that uncontrollable tumors may develop as a result of TACE, and "curative TACE" is necessary to realize a good prognosis.

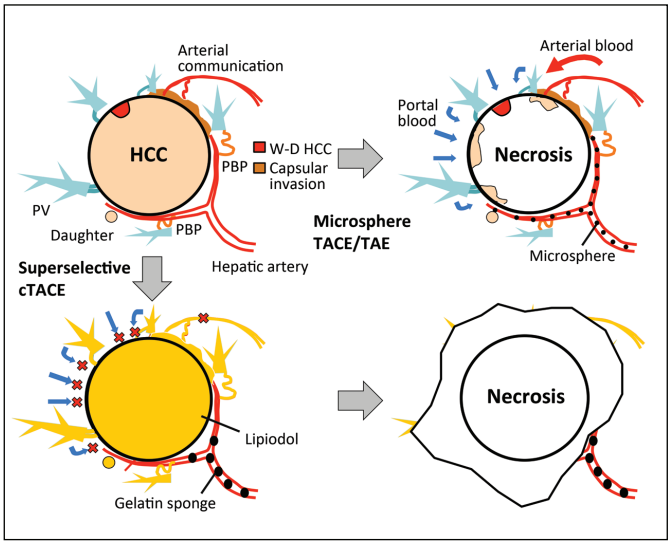

Figure 1. The rationale for microsphere TACE/transarterial embolization and superselective cTACE. PBP, peribiliary plexus; PV, portal vein; W-D HCC, well-differentiated hepatocellular carcinoma.

LIMITATIONS OF PARTICLE TACE

Moderately to poorly differentiated HCC is predominantly supplied by arterial blood. However, capsular and/or extracapsular tumor invasions and microsatellite lesions, as well as well-differentiated tumor portions in early stage HCC, are also supplied by the portal vein.[6] Additionally, portal blood flows into tumors and promotes tumor survival via the portal venules and surrounding hepatic sinusoids (drainage route from HCC) during TACE.[7] Some arterial blood may also reach the tumor through arterial communications. As a result, tumor tissues supplied by both arterial and portal blood as well as collateral flows, including portal blood, may survive at the periphery when the arterial side is simply embolized with a particulate embolus (Figure 1). When using drug-eluting beads for TACE, doxorubicin is slowly released and may kill some surviving tumor cells; however, it is unclear how the drug reaches these viable tumor portions.

SUPERSELECTIVE CONVENTIONAL TACE

Conventional TACE (cTACE) uses a mixture of Lipiodol (Guerbet LLC), chemotherapeutics, and gelatin sponge (GS) particles. Lipiodol is a semifluid embolic agent that enhances the ischemic effects of TACE. When Lipiodol is injected into the hepatic artery, it is first retained in the tumor sinusoids. If too much Lipiodol pools in the tumor sinusoids, some of it can flow into the portal veins through the peribiliary plexus and tumor drainage.[8,9] As a result, the flow of portal blood into the tumor can be temporarily blocked. By adding GS particles to block the artery, both the hepatic artery and portal vein can be embolized. In addition to inflow in the portal vein, some Lipiodol can also flow into the neigh-

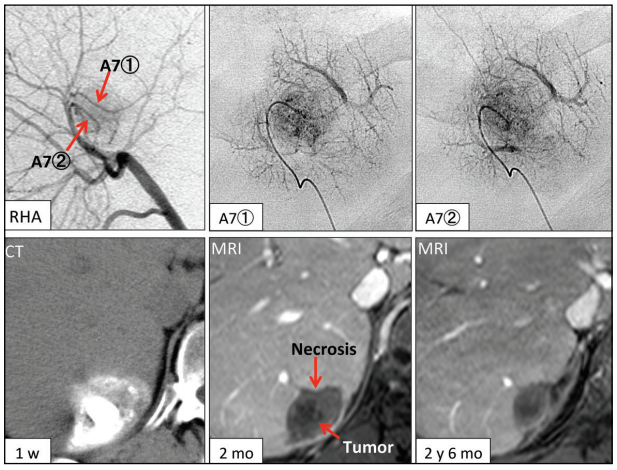

Figure 2. Ultraselective cTACE was performed for small a HCC via two branches of the A7. Portal veins were markedly opacified with Lipiodol, and complete tumor necrosis and peritumoral necrosis were achieved. The tumor has been well controlled for 2 years and 6 months. RHA, right hepatic artery. Upper left, right, and lower left figures reprinted with permission from Sangyo Kaihatsu Kiko: Miyayama S. TACE for hepatocellular carcinoma [in Japanese]. Eizojoho Med. 2014;46:719–726.

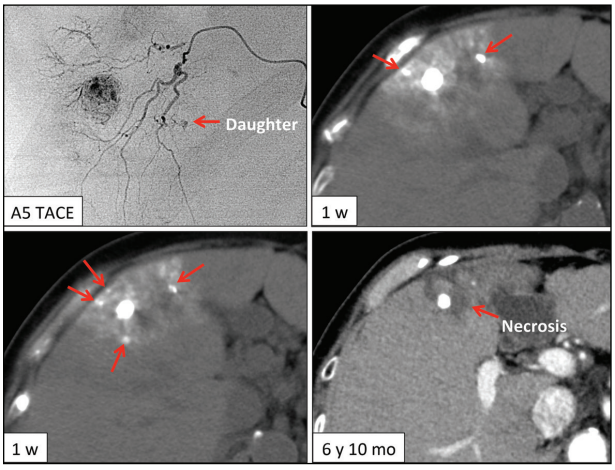

Figure 3. Dense Lipiodol accumulation in small metastatic lesions (arrows) was demonstrated around a small HCC after ultraselective cTACE. The tumors have remained well controlled for 6 years and 10 months.

boring hepatic arterial branches and sometimes into the extrahepatic collateral arteries,[10] possibly through the vascular network and isolated artery. This allows the embolization or identification of "an occult tumor feeder." As a result, cTACE causes complete tumor necrosis as well as peritumoral necrosis (Figures 1–3); however, nonselective cTACE may require a large amount of Lipiodol to achieve sufficient therapeutic effects, and this could severely damage the normal liver.

Selective catheterization is essential to reduce the total dose of Lipiodol and minimize liver toxicity associated with cTACE.[11] Selective cTACE is defined as cTACE at the segmental hepatic artery, whereas superselective cTACE is defined as cTACE at the subsegmental hepatic artery. cTACE at the most distal level of the subsubsegmental hepatic artery is termed *ultraselective cTACE*.[9] In ultraselective cTACE, embolic agents flow distally not only by physiologic blood flow but also by the injection force because the backflow of embolic agents can be blocked due to a catheter's mass effect (semi-wedged condition). This enables passive injection of the embolic agent, and thus, an increased dose of Lipiodol reaches the portal veins.[9,12]

HCC cells form intrahepatic satellite lesions, mainly in the drainage area of tumor blood (corona).[13,14] Therefore, the corona should be included in the treatment area because cancer cells first spread there before entering the systemic circulation. In most tumors, superselective cTACE can simultaneously treat micrometastases in the corona because the corona is usually included in the vascular territory of the tumor feeder (Figure 3).[8] However, in some cases, the corona is supplied by another arterial branch, and subsequent selective embolization of this branch is required.

INDICATIONS FOR SUPERSELECTIVE CONVENTIONAL TACE

cTACE techniques influence patient survival, and selective/superselective cTACE can achieve a significantly better prognosis compared with nonselective cTACE in patients with HCC ≤ 7 cm and five or fewer lesions.[15] TACE is recommended for patients with Barcelona Clinic Liver Cancer stage B (BCLC-B) HCC; however, this stage includes various tumor conditions, and there is no consensus regarding which specific types of tumors warrant treatment with superselective cTACE. Patients with BCLC-B HCC treated with cTACE had a better overall survival if they were classified as Child-Pugh class A, had tumors ≤ 7 cm, and had four lesions or fewer.[16] Additionally, cTACE may do more harm than good in HCC patients with a Child-Pugh score of 9,[17] which suggests that patients with Child-Pugh scores ≤ 8, tumors ≤ 7 cm, and five or fewer lesions are good candidates for superselective cTACE. Stepwise superselective cTACE is also indicated for localized tumors > 7 cm.[18] Ultraselective cTACE is an alternative treatment for selected patients with BCLC stage 0–A HCC because it can be used to passively inject embolic agents into a tiny tumor feeder.[19]

TIPS FOR EFFECTIVE ADMINISTRATION OF SUPERSELECTIVE cTACE

- Inject Lipiodol slowly to avoid oil cast formation in the arteries.
- When the flow of the tumor-feeding branch unexpectedly stops before the portal vein is adequately visualized, the Lipiodol injection is paused, and the following steps should be performed:
  - Administer 0.5 μg of prostaglandin E1 or 0.5 mL of 2% lidocaine through the catheter to increase arterial flow.
  - Advance the microcatheter more distally to achieve a semiwedged condition, if possible.[9,28]
- In tumors with multiple feeders, the main tumor feeder should be embolized last—it is difficult to confirm a residual tumor stain and other small feeders because of the dense retention of Lipiodol and contrast medium in the surrounding liver parenchyma immediately after cTACE.[9] In addition, embolic agents injected into the main tumor feeder are sometimes pushed back by the reversed flow via the minor tumor feeder.
- The distal tumor feeder should be embolized first, and the proximal tumor feeder should be embolized last to avoid inadvertently occluding the tumor feeders with overflowing embolic agents.
- To minimize the risk of systemic embolization and acute tumor lysis syndrome in large HCCs, schedule two to three sessions of superselective cTACE based on vascular anatomy.
  - Each session should be performed at 3- to 10-week intervals based on patient and tumor characteristics (stepwise TACE).[18]
  - The tumor feeder supplying the tumor portions at the liver surface should be embolized first to prevent tumor rupture.
  - The next target is the proximal tumor feeder to prevent tumor invasion into the main portal vein.

SUPERSELECTIVE CONVENTIONAL TACE TECHNIQUES

Tumors with obvious staining on the arteriogram at the periphery of the liver are relatively easy when selecting cases for superselective cTACE early in your experience. On the other hand, tumors with less vascularity and those located in the central portion and/or watershed area, such as the caudate lobe and the medial subsegment of the left hepatic lobe, require more experience to complete this technique.

The embolic effect of Lipiodol emulsion can be changed by the preparation technique. The yield stress values of water-in-oil emulsions are more than 47 times higher than those of oil-in-water emulsions.[20] Therefore, water-in-oil emulsions have a stronger embolic effect than oil-in-water emulsions and pure Lipiodol.[21] Moreover, the combined use of Lipiodol emulsion and GS particles can increase the intratumoral concentration of chemotherapeutics.[22] The average dose (mL) of Lipiodol in a single session is roughly equal to the sum of the target tumor diameters (cm). The reported maximum dose of Lipiodol per session is 10 mL in Japan[18] or 15 mL in Western countries.[23] The difference may be due to variations in physique and tumor size between patients in the regions, as well as a different catheter position during TACE. It is important to note that the use of a larger amount of Lipiodol may cause severe complications, such as hepatic failure and systemic embolization.

After advancing a microcatheter into the tumor feeder, 0.5 mL of 2% lidocaine is injected through the catheter to prevent pain and vasospasm. Then, a Lipiodol emulsion is slowly injected, followed by GS particles. A recent study reported that the diameter of tumor feeders ranged from 0.12 to 1.79 mm (mean, 0.41 ± 0.32 mm) for tumors that were 7 to 63 mm (mean, 20.3 ± 12.7 mm) in diameter.[24] Therefore, GS particles of approximately 0.2 to 0.5 mm in diameter are mainly used in superselective cTACE.[9,12] The endpoint of Lipiodol injection is portal vein visualization adjacent to the tumor (grade 1),[9] not marked portal vein visualization in the entire embolized area (grade 2),[9] because Lipiodol in the tumor and normal liver is pushed into the portal vein by GS injection and widely distributes throughout the entire embolized area, frequently spreading beyond the embolized area. As a result, grade 2 visualization is achieved. The endpoint of GS injection is complete occlusion of the tumor feeder. Confirmation of the embolized areas using CT or cone-beam CT is useful for determining the endpoint. A safety margin of at least 5 mm wide for HCC < 25 mm and 10 mm wide for HCC ≥ 25 mm should be achieved

in each tumor.[25,26] TACE guidance software, including automated tumor-feeder detection, can also reduce the physician's work and improve the treatment accuracy.[27]

cTACE also damages the hepatic artery by causing arteritis, and attenuation of the hepatic artery reduces the hepatic function and exaggerates the development of extrahepatic collaterals. Therefore, damage to the hepatic artery by cTACE should be kept to a minimum to prolong the duration of transcatheter management. Technical tips for effectively administering superselective cTACE are outlined in the *Tips for Effective Administration of Superselective cTACE* sidebar.[9,18,28]

FUTURE DIRECTIONS

With the potential of superselective cTACE to cure small HCC, we believe that it can replace surgical resection and radiofrequency ablation in selected patients. Catheterization into the tumor feeders and determination of the optimal catheter position, as well as identification of tumor feeders, are key in order to widely distribute this technique. Now, we have used a 1.5-F tip microcatheter system (Asahi Veloute Ultra and Asahi Meister S14, Asahi Intecc) in ultraselective cTACE to facilitate catheterization into tiny tumor feeders. In addition, the clinical application of novel virtual parenchymal perfusion software (Virtual Injection, Philips Healthcare) to visualize embolized areas has been introduced.[29] We believe that advancement of such technologies can improve the technical accuracy and outcomes of ultraselective cTACE. ■

1. Kim BK, Kim SU, Kim KA, et al. Complete response at first chemoembolization is still the most robust predictor for favorable outcome in hepatocellular carcinoma. J Hepatol. 2015;62:1304-1310.
2. Kojiro M, Sugihara S, Kakizoe S, et al. Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy. Cancer Chemother Pharmacol. 1989;23:S4-S8.
3. Zen C, Zen Y, Mitry RR, et al. Mixed phenotype hepatocellular carcinoma after transarterial chemoembolization and liver transplantation. Liver Transpl. 2011;17:943-954.
4. Wang B, Xu H, Gao ZQ, at al. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization. Acta Radiol. 2008;49:523-529.
5. Miyayama S, Matsui O, Zen Y, et al. Portal blood supply to locally progressed hepatocellular carcinoma after transcatheter arterial chemoembolization: observation on CT during arterial portography. Hepatol Res. 2011;41:853-866.
6. Kuroda C, Sakurai M, Monden M, et al. Limitation of transcatheter arterial chemoembolization using iodized oil for small hepatocellular carcinoma. A study in resected cases. Cancer. 1991;67:81-86.
7. Goseki N, Nosaka T, Endo M, et al. Nourishment of hepatocellular carcinoma cells through the portal blood flow with and without transcatheter arterial embolization. Cancer. 1995;76:736-742.
8. Terayama N, Matsui O, Gabata T, et al. Accumulation of iodized oil within the nonneoplastic liver adjacent to hepatocellular carcinoma via the drainage routes of the tumor after transcatheter arterial embolization. Cardiovasc Intervent Radiol. 2001;24:383-387.
9. Miyayama S, Matsui O, Yamashiro M, et al. Ultraselective transcatheter arterial chemoembolization with a 2-F tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of the portal vein with iodized oil. J Vasc Interv Radiol. 2007;18:365-376.
10. Miyayama S, Yamashiro S, Okuda M, et al. Anastomosis between the hepatic artery and the extrahepatic collateral or between extrahepatic collaterals: observation on angiography. J Med Imag Radiat Oncol. 2009;53:271-282.
11. Matsui O, Kadoya M, Yoshikawa J, et al. Small hepatocellular carcinoma: treatment with subsegmental transcatheter arterial embolization. Radiology. 1993;188:79-83.
12. Miyayama S, Mitsui T, Zen Y, et al. Histopathological findings after ultraselective transcatheter arterial chemoembolization for hepatocellular carcinoma. Hepatol Res. 2009;39:374-381.
13. Ueda K, Matsui O, Kawamori Y, et al. Hypervascular hepatocellular carcinoma: evaluation of hemodynamics with dynamic CT during hepatic arteriography. Radiology. 1998;206:161-166.
14. Sakon M, Nagano H, Nakamori S, et al. Intrahepatic recurrences of hepatocellular carcinoma after hepatectomy: analysis based on tumor hemodynamics. Arch Surg. 2002;137:94-99.
15. Yamakado K, Miyayama S, Hirota S, et al. Hepatic arterial embolization for unresectable hepatocellular carcinomas: do technical factors affect prognosis? Jpn J Radiol. 2012;30:560-566.
16. Yamakado K, Miyayama S, Hirota S, et al. Subgrouping of intermediate-stage (BCLC stage B) hepatocellular carcinoma based on tumor number and size and Child-Pugh grade correlated with prognosis after transarterial chemoembolization. Jpn J Radiol. 2014;32:260-265.
17. Yamakado K, Miyayama S, Hirota S, et al. Prognosis of patients with intermediate-stage hepatocellular carcinomas based on the Child-Pugh score: subclassifying the intermediate stage (Barcelona Clinic Liver Cancer stage B). Jpn J Radiol. 2014;32:644-649.
18. Miyayama S, Yamashiro M, Okuda M, et al. Chemoembolization for the treatment of large hepatocellular carcinoma. J Vasc Interv Radiol. 2010;21:1226-1234.
19. Miyayama S, Matsui S, Yamashiro M, et al. Iodized oil accumulation in the hypovascular tumor portion of early-stage hepatocellular carcinoma after ultraselective transcatheter arterial chemoembolization. Hepatol Int. 2007;1:451-459.
20. Demachi H, Matsui O, Abo H, Tatsu H. Simulation model based on non-Newtonian fluid mechanics applied to the evaluation of the embolic effect of emulsions of iodized oil and anticancer drug. Cardiovasc Intervent Radiol. 2000;23:285-290.
21. de Baere T, Zhang X, Aubert B, et al. Quantification of tumor uptake of iodized oils and emulsions of iodized oils: experimental study. Radiology. 1996;201:731-735.
22. Raoul JL, Heresbach D, Bretagne JF, et al. Chemoembolization of hepatocellular carcinomas. A study of the biodistribution and pharmacokinetics of doxorubicin. Cancer. 1992;70:585-590.
23. de Baere T, Arai Y, Lencioni R, et al. Treatment of liver tumors with lipiodol TACE: technical recommendations from experts opinion. Cardiovasc Intervent Radiol. 2016;39:334-343.
24. Irie T, Kuramochi M, Takahashi N. Diameter of main tumor feeding artery of a hepatocellular carcinoma: measurement at the entry site into the nodule. Hepatol Res. 2016;46:E100-104.
25. Sasaki A, Kai S, Iwashita Y, et al. Microsatellite distribution and indication for locoregional therapy in small hepatocellular carcinoma. Cancer. 2005;103:299-306.
26. Miyayama S, Yamashiro M, Hashimoto M, et al. Comparison of local control in transcatheter arterial chemoembolization of hepatocellular carcinoma ≤6 cm with or without intraprocedural monitoring of the embolized area using cone-beam computed tomography. Cardiovasc Intervent Radiol. 2014;37:388-395.
27. Miyayama S, Yamashiro M, Ikuno M, et al. Ultraselective transcatheter arterial chemoembolization for small hepatocellular carcinoma guided by automated tumor-feeders detection software: technical success and short-term tumor response. Abdom Imaging. 2014;39:645-656.
28. Miyayama S, Matsui O. Superselective conventional transarterial chemoembolization for hepatocellular carcinoma: rationale, technique, and outcome. J Vasc Interv Radiol. 2016;27:1269-1278.
29. Miyayama S, Yamashiro M, Nagai K, et al. Performance of novel virtual parenchymal perfusion software visualizing embolized areas of transcatheter arterial chemoembolization for hepatocellular carcinoma [published online June 28, 2016]. Hepatol Res.

Shiro Miyayama, MD
Department of Diagnostic Radiology
Fukuiken Saiseikai Hospital
Funabashi, Wadanaka-cho, Fukui, Japan
s-miyayama@fukui.saiseikai.or.jp
Disclosures: None.

Osamu Matsui, MD
Department of Radiology
Kanazawa University, Graduate School of Medical Science
Takara-machi, Kanazawa, Japan
matsuio@med.kanazawa-u.ac.jp
Disclosures: None.