REVIEW ARTICLE

# Superselective Conventional Transarterial Chemoembolization for Hepatocellular Carcinoma: Rationale, Technique, and Outcome

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## ABSTRACT

Conventional transarterial chemoembolization with ethiodized oil and gelatin sponge (GS) particles is a standard technique for hepatocellular carcinoma. Ethiodized oil can temporarily block tumor sinusoids, portal venules, hepatic sinusoids, and arterial microcommunications. By adding GS embolization, strong ischemic effects not only on the tumor but also on the surrounding liver parenchyma can be achieved. Superselective conventional transarterial chemoembolization is mainly indicated for patients with Child-Pugh scores of 5–8, tumors $\leq$ 7 cm, and $\leq$ 5 lesions. According to a Japanese nationwide survey, the 5-year survival rate of patients with Child-Pugh class A and a single tumor was 52%.


## ABBREVIATIONS

CR = complete remission, DEB = drug-eluting bead, GS = gelatin sponge, HCC = hepatocellular carcinoma, PBP = peribiliary vascular plexus

Transarterial chemoembolization has been performed worldwide for inoperable hepatocellular carcinoma (HCC) since the first report by Yamada et al (1) in 1983. In 2002, two randomized controlled trials demonstrated that transarterial chemoembolization showed a survival benefit compared with best supportive care (2,3). Two meta-analyses also demonstrated the clinical efficacy of transarterial chemoembolization (4,5). At the present time, transarterial chemoembolization is the most commonly performed therapy for inoperable HCC (6), although the necessity of chemotherapeutics is controversial (7).

A wide variety of transarterial chemoembolization techniques is available. Superselective transarterial chemoembolization (transarterial chemoembolization at the distal portion of the tumor-feeding subsegmental hepatic artery) using ethiodized oil (Lipiodol 480; Guerbet Japan, Tokyo, Japan) and gelatin sponge (GS) particles (conventional transarterial chemoembolization) is a standard technique for localized HCCs in Asia, especially in Japan (8–10), and a contemporary multiinstitutional prospective study reported good outcomes (11). The purpose of this article is to describe the rationale, technique, and outcomes of superselective conventional transarterial chemoembolization.

## RATIONALE AND LIMITATION OF TRANSARTERIAL CHEMOEMBOLIZATION

Moderately to poorly differentiated HCC tissue is predominantly supplied by arterial blood (1,12). The normal liver parenchyma is supplied by arterial and portal blood. Therefore, blockage of the hepatic artery can theoretically achieve selective ischemic necrosis of the tumor tissues alone.

However, HCC frequently recurs after transarterial chemoembolization. One important cause of tumor tissue survival after transarterial chemoembolization is thought to be portal venous supply to tumors via the portal venules and surrounding hepatic sinusoids as a result of the reversal of portal flow through the drainage route from HCC appearing when embolization of the hepatic artery is performed (13,14). Additionally, some

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capsular tumor invasions, microsatellite lesions, and well-differentiated tumor portions in early-stage HCC are supplied by both the hepatic artery and the portal vein (14). Additionally, arterial collateral supply after transarterial chemoembolization helps tumor survival (15). Therefore, residual tumor tissues may be present after embolization of the hepatic artery, particularly when it is performed nonselectively (13,14).

Transarterial chemoembolization loads hypoxic stress on HCC and stimulates vascular endothelial growth factor production by the residual tumor cells (16). Additionally, the surviving tumors frequently change to sarcomatous appearances or mixed hepatocholangiocellular phenotypes (17,18). Furthermore, some residual tumors are fed by portal blood if the arterial branches reaching the tumor, including extrahepatic collaterals, are occluded (19). Hence, it is suggested that transarterial chemoembolization also has a risk of leading to uncontrollable tumors, and complete remission (CR) of tumors after embolization is necessary to improve patient outcomes (20).

## EMBOLIC AGENTS USED IN CONVENTIONAL TRANSARTERIAL CHEMOEMBOLIZATION

### Ethiodized Oil

Ethiodized oil is poppyseed oil that is used as a semifluid embolic material. Although definitive evidence is lacking regarding treatment with or without chemotherapy (3–5,7), several chemotherapeutics are mixed with ethiodized oil in conventional transarterial chemoembolization. Doxorubicin is the most commonly used chemotherapeutic worldwide (5). In Japan, epirubicin is the most common (74%) chemotherapeutic, followed by doxorubicin, mitomycin C, cisplatin, and others (21). Although conventional transarterial chemoembolization has a long history, the most effective and least toxic regimen has not yet been established. Mixed hydrophilic chemotherapeutics are lost from ethiodized oil within 4 hours, in contrast to drug-eluting beads (DEBs) (22). Therefore, systemic toxicities may develop when a large amount of doxorubicin is used in conventional transarterial chemoembolization (23).

Two types of ethiodized oil emulsion can be prepared: water-in-oil emulsion and oil-in-water emulsion. Water-in-oil emulsion has a higher yield stress and can occlude a thin tube at a lower pressure gradient compared with oil-in-water emulsion, and oil droplet size is larger than that of oil-in-water emulsion; therefore, water-in-oil emulsion has stronger embolic effects than oil-in-water emulsion (**Fig 1**) (24). Although there are also no standard techniques for preparing ethiodized oil emulsion, we usually mix 2–10 mL of ethiodized oil with contrast medium one-third the quantity of ethiodized oil that dissolves 10–30 mg of epirubicin and 2–6 mg of mitomycin C by a pumping method.

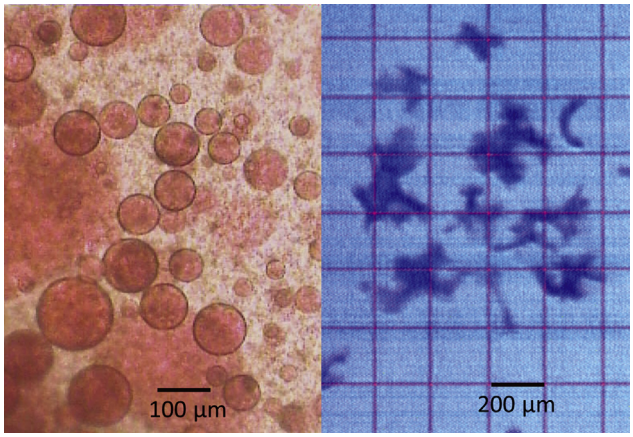


**Figure 1.** Embolic materials used in conventional transarterial chemoembolization. Water-in-oil emulsion (left panel) and GS particles crushed by a pumping method (right panel). (Left panel image courtesy of Toshihiro Tanaka, MD, Department of Radiology, Nara Medical University, Nara Kashihara, Japan.)

Ethiodized oil is retained in necrotic tumor tissues over several years (25) as well as in the hepatic parenchymal necrosis induced by conventional transarterial chemoembolization (**Fig 2a–c**) (10). Artifacts from dense ethiodized oil accumulation deteriorate the image quality of computed tomography (CT), whereas ethiodized oil does not influence the quality of magnetic resonance imaging (26).

### GS Particles

GS is a temporary occlusive agent because it is absolvable 2–6 weeks after injection. GS is composed of bovine or porcine collagen (27); therefore, it causes many antibody-mediated reactions, and attenuation of vessels after embolization occurs as a result of granulomatous arteritis and intimal proliferation (28). Permanent vascular occlusion may also develop when dense packing of GS is performed (27).

In Japan, a 1- or 2-mm-diameter, ready-made spherical GS particle (Gelpart; Nippon Kayaku Co, Ltd, Tokyo, Japan) is commercially available; however, the size is too large for embolization of tumor vessels (29). Crushed GS particles of approximately 0.2–0.5 mm in diameter that are produced by a pumping method are mainly used in superselective conventional transarterial chemoembolization (10). However, the crushed GS particles are not uniform in size and have jagged edges (**Fig 1**); therefore, the occluding level of targeted vessels cannot be controlled (27).

## RATIONALE FOR SUPERSELECTIVE CONVENTIONAL TRANSARTERIAL CHEMOEMBOLIZATION

There are two major types of the terminal hepatic artery: one terminates within the portal tract supplying the bile duct (peribiliary vascular plexus [PBP]), portal tract

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