Review Article

Recent technical advances in conventional transarterial chemoembolization for hepatocellular carcinoma in Japan

Hiroki Higashihara*, Yusuke Ono, Kaisyu Tanaka, Kosuke Tomotake, and Noriyuki Tomiyama

ABSTRACT

Conventional transarterial chemoembolization (TACE) using ethiodized oil and gelatin sponge (GS) particles is a standard treatment for unresectable BCLC-B stage hepatocellular carcinoma (HCC). Ethiodized oil can cause temporary embolic micro-interactions in tumor sinuses, portal veins, hepatic venous sinuses, and arteries as a temporary embolic material for the microvasculature. Using GS particles as an added embolic material, strong ischemic effects can be achieved not only in HCC, but also in the surrounding liver parenchyma. In recent years, various technical innovations in TACE using ethiodized oil have been made in Japan to improve the outcomes of TACE, such as a device for emulsifying ethiodized oil and water-soluble anticancer drugs, the use of intraoperative embolization guidance software to plan embolization during TACE, and the introduction of various microcatheters. This report examines some of the technical innovations that have been adopted to improve TACE outcomes.

Keywords: Carcinoma, hepatocellular; Conventional transarterial chemoembolization; Ethiodized oil; Radiology, interventional; Transarterial chemoembolization

Introduction

Each year, primary liver cancer accounts for more than 38,000 deaths in Japan and more than 15,000 deaths in Korea, representing the fourth most common cause of death in Japan, and the third most common in Korea. Among primary liver cancers, about 95% in Japan and 85% in Korea are hepatocellular carcinoma (HCC), most of which are caused by chronic hepatitis or cirrhosis due to persistent viral infection. The main cause is chronic hepatitis or cirrhosis caused by persistent infection with hepatitis C or B virus.

Since Yamada et al. first reported transarterial chemoembolization (TACE) in 1983, the Japanese development of TACE using ethiodized oil (Lipiodol 480; Guerbet Japan, Tokyo, Japan) has been widely adopted worldwide. In particular, Asian countries took up this method long before the confirmation of its survival benefit in randomized controlled trials. In this manuscript, TACE using ethiodized oil and gelatin sponge particles was considered to represent "conventional TACE."

In a multicenter, prospective study conducted jointly by Japan and Korea and involving 99 patients with HCC in the early to intermediate stage according to BCLC classification who underwent conventional TACE, the median survival and 1- and 2-year survival rates were 3.1 years, 89.6% and 75.0%, respectively. For the past 30 years, conventional TACE has been referenced in many publications, with varying levels of detail regarding preparation and administration. In 2016, a global expert panel published consensus technical recommendations to encourage standardization and promote conventional TACE. In addition, multiple molecularly targeted drugs have been introduced for HCC, causing a paradigm shift in the treatment strategy for HCC in the BCLC-B stage. New applications, devices and microcatheters have emerged in Japan to enhance local control of individual HCC lesions. In this review, we mention and introduce the technically advanced progress of conventional TACE in Japan.

Recent Concepts in Conventional Transarterial Chemoembolization for Hepatocellular Carcinoma

A HCC is usually a hypervascularized tumor with arterial dominance. The goal of conventional TACE is to achieve antitumor effects with anti-cancer drugs and cytotoxic effects by...
achieving ischemia in tumor tissue with arterial embolization. Ethiodized oil injected into the hepatic artery has been found to accumulate predominantly in HCCs and to show long-lasting retention in tumors.\textsuperscript{18–20} Ethiodized oil circulates beyond the feeding arteries of the tumor to the distal portal vein through the peribiliary capillary plexus and drainage channels from the tumor.\textsuperscript{1,22} Ethiodized oil infused from the hepatic artery exerts temporary embolic effects on both the hepatic artery and portal vein branches when it flows out to the portal vein side.\textsuperscript{23} When ethiodized oil is used as a means of delivering chemotherapeutic agents, an ethiodized oil-anticancer drug emulsion followed by embolization with particles shows better pharmacokinetics than either ethiodized oil-anticancer drugs alone without ethiodized oil\textsuperscript{24} and induces significant necrosis of the main tumor and satellite tumor nodules compared to either ethiodized oil or anticancer drug injected alone.

Uchida et al\textsuperscript{4} and Matsui et al\textsuperscript{5} established the so-called segmental TACE and subsegmental TACE techniques to embolize a segment or sub-segment of the liver parenchyma containing a tumor using ethiodized oil.

In recent years, in Japan, with improvements to microcatheters and the development of thinner microcatheter tips, active injection of ethiodized oil to more distal sub-segment levels has become possible in line with the concept of superselective TACE proposed by Miyayama et al\textsuperscript{25} The development of microballoon has also led to balloon occlusion TACE, in which the pressure gradient between the artery and portal vein is reduced before the ethiodized oil is injected.\textsuperscript{26} Both of these methods will be described later.

\textbf{Ingenuity in Preparing a Stable Micro-Shaped Ethiodized Oil Emulsion}

The standard method of conventional TACE involves pumping emulsified ethiodized oil and a cytotoxic drug back and forth using two syringes and a three-way stopcock to create an ethiodized oil-anticancer drug emulsion.\textsuperscript{19,27–31} The physicochemical properties of the emulsion influence the therapeutic effect.

Water-in-oil (W/O) emulsion can achieve high embolization efficacy by slowly releasing the drug, while offering enhanced tumor retention due to the high viscosity of the emulsion.\textsuperscript{19,27–31} However, emulsions produced by the current pump method using three-way cocks have an important limitation, in that they can only achieve a W/O ratio of about 70%.\textsuperscript{32}

Emulsification devices were developed to improve the properties of ethiodized oil emulsions formed by the pumping method. In 1995, Higashi et al\textsuperscript{33} first reported a membrane emulsification technique to form W/O emulsion for use in intra-arterial injection therapy. This technology requires a dedicated metal module with a nitrogen gas inlet and a stirring rotor. Tanaka et al\textsuperscript{34} developed and reported a simple pump emulsifier equipped with a membrane to form W/O emulsions.

This pumped emulsifier comprises a microporous glass membrane made from volcanic ash from southern Kyushu, formed of a porous glass material consisting of $\text{Al}_2\text{O}_3\cdot\text{SiO}_2$. The disk-shaped glass-glass membrane had numerous micron-sized pores with a diameter of 50 $\mu$m as of the first report, but they later changed to micron-sized pores with a diameter of 100 $\mu$m. The membrane is coated with silicon to make it hydrophobic and to facilitate formation of the W/O emulsion. This membrane is placed between two syringe adapters made of rigid polyvinyl chloride resin (Fig. 1A).

The emulsion was prepared and emulsified by mixing ethiodized oil with an epirubicin solution comprising 50 mg of epirubicin hydrochloride powder (Epirubicin; Nippon Kayaku, Tokyo, Japan) dissolved in 6 mL of contrast medium (250 mg/mL).

Emulsions were prepared at different concentrations using either a three-way cock or the pump emulsifier with glass membrane to evaluate the physicochemical properties of the results. The percentage of each W/O emulsion at 30 minutes showed that the pump emulsifier with glass membrane was significantly higher than the three-way cock at any W/O concentration ratio.\textsuperscript{35}

Tanaka et al\textsuperscript{36} also reported the drug elution ability of an emulsion of epirubicin–ethiodized oil using either a pump emulsifier with glass membrane or a three-way cock. Immediately after preparing the emulsion (0 min), 1.73% ± 1.05% of epirubicin was released from the emulsion prepared by the pump emulsifier with glass membrane, while 41.02% ± 7.27% of epirubicin was already eluted by the 3-way cock, representing a significant difference ($P < 0.001$). In addition, the release half-life (50%) was significantly longer with the emulsifier than with the three-way cock (175 ± 25 vs 8 ± 6 min; $P < 0.001$), suggesting a sustained release effect of the drug. When epirubicin solution and ethiodized oil were mixed at a ratio of 1 : 2 and pumped exchange was performed in the device, the W/O ratio was 98.49% ± 0.03%. Median droplet size was

\begin{figure}[h]
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\includegraphics[width=\textwidth]{fig1.png}
\caption{A new device for making ethiodized oil-anticancer drug emulsion and microscopic images of the water-in-oil emulsion. (A) Appearance of a V-shaped emulsification device with a glass membrane with small pores of 100 $\mu$m sandwiched in the center. (B) After agitation by pumping the syringe 20 times, an emulsion eluted by the 3-way cock, representing a significant difference ($P < 0.001$). (C) Microscopic image of the emulsions produced, showing spherical water-in-oil emulsions of approximately 100 $\mu$m. Reused from the article of Tanaka et al [Eur Radiol. 2018;28:2203-7]\textsuperscript{35} with original copyright holder’s permission.}
\end{figure}
This pump emulsifier with glass membrane can be used to create W/O emulsions with almost-uniform droplet size and slower drug elution capacity than the conventional method with three-way cocks. Currently, the MicroMagic emulsifier (Piolax Co., Yokohama, Japan) is being marketed and is actively used in Japan, and the design has been changed to a V-shape with a glass membrane containing numerous 100-μm holes (Fig. 1). The results of conventional TACE using this device are expected to be reported in the near future, and are expected to contribute to the improvement of therapeutic outcomes for conventional TACE.

Advances in Assistive Reference Imaging during Interventional Radiology Procedure: Novel Software for Planning and Guidance in Transarterial Chemoembolization

In recent years, cone-beam computed tomography (CBCT) has become available by rotating the angiography unit. In addition, CT images can be obtained during interventional radiological procedures using an interventional radiology CT (IVR-CT)-equipped angiographic unit. These images during hepatic arteriography are now often widely taken in TACE for tumor delineation and decisions on embolization, and can be referred to as support images during TACE to improve local tumor control.36,37

In addition, TACE guidance software, including 3-dimensional automatic tumor feeding artery detection (AFD) software using either CBCT or IVR-CT data, has been developed. Such software can identify 85% to 93% of feeding arteries and improve the rates of technical success of TACE and early tumor response.38–42

Miyayama et al43 performed conventional TACE using AFD software and reported the evaluation of technical success for TACE and local tumor control rates and overall survival (OS) rates using unenhanced CT 1-week after TACE to determine the degree of ethiodized oil retention in HCC nodules. They reported that complete embolization with a safety margin (grade A) was achieved in 82.1% of HCCs treated with TACE, and 13.7% of HCCs were embolized without a safety margin (grade B). The rate of incomplete embolization was only 4.2% (grade C). Regarding OS and intrahepatic tumor recurrence [local tumor progression (LTP) or intrahepatic distant recurrence (IDR)] rates according to the degree of technical success, LTP and IDR rates at 1, 3, and 5 years were 31.7%, 49.4%, and 59.4%; and 33.9%, 58.2%, and 73.3%; respectively. LTP occurred more frequently in HCCs classified as grade B than in those classified as Grade A (P = 0.016). OS rates were 96.1%, 71.1%, and 60% at 1, 3, and 5 years, respectively, and the presence or absence of LTP of treated HCCs did not result in significant differences in OS. Active use of AFD software during TACE may result in high technical success rates and good local control for patients with localized HCC lesions, resulting in good survival (Fig. 2).

Fig. 2. A 70-year-old male with three hypervascular hepatocellular carcinomas (HCCs). (A) In the early phase of computed tomography during hepatic arteriography at the time of transarterial chemoembolization (TACE), one hypervascular nodule was depicted in each of the medial segment (white arrow) in the medial segment which diagnosed as HCC. (B) Tumor staining was not obvious on angiography at proper hepatic artery. (C) For embolization planning as TACE guidance software, regions of interest (ROI) (blue circles) were set for three HCCs in order to use the automatic tumor feeding artery detection (AFD). (D) By using the AFD function, the three feeding arteries to be embolized were automatically displayed for the three ROI set as embolization targets in the 3-dimensional volume rendering image. (E) Angiography with medial segmental branch depicted two branches delineated by AFD function. Angiographically, the caudal branch (white arrow) was suspected to be involved in tumor staining, while the cephalic branch (white arrowhead) appeared to be poorly involved in tumor staining. (F) Two hyper-dense accumulations of ethiodized oil in each HCC were shown on computed tomography after TACE [white arrow and white arrowhead].
the HCC at the sub-segmental level, the emulsion of ethiodized oil and anticancer drugs is slowly injected, followed by gelatin sponge particles. The dose (in milliliters) of ethiodized oil per dose of conventional TACE is approximately equal to the total diameter (in centimeters) of the target HCC.5 The maximum reported dosage per dose is 10 mL.45 or 15 mL.46 The endpoint of conventional TACE is cessation of blood flow in the arteries feeding the tumor and disappearance of staining for the target HCC on DSA, although confirmation of the embolized area using CT or CBCT is also useful in determining the endpoint.44,46 A safety margin (at least 5 mm wide for tumors greater than 25-mm and 10-mm wide for tumors greater than 25 mm, corresponding to the coronal enhancement area) should be secured around the HCC.44,46,47 If the HCC is fed by multiple feeding arteries or if there are multiple HCCs, superselective conventional TACE should be performed for each feeding artery whenever possible.

As for technical innovations during the injection of the ethiodized oil emulsion, injecting the ethiodized oil emulsion slowly is important to avoid formation of an “oil cast” in the feeding artery. Also, if possible, the microcatheter should be advanced more distally to achieve a “semi-wedged condition,”45 so that the ethiodized oil emulsion can reach the portal vein circulation from the feeding arteries of the HCC across the peribiliary arteries, and enough ethiodized oil emulsion can be stored in the embolic region, as ethiodized oil may act as a temporary embolic material (Fig. 3). If multiple feeding branches are present, embolization of the main feeding branch should be performed at the very end. This is because immediately after ethiodized oil TACE, the surrounding hepatic parenchyma may be densely accumulated with ethiodized oil and contrast media, making residual tumor staining and the involvement of small feeding branches difficult to identify.46

In cases of conventional TACE for large HCCs, the use of a large amount of ethiodized oil in a single procedure may expose a certain risk of serious complications such as systemic embolism and tumor lysis syndrome.46–50 For localized tumors larger than 6 cm in diameter, repeated conventional TACE at regular intervals may be effective. Two to three sessions should be scheduled depending on the vascular structure of the feeding arteries, and each session should be performed superselectively at intervals of 3 to 10 weeks, considering the symptoms and laboratory data of the patient.45

**Concepts of Microcatheter Selection and Selection of Unique Microcatheters**

An important concept of superselective conventional TACE is to increase the local control rate for individual HCCs targeted for embolization. The local recurrence rate of HCCs with significant visualization of portal veins by ethiodized oil has been reported to be significantly lower than that of tumors with little or no portal vein visualization ($P = 0.0485$ and $P < 0.0001$, respectively),45 suggesting that reaching the portal vein circulation with ethiodized oil may lead to local control of the HCC in TACE (Fig. 3E). Advancing the microcatheter more distally is therefore important for achieving a “semi-wedged condition.” For this purpose, small-diameter microcatheters have been actively used in Japan in recent years. We can use a thinner microcatheter with a tip diameter of 1.5 Fr (Asahi Veloute ultra; Asahi Intecc, Nagoya, Japan) using a 0.014-inch guidewire via a 4-Fr catheter to advance to the feeding artery in the subsegmental branch (Fig. 4).

However, several difficult situations can provide obstacles to super-selective TACE, such as sharp-angled bifurcation of the vessels, tortuosity of the hepatic artery, or a small diameter of the feeding artery from the proximal hepatic artery.

When dealing with sharp-angled bifurcations from tortuous vessels, selective catheter insertion can be very difficult. Even if the shape of the guidewire and catheter is selected to fit the de-
sired bifurcations of vessels, selective catheter insertion is sometimes difficult and could be disrupted. In such situations, selective catheterization may be difficult and end up being abandoned.

In such cases, the use of a microcatheter with a steerable-tip (SwiftNINJA; Sumitomo Bakelite, Tokyo, Japan) may be one option (Fig. 5). Steerable microcatheters were developed in Japan in 2014. The SwiftNINJA has a remotely operated flexible tip with a steering dial at the proximal part of the grip, allowing the operator to optimally control the direction of the 2.4-Fr steerable tip, up to 180° in the opposite direction (Fig. 5A, 5B). The steering dial and tip are connected by two wires inserted from each lumen in the wall of the catheter shaft. If we want the tip of this catheter to tilt to a specific angle, turning the dial applies tension to either of the wires, causing the steerable tip to bend by a certain angle. Once the direction of the steerable tip is determined, the steering dial can be locked with the dial stopper to maintain the intended direction and orientation. This steerable microcatheter may facilitate more selective catheter insertion than a conventional micro-

Fig. 4. A 70-year-old male with liver cirrhosis caused by hepatitis C virus. (A) Contrast enhanced computed tomography showed hyperattenuation under the liver capsule in anterior inferior segment (white arrow) which was diagnosed as hepatocellular carcinoma. Portal-hepatic venous shunt was also shown in posterior inferior segment (open arrow). (B) The tip of 1.5-Fr microcatheter was superselectively inserted to the distal portion of anterior inferior segment. The tumor stain was well depicted (arrow). (C) After conventional transarterial chemoembolization, the tumor stain disappeared and other branches of the hepatic artery within the anterior inferior segment of the non-embolized area are delineated, and the hepatic parenchyma remains densely stained (open arrow).

Fig. 5. (A) The steerable microcatheter. The operator can optimally control the direction of the steerable tip by turning the steerable dial (white arrow) attached to the proximal end. A steerable dial lock (white arrowhead) is used to maintain the intended orientation. When the operator is not operating the steerable dial, the shape of the steerable tip is straight. The steerable dial at hand can be adjusted and rotated to any position at the operator’s intention, and the tip of the microcatheter can be bent to a range of angles up to 180°. (B) A 78-year-old male presented with hepatocellular carcinoma (HCC). Contrast enhanced computed tomography showed multiple hypervascular tumors indicating as multiple HCCs. A2 bifurcated independently from the left hepatic artery, A3 and A4 bifurcated from the next bifurcating middle hepatic artery, and then the right hepatic artery bifurcates. The origin of the middle hepatic artery ran in an inverted, steep shape (open arrow), making it difficult to insert a microcatheter with a micro guide-wire. (C) The tip of the steerable microcatheter was bent to a steep angle at the origin of the middle hepatic artery by turning a dial at the hub of microcatheter. The steeply bent microcatheter tip (white arrow) could be inserted directly into the origin of the middle hepatic artery.
catheter because of the controllable mechanism for the tip shape (Fig. 5). In addition, when an occlusion point is present in the route from the aorta to the hepatic artery, the catheter needs to be inserted through a collateral pathway such as the pancreatic arcade. The collateral pathway is often tortuous with sharp angles, and the stability of the parent catheter is sometimes impaired due to the kickback with counter-tension during microcatheter insertion, causing the parent catheter to become dislodged. The tip of the microcatheter thus may not reach the intended peripheral location of the hepatic artery.

In such cases, a triple co-axial catheter system may be able to stably advance the tip of microcatheter more distally (Fig. 6). This catheter system consists of a small microcatheter with a 1.6 or 1.9-Fr non-tapered tip inserted into a large microcatheter with a large inner diameter of 2.7 Fr (high-flow type) into a 4- or 5-Fr parent catheter, as the so-called “tri-axial catheter technique.” The insertion of the microcatheter with the tri-axial catheter system enables stable catheter insertion into vessels with strong bending and tortuosity. Shimohira et al. reported the initial results of using this catheter system for conventional TACE in HCCs. They reported that 30 patients with HCCs underwent TACE using this catheter system, and the level of embolization was sub-segmental TACE in 26.7% (8/30), more sub-sub-segmental TACE in 43.3% (13/30), and more distal TACE in 23.3% (7/30). Shimohira et al. reported that they were able to insert the catheter more distally than the embolization site, where TACE was performed using a conventional microcatheter. When arteries are tortuous, or when a microcatheter has to be advanced via collateral pathways, sagging of the microcatheter may occur, and consideration of using this tri-axial catheter system may be an option (Fig. 6).

Furthermore, even with such catheters as the small-diameter microcatheter and the triaxial catheter system, we have empirically encountered cases in which selective catheter insertion into the feeding artery was difficult when the very thin feeding artery branched abruptly from the proximal hepatic artery. Conventional TACE is often difficult to perform in other cases where the HCC appears with the region of an arterial-portal (AP) shunt in the liver, due to changes associated with the deterioration and fibrosis of normal intrahepatic tissues associated with cirrhosis or repeated conventional TACE or radiofrequency ablation. This is the cause of the AP shunt, which is characterized by a high volume of blood flowing through the AP shunt to the portal vein region and a high blood flow velocity. Therefore, when ethiodized oil emulsion is injected from the proximal position to the AP shunt, most of the emulsion escapes into the portal vein without accumulating in the liver parenchyma around the HCC. To improve the efficiency of ethiodized oil emulsion retention in a HCC in this situation, conventional TACE under microballoon perfusion control may be one option. In this situation, a temporary reduction in blood flow

![Figure 6](image_url)

**Fig. 6.** A 81-year-old male presented with hepatocellular carcinoma (HCC) in caudate lobe treated by triaxial microcatheter system. (A) The distal portion of triaxial microcatheter system consists of a non-tapered 1.9-Fr microcatheter (open white arrow), a 2.6–2.9 Fr high-flow microcatheter (white arrow), and a 4-Fr Catheter (black arrow). A 0.014 inch micro guide wire can be inserted into this catheter system (white arrow head). (B) The contrast enhanced computed tomography (CT) image in arterial phase showed 6cm enhancement of HCC at the caudate lobe (arrow). (C) The contrast enhanced CT image in arterial phase showed 6cm enhancement of HCC at the caudate lobe (arrow). (C) An accumulation of contrast material injected from the tip of the 4Fr catheter at the origin of the celiac artery was depicted. (D) In superior mesenteric arteriography, left hepatic artery (white open arrowhead) from common hepatic artery (white arrow), and splenic artery (white open arrow) which branch from the celiac artery via the pancreatic arcade and collateral tract of the dorsal pancreatic artery (black arrow), are depicted from the origin of right hepatic artery. (E) The tip of the triaxial microcatheter system was advanced to A4 via the dorsal pancreatic artery arising from superior mesenteric artery to splenic artery and common hepatic artery. The tip of a non-tapered 1.9-Fr microcatheter was at the axis of A4 (white open arrow) and the tip of high-flow microcatheter was at the dorsal pancreatic artery (white arrow). (F) Contrast-enhanced CT images after treatment with 3 transarterial chemoinfusion (TAI) and 4 combined TAI and transarterial embolization showed shrinkage of HCC in the caudate lobe.
through the hepatic artery using a microballoon catheter is necessary to block the distal portion from the orifice of the feeding artery for the HCC. The injection of ethiodized oil emulsion through the proximal radiopaque marker is located 17 mm from the tip of the microballoon catheter and has a diameter of 0.48 mm. (B) With the microballoon inflation, material injected through the lumen of the catheter tip flows only through the side hole (white arrow). (C) A 81-year-old female presented with hepatocellular carcinoma (HCC) at the border of the posterior segment and caudate lobe. Contrast-enhanced computed tomography (CT) imaging of the arterial phase showed hypervascular tumor (white arrow) and the right branch of the portal vein was clearly delineated, and arterial-portal (AP) shunt formation was suspected (white arrow head). A small feeding artery (white arrow) was visualized proximal to the side-hole, and tumor staining (white open arrow) was depicted. A slight AP shunt was observed (white arrowhead). (D) A side-hole opened microballoon catheter was inserted into the proximal portion of the posterior segment branch, and angiography was performed under balloon inflation (black arrowhead). A small feeding artery (white arrow) was visualized proximal to the side-hole, and tumor staining (white open arrow) was depicted. A slight AP shunt was observed (white arrowhead). (E) The sufficient accumulation of ethiodized oil was well depicted in HCC 1 week and 1 year (G) after conventional transarterial chemoembolization. There was no local recurrence of HCC.

**Conclusion**

Superselective conventional TACE provides excellent antitumor efficacy for localized HCCs. Stabilization of ethiodized oil emulsions may be the key to conventional TACE. The position of the catheter is important for safe and effective TACE. Preparation of various types of characteristic microcatheter is also important in cases where advancing the catheter tip to the appropriate position is not possible.
References

1. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T. Cancer incidence and mortality in Japan in 2005: based on data from 12 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCII) project. Jpn J Clin Oncol. 2011;41:139-47.

2. Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatocarcinoma. Radiology. 1983;148:297-401.

3. Konno T, Maeda H, Iwai K, Tashiro S, Maki S, Morinaga T, et al. Effect of arterial administration of high-molecular-weight anticoagulant agent SMANCS with lipymphographic agent on hepaticoma: a preliminary report. Eur J Cancer Clin Oncol. 1983;19:955-65.

4. Nakamura H, Hashimoto T, Oh H, Sawada S. Transcatheter oily chemoembolization of hepatocellular carcinoma. Radiology. 1989;170:Pt 1:783-6.

5. Uchida H, Ohishi H, Matsuo N, Nishimine K, Ohue S, Nishimura Y, et al. Transcatheter hepatic segmental arterial embolization using lipiodol mixed with an anticancer drug and Gelfoam particles for hepatocellular carcinoma. Cardiovasc Intervent Radiol. 1990;13:140-5.

6. Matsui O, Kadoya M, Yoshikawa J, Gabata T, Arai K, Demachi H, et al. Small hepatocellular carcinoma: treatment with subsegmental transcatheter arterial embolization. Radiology. 1993;188:79-83.

7. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma—a randomized controlled trial. Gastroenterology. 1988;94:453-6.

8. Pelletier G, Roche A, Ink O, Anciaux MI, Derby S, Rougier P, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol. 1990;11:181-4.

9. Groupe d’Etude et de Traitement du Carcinoide Hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med. 1995;332:1256-61.

10. Pelletier G, Ducrée S, Martin L, Lusinchi J, Bache J, Huang P, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. J Hepatol. 1998;29:129-34.

11. Bruix J, Llovet JM, Castells A, Montaña X, Bru C, Ayuso MC, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology. 1998;27:1578-83.

12. Lo CM, Nian H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35:1164-71.

13. Llovet JM, Real MI, Montaño X, Planas R, Coll S, Apointe J, et al. Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet. 2002;359:1734-9.

14. Doffoël M, Bonnetain F, Bouché O, Vetter D, Abergel A, Fratté S, et al. Multicentre study of adriamycin in the emulsion mixed with lipiodol-difference resulting from composition and methods of preparation, and behavior after mesenteric arterial injection in rat. Gan To Kagaku Ryoho. 1991;18:1349-55.

15. Masuda T, Tanaka T, Nishiofuku H, Masada T, Fukuzuka Y, Sato T, Tatsumoto S, et al. Technical and pharmacokinetic study of adriamycin in the emulsion mixed with lipiodol-difference resulting from composition and methods of preparation, and behavior after mesenteric arterial injection in rat. Gan To Kagaku Ryoho. 1991;18:1349-55.

16. Masuda T, Tanaka T, Nishiofuku H, Masada T, Fukuzuka Y, Sato T, Tatsumoto S, et al. Drug release property of Lipiodol emulsion formed by glass membrane emulsification device for transcatheter chemoembolization. Cardiovasc Intervent Radiol. 2020;43:135-9.

17. Miyayama S, Yamashiro M, Hashimoto M, Hashimoto N, Ikuno M, Okumura K, 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;37:288-95.

18. Iwazawa J, Ohue S, Hashimoto N, Muramoto O, Mittai T. Survival after C-arm CT-assisted chemoembolization of unresectable hepatocellular carcinoma. Eur Radiol. 2012;21:2985-92.

19. Deschamps F, Solomon SB, Thornton RH, Rao P, Hakkine A, Kuech V, et al. Computed analysis of three-dimensional cone-beam computed tomography angiography for discrimination of tumor-feeding vessels during chemoembolization of liver tumor: a pilot study. Cardiovasc Intervent Radiol. 2010;33:233-42.

20. Ihazawa J, Ohue S, Hashimoto N, Muramoto O, Mittan T. Clinical utility and limitations of tumor-feeder detection software for liver cancer embolization. Eur J Radiol. 2011;82:1665-71.

21. Miyayama S, Yamashiro M, Hashimoto M, Hashimoto N, Ikuno M, Okumura K, et al. Identification of small nodular hepatocellular carcinoma and tumor-feeding branches with cone-beam CT guidance technology during transcatheter arterial chemoembolization. J Vasc Interv Radiol. 2013;24:501-8.

22. Minami Y, Yagiya Y, Murakami T, Kudo M. Tracking navigation imaging of transcatheter arterial chemoembolization for hepatocellular carcinoma using three-dimensional cone-beam CT angiography. Liver Cancer. 2014;3:53-61.
42. Miyayama S, Yamashiro M, Ikuno M, Okumura K, Yoshida M. 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;39:645-56.

43. Miyayama S, Yamashiro M, Sugimori N, Ikeda R, Okimura K, Sakuragawa N. Outcomes of patients with hepatocellular carcinoma treated with conventional transcatheter arterial chemoembolization using guidance software. J Vasc Interv Radiol. 2019;30:10-8.

44. Takayasu K, Muramatsu Y, Maeda T, Iwata R, Furukawa H, Muramatsu Y, et al. Targeted transarterial oily chemoembolization for small foci of hepatocellular carcinoma using a unified helical CT and angiography system: analysis of factors affecting local recurrence and survival rates. AJR Am J Roentgenol. 2001;176:681-8.

45. Miyayama S, Yamashiro M, Okuda M, Yoshie Y, Sugimori N, Igarashi S, et al. Chemoembolization for the treatment of large hepatocellular carcinoma. J Vasc Interv Radiol. 2010;21:1226-34.

46. Miyayama S, Matsui O, Yamashiro M, Ryu Y, Takata H, Takeda T, et al. Visualization of hepatic lymphatic vessels during transcatheter arterial chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol. 2007;18:1111-7.

47. Sasaki A, Kai S, Iwashita Y, Hirano S, Ohta M, Kitano S. Microsatellite distribution and indication for locoregional therapy in small hepatocellular carcinoma. Cancer. 2005;101:299-306.

48. Chung JW, Park JH, Im JG, Han JK, Han MC. Pulmonary oil embolism after transcatheter oily chemoembolization of hepatocellular carcinoma. Radiology. 1993;187:689-93.

49. Li Z, Ni RF, Busireddy KK, Jin YH, Zhao X, Li MM, et al. Cerebral lipiodol embolism following transcatheter arterial chemoembolization for hepatocellular carcinoma: a report of two cases and literature review. Chin Med J (Engl). 2011;124:4355-8.

50. Hsieh PM, Hung KC, Chen YS. Tumor lysis syndrome after transarterial chemoembolization of hepatocellular carcinoma: case reports and literature review. World J Gastroenterol. 2009;15:4726-8.

51. Soyama T, Yoshida D, Sakaiura Y, Morita R, Abo D, Kudo K. The steerable microcatheter: a new device for selective catheterisation. Cardiovasc Intervent Radiol. 2017;40:947-52.

52. Horikawa M, Miyayama S, Irie T, Kaji T, Arai Y. Development of conventional transarterial chemoembolization for hepatocellular carcinomas in Japan: historical, strategic, and technical review. AJR Am J Roentgenol. 2015;205:764-73.

53. Shimohira M, Ogino H, Kawai T, Kushita A, Watanabe M, Kawaguchi T, et al. Use of the triaxial microcatheter method in super-selective transcatheter arterial chemoembolization for hepatocellular carcinoma. Br J Radiol. 2011;84:184-7.

54. Yamagami T, Yoshimatsu R, Nishimoto M, Ogi K, Tamura T, Iwasaki S, et al. Use of proximal side-hole micro-balloon catheter in transcatheter hepatic arterial chemoembolization. Minim Invasive Ther Allied Technol. 2017;26:372-6.