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Review Article

Balloon-occluded transarterial chemoembolization for hepatocellular carcinoma: History, background, and the roles

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A B S T R A C T

Super-selective lipiodol balloon-occluded transarterial chemoembolization (SSLB-TACE) increases lipiodol accumulation in the targeted nodule. To understand the mechanism of increased accumulation, it is necessary to understand intra-hepatic collateral system and rheology of lipiodol. Although SSLB-TACE is thought to be a promising technique, randomized prospective controlled trials to compare local control rates with conventional super-selective lipiodol (c-TACE) are still lacking. Another problem for SSLB-TACE is change of TACE candidates by development of radiofrequency ablation (RFA) technology. Patients with limited number of small nodules are good candidates for both SSLB-TACE and c-TACE, but these are also good candidates for RFA. Because higher priority is given to RFA, TACE is usually indicated for patients with 4 or more nodules, with large nodule(s), and/or with proximal Glisson attaching nodule(s). However, these cases are known as TACE-refractory, and the chance to perform SSLB-TACE or c-TACE would be markedly decreased in institutions where RFA is aggressively performed. In the past, paradigm shift from non-selective TACE to super-selective TACE occurred, and the goal of SSLB-TACE and c-TACE is prolonged complete remission of the treated nodules while sacrificing small volume of liver parenchyma. But another TACE technique, aiming treatment of wide region (hemi-lobe or more) and effective tumor volume reduction while minimizing liver parenchymal damage, is mandatory in RFA era. For this purpose, we developed a new balloon-occluded TACE without using lipiodol; alternate infusion of cisplatin solution and sparse gelatin slurry was repeated under balloon-occlusion (RAIB-TACE) until stasis of gelatin slurry in proximal hepatic arteries was seen. However, not only RFA but also recent development of molecular targeted drugs strongly influences on the indication and the aim of TACE. The goal and technique of TACE should be properly selected in each era, in each institution, and for each patient.

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Keywords: Balloon occlusion; Chemoembolization, therapeutic; Hepatocellular carcinoma

Introduction

Super-selective balloon-occluded transarterial chemoembolization (TACE) increases lipiodol accumulation in hepatocellular carcinoma (HCC) nodule (Fig. 1). To understand this mechanism, knowledge about angio-architecture of tumor feeders, intra-hepatic collaterals, and rheology of lipiodol emulsion are necessary. These knowledges are also helpful to improve conventional super-selective lipiodol TACE (c-TACE) technique using a microcatheter and to develop new TACE technique.

Background of Super-Selective Lipiodol Balloon-Occluded TACE

As far as we know, use of balloon catheter for TACE of HCC was first reported in 1985 by Nakamura et al.[1] A balloon catheter was placed at common hepatic artery, the flow direction of gastroduodenal artery was reversed, and TACE could be done while preventing inflow of embolization material into pancreas and duodenum. This technique could be also applied for radioembolization[2] while common hepatic artery is occluded with balloon to reverse the flow of right gastric artery. Right gastric and gastroduodenal arteries are large and visible collaterals, but invisible small collaterals such as peri-biliary arterial plexus[3] and isolated

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arteries[4] are diffusely equipped in peripheral hepatic arterial system. Thus, balloon-occlusion of peripheral hepatic artery only decreases hepatic arterial flow, but could not achieve complete cease of hepatic arterial flow. This phenomenon was first reported by Sugai et al.[5] They performed balloon-occluded angiography via proper or right hepatic artery in more than 50 cases and showed that complete cease of hepatic arterial flow could not be achieved. They also proposed a hypothesis that peri-biliary plexus worked as collaterals and arterial flow could not be ceased by balloon inflation.

Peri-biliary arterial plexus is well known intra-hepatic collateral arterial system, but it is seldom seen on digital subtraction angiography (DSA) during TACE procedures and the reason is still unknown. The arterial diameter of peribiliary plexus would be too small for depiction, or it might be a dynamic system. Peri-biliary plexus might be closed in ordinary statue and opened in ischemic statue (Fig. 2).

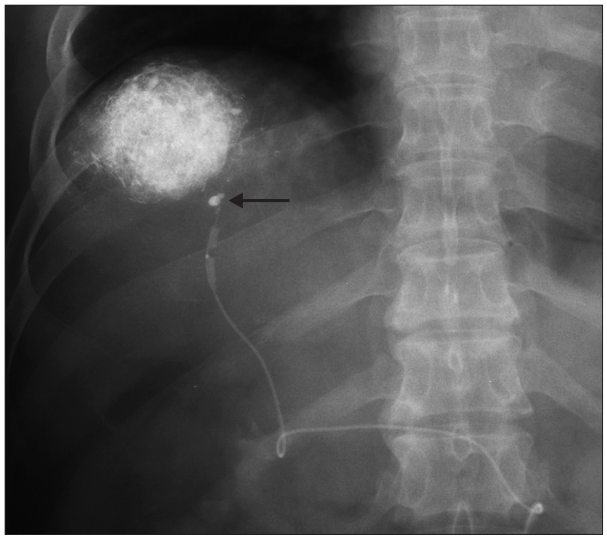


Fig. 1. The first case of super-selective lipiodol balloon-occluded transarterial chemoembolization performed in 1991 using a coronary angioplasty balloon catheter. A coronary angioplasty catheter was passed through a 7 F guiding catheter and placed in subsegment 8 artery. Lipiodol emulsion was infused under balloon-occlusion and a spot radiography was obtained before embolization of gelatin fragments. Densely accumulated lipiodol in hepatocellular carcinoma nodule and adhesion of a lipiodol droplet at the catheter tip were seen (arrow).

At the beginning of our balloon-occluded TACE (B-TACE) experiences, we did not know why arterial flow could not be ceased by balloon-occlusion. Initially, we considered that incomplete inflation of the balloon might be the cause of maintained arterial flow. However, adhesion of lipiodol droplet at the tip of inflated balloon catheter was frequently seen. Actually, this lipiodol adhesion was seen in the initial super-selective lipiodol B-TACE (SSLB-TACE) case performed in 1991 using a coronary angioplasty balloon catheter (Fig. 1). Adhesion of lipiodol droplet indicated that no arterial flow existed between the inflated balloon and arterial wall, and incomplete inflation was not the cause of maintained blood flow beyond the balloon catheter. Then, we performed clinical study to explain this phenomenon;[6] we measured the arterial stump pressure at the tip of the balloon catheter before and after balloon inflation, confirmed that arterial stump pressure was decreased after balloon inflation, and found that increased lipiodol accumulation was seen when balloon-occluded arterial stump pressure was decreased to 64 mmHg or less. Proximal portion of each segmental level artery was often connected with communicating arcades (Fig. 3),[7] and super-selective placement of a balloon catheter beyond the communicating arcades was necessary to decrease balloon-occluded arterial stump pressure. Based on these results, we made a hypothesis to explain increased lipiodol accumulation by SSLB-TACE as follows: compared with blood, lipiodol emulsion was viscous. Tumor feeder was directly connected with tumor vessel within the HCC nodule, and the diameter was larger compared with that of arterial branch supplying liver parenchyma (Fig. 4). Thus, flow resistance of tumor feeder was lower than that of artery supplying liver parenchyma. Balloon-occlusion of peripheral hepatic artery decreased arterial stump pressure at the catheter tip. Arterial flow beyond the catheter was still maintained by intra-hepatic collaterals, and viscous lipiodol emulsion was pushed into the nodule even by the decreased arterial stump pressure. But lipiodol emulsion could not be pushed into normal liver parenchyma efficiently by the decreased arterial stump pressure. Thus, lipiodol accumulation in liver parenchyma ceased soon, while accumulation in the HCC nodule continued.

The viscosity of lipiodol emulsion could be controlled by changing the ratio of lipiodol to drug solution.[8] Increasing the ratio of lipiodol to drug solution enables to prepare lipiodol emulsion more viscous. Increased viscosity is feasible for SSLB-TACE to increase lipiodol accumulation in the nodule. Typically, we mix 10 mL lipiodol with 2–3 mL drug solution. In Japan, lipiodol suspension with lipophilic cisplatin (MIRIPLA; Dainippon Sumitomo

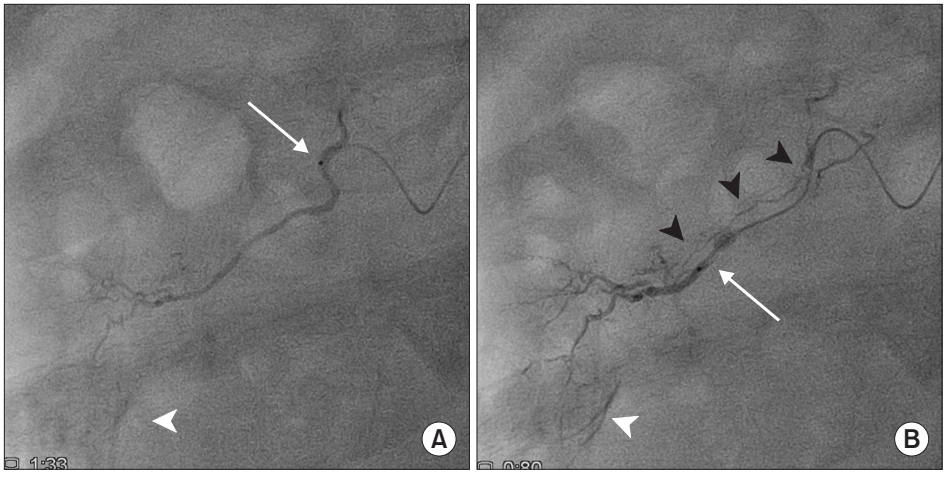


Fig. 2. Peri-biliary arterial plexus. Super-selective digital angiography depicted a tumor stain (arrowhead; A). A microballoon catheter was deeply placed adjacent to the nodule (arrow; B) and lipiodol-balloon-occluded transarterial chemoembolization (B-TACE) was performed. Digital angiography during lipiodol infusion depicted a tumor (white arrowhead; B) and retrograde filling of lipiodol in small arteries accompanying with the tumor feeder (black arrowheads; B). But these small arteries were not depicted on the digital angiography performed via proximal portion (arrow; A). We speculated that the small arteries, peribiliary plexus were opened to supply ischemic portion produced by B-TACE.

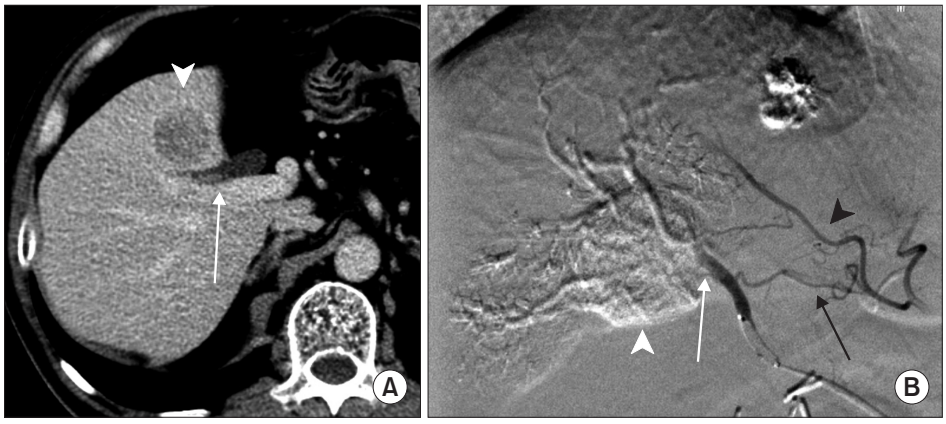


Fig. 3. Communicating arcade depicted during selective lipiodol-balloon-occluded transarterial chemoembolization (Lip-B-TACE). The targeted nodule (arrowhead; A) was attached to the right hepatic duct (arrow; A) on computed tomography. At first, Lip-B-TACE was done via anterior segment artery and lipiodol accumulation in the nodule was seen (white arrowhead; B). The balloon catheter was slightly withdrawn and balloon-occluded digital subtraction angiography (DSA) was performed (B). A small tumor feeding artery (white arrow; B) branching from the trunk of anterior segment artery and a communicating arcade (black arrow; B) between anterior segment and medial segment arteries (black arrowhead; B) were depicted. Immediately after DSA, lipiodol emulsion was forcefully injected to infuse into the small tumor feeder while regurgitating lipiodol into medial segment artery. Much volume of liver parenchyma, anterior, and medial segments, was affected by lipiodol.

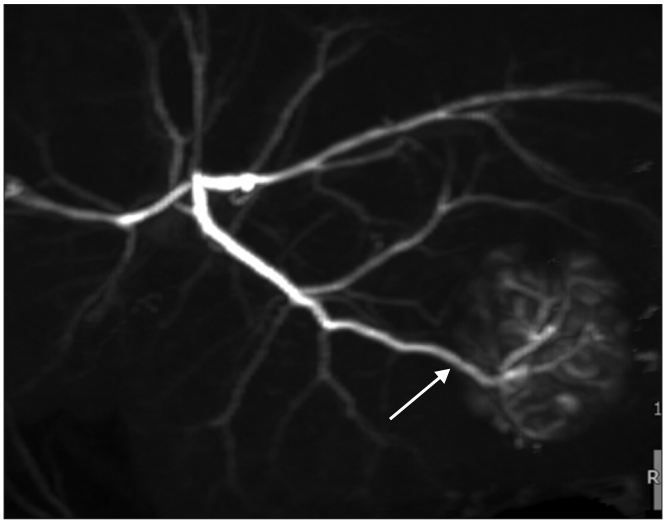


Fig. 4. Structure of tumor feeder to a peripheral nodule apart from proximal Glisson sheath. A main tumor feeder was connected with intra-nodular tumor vessels on slab maximum intensity projection image of trans-arterial multidetector computed tomography (arrow). The diameter of intra-nodular tumor vessel was larger than that of the tumor feeder.

Pharma, Osaka, Japan) is available. This suspension, mixture of lipiodol with cisplatin powder, is more viscous than lipiodol emulsion, and suitable for SSLB-TACE.[9,10]

TACE-Refractory Factors

There are several weak points in c-TACE. It is well known as "up-to-seven rule" that large size and multiplicity are TACE-refractory factors.[11] When a microcatheter is deeply placed in a peripheral tumor feeder for infusion of much lipiodol, c-TACE is highly effective to control the targeted nodule sacrificing small volume of liver parenchyma.[12] But there are many tumor feeders in large and/or multiple nodules, and it is impractical to place a microcatheter in each tumor feeder. This would be one of the reasons why large and multiple nodules are TACE refractory.[13] SSLB-TACE increases lipiodol accumulation in nodules and decreases the number of arteries in which catheter should be placed, but it is still time-consuming and technically difficult to treat many tumor feeders. Another TACE-refractory factor is central location of the nodule.[14,15] Nodule attached to proximal Glisson sheath is often supplied via very small arteries directly branching from the large trunk artery.[14] It is difficult to perform c-TACE for each small tumor feeder using a microcatheter. It is sometimes difficult for SSLB-TACE to inject lipiodol emulsion and embolization materials into these small tortuous feeders via the trunk artery. Because lipiodol emulsion forms round droplets in a large artery and the droplet has surface tension keeping its shape round and preventing its fragmentation (Fig. 5), most of droplets inflow beyond the small feeders into normal liver parenchyma. Thus, nodule attaching to proximal Glisson sheath is TACE-refractory. TACE-refractory factors in c-TACE are also those in SSLB-TACE.

Influence of Radiofrequency Ablation Technology on the Indication of TACE

Surgery and radiofrequency ablation (RFA) are curative treatments compared with TACE, and higher priority for treatment indication is given to them. Patients with limited number of small nodules are usually treated by surgery or RFA.[16] When c-TACE was first developed by Matsui et al[17] and Uchida et al,[18] RFA technology was unavailable. At that era, the role of c-TACE was to achieve prolonged complete remission (CR) in patients with limited number of small nodules. Actually, limited number of small nodules could be well controlled by c-TACE, and paradigm shift from non-selective lipiodol TACE to c-TACE occurred with the development of a microcatheter and various imaging modalities to detect small nodules. However, development of RFA technology took away the chance to perform c-TACE for these patients with limited number of small nodules. Although recent development of RFA technology expanded its indication, one of contraindications for RFA is nodules attached to proximal Glisson sheath because RFA causes thermal damage on biliary tract.[19,20] These cases are also known as TACE-refractory.[14,15]

In institutions where RFA is properly performed, TACE is of-

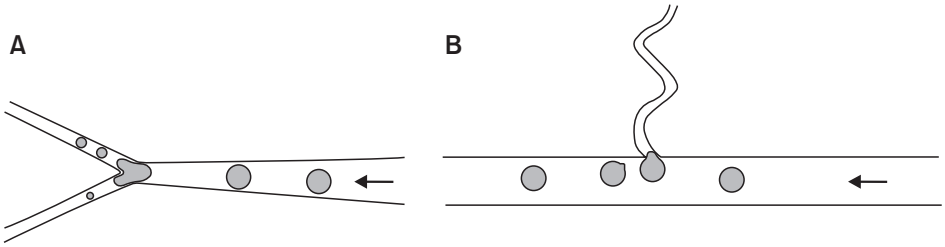


Fig. 5. Illustrations showing difference in tumor feeder structure. When a trunk artery diverges into several similar size arteries, lipiodol droplets are fragmented at the diverging point (A). Thus, lipiodol droplets could flow into the tumor feeders. When very small tumor feeders branch out from a large trunk artery, lipiodol droplets could not be fragmented due to its surface tension, nor could not flow into the small tumor feeders (B).

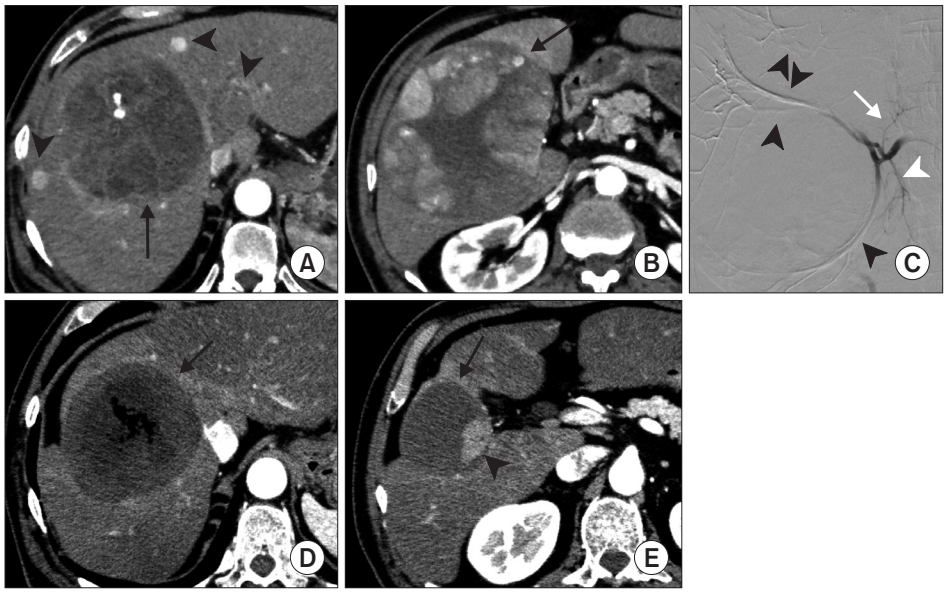


Fig. 6. Repeated alternate infusion of cisplatin and sparse gelatin slurry under balloon-occlusion (RAIB-TACE) for large nodules. Dynamic computed tomography (CT) showed 2 large nodules (arrow; A, B) more than 10 cm in diameter and multiple small nodules (arrowheads; A). First session of RAIB-TACE was performed for right and left hepatic arteries. On digital subtraction angiography after first session of RAIB-TACE (C), caudal segment (white arrow; C) and gall bladder arteries (white arrowhead; C) were patent. Arterial branches were filled with gelatin slurry (black arrowheads; C). Second session of RAIB-TACE was performed 3 months after the first one. Dynamic CT 5 months after second session of RAIB-TACE showed complete remission (arrow; D) and partial remission (black arrow; E) of each large nodule. The viable part (arrowhead; E) would be supplied via gall bladder artery.

ten indicated for TACE-refractory nodules/patients. Thus, before performing TACE, we should remind and understand that the targeted nodules and patients are TACE-refractory or not. Finally, proper TACE technique should be selected and performed. We now perform 2 types of B-TACE, 1) SSLB-TACE to intend prolonged CR while sacrificing small volume of liver parenchyma, and 2) repeated alternate infusion of cisplatin and sparse gelatin slurry under balloon-occlusion (RAIB-TACE) to intend CR or near CR partial remission while minimizing liver parenchymal damage.

Indication of SSLB-TACE

SSLB-TACE could improve local control rates in patients with 1–2 nodules compared with c-TACE.[21] We consider that SSLB-TACE is especially effective to control nodules 4 cm or less in diameter and located apart from proximal Glisson sheath. Because patients with 1–3 nodules less than 3 cm in diameter were usually treated by RFA, the chance to perform SSLB-TACE is markedly decreased. A good review paper about clinical results of SSLB-TACE is available.[22] Although SSLB-TACE is thought to be a promising technique, randomized prospective controlled trials to compare local control rates with c-TACE are still lacking.

The Concept and Indication of RAIB-TACE

To include entire nodules completely within treatment region, TACE for wide region (segmental to whole liver) is one of the options. However, much volume of liver parenchyma is affected by TACE. Anti-tumor effect of lipiodol emulsion is great, but infusion via proximal level artery causes damage of much volume of liver parenchyma.[23] Most Japanese interventional radiologists do not prefer lipiodol TACE for wide region because the demerit of widespread liver damage by lipiodol often overcomes the merit of limited anti-tumor effect.

RAIB-TACE is a new B-TACE technique for wide region without using lipiodol. The concept of RAIB-TACE is improvement of non-selective TACE.[14,24] The original TACE technique for whole liver reported by Yamada et al[25] was non-selective TACE via a single artery, proper hepatic artery. In this technique, gall bladder artery was also embolized that often caused ischemic cholecystitis.[26] In RAIB-TACE for whole liver, 2 or more arteries were selected to avoid embolization of gall bladder artery. For example, when caudate and/or medial segment arteries branched directly from right hepatic artery, each artery was selected for embolization. Cisplatin solution and sparse gelatin slurry was alternately infused under balloon-occlusion. The end-point of RAIB-TACE is stasis of sparse gelatin slurry in proximal hepatic arteries like tree structure beyond the balloon catheter. This technique was developed to treat TACE-refractory nodules. Non-use of lipiodol would decrease anti-tumor effect, but also decrease liver parenchymal damage. Thus, wide region could be safely treated and entire TACE-refractory nodules could be included within the treatment region. Lipiodol emulsion is viscous and does not inflow efficiently into very small or tortuous corkscrew arteries. But non-viscous drug solution could inflow into these arteries. We use cisplatin, not epirubicin nor doxorubicin, for RAIB-TACE. Although both drugs are most widely used for creation of lipiodol emulsion, cisplatin is used in almost all cases for repeated intra-arterial infusion treatment.[27] The great merit of intra-arterial administration of cisplatin compared with trans-venous administration is higher ac-

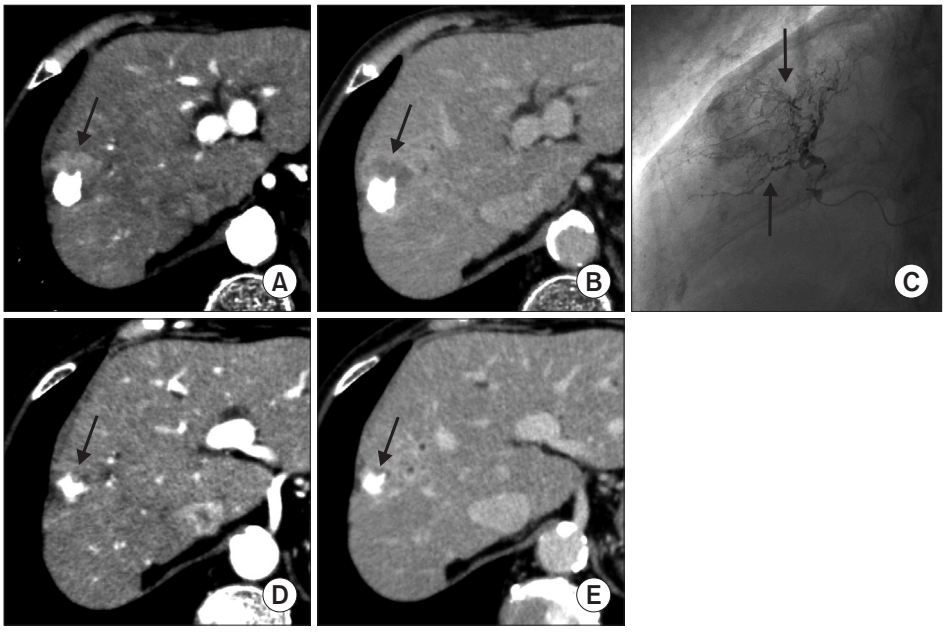


Fig. 7. Repeated alternate infusion of cisplatin and sparse gelatin slurry under balloon-occlusion (RAIB-TACE) for a recurred nodule after conventional super-selective lipiodol (c-TACE). Dynamic computed tomography (CT) showed a recurred nodule (arrow; A, B) 1 month after c-TACE performed at a neighboring hospital. Selective digital angiography showed tortuous corkscrew tumor feeders (arrows; C), and RAIB-TACE was performed via anterior superior subsegment artery. Dynamic CT 1 year after RAIB-TACE showed complete remission of the nodule (black arrow; D, E).

tivity of cisplatin. Albumin-bound platinum is considered as therapeutically inactive. Transarterial infusion decreases the bounding chance between albumin and cisplatin, and increases the ratio of free cisplatin.[28] Additionally, balloon-occluded infusion increases the concentration of cisplatin.

To prevent collateral supplies, embolization of tumor vessels inside the nodule is effective. We consider 100–200 μm gelatin particle is suitable.[29] Commercially available 1 mm particles are crushed by pumping method to create 100–200 μm fragments.[30]

RAIB-TACE increases control rate of small nodule attaching to proximal Glisson sheath.[14] RAIB-TACE is also useful to control large nodules (Fig. 6).[24] It would be worth to try to treat c-TACE-refractory nodule by RAIB-TACE (Fig. 7).

Role of TACE in Future

As described above, the indication and role of TACE are strongly influenced by the development of other treatment strategies. In institutions where RFA is aggressively performed, the chance to perform c-TACE and SSLB-TACE would be markedly decreased. In such institutions, one of the main roles of TACE is to treat multiple nodules. However, recently, development of molecular targeted drugs (MTD) is also influencing on the indication of TACE. While TACE could be repeated and temporal tumor volume reduction could be achieved, liver function gradually decreases by repetition of TACE and advancement of the tumor stage. For administration of MTD, liver function should be preserved. Thus, liver parenchymal damage by TACE should be minimized. The objective ratio of MTD is 60% or more, and MTD is replacing the role of TACE.[31] When TACE is performed as substitute of MTD, the goals are both partial remission in more than 60% patients and preservation of liver function. The goal and technique of TACE should be properly selected in each era, in each institution, and for each patient. Development and improvement of TACE technique for wide region is mandatory. In MTD era, the role of TACE should be a good bridge from RFA/surgery to MTD.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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