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REVIEW

Effective Utilization of Conventional Transarterial Chemoembolization and Drug-eluting Bead Transarterial Chemoembolization in Hepatocellular Carcinoma: A Guide to Proper Usage

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Abstract:
Transarterial chemoembolization is still an effective treatment option for hepatocellular carcinoma worldwide and is categorized into conventional transarterial chemoembolization with ethiodized oil transarterial chemoembolization and transarterial chemoembolization with drug-eluting spherical material transarterial chemoembolization. Several randomized controlled trials conducted in Europe have shown the equivalent efficacy of ethiodized oil transarterial chemoembolization and drug-eluting spherical material transarterial chemoembolization. However, a recent randomized controlled trials in Japan established the superiority of ethiodized oil transarterial chemoembolization in terms of complete response rates although higher liver toxicity for ethiodized oil transarterial chemoembolization. Nevertheless, the survival advantage of ethiodized oil transarterial chemoembolization is yet to be substantiated. The adverse effects of drug-eluting spherical material transarterial chemoembolization are milder than those of ethiodized oil transarterial chemoembolization, rendering drug-eluting spherical material transarterial chemoembolization an advantageous option for patients with bilobar tumors and impaired liver function/performance status. This article aims to provide an overview of these embolization techniques and a review of recent literature.

Keywords:
hepatocellular carcinoma, transarterial chemoembolization, drug-eluting beads-transarterial chemoembolization

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Introduction

In 1983, Yamada et al. pioneered the use of transarterial embolization (TAE) for hepatocellular carcinoma (HCC) by reporting on 120 cases, thereby laying the foundation for its widespread implementation [1]. In 1985, Onishi et al. introduced a novel technique that involves injection of a mixture of ethiodized oil and anticancer drugs, followed by TAE using a gelatin sponge [2], which served as the prototype for the current standard of transarterial chemoembolization (cTACE). In this article, TACE using ethiodized oil is referred to as cTACE. Onishi et al. reported that ethiodized oil was mainly used as a standalone anticancer drug and exhibited enhanced antitumor effects, but they also highlighted its utility in the diagnosis of HCC, leading to the clinical application of cTACE. Nakamura et al. investigated the role of ethiodized oil as a drug-delivery carrier for anticancer drugs and reported that ethiodized oil flowed into the portal vein of the injected area at a high rate, resulting in favorable antitumor effects when ethiodized oil was detected [3, 4]. At the time, cTACE for HCC only entailed embolizing the entire liver or a single lobe, necessitating large amounts of ethiodized oil to reach the portal vein area, which had a significant effect on liver function and caused liver damage. The introduction of digital substraction angiography in the 1980s and advancements in catheter technology enabled selective catheter insertion, whereas screening tests for HCC became more common and localized HCC became a target for treatment. In the late 1980s, segmental TACE for HCC was introduced by Uchida et al. [5, 6]. In 1993, Matsui et al. reported that the introduction of a microcatheter in cTACE allowed for TACE in the periphery rather than in the

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subsegmental region, thus improving the therapeutic efficacy of HCC smaller than 4 cm in diameter [7]. In Japan and other Asian countries, cTACE has become the standard treatment for TACE of HCC. In Japan, further miniaturization of microcatheter tip diameter has made it possible to insert microcatheters into the third and fourth branches of subsegmental arteries, resulting in a more localized stagnation of ethiodized oil and a stronger embolic effect, as reported by Miyayama et al. with the term "ultraselective cTACE" [8]. Conversely, a microspherical embolization material (microsphere) has been widely used as an embolization material for TACE for HCC since 2000, mainly in Europe and the United States, giving rise to TACE using drug-eluting beads (DEB-TACE) [9]. Several large-scale clinical trials have been conducted to evaluate the use of TACE and the superiority of its therapeutic effects [10-12].

In this review article, we will discuss the evidence-based use of TACE for HCC, including prevalent modifications aimed at therapeutic efficacy enhancement, as well as recent advancements in each TACE technique.

Utilization of cTACE and DEB-TACE: A Review of the Outcomes of Prior Clinical Trials

In the past, the outcomes of large-scale clinical trials pertaining to the use of cTACE or DEB-TACE have been largely equivocal regarding the superiority or inferiority of the two, and no definitive opinion has been reached for their use. Three randomized controlled trials and retrospective studies have been conducted to compare the efficacy of cTACE and DEB-TACE (**Table 1**) [10-14]. Lammer et al. conducted a randomized comparative study of cTACE and DEB-TACE in 212 patients with HCC (PRECISION V) [10]. The results indicated that the response rates at 6 months, the primary endpoint, were 51.6% and 43.5% in the DEB-TACE and cTACE groups (p = 0.11), with no significant difference. However, the response rate was significantly higher in the DEB-TACE group in patients with Child-Pugh B, Eastern Cooperative Oncology Group Performance Status Scale 1, bilateral lobe disease, and recurrent disease (p = 0.038). The DEB-TACE group had significantly fewer hepatotoxic and doxorubicin-related adverse events (p < 0.001, p = 0.0001) and was better tolerated. Golfieri et al. conducted a randomized, comparative study of cTACE and DEB-TACE in 177 patients with Barcelona Clinic Liver Cancer stage B HCC (PRECISION ITALY) [12]. The results indicated no significant differences in the progression-free period (cTACE: 9 months vs. DEB-TACE: 9 months, p = 0.766) or survival (2-year survival rate, cTACE: 56.8% vs. DEB-TACE: 55.4%, p = 0.949), and only postembolization pain was more frequent in the cTACE group (p < 0.001). A randomized comparative study of selective TACE with cTACE and DEB-TACE conducted by the Japan Interventional Radiology in Oncology Study Group were conducted in 200 patients with liver cancer [15]. The complete remission (CR) rate at 3 months was defined as the primary endpoint, whereas the CR rate at 1 month and the incidence of ad-

Table 1. Comparison of DEB-TACE and c-TACE Outcomes.

Report (year)		Group	Patient	BCLC stage	Embolic material/ particle size	Anticancer drug	Ethiodized oil	Local control effect (%)			*P*-value	Survival rate (%)		
			(n)	(A/B/C)	(μm)	(mg) (Average)	(ml) (Average)	CR (%)	PR (%)	Response (%)		1y	2y	*P*-value
Lammer/2010 (PrecisionV)	Overall	DEB-TACE	93	24/69/0	DC-Bead 300-500, 500-700	DOX ≤ 150	-	26.9	24.7	51.6	0.11	-	-	-
		cTACE	108	29/79/0		DOX ≤ 150	-	22.2	21.3	43.5		-	-	
	Advanced Case	DEB-TACE	63	-	DC-Bead 300-500, 500-700	DOX ≤ 150	-	25.4	27.0	52.4	0.038	-	-	-
		cTACE	72	-		DOX ≤ 150	-	13.9	20.8	34.7		-	-	
Sacco/2011		DEB-TACE	33	22/11/0	DC-Bead 100-300	DOX 25-150 (55)	-	51.5	48.5	100	0.1	-	86.8	0.96
		cTACE	34	22/12/0	GS	DOX 50-75 (57)	10-25 (16.6)	70.6	29.4	100		-	83.6	
Golfieri/2014 (Precision Italia)		DEB-TACE	89	41/26/22	DC-Bead 100-300	EPIR 50/vial	-	55.7	19.0	74.7	>0.999	86.2	56.8	0.949
		cTACE	88	41/23/24	GS	EPIR ≤ 75	≤15	58.0	16.1	74.1		83.5	55.4	
Ikeda/2020 (PRESIDENT)		DEB-TACE	98	64/34/0	DC-Beaad 100-300	EPIR 1.5-150 (22.5)	-	27.5	-	-	<0.0001	-	-	-
		cTACE	101	73/25/3	GS	EPIR 2.3-85 (25)	0.47-10 (3.0)	75.2	-	-		-	-	

GS: gelatin sponge DOX: Doxorubicin, EPIR: Epirubicin

verse events were evaluated as secondary endpoints. The results indicated that the CR rates at 3 and 1 months were significantly higher in the cTACE group (75.2% and 84.2%) than in the DEB-TACE group (27.6% and 35.7%) [15]. However, the frequency of all grades of adverse events, including fever, fatigue, anorexia, and abdominal pain, was higher in the cTACE group. Hypoalbuminemia (43.4% vs. 60.3%, $p = 0.0154$), increased serum aspartate aminotransferase (35.7% vs. 81.2%, $p < 0.0001$), and increased serum alanine aminotransferase (35.7% vs. 77.2, $p < 0.001$) were also observed [15]. At present, selective cTACE for HCC appears to have a superior rate of complete response for local tumor control in comparison with selective DEB-TACE, yet the incidence of postembolization syndrome is also significantly higher in the cTACE group than in the DEB-TACE group. On the other hand, several studies have reported that bile duct injury [16], arterial portal shunt [17], and portal vein damage [18] occur more frequently following DEB-TACE. In light of these recent findings, cTACE should be considered as the preferred treatment option for patients able to tolerate the postembolic syndrome to achieve complete response.

Innovative Techniques Employed during the Implementation of cTACE and DEB-TACE for the Treatment of HCC

There are various factors that may play a role in the technical accuracy and efficacy of cTACE and DEB-TACE. Among them, advancements in catheter technology are considered as a crucial determinant of treatment success. Of particular significance is the role of microcatheter in enhancing TACE outcomes, as they have undergone significant advancements in Japan [19].

As the development of microcatheters progressed, the utilization of Interventional Radiological Angiography units equipped with computed tomography (CT) (commonly referred to as IVR-CT) [20] as well as cone-beam CT images obtained through rotational imaging and equipped with flat panel detector equipment has also significantly contributed to the advancement of diagnostic imaging during TACE [21-23]. Both CT and cone-beam CT have been instrumental in enhancing the diagnosis of HCC and identification of feeding arteries through the utilization of CT imaging with hepatic arteriography (CTHA) during TACE (**Fig. 1**). Furthermore, CTHA image data are transferred to a specialized workstation, and guidance software for arterial embolization, referred to as 3D automated tumor-feeder detection (AFD) software, is now readily available. This software has been reported to improve the technical success of TACE and early tumor response by accurately recognizing the feeding arteries of HCC; it has an accuracy of 85%-93% [24-27].

Miyayama et al. employed unenhanced CT at 1 week after cTACE using guidance software to evaluate the degree of ethiodized oil retention in HCC and reported on the technical success of cTACE and rates of local tumor control and overall survival [28]. They found that complete embolization with and without a safety margin was achieved in 82.1% and 13.7% of HCCs treated with cTACE, respectively. Incomplete embolization was achieved in only 4.2%. According to the degree of technical success, the rates of intrahepatic tumor recurrence (local tumor progression [LTP]) were 31.7%, 49.4%, and 59.4% at 1, 3, and 5 years, respectively, although the overall survival did not significantly differ. Notably, LTP occurred more frequently in the HCC group that achieved complete embolization without a safety margin than in the HCC group that achieved complete embolization with a safety margin ($p = 0.016$), and intrahepatic distant recurrence (IDR) also developed more frequently in patients with LPT ($p = 0.0004$). This indicates that some IDR may be metastases from LTP or promoted mainly by high expression of vascular endothelial growth factor from residual tumor cells. The use of the 3D AFD software during TACE appears to result in high technical success rates and good local control in patients with localized HCC (**Fig. 2**).

Tips on cTACE for HCC

The objective of cTACE is to achieve CR in the target HCC. Recent studies have demonstrated that patients exhibit improved prognosis when CR is achieved as a first-line TACE therapy [29, 30]. In Japan, cTACE is performed using a technique named superselective TACE, which is typically performed by using IVR-CT or cone-beam CT imaging as a guide to locate the HCC and identify its feeding arteries, then using a conventional 1.7 to 2.4 Fr microcatheter inserted into the more peripheral hepatic artery from the segmental branch for embolization [31]. Various other technical innovations of microcatheters have been developed in Japan, including TACE under blood flow control using microballoons and microballoons with side holes [32, 33]. For further information, please refer to other articles in this special issue. The recent development of microcatheters with a smaller 1.5 F tip has enabled the catheter tip to reach the more distal level of the feeding artery during cTACE (**Fig. 3**) [34]. There are also reports of variable tip microcatheters that enable the insertion of microcatheters into steep arterial branches that were previously challenging to catheterize; this may serve as an alternative option for microcatheterization [35].

Optimizing the Utilization and Stability of Ethiodized Oil Emulsions

With regard to the use of ethiodized oil during cTACE, previous studies have suggested that the amount of ethiodized oil used should be proportional to the largest total tumor diameter (in centimeters) of the targeted HCCs [5], whereas others have posited that complete necrosis can be achieved by administering an appropriate amount of ethiodized oil emulsion exceeding the tumor diameter [36]. However, to preserve liver function, it is generally recommended to limit the maximum dose of ethiodized oil per session to 10 mL in Japan [5, 37] and 15 mL in Western countries

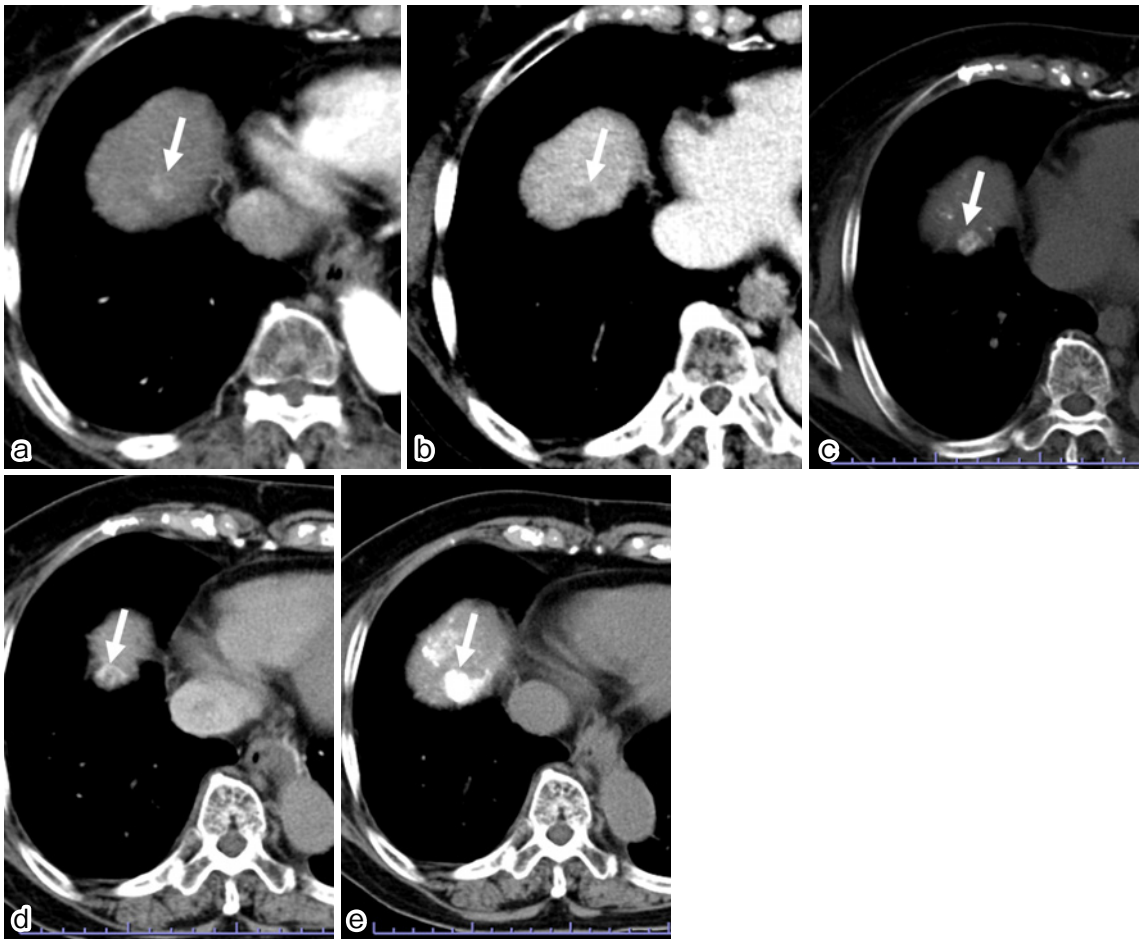

Figure 1. 82 y.o. Female with hepatitis C and B who has been repeatedly treated with TACE, radiofrequency ablation, and percutaneous ethanol injection therapy.
a/b. Intravenously administered contrast-enhanced dynamic CT scans showed the presence of a 1-cm hypervascular solitary nodule (a. white arrow) in segment 8 of the right diaphragm. The portal venous phase revealed washout within the nodule (b. white arrow), indicating a potential recurrence of hepatocellular carcinoma (HCC).
c/d. The preoperative diagnosis of HCC was visualized as a hypervascular nodule during the early phase of computed tomography hepatic arteriography (CTHA) (c. white arrow), with washout within the nodule and corona enhancement surrounding it being depicted during the delayed phase (d. white arrow).
e. The well retention of ethiodized oil within the HCC nodule was demonstrated.

[38].

The preparation of stable ethiodized oil emulsion in cTACE has been widely reported since the advent of TACE using ethiodized oil [39-43]. Recently, Tanaka et al. developed a novel and simple pumping glass-membrane emulsification device (GMD) with a membrane for forming water-in-oil emulsions [44, 45]. They reported that the drug elution capacity of the epirubicin-ethiodized oil emulsion created by this pump emulsifier with a glass membrane had a significantly longer release half-life than that using a three-way cock, suggesting a sustained drug release effect (175 ± 25 min vs. 8 ± 6 min, $p < 0.001$). In addition, several centers have recently reported treatment results of cTACE using this pump emulsifier with glass membrane [46, 47]. Ishikawa et al. compared the local recurrence rate of cTACE with and without GMD [48]. The local recurrence rate of TACE without GMD was 3.0% at 6 months, 16.7% at 12 months, and 35.0% at 18 months, with a plateau state around this. In the GMD-cTACE group, the local recurrence rates were 7.7% at 14 months and 23.1% at 20 months [48]. Further reports on the outcomes of cTACE using this GMD are expected to be published in the future.

Strategies for Executing Efficient and Superselective cTACE

When performing superselective TACE, it is necessary to keep in mind certain technical considerations to optimize therapeutic efficacy. First, ethiodized oil should be administered at a slow pace to prevent the formation of an "oil film" within the artery. In the event that the flow of the tumor-supplying branch unexpectedly ceases prior to the portal vein becoming fully visible, it is recommended to increase arterial flow by administering 0.5 μg of prostaglandin E 1 (Liple; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) or 0.5 mL of 2% lidocaine *via* catheter. In addition, it is recommended to advance the microcatheter as distally as possible to achieve a "semiwedged condition" [49]. Fur-

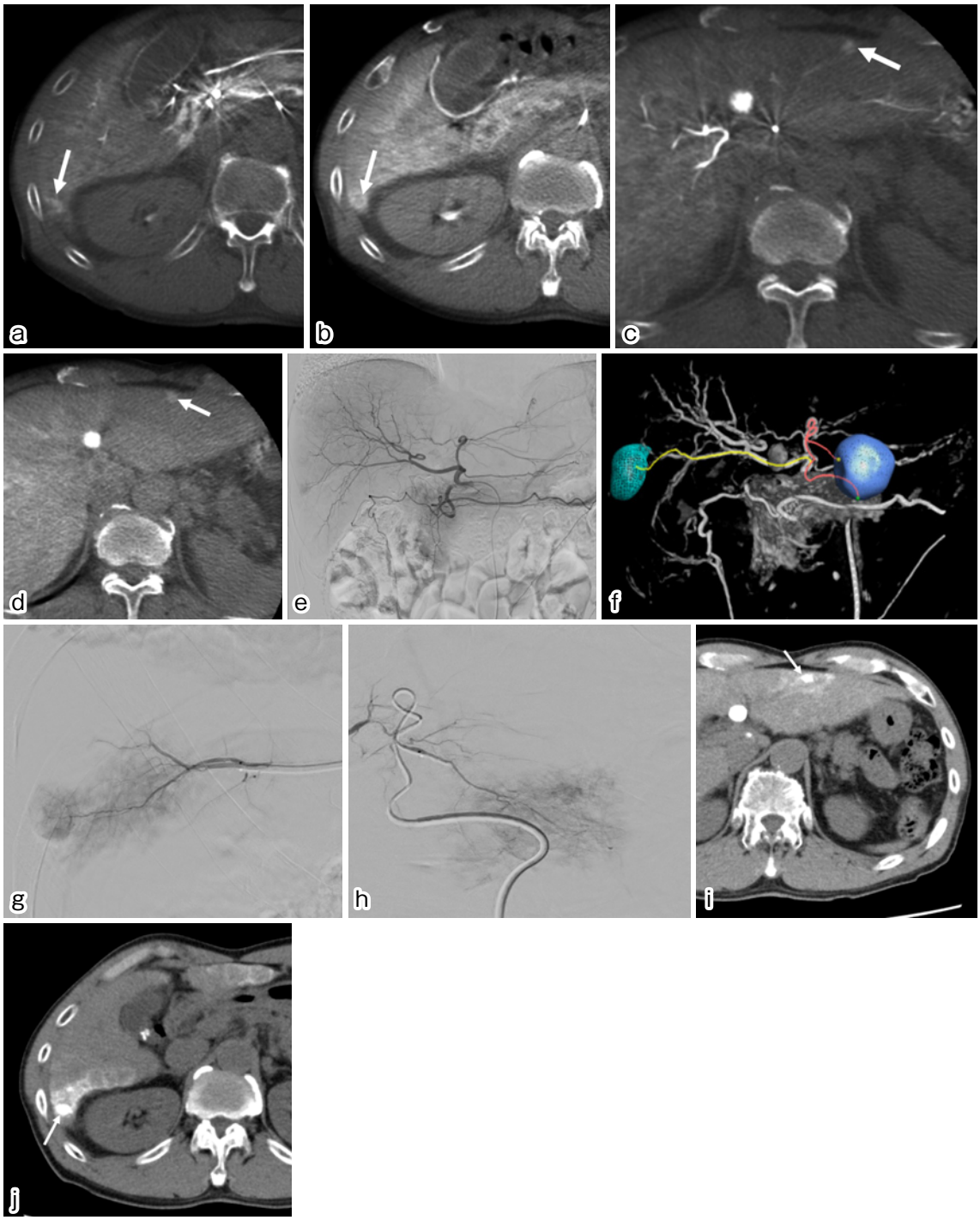

Figure 2. 73 y.o. Male patient with hepatitis C who has been repeatedly treated with TACE.
a/b. In the early phase of cone-beam computed tomography during hepatic arteriography at the time of TACE, a hypervascular nodule was visualized in segment 6 (a. white arrow), with evidence of washout within the nodule (b. white arrow).
c/d. An additional hypervascular nodule exhibiting similar contrast characteristics was detected beneath the capsule in the S3 area of the liver and was diagnosed as HCC (white arrow).
e. Angiography derived from the common hepatic artery demonstrated evidence of tumor staining within the capsule of the right lobe of the liver, consistent with HCC located in segment 6. The HCC in segment 3 was obscure.
f. In preparation for TACE, the regions of interest were defined as green and blue circles for two HCCs using the TACE guidance software. The 3D AFD software was then used to visualize the feeding artery supplying each HCC in the form of yellow and red lines, depicted in the three-dimensional volume rendering image, as targeted for embolization.
g/h. The tip of a 1.7 Fr microcatheter was inserted with superselective precision under the segmental plane, resulting in a clear and distinct delineation of each neoplastic lesion.
i/j. Each HCC exhibited a clear retention of ethiodized oil following cTACE.

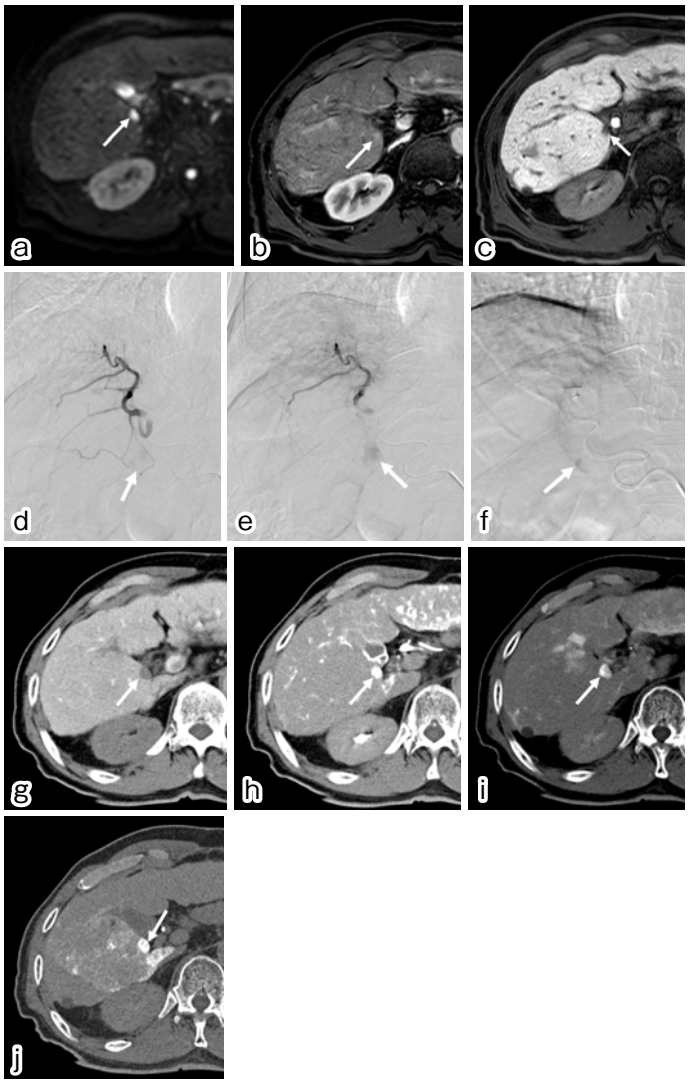

Figure 3. 71 y.o. Male with hepatitis C who has been repeatedly treated with cTACE.

a. The diffusion-weighted imaging depicted a nodule with high signal intensity at the marginal hilar region in S5.

b. Gd-EOB-DTPA-enhanced MRI with early phase depicted as a hypervascular nodule (white arrow).

c. Gd-EOB-DTPA-enhanced MRI with hepatobiliary phase depicted as a hypointensity nodule for decreased uptake of EOB, diagnosed as HCC (white arrow).

d. An angiography performed from the anterior segment branch revealed a finely stained tumor.

e. A 1.5 Fr microcatheter was superselectively inserted into the distal region of the anterior segment, and the tumor stain was clearly depicted (white arrow).

f. The 1.5 Fr microcatheter was inserted even further distally into the sub segmental branch, with the sole depiction of the tumor stain (white arrow).

g. Arterial portography CT scans displayed the HCC as a low-attenuation region indicative of a perfusion defect (white arrow).

h. Early-phase hepatic arteriography CT scans revealed the HCC as a hyperattenuation region, signifying hypervascularity (white arrow).

i. The delayed-phase hepatic arteriography CT scans displayed washout in the HCC nodule (white arrow).

j. Well-ethiodized oil retention of the HCC (white arrow) was visible with a sufficient embolic margin after cTACE.

thermore, in cases where multiple nutrient branches are present, it is prudent to perform embolization of the main nutrient branch last, as immediately after routine TACE, it can be challenging to identify residual tumor staining and other small trophic branches due to the dense concentration of ethiodized oil and contrast medium in the surrounding liver parenchyma [49]. Moreover, the use of large volumes of ethiodized oil for large tumors carries the risk of serious complications such as systemic embolization and acute tumor lysis syndrome [50-52]. For localized tumors larger than 6 or 7 cm, staged superselective cTACE is an effective option and can be performed in two to three sessions depending on the vessel anatomy, each session being superselective and scheduled at intervals of 3 to 10 weeks, depending on the patient's symptoms and laboratory data [49, 53].

The Ingenuity of TACE Using Drug-eluting Beads (DEB-TACE)

Since 2000, spherical embolization materials known as microspheres have gained popularity in both Europe and the United States as an alternative to traditional polyvinyl alcohol and gelatin sponge materials. Among these microspheres, DEBs impregnated with anticancer drugs have become widely used in TACE for the treatment of HCC [54]. DEBs, primarily composed of synthetic resin, possess smooth surfaces and are uniform in size, enabling them to reach peripheral vessels with increased precision, particularly in the embolization of narrower target arteries. In the case of TACE using DEBs, positively charged anticancer drugs such as epirubicin, doxorubicin, and irinotecan can be impregnated into DC Bead® (BTG, London, UK) or Hepa Sphere™ (Merit Medical, South Jordan, UT, USA). In addition, anticancer drugs such as cisplatin and oxaliplatin, which do not possess surface charge, can be impregnated into HepaSphere™ owing to its water absorption capacity as a superabsorbent polymer.

The optimal size of beads used in DEB-TACE is typically within the range of 100-300 μm in diameter [55]. Based on the particle size, the beads embolize the arteries within the tumor or at the tumor periphery and consistently deliver anticancer agents to the embolization site. Owing to its spherical, permanent embolic properties, DEB possesses a potent embolic effect on peripheral arteries. Because it does not penetrate the tumor drainage vessels or portal vein, it tends to persist and recur at the tumor margins more frequently than cTACE [56]. A histopathological evaluation of the localized effects of doxorubicin-loaded DC Bead® and bland embolization with Embosphere® in explanted livers undergoing liver transplantation showed that necrosis in the bland embolization with the Embosphere® group was confined to the tumor nucleus, whereas the DEB-TACE group exhibited a notably higher incidence of tumor necrosis and necrosis in adjacent nontumoral regions. This outcome implies that DEB-TACE is a prolonged-release anticancer agent that amplifies the efficacy of DEB [57]. A study evaluating the distribution of DEB and concentration of the anticancer agent in tissue following DEB-TACE demonstrated that DEB was dispersed within an approximate radius of 1 cm from the tumor boundary at a rate of 42% within the tumor and 58% outside, and doxorubicin in the tissue eluted from the DEB also exhibited an efficacious concentration [58]. In an initial phase II trial comparing peripheral blood pharmacokinetics between DEB-TACE and cTACE, both the mean C_{max} and mean AUC were significantly lower in the DEB-TACE group, indicating the superior sustained drug release capabilities of DEB [59]. However, there is no evidence whether slow release of chemotherapeutics is more effective for HCC.

Does the size of DEB influence therapeutic efficacy?

Several studies have determined whether the size of DEBs influences the therapeutic efficacy of DEB-TACE for HCC. Notably, the utilization of smaller DEBs (100-300 μm) has been linked to higher overall survival rates and lower TACE toxicity in patients with poor liver function (Child-Pugh classifications B and C) and advanced HCC, particularly during the era when DEBs larger than 100 μm were utilized [60, 61]. More recently, the use of smaller DEBs (<100 μm) has resulted in significant enhancements in treatment response rate, procedure-related complications, and postembolization syndrome when administered to patients [62-64]. However, compared with cTACE, the use of smaller DEBs is associated with a heightened risk of hepatobiliary injury, including bile duct dilation, portal vein stenosis, and liver failure [62-64]. As a result, the optimal bead size for patients with HCC receiving DEB-TACE remains elusive and has yet to be thoroughly investigated. The absence of multicenter phase 2 or 3 clinical trials has resulted in a lack of established guidelines for selecting small-diameter DEBs in TACE for HCC. The use of commercially available small-caliber DEBs is mainly predicated on the experience of interventional radiologists.

Factors to Be Considered in DEB-TACE for HCC

To execute DEB-TACE with efficacy, it is important that the beads are properly diluted with a sufficient amount of contrast medium and administered at a slow rate to prevent aggregation, which can lead to a premature cessation of blood flow. Careful attention should be paid to the injection rate and increments to prevent backflow of the beads and prolonged injection process. This approach may increase the duration of the procedure and volume of contrast medium used, which may pose a challenge for the operator. The embolization endpoint should ideally be attained after five cardiac cycles of stagnation of contrast within the nutrient artery following a test injection of a small amount of contrast material. During the embolization process, a pooling image of contrast material referred to as a vascular lake may appear in the tumor area, and if such an image is seen, additional embolization with gelatin sponge particle should be added to mitigate the risk of intratumoral bleeding (**Fig. 4**). Western guidelines for the use of DC Bead® suggest the use

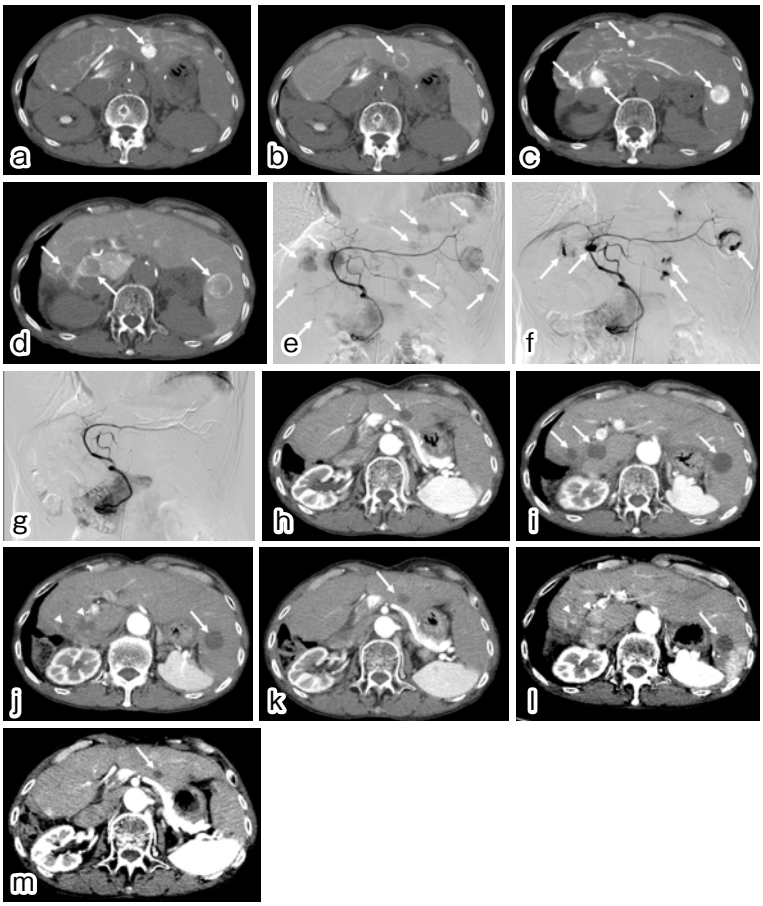

Figure 4. 78 y.o. Male with HCC in the setting of alcohol-related liver disease after right hepatectomy.

a. The early-phase CTHA of the liver demonstrated a hypervascular nodule in segment 3, characterized by hyperattenuation and identified as an HCC (white arrow).

b. The delayed-phase CTHA showed washout of contrast material within the nodule and a corona of enhancement around its margins, confirming the diagnosis of HCC (white arrow).

c/d. Further examination of the early-phase CTHA demonstrated multiple hypervascular nodules (c. white arrow) with washout of contrast material and corona enhancement (d. white arrow).

e. An angiography of the left hepatic artery demonstrated multiple tumor stains (white arrow).

f. TACE using drug-eluting beads (DEB-TACE) resulted in the pooling of contrast material within several HCCs, referred to as vascular lakes, thought to be indicative of hemorrhage within HCCs during DEB-TACE.

g. Subsequent embolization with gelatin sponge resulted in the disappearance of the vascular lakes, confirmation of tumor staining, and preservation of the central hepatic artery.

h/i. 1 week after DEB-TACE, multiple HCCs exhibited low attenuation on contrast-enhanced CT and were considered indicative of tumor necrosis (h/i. white arrows).

j/k. Three months after DEB-TACE, contrast-enhanced CT revealed partially enhanced lesions at the margins of HCC in the hepatic hilum, suggesting local recurrence (j. white arrowheads). Other HCC lesions remained necrotic and displayed complete hypoattenuation (j/k. white arrows).

l/m. Six months after DEB-TACE, contrast-enhanced CT revealed increased enhancement in the area of local recurrence of HCC in the hepatic hilum (l. white arrowhead). Other HCCs exhibited complete low attenuation, reflecting regression and complete necrosis (l/m. white arrows).

of up to 150 mg of doxorubicin (equivalent to two vials of DC Bead®) depending on the volume of the tumor, selective insertion of microcatheters at the regional and subregional levels whenever feasible, and administration of treatment in 2-4-week intervals for multiple lesions in both lobes and large lesions. This recommended treatment regimen is similar to hepatic infusion chemotherapy in that large doses of anticancer drugs are periodically administered [65].

Factors that Contribute to the Successful Implementation of DEB-TACE

Vesselle et al. conducted a multivariate analysis of response factors in 108 (36%) of 315 nodes from 172 cases of HCC treated with doxorubicin-impregnated DC Bead® and found that tumor diameter less than 5 cm and localization other than segments 1 and 4 of the liver were significant response factors [66]. Similarly, Seki et al. studied 338 nodules in 123 cases of HCC treated with ebirubicin-impregnated HepaSphere™ and found that the response rate was significantly higher in tumors with vascular lakes and that tumor diameter greater than 3 cm was a significant predictor of the appearance of vascular lakes [67]. Conversely, Odisio et al. conducted a pathological examination of 27 nodules in 23 patients treated with doxorubicin-impregnated DC Bead® prior to liver transplantation and found that tumors with a necrosis rate of greater than 50% had a significantly larger mean diameter than those with less than 50% (3.2 vs. 2.1 cm, $p = 0.030$) and were significantly more frequently capsular (78% vs. 22%, $p = 0.0027$), suggesting that DEB-TACE may be less effective in small-diameter HCCs with poor capsular formation [68]. Cannon et al. retrospectively compared 42 patients with more than 10 multiple HCCs to 134 patients with less than 10 HCCs who were repeatedly treated with doxorubicin-impregnated DC Bead® and found no significant difference in response rate (56% vs. 57%) between the two groups and no deterioration of liver function in the group with more than 10 multiple HCCs despite a larger embolization extent. This suggests the usefulness of DEB-TACE for multiple HCCs in both lobes [69]. These reports suggest that DEB-TACE is most likely to be effective in tumors 3-5 cm in size with well-formed capsules, whereas a certain level of efficacy can be expected in multiple bilobar HCCs without impairing liver function with repeated treatment.

The Efficacy of the Combined Use of DEB-TACE and cTACE for Large HCC

At present, there is no consensus regarding the most effective TACE treatment for unresectable HCCs larger than 5 cm in size. Owing to the considerable size of the HCC, it is important to embolize extensive areas of the liver parenchyma to enhance local tumor control, which can result in severe liver dysfunction. Recently, Chen et al. conducted a retrospective analysis comparing the effectiveness and safety of cTACE alone versus combined treatment of DEB-TACE and cTACE for unresectable large HCCs greater than 5 cm in size [70]. The researchers compared 55 patients who underwent combined DEB-TACE and cTACE with a control group of 110 patients treated with cTACE alone. The tumor response rates were evaluated at 1 and 3 months post-TACE, as well as the time to progression (TTP), and adverse events were compared between the two groups. The combination of DEB-TACE and cTACE resulted in a higher objective response rate than cTACE alone (39 out of 55 patients [70.9%] versus 57 out of 110 patients [51.8%], $p = 0.019$) at 1 and 3 months (27 out of 43 patients [62.8%] versus 31 out of 71 patients [43.7%], $p = 0.048$). The median TTP was also significantly longer in the combined DEB-TACE and cTACE group than in the cTACE group (7.2 versus 5.3 months, $p = 0.039$). In terms of safety, abdominal pain, nausea, and vomiting were less common in the combination therapy group than in the cTACE group, whereas constipation was significantly more frequent in the combination therapy group. The combined use of DEB-TACE and cTACE significantly improved the objective response rates and prolonged TTP at 1 and 3 months posttreatment while maintaining safety, making it an effective treatment option for unresectable large HCC. However, the cTACE technique combined with DEB-TACE in their report involves additional embolization with gelatin sponge particles without ethiodized oil during a single TACE session when residual tumor staining is observed after the endpoint of DEB-TACE embolization. Future studies on the effectiveness of combination therapy using DEB-TACE and cTACE for each session in a series of consecutive treatments for unresectable large HCC are anticipated.

Conclusion

In conclusion, it appears that a clear trajectory has been established with regard to the appropriate use of cTACE and DEB-TACE. However, it is important to conduct effective embolization through the utilization of the appropriate technique for each type of TACE, and standardization of these techniques is imperative. In addition, future research is anticipated to explore the combination of TACE techniques with molecular targeted drug therapy.

Conflict of Interest: None

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