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Transcatheter Arterial Chemoembolization for Liver Cancer: Is It Time to Distinguish Conventional from Drug-Eluting Chemoembolization?

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Abstract

Conventional transcatheter arterial chemoembolization and chemoembolization with drug-eluting beads are increasingly being performed interchangeably in many institutions throughout the world. As both therapies continue to being tested in many phase II and III studies and in combination with other therapies, especially targeted agents, for treatment of primary and metastatic liver cancer, it is imperative to review their current status and evaluate their impact on patient survival. This review critically assesses patient selection, indications, contraindications, techniques, materials, safety, and clinical outcomes of patients treated with conventional chemoembolization and chemoembolization with drug-eluting beads.

Keywords

Interventional radiology; Liver cancer; Chemoembolization

Introduction

Transcatheter arterial chemoembolization (TACE) is the mainstay of catheter-based therapies for unresectable primary liver cancer, and its use is expanding for other hepatic

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metastatic malignancies [1, 2]. The procedure of TACE has technically and scientifically evolved since its introduction almost 30 years ago. Conventional TACE typically involves the injection of chemotherapeutic agents mixed with lipiodol and embolic particles into the branch of the hepatic artery that feeds the tumor [3]. TACE with drug-eluting beads (DEB) involves the injection of DEBs into the tumor-feeding artery, offering simultaneous delivery of chemotherapy and embolization with sustained and controlled drug release over time.

Conventional TACE and DEB-TACE are increasingly being performed interchangeably in many institutions throughout the world. As both therapies continue to being tested in many phase II and III studies and in combination with other therapies, especially targeted agents, for treatment of primary and metastatic liver cancer, it is imperative to review their current status and evaluate their impact on patient survival. In this review, we critically assess patient selection, indications, contraindications, techniques, materials, safety, and clinical outcomes of patients treated with conventional TACE and DEB-TACE.

Patient Selection for TACE and DEB-TACE

Conventional TACE is used for palliative treatment of unresectable hepatocellular carcinoma (HCC), as well as an adjunctive therapy to liver resection, as a bridge to liver transplantation, and before or after radiofrequency ablation [4–10]. TACE is also used for palliative treatment of unresectable cholangiocarcinoma [11], hepatic metastatic neuroendocrine tumors, sarcomas metastatic to the liver, breast hepatic metastases, and hepatic colorectal metastases [12–16]. Similarly, DEB-TACE has been performed for patients with unresectable HCC, cholangiocarcinoma, neuroendocrine tumors, and hepatic colorectal metastases [17–23].

Not every patient with unresectable primary or meta-static liver tumor may benefit from these procedures. One important aspect in the selection of patients is the presence of adequate liver function. In patients with advanced liver disease, treatment-induced liver failure may offset the anti-tumoral effect or survival benefit of the intervention. Predictors of outcome are related to tumor burden (tumor size, vascular invasion, and alfa-fetoprotein levels), liver functional impairment (Child-Pugh score, bilirubin, ascites), performance status (Karnofsky index, East Coast Oncology Group performance status [ECOG]), and response to treatment [24, 25]. Thus, the best candidates are patients with preserved liver function and asymptomatic lesions without vascular invasion or extrahepatic spread.

Contraindications for TACE and DEB-TACE

Contraindications to both techniques are similar. Current absolute contraindications to conventional TACE include tumor resectability, intractable systemic infection, an uncorrectable bleeding disorder, uncorrectable contrast sensitivity, leukopenia (white blood cell count <1000/μl), cardiac or renal insufficiency (serum creatinine >2.0 mg/dl), hepatic encephalopathy, or ECOG performance status >2. Contraindications such as absence of hepatopetal blood flow and presence of encephalopathy and biliary obstruction have been recently reclassified as relative ones. Portal vein thrombosis (PVT) should not be considered a contraindication to TACE. A study by Georgiades et al. reported that TACE is safe to perform in patients with PVT and identified that they key prognostic factor to survival was

the Child-Pugh numerical disease stage [26]. In the presence of PVT, a highly selective approach and adjustment of the chemotherapeutic dosage may minimize liver damage.

Relative contraindications to conventional TACE include a variety of other factors including, but not limited to: serum bilirubin >3 mg/dl, lactate dehydrogenase >425 U/l, aspartate aminotransferase more than five times the upper limit of normal, tumor burden involving>50% of the liver, presence of extrahepatic metastases, poor performance status, cardiac or renal insufficiency, ascites, recent variceal bleeding, or significant thrombocytopenia, intractable arteriovenous fistula, surgical portocaval anastomosis, severe portal vein thrombosis, and tumor invasion to inferior vena cava and right atrium.

Because DEB-TACE is still relatively new and thus clinical data have not been collected for as long as for conventional TACE, the list of exclusion criteria is more extensive for DEB-TACE. Currently, most investigators will not treat patients with Child-Pugh class C, diffuse tumors, or portal vein thrombosis. Table 1 summarizes the list of exclusion criteria for conventional TACE and DEB-TACE.

Materials for TACE

Chemotherapeutic Agents and Combinations

Both single-drug therapy and combination chemotherapy have been used as part of the drug regimen in chemoembolization. The most widely used single chemotherapeutic agent is doxorubicin, and the combination of cisplatin, doxorubicin, and mitomycin C is the most common drug combination used in the United States. Although none of these agents is extracted by the liver during the first pass, their pharmacokinetic profile is modified when they are combined with lipiodol. The emulsion allows prolonged transit of the drugs within the tumor bed, leading to greater contact time between the cancer cells and the chemotherapeutic agents. As a result, favorable tumor drug concentration with concurrent low systematic drug load can be achieved. Despite their favorable and high intratumoral concentrations, most initial randomized, controlled trials have failed to demonstrate advantage of one agent over another, or monotherapy over combination chemotherapy [27]. It is, however, clear that maintaining long-term arterial patency is critically important in order to allow for retreatment if it is necessary. This can be accomplished by embolizing the tumor-feeding vessel or vessels only after the entire dose of chemotherapy has been delivered [28]. In the United States, the most common combination is the mixture of cisplatin 100 mg (Bristol Myers Squibb, Princeton, NJ), doxorubicin 50 mg (Adriamycin; Pharmacia-Upjohn, Kalamazoo, MI), and mitomycin C 10 mg (Bedford Laboratories, Bedford, OH) diluted in 10 ml of water-soluble contrast medium (Omnipaque; Winthrop Pharmaceuticals, New York, NY) [29–31]. This mixture is then emulsified in an equivalent volume of lipiodol.

Lipiodol

The oily medium of lipiodol is a key ingredient to the chemoembolization procedure because of its unique combination of properties as a drug-carrying, tumor-seeking, and embolizing agent. Even though lipiodol has been used for more than 20 years for chemoembolization of HCC and hepatic metastatic lesions, the mechanism of its uptake by

cancer cells is not clearly understood. A pump in the tumor cell wall is thought to absorb the lipiodol and then transfer it inside the intracellular space. This pump is subsequently disabled by hypoxia within the tumor, thus trapping the oily emulsion within the cell. Lipiodol localizes in hepatic tumors when administered via the hepatic artery, and it is typically retained by HCC for months, even up to a year, while it is cleared from normal or cirrhotic liver within 4 weeks. When injected into the hepatic artery, it traverses the peribiliary plexus to the portal veins, resulting in a dual embolization [32]. The amount of lipiodol emulsion to be injected has been shown to be related to the tumor size. However, hepatic parenchymal damage or bile duct ischemia have been reported by use of large amounts of lipiodol [33]. Individualized adjustment of lipiodol dose, according to blood supply pattern and tumor diameter as measured by computed tomographic (CT) scan, has been suggested in a randomized, controlled trial [34]. The degree of lipiodol accumulation at CT has been shown to be an independent indicator of improved survival [35].

Embolic Agents

Several embolic agents have been used over the past three decades in conjunction with intra-arterial drug delivery. The intended purpose of embolization is twofold: to prevent washout of the drug at the site of tumor, and to induce ischemic necrosis. These agents may produce different effects on vasculature, resulting in permanent or transient obstruction, by acting at different levels in the arterial system. Usually the injection of embolic agents follows the injection of the chemotherapeutic mixture, yet some centers favor mixing the embolic materials in a slurry with the chemotherapeutic drugs and oil [28]. Embolic materials for TACE can be spherical or nonspherical agents.

Nonspherical Embolic Agents for TACE

Gelfoam

Gelatin bioabsorbable embolic agents, in the form of Gelfoam sponge, pledgets, cubes, or powder, have been extensively used as an intravascular embolization agent for TACE. Improved overall patient survival rates with the addition of Gelfoam sponge to the lipiodol emulsion were initially described by Nakao et al. in a retrospective study on 343 patients [36]. In Japan, Gelfoam represents the most used occlusive agent for TACE. Gelatin sponge blocks circulation transiently and is absorbed within 48–72 h, and it is currently the most commonly used material worldwide. Gelatin sponge causes a temporary vascular occlusion, with recanalization occurring in approximately 2 weeks [28]. When compared to powder, Gelfoam sponge provides a more proximal obstruction of the arterial supply. However, proximal obstruction may enhance the development of revascularization of treated lesions through recruited arterial collaterals, making it more difficult to retreat patients if it becomes necessary. On the other hand, Gelfoam powder can induce ischemic bile ducts necrosis. The use of gelatin sponge allows chemoembolization procedures to be repeated because it does not occlude the artery permanently, which is generally desirable [28].

Polyvinyl Alcohol Particles

Polyvinyl alcohol (PVA) particles have been used successfully since 1974 as an intravascular embolic agent, and for many years, it has been considered the standard embolic

agent for TACE [37]. PVA is considered to be a permanent embolic agent because it is not biodegradable. The histologic effects of PVA particles embolization have been well documented, varying from inflammatory and foreign body reactions to focal angionecrosis of the vessel wall [38]. The duration of the vascular occlusion induced by PVA is variable. Occlusions may last for several months as a result of organization of the thrombus, with recanalization attributed to thrombus resorption and angioneogenesis [38]. In a study testing the effects of various embolization protocols on the injectable volume of chemotherapy and subsequent arterial patency, the type of chemoembolization protocol rather than the type of embolic material had a significant impact on the rate of arterial recanalization or arterial patency [28]. Surprisingly, the assumption that PVA particles result in deeper penetration when compared to Gelfoam pledgets was not confirmed in this study [28].

Spherical Embolic Agents for TACE

Spherical microspheres have a single dimension; moreover, depending on their size, they may block the arterioles tightly and gradually seal the vascular lumen. The optimal size of these embolic agents for chemoembolization has yet to be established. In terms of intratumoral drug concentration achieved during TACE, a single study performed in an animal model of liver cancer demonstrated that calibrated tris-acryl gelatin microspheres were superior to PVA nonspherical particles [39].

Tris-acryl Gelatin Microspheres

Tris-acryl gel microspheres were the first spherical embolic agents to be commercially available [40]. Tris-acryl is an entirely synthetic, hydrophilic, and nonresorbable material. It has been demonstrated that this material produces non-toxic tissue reaction, thus allowing absorption and cellular adhesion [40]. Colored and noncolored tris-acryl gelatin microspheres (Embogold and Embosphere Microspheres; Biosphere Medical, Rockland, MA) are currently commercially available. These microspheres are precisely calibrated, spherical, hydrophilic, microporous beads made of tris-acryl co-polymer coated with gelatin. They come in defined range of sizes, ranging from 40 to 1200 μm in diameter. Their smooth hydrophilic surface, deformability, and minimal aggregation tendency have been shown to result in a lower rate of catheter occlusion and more distal penetration into the small vessels [40]. Their efficacy has been evaluated in several conditions, and when compared to the standard PVA particles, a deeper penetration and embolization of smaller and more peripheral vessels may be achieved. In a study where PVA particles and tris-acryl microspheres of similar size were compared, the level of vascular occlusion with calibrated tris-acryl microspheres precisely correlated with particle size, whereas the level of vascular occlusion with PVA particles did not. Another study demonstrated that in embolized tumors, most occluded vessels were located within the tumor tissue, whereas vessels located outside the tumor were rarely occluded [40]. Tris-acryl gelatin microspheres have also been tested for compatibility with several chemotherapeutic agents and can be mixed with carboplatin, mitomycin C, 5-fluorouracil, or pirarubicin for chemoembolization without any risk of harmful alteration in their morphology [41].

PVA Microspheres

The long track record of safety and efficacy of PVA led to the design of spherical PVA. PVA (Contour SE Micro-spheres; Boston Scientific, Natick, MA) and PVA hydrogel (Bead Block; Biocompatibles, Farnham, UK) are currently available for transcatheter use. Interestingly, PVA micro-spheres have been found to cause a mild inflammatory response [42]. This finding seems counterintuitive and unexpected, considering the aggressive inflammatory reaction that have been described with PVA particles. However, further studies should be conducted to assess whether this reduced intravascular and perivascular inflammation may have significant favorable clinical implications [42].

Drug-Eluting Microspheres Commercially Available for DEB-TACE

DC Bead/Precision Bead Microspheres/Paragon Bead Microspheres

DC Bead microspheres (Biocompatibles, UK) are nonbiodegradaple PVA microspheres that are CE Mark-approved for the treatment of malignant hypervascular tumors and loading with doxorubicin. These microspheres may also be loaded with irinotecan for the palliative treatment of patients with metastatic colorectal cancer. Precision Bead (Biocompatibles, UK) microspheres are the first micro-spheres to be factory preloaded with doxorubicin (37.5 mg/ml). They comprise a PVA polymer hydrogel that has been modified by the addition of a sulfonic acid-containing component. They can be polymerized to formulate different-size spheres, ranging in maximal diameter from 100 to 900 μm.

DC Bead microspheres actively sequester oppositely charged drugs through an ion-exchange mechanism. Initial in vitro studies showed that doxorubicin can be efficiently sequestered by the DC Beads to a maximum loading of approximately 45 mg/ml hydrated beads, irrespective of the size range of beads used [43]. The rate at which the beads sequester the doxorubicin is dependent on bead size, drug concentration, and salt-loading solution concentration. Larger-size (700–900 μm) beads show an approximately 35% decrease in average diameter when loaded with the maximum dose of drug, whereas smaller-size microspheres (100–300 μm) shrink less after drug loading. Moreover, larger-size beads (700–900 μm) release the drug more slowly than the smaller 100–300-μm beads [43]. DC Bead microspheres can load a maximum of approximately 45 mg doxorubicin/ml, with >99% of drug being sequestered from the doxorubicin solution [44]. A loading of 37.5 mg doxorubicin/ml beads is currently recommended, combining a practical therapeutic dose and optimum handling characteristics. An animal pharmacokinetic study compared two sizes of doxorubicin-eluting beads (DEB; 100–300 and 700–900 μm) loaded with 37.5 mg doxorubicin/ml hydrated beads and demonstrated that higher doxorubicin plasma levels were detected in the smaller-size (100–300 μm) beads group [45]. This was attributed to the increased surface area of the smaller beads, inducing a greater burst release of doxorubicin.

Paragon Bead microspheres (Biocompatibles, UK) are irinotecan-loaded drug-eluting microspheres for palliation of hepatic colorectal metastases. Initial in vitro experiments of irinotecan DEBs, prepared by combining embolization beads (DC Bead, Biocompatibles, UK) with irinotecan hydrochloride solution, showed that the rate of drug uptake was seen to be bead size dependent, the smaller beads loading more quickly as a result of increased

surface area-to-volume ratio. The maximum loading of bound drug was shown to be approximately 50–60 mg irinotecan/ml beads for all sizes [46]. The time required to reach suspension in contrast agent–saline mixture was both bead size- and drug dose-dependent, ranging 1–12 min. In another study, irinotecan-loaded beads were shown to decrease in size (by a maximum 25–30%) with a concomitant increase in their modulus of compression and drug loading [47].

Superabsorbent Polymer Quadrasphere (Hepasphere for Europe)

Superabsorbent polymer (SAP) Quadrasphere (Hepasphere for Europe) microspheres (Biosphere Medical) are biocompatible, hydrophilic (absorbent), nonresorbable, acrylic copolymer microspheres designed for hepatic arterial embolization with an ability to absorb fluids, up to 64 times their dry-state volume. The expansion rate is dependent on ionic concentration of their surrounding media. The size of dry particles ranges 50–200 μm, corresponding to an expanded size range of 200 and 800 μm. The SAP micro-spheres can be loaded with doxorubicin or cisplatin for drug delivery during TACE [48]. Initial in vitro and in vivo studies showed encouraging results, and these microspheres now have CE Mark approval for TACE of unresectable HCC in combination with doxorubicin.

An in vitro study tested the reservoir capacity of SAP using two different contrast media and optimal loading doses of cisplatin powder into SAP for hepatic arterial embolization. Interestingly, 100 mg of SAP, when mixed with iohexol, could carry a 10 times larger dose of cisplatin powder than when mixed with ioxaglic acid. Moreover, cisplatin powder-loaded SAP with ioxaglic acid were double in size than those loaded with iohexol, suggesting that they may occlude vessels at a more proximal level than required.

Technique

TACE and DEB-TACE procedures share many common steps. Diagnostic angiograms are initially performed to determine the hepatic arterial anatomy, the arterial supply of the tumor and any arteriovenous shunting. The issue of how selectively the catheter should be placed (lobar or segmental) during conventional TACE remains controversial, whereas most DEB-TACE protocols favor highly selective catheter positioning. Nonocclusive and occlusive techniques have been described for both TACE and DEB-TACE [9, 21, 23, 49, 50]. Improved tumor response has been shown when TACE can be repeated multiple times with maintenance of long-term arterial patency [28, 51]. Obviously, treatment is discontinued if any exclusion criteria develop. When performing multiple procedures, one should also take into account that the maximum lifetime dose of doxorubicin is 450 mg/m^2.

TACE Technique

Here, we describe the Johns Hopkins Hospital protocol, which consists of segmental or subsegmental TACE with use of the triple chemotherapeutic cocktail of doxorubicin, mitomycin, and cisplatin with lipiodol, followed by the injection of tris-acryl gelatin microspheres. The initial diagnostic angiographic steps are common to TACE and DEB-TACE and have been extensively described elsewhere [52].

After the initial visceral vascular evaluation has been performed, the vessel of interest targeting the specific tumor bed is subsequently accessed. A solution containing cisplatin 100 mg, doxorubicin 50 mg, and mitomycin C 10 mg in a 1:1–2:1 mixture with Ethiodol is subsequently injected until stasis is achieved. Then 15–20 ml of intra-arterial lidocaine is injected for immediate analgesia and to diminish postprocedural symptoms. This is followed by injection of 3–6 ml of a mixture containing tris-acryl gelatin microspheres (100–300 μm in size) suspended in 1:1 ratio of contrast medium. The embolization end point is not artery occlusion, but rather reduction in arterial inflow, to prevent the rapid washout of chemotherapy. This can be measured by counting the number of heartbeats it takes to clear the column of contrast media after the TACE procedure is nearly completed (2–5 being ideal). Closure of femoral artery access is then typically achieved by means of a closure device provided the common femoral artery anatomy is favorable [53].

DEB-TACE Technique at Johns Hopkins

The diagnostic angiographic steps for DEB-TACE are similar to the ones of TACE. DEBs can be loaded with drug before the procedure or can be supplied preloaded. DEB-TACE does not involve the injection of lipiodol and does not require intra-arterial injection of lidocaine because the pain typically associated with the slow transit of the lipiodol–chemotherapy mixture through the arterial bed is not present when injecting the DEBs. After performing diagnostic angiograms to characterize the hepatic arterial anatomy and tumor vascularity, and after having retrieved the DEBs that had been loaded with doxorubicin in the central oncology pharmacy, the DEBs are suspended in a saline contrast 50:50 (v:v) mixture using a three-way stopcock and left for a few minutes to become homogeneously distributed within the syringe. This dilution has to be taken into account by the operator. Because the number of microspheres per millimeter of sediment is high and may reach approximately 1 million for small calibers, there is a high risk that without dilution, microspheres will travel grouped together and block the feeding artery as clusters, with subsequent compromise of tumor targeting. Once the catheter is in place within the artery feeding the tumor, the DEBs are injected into the artery. Currently, there is no consensus regarding the choice of DEB size. Initial studies were performed with larger-size beads (500–700 μm) on the basis of the observation that doxorubicin is released more slowly from larger beads compared with smaller ones [43]. Several investigators recommend starting with smaller (100–300- or 300–500-μm) beads, followed by larger (500–700 μm) ones [21, 49]. In one study, the diameter of the beads chosen was on the basis of the size of the lesion, the diameter of the feeding artery, and tumor vascularity [49]. In our institution, we favor injection of the smallest-size beads only (100–300 μm), leading to more distal lodging of beads inside the tumor [23], thereby allowing (at least in theory) greater delivery of drug to the tumor bed.

Currently there is no consensus whether embolization should be totally occlusive or nonocclusive. Recanalization of tumor feeders may occur in occlusive embolization protocols. In nonocclusive protocols, such as the Johns Hopkins protocol, the procedure successfully ends when a total of 4 ml of DEBs and 4 ml of contrast medium are delivered (maximum doxorubicin dose 150 mg, at 37.5 mg/ml) or when the blood flow of the feeding artery slows down substantially. It is critically important when DEBs are used to ensure that

forward flow exists at all times to avoid reflux along the catheter, which could result in nontarget embolization and possible dire consequences (gastroduodenal ulceration, pancreatitis, cholecystitis). In addition, the catheter or microcatheter (highly recommended to achieve better control during delivery of the DEBs) should be placed selectively in extremely close proximity to the tumor. Complete occlusion of the main feeding artery should be avoided to allow for retreatment if it is necessary. An average of two treatments (range 1–3) per targeted tumor or tumors is usually necessary to complete a DEB-TACE cycle. Regardless of the DEB-TACE protocol, it is important to ensure that the intended amount of drug be delivered to the tumor.

Complications

TACE is generally well tolerated, with major complications in 4–7% of procedures and a 30-day mortality of approximately 1%. Postembolization syndrome (PES), characterized by nausea, vomiting, abdominal pain, and fever, occurs in up to 90% of patients after the procedure and may last up to 3 days. The etiology of PES is not fully understood but it is thought to be caused by a combination of tissue ischemia and an inflammatory response to chemoembolization [54]. The most common serious adverse events of TACE are liver abscess or liver infarction and cholecystitis, which occur in approximately 2% of the patients, despite antibiotic prophylaxis treatment and the absence of risk factors for abscess formation. An intrahepatic abscess is likely to occur (30–80%) in patients with a history of sphincter of Oddi dysfunction, sphincterectomy, or any type of biliary-enteric reconstructive surgery. Such patients have their biliary tree colonized by bacteria traveling freely from the gut. Because the biliary plexus is supplied by the hepatic artery, the ischemic effects of TACE exacerbate the situation, trapping the bacteria within the biliary tree and causing abscess formation. Nontarget embolization (gastroduodenal, left, or right gastric arteries, or other arteries) is a rare but serious complication. Variant vascular anatomy increases the risk of this complication, which may manifest as transient abdominal pain, ulcer, gastrointestinal bleeding, or ischemic mucosal necrosis. Other possible complications include liver failure, main bile duct strictures, cerebral or pulmonary lipiodol embolism, or even death (1%) [55–57]. In conventional TACE, a transient increase of liver enzymes after the procedure is expected and has been well documented.

Complications of DEB-TACE include cholecystitis, liver abscess formation, tumor rupture, pancreatitis, pleural effusion, gastric ulcer bleeding, esophageal variceal bleeding, and spontaneous bacterial peritonitis. The list of complications of DEB-TACE is relatively shorter than the one for conventional TACE, mainly because DEB-TACE is a relatively new procedure and not practiced as widely as TACE, but also likely because of the lack of lipiodol. Table 2 summarizes the complications encountered so far with DEB-TACE.

Clinical Outcomes

Clinical Outcomes for TACE

TACE for HCC—Until 2002, the use of TACE was largely based on phase II data that showed efficacy using tumor response [5, 31, 58]. In 2002, however, two landmark studies showed that TACE provided a statistically significant survival advantage over that of best

supportive care in selected patients with well-preserved liver function [59, 60]. The first of these studies, by Llovet et al., prospectively evaluated the survival outcomes in patients treated with fixed interval chemoembolization, embolization, and supportive measures [59]. This trial ended when a survival benefit of patients treated with chemoembolization compared to those treated conservatively was shown. In the second randomized, controlled trial, Lo et al. reported on a select group of patients with unresectable HCC treated with TACE or supportive care, demonstrating that TACE significantly improved survival over supportive care [60]. In this trial, the most common complications of patients treated with TACE were fever 33%, abdominal pain 26%, vomiting 16.7%, ascites 5.2%, and gastrointestinal bleeding 4.2%.

The largest case series ever reported (8510 patients) on patients treated with TACE comes from Japan [61]. TACE was performed with an emulsion of lipiodol and anticancer agents followed by gelatin sponge particles. Median survival in this series was 34 months. Both the degree of liver damage and the tumor, node, metastasis system proposed by the Liver Cancer Study Group of Japan demonstrated good stratification of survivals ($P = 0.0001$). Multivariate analysis showed significant difference in degree of liver damage, alfa-fetoprotein levels, largest tumor diameter, number of lesions, and portal vein invasion. Several other large case series have been reported since then, confirming the efficacy of TACE (Table 3) [23, 24, 52, 62–64]. Future prospective randomized studies should include TACE as the standard-of-care study arm for patients with unresectable HCC.

TACE for Neuroendocrine Hepatic Metastases—Among the various palliative options for metastatic neuroendocrine hepatic metastases, TACE has been shown to be effective in controlling hormonal symptoms and tumor growth [13, 65–67].

One study retrospectively evaluated the effectiveness of hepatic transarterial chemotherapy using two therapeutic protocols—mitomycin C alone and combined mitomycin C and gemcitabine—on local tumor control and survival rate in patients with liver metastases from neuroendocrine tumors [66]. Both treatment protocols were well tolerated by all patients. The combination of mitomycin C and gemcitabine was found to locally control tumor better than the monotherapy with improved 5-year survival rate (46.67% vs. 11.11%).

TACE for Hepatic Colorectal Metastases—In 1998, Tellez et al. reported on 30 patients with meta-static colorectal cancer treated with TACE after their disease failed to respond to standard-of-care chemotherapy [68]. After TACE, a radiographic response defined as a decrease in lesion density of 75% or a decrease in lesion size of 25% occurred in 63% of patients. In 95% of patients, there was at least a 25% decrease from baseline carcinoembryonic antigen levels. All patients experienced PES. One study demonstrated that TACE can prolong survival of patients with colorectal metastases. Most of the patients in this cohort had previously been treated with systemic chemotherapy [69].

TACE for Primary Cholangiocarcinoma—In 2005, Burger et al. reported on 17 patients with unresectable cholangiocarcinoma treated with TACE. The median survival was 23 months, with two of the patients being downstaged to resection. Minor complications were present in 12% of the patients, and a major complication resulting in death was seen in

6%. The authors concluded that TACE was effective in prolonging survival in this patient population [11].

TACE for Hepatic Breast Cancer and Other Metastases—Giroux et al. performed TACE on eight patients with breast cancer liver metastases that were unresponsive to previous standard-of-care chemotherapy [70]. Tumor regression was shown in five of eight patients, while half of the patients experienced relief of symptoms after TACE. All patients died within 13 months of treatment, mainly as a result of development of other metastatic sites.

Unresectable sarcomas metastatic to the liver may also respond well to TACE. Rajan et al. evaluated the survival and response to chemoembolization of 16 patients with sarcomas (gastrointestinal leiomyosarcomas, splenic angiosarcomas, leiomyosarcoma of the broad ligament, leiomyosarcoma of the inferior vena cava, and malignant fibrous histiocytoma of the colon) metastatic to the liver that were surgically unresectable [71]. Most patients (69%) remained morphologically stable 30 days after treatment. Cumulative survival from time of diagnosis was 81, 54, and 40% at 1, 2, and 3 years, respectively. Median survival time was 20 months. Cumulative survival from initial chemoembolization was 67, 50, and 40% at 1, 2, and 3 years, respectively, with a median survival of 13 months. Vossen et al. evaluated the imaging response of leiomyosarcomas metastatic to the liver in patients treated with TACE using morphological and functional (diffusion weighted) magnetic resonance imaging techniques [16]. Immediately after treatment, tumor size decreased by 2%, whereas arterial and portal venous enhancement decreased by 69 and 64%, respectively. After TACE, mean tumor apparent diffusion co-efficient (ADC) increased by 20% ($P = 0.0015$). Patient survival from time of first TACE was 21 months for the entire cohort.

Clinical Outcomes for DEB-TACE

DEB-TACE for HCC—DEB-TACE with doxorubicin-eluting beads (DC Beads, Biocompatibles, UK) was initially tested in a phase I/II study from China. In this study, patients with unresectable HCC and Child-Pugh class A cirrhosis were treated with two sessions of DEB-TACE at an interval of 2 months [50]. The phase I trial was a dose-escalating study from 25 mg to 150 mg doxorubicin in cohorts of 3 patients (total of 15 patients). The 150-mg doxorubicin dose was used for the phase II study. Primary end points for the phase II study were treatment-related complications and death. Secondary end points included tumor response and pharmacokinetics of doxorubicin. No dose-limiting toxicity was observed for up to 150 mg doxorubicin, which was used for 20 patients in the phase II study. The pharmacokinetic study showed a low peak plasma doxorubicin concentration (49.4 ± 23.7 ng/ml) without any evidence of systemic toxicity. Treatment-related complications were reported in 11.4% of cases. However, there was no treatment-related death. Among 30 patients who received two courses of TACE, the partial and complete response rates were 50 and 0%, respectively, according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria at 1 month after the second TACE. By modified RECIST criteria, taking into account the extent of tumor necrosis, the disease of 19 patients (63.3%) showed a partial response and the disease of 2 (6.7%) showed a complete response.

The Barcelona Center for Liver Cancer (BCLC) was the first center to report midterm results of 27 patients with Child-Pugh class A and cirrhosis (76% male, 59% hepatitis C virus) with large/multifocal HCC that received chemo-embolization with doxorubicin-loaded microspheres at doses adjusted for bilirubin and body surface (range 47–150 mg) [9] (response rate, as assessed by CT at 6 months, was 75%, or 66.6% at intention to treat). After a median follow-up of 27.6 months, 1- and 2-year survival was 92.5 and 88.9%, respectively.

A study from Greece presented the results of an open-label, single-center, single-arm study included 62 patients with cirrhosis with a single unresectable HCC [21]. Patients received repeat chemoembolization with doxorubicin-loaded beads (maximum dose, 150 mg per session, 100–300 or 300–500 μm) every 3 months (up to three sessions). Overall objective response according to the European Association for the Study of the Liver (EASL) criteria was observed in 59.6, 81.8, and 70.8% across three treatments. A complete response was observed in 4.8% after the first procedure and 3.6 and 8.3% after the second and third procedures, respectively. At 9 months, complete response was seen in 12.2%, objective response in 80.7%, progressive disease in 6.8%, and stable disease in 12.2%. Severe procedure-related complications were seen in 3.2% (cholecystitis, $n = 1$; liver abscess, $n = 1$). PES was observed in all patients.

The results from the PRECISION V trial, which is the only prospective, controlled, randomized study involving the efficacy of DEB-TACE, were recently published [20]. In this trial, a total of 212 patients were enrolled and received either TACE with doxorubicin or TACE with doxorubicin-loaded microspheres. DEB-TACE with doxorubicin showed a higher rate of complete response, objective response, and disease control compared with conventional TACE (27 vs. 22%; 52 vs. 44% and 63 vs. 52% respectively, $P > 0.05$). Patients with Child-Pugh class B, ECOG score 1, bilobar disease, and recurrence after curative treatment benefited more from the DEB-TACE procedure than they did from conventional TACE, as demonstrated by a significant increase in objective response ($P = 0.038$). There was a marked reduction in serious liver toxicity in patients treated with DEB-TACE. The rate of doxorubicin-related side effects were significantly lower ($P = 0.0001$) in the DEB group than in the conventional TACE one. Results about the survival benefits of each therapy will be reported within the next 2 years.

The first U.S. prospective phase II study designed to evaluate safety and efficacy of DEB-TACE for unresectable HCC was recently published [23]. This study involved 20 patients (75% Child-Pugh class A, 95% ECOG performance status score 0 to 1, 60% BCLC class C, and tumor size 6.9 cm) who underwent 34 DEB-TACE sessions. At 1-month follow-up magnetic resonance imaging, treated lesions had a mean decrease in size of 4% ($P = 0.1129$). Partial response was 10% by RECIST criteria, while 90% of patients had stable disease. By EASL criteria, 60% had objective tumor response and 40% had stable disease. No patients had progression of a treated lesion while undergoing treatment. At 6 months' follow-up, the disease control rate was 95% by RECIST criteria. Overall survival rates at 1 and 2 years were 65 and 55%, respectively; median overall survival was 26 months. The authors concluded that DEB-TACE is safe and effective in achieving local tumor control in patients with unresectable HCC (Table 4).

Early results of a multicenter registry in Italy that used HepaSphere loaded with a single chemotherapeutic agent for TACE in patients with unresectable HCC have been presented [73]. Forty-four patients with up to three HCC lesions were treated by selective TACE using HepaSphere loaded with doxorubicin or epirubicin (50 mg in 5 ml NaCl 0.9% or in 5 ml nonionic isotonic contrast medium). Follow-up included laboratory tests and CT scans performed at 1, 3, 6, and 12 months. No major complications occurred, except for a mild pancreatitis. Eleven patients had a PES, which seemed to be less severe than after conventional TACE. Thirty-day mortality was 0% and overall mortality was 11.1%. Technical success rate was 100%, with complete devascularization of the lesions at the end of all procedures. One-month follow-up CT scans showed good response with complete necrosis (100%) of lesions in 43.9% of patients, partial necrosis (50–90%) in 39% of patients, and incomplete necrosis (0–49%) in 17.1% of patients. Six-month follow-up CT scans showed complete necrosis in 42.3% of patients, partial necrosis in 15.4% of patients, and incomplete necrosis in 42.3% of patients with local recurrence and/or satellite lesions. Further patient enrollment is underway to confirm and investigate the long-term efficacy of this new drug carrier.

DEB-TACE for Neuroendocrine Hepatic Metastases—A study with 20 patients that had metastatic gastroentero-pancreatic endocrine tumors was recently completed [18]. These patients underwent 34 sessions of TACE with DEBs (500–700 μm) loaded with doxorubicin. Morphologic response was evaluated with CT scanning at 1 and 3 months according to RECIST criteria. Three months after TACE, disease of 16 (80%) of 20 patients exhibited a partial response, 3 (15%) stable disease, and 1 (5%) progressive disease. After a median follow-up of 15 months, the disease of 9 patients remained controlled without tumor progression, and 10 patients had progressive disease. The median time to progression was 15 months.

DEB-TACE for Hepatic Colorectal Metastases—Ten patients with liver metastases from colorectal cancer were prospectively enrolled and treated with irinotecaneluting bead embolization (DEB-TACE) at a dose of 100 mg every 3 weeks with up to three treatments [17]. Tumor response was assessed by CT 1 month after the end of treatments. DEB-TACE with irinotecaneluting beads was found to be feasible and well tolerated. Right upper quadrant pain was reported by all the patients. After 30 days, a reduction of >50% of carcinoembryonic antigen levels and in the tumor contrast enhancement was observed in all the patients. Further clinical studies should verify these initial encouraging results.

Conclusion

Both TACE and DEB-TACE are potent palliative options for the treatment of primary and metastatic liver cancer. Initial results in patients with unresectable HCC, including a randomized phase II study, have shown that DEB-TACE is superior to TACE in terms of local tumor response, liver toxicity, and systemic toxicity. Results regarding the potential survival benefits of DEB-TACE in patients with HCC are to be reported within the next 2 years. Results regarding the potential survival benefit of patients with hepatic metastases treated with DEB-TACE should also become available in the near future.

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Table 1

Exclusion criteria for TACE and DEB-TACE

Characteristic	DEB-TACE	TACE
Liver disease	• Child-Pugh class C (except with isolated tumor feeder) • Active gastrointestinal bleeding • Encephalopathy • Mild or severe ascites • Bilirubin levels >3 mg/dl • Albumin <2.5 g/dl • ALT and AST >5 times upper limit of normal	• Child-Pugh class >C11 • Active gastrointestinal bleeding
Tumor status	• Tumor resectability • BCLC class C (vascular invasion including segmental portal obstruction, extrahepatic spread) • BCLC class D • Main PVT or portal vein occlusion • Extensive tumor involvement (>50% of the liver) • Extrahepatic metastases	• Tumor resectability • BCLC class D
Patient performance status	• ECOG >3	• ECOG >3
Doxorubicin related	• WBC <3000 cells/mm^3 Neutrophils <1500 cells/mm^3 • LV ejection fraction <50%	• WBC <3000 cells/mm^3 Neutrophils <1500 cells/mm^3 • LV ejection fraction <50%
Procedural	• Portosystemic shunt • Hepatofugal blood flow • Platelet count <50,000/mm^3 • Prothrombin activity <50%) • Renal insufficiency/failure • Serum creatinine >2 mg/dl (177 lmol/l)	• Renal insufficiency/failure • Serum creatinine >2 mg/dl (177 lmol/l) • Uncorrectable bleeding disorder

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *WBC* white blood cell count, *LV* left ventricle

Table 2

Periprocedural complications and reported toxicities in DEB-TACE studies of patients with unresectable HCC

Study	No. of patients	Complications	PES	Toxicities
Varela et al. [9]	27	• Liver abscess (2/27) • Liver failure (1/27) • Hepatic artery dissection (1/27)	NA	• Transient increase in AST and bilirubin
Reyes et al. [23]	20	• Tumor rupture (1/20) • Pancreatitis (1/20)	1/20	• Leukocytopenia grade 3 (1/20)
Poon et al. [50]	35	• Tumor rupture • Liver failure • Pleural effusion • Gastric ulcer bleeding, esophageal variceal bleeding • Spontaneous bacterial peritonitis	27/35	• None, transient increase in bilirubin, AST, ALT, and WBC
Grosso et al. [74]	50	• Pancreatitis	9/50	• Transient increase in AST, ALT, GTT
Malagari et al. [21]	62	• Cholecystitis (1/62) • Liver abscess (1/62)	62/62	• Transient increase in AST, ALT, GTT
Forner et al. [19]	27	• Arterial dissection (1/27) • Liver abscess (1/27)	NA	• NA
Lammer et al.—PRECISION V [20]	212 (102 DEB)	• Liver failure • GI bleeding • Infection	NA	• Alopecia (1.1%) • Marrow suppression (5.4%) • Mucositis (4.3%) • Skin discoloration (2.2%)

NA not applicable, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GTT* glucose tolerance test, *WBC* white blood cell count

Table 3

Brief review of literature on the treatment of unresectable HCC with TACE in patients with unresectable HCC

Study	No. of patients	Child-Pugh class	CR and PR	Survival
Lo et al. [60]	80 (40 TACE)	NA, OKUDA I (*n* = 19)/II (*n* = 21)	39% (WHO and/or AFP)	2 years 31%
Llovet et al. [59]	112 (40 TACE)	A (*n* = 31)/B (*n* = 9)	35% (WHO)	2 years 63%
Camma et al. [75]	2446 (2268 TACE)	A (59%)	38.7% (WHO)	OR 0.54, *P* = 0.015
Llovet et al. [59]	1443 (545 TACE)	A (82%)	35% (WHO)	2 years 41%, OR 0.53, *P* = 0.017
Yuen et al. [76]	96 (80 TACE)	A (*n* = 64)/B(*n* = 16)	28%[a]	2 years 78.8%, median 31.2 months
Takayasu et al. [61]	8542	A (51%)/B(39%)/C (10%)	NA	2 years 63%, median 34 months
Brown et al. [77]	209	A (*n* = 132)/B (*n* = 65)/C (*n* = 4)	NA	Median 12.6 months
Liapi et al. [13]	347	A (66%)/B (31%)/C (3%)	32% (RECIST)	Median 20.25 months

CR complete response, *PR* partial response, *WHO* World Health Organization, *AFP* alfa-fetoprotein, *OR* odds ratio, *NA* not applicable

[a]Tumor size by angiogram

Table 4

Review of studies evaluating treatment of unresectable HCC with TACE with DEB

Study	No. of patients	Child-Pugh class A/B (no. of patients)	BCLC score (A/B/C, %)	No. procedures/patient	Doxorubicin dose	Bead diameter	Technique	CR and PR at 6 months	Survival
Varela et al. [9]	27	27/0	0/100/0	2	Adjusted for body surface and bilirubin (25–100 mg/m^2, up to 150 mg, mean 128 mg)	500–700 μm	Highly selective, completely occlusive	75% (EASL)	2 years 88.9%
Reyes et al. [23]	20	15/5	30/10/60	2 (1–3)	97 mg (range 50–100 mg)	100–300 or 500–700 μm	Highly selective, nonocclusive	10% (RECIST) 60% (EASL)	2 years 55%
Poon et al. [50]	35	35/0	5/30	2	Phase I: dose escalating (25–150 mg), Phase II: 150 mg	500–700 μm	Selective, almost occlusive	50% (RECIST) 70% (EASL)	NA
Grosso et al. [74]	50	46/4	NA	1 (1–3)	50 mg doxorubicin or epirubicin	100–150 μm	Highly selective, occlusive	77.4% (EASL)	NA
Malagari et al. [21]	62		NA	2.2 (1–3)	112.5 mg	100–300 followed by 300–500 μm	Highly selective, completely occlusive	80.6% (EASL)	2 years 91.1%
Forner et al. [19]	27	27/0	0/100/0	2	Adjusted for body surface and bilirubin (100 mg/m^2 when bilirubin <1.5 and 75 mg/m^2 when bilirubin 1.5–3 mg/dl, up to 150 mg, median: 143 mg).	500–700 μm		75% (EASL) 50% (RECIST)	NA
Kettenbach et al. [78]	30	26/4	NA	NA	75 mg/m^2 for bilirubin levels <1.5 mg/dl and 50 mg/m^2 for levels >1.5 mg/dl	NA	NA	40% (RECIST) 44% (EASL)	Mean 376 days
Lammer et al.—PRECISION V [20]	212 (102 DEB)	83/19	24/69/0	1–3	150 mg per procedure	4 ml DC Bead (1 vial of 300–500 μm first, followed by 1 vial of 500–700 μm)	Highly selective to stasis	52% (RECIST)	NA

CR complete response, *PR* partial response, *NA* not applicable