

Transcatheter Arterial Chemoembolization: Current Technique and Future Promise

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Transarterial chemoembolization is the mainstay of catheter based interventional oncologic therapies. This article describes the history of the procedure, selection of appropriate candidates, technical aspects of procedure performance, results, complications, and appropriate follow-up. In addition, the limitations and challenges of the procedure are outlined. Finally, the reader is introduced to novel and promising techniques and devices that hold future promise for transarterial therapy of malignancies.

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Transcatheter arterial chemoembolization (TACE) has significantly contributed to the evolution of interventional radiology, as it proficiently represents the novel group of minimally invasive catheter-directed oncologic therapies. Based on the initial observation that most hepatic malignant lesions receive their blood supply by the hepatic artery, TACE may effectively deliver highly concentrated doses of chemotherapy to the tumor bed, whereas sparing the surrounding hepatic parenchyma.^{1,2}

In practice, despite its promising concept of design, TACE has not proved to be as effective and potent as in theory. Among several challenging obstacles that have not yet been exceeded, is the heterogeneity of chemotherapeutic agents employed and the several variations in the application of the technique. This disparity hinders the conduct of systematic meta-analyses or the design of randomized trials that would demonstrate a clear survival benefit.³ Despite controversy and diversity, TACE has gained wide acceptance over the past 20 years and is currently considered as the mainstay therapy for unresectable primary and metastatic liver cancer.^{4,5} In this article, we attempt to review the technical and clinical part of the procedure, as well as current results, effectiveness, and future potential of TACE.

Brief History and Review of Underlying Mechanisms for Tumor Damage

TACE was introduced in 1977 by Dr. Yamada, who first exploited hepatocellular carcinoma's preferential blood supply from the hepatic artery to deliver antitumor therapy, without damaging the surrounding liver parenchyma.^{1,2} A decade later, the observation that the injection of lipiodol, an iodinated ester derived from poppy-seed oil, can be selectively up-taken and retained by primary hepatocellular carcinoma (HCC) and hepatic metastases of colonic and neuroendocrine tumors, led to the establishment of this compound as an important part of the injected chemotherapeutic cocktail.⁶⁻⁸ Moreover, lipiodol was found to effectively engage the chemotherapeutic agents, whereas leading to dual embolization and tumor necrosis.

Theoretically, embolization of the feeding vessel causes ischemia of the tumor, and when combined with chemotherapy, results in tumor necrosis. Despite this promising observation, only 44% of large treated lesions demonstrate extensive necrosis in pathology, leading to further questioning of the true mechanism of producing tumor necrosis.⁹ Recent studies have shown that tumor ischemia and hypoxia up-regulate several molecular factors, such as the vascular endothelial growth factor (VEGF), and hypoxia inducible factor-1 (HIF-1), thereby preventing cell apoptosis and stimulating tumor growth.^{10,11} These novel observations need to be further tested in the clinical setting so as to demonstrate the role of possible interactions between hypoxia and the effect of embolization during a chemoembolization procedure.

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Patient Selection and Indications for TACE

Nowadays, chemoembolization is the preferred treatment for unresectable HCC.¹²⁻¹⁴ Despite the recently encouraging intention-to-treat studies, TACE is still considered a palliative option. TACE is also employed as an adjunctive therapy to liver resection or as a bridge to liver transplantation, as well as before radiofrequency ablation.¹⁵⁻¹⁹ Promising results have been recently demonstrated with unresectable cholangiocarcinoma treated with chemoembolization.²⁰ Chemoembolization has also successfully been employed for patients with carcinoid tumor, pancreatic islet tumor and sarcoma metastatic to the liver, whereas the efficacy of TACE in patients with colorectal metastases is less established. Promising results have been recently demonstrated with unresectable cholangiocarcinoma treated with chemoembolization.²⁰

Not every patient with unresectable primary or metastatic liver tumor may benefit from chemoembolization. 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 antitumoral effect or survival benefit of the intervention. Predictors of outcome are related to tumor burden (tumor size, vascular invasion, and AFP levels), liver functional impairment (Child-Pugh, bilirubin, ascites), performance status (Karnofsky index, ECOG), and response to treatment. Thus, the best candidates are patients with preserved liver function and asymptomatic lesions without vascular invasion or extrahepatic spread.

Contraindications for TACE

Absolute contraindications for TACE such as absence of hepatopedal blood flow and presence of encephalopathy and biliary obstruction have been recently reclassified as relative ones. Several articles have demonstrated little negative impact on hepatic function in cases of portal vein tumoral thrombosis and chemoembolization can be safely performed if hepatopedal collateral flow is present.^{21,22} In such cases, a superselective approach as well as an adjustment of the chemotherapeutic dosage may minimize liver damage.

Current absolute contraindications for TACE now include tumor resectability, intractable systemic infection, and extensive hepatic disease (Child-Pugh C). Relative contraindications include a variety of other factors including, but not limited to: serum bilirubin >2 mg/dL, lactate dehydrogenase >425 U/L, aspartate aminotransferase >100 U/L, tumor burden involving more than 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 IVC and right atrium. Table 1 summarizes the list of absolute and relative contraindications for TACE.

Patient Preparation

Before TACE all patients should undergo a gadolinium-enhanced magnetic resonance imaging (MRI) study of the liver, preferably with perfusion/diffusion sequences. This will de-

Table 1 Contraindications for TACE

Absolute
1. Tumor resectability
2. Extensive intractable infection
3. Extensive liver disease
Relative
1. Borderline liver function
2. Total bilirubin >4 mg/dL
3. Portal vein thrombosis
4. Uncorrectable coagulopathy
5. Poor general health
6. Significant arterio-venous shunting through the tumor
7. Encephalopathy

lineate the extent and viability of tumor and serve as a baseline study to plan future treatment. A dual phase MRI or computed tomography (CT) are also acceptable but the addition of the diffusion sequences may demonstrate and quantify tumor necrosis.²³ In addition to information regarding tumor viability, cross-sectional imaging may add valuable information regarding its vascular supply. For example, the presence of portal vein thrombosis and/or variant vascular anatomy may alter the embolization part of the procedure or reduce the procedure time and contrast load.

Patients are premedicated depending on the tumor histology, renal function, and prior surgical and medical history. Patients whose sphincter of Oddi function have been eliminated, that is, hepatojejunostomy, sphincterotomy patients, or patients with percutaneous or internal biliary stents, are at high risk for developing a hepatic abscess after TACE. Stringent 24-hour bowel preparation and intravenous administration of broad-spectrum intravenous antibiotics before the procedure all but eliminate this possibility. Because the procedure is performed under conscious sedation, an 8-hour NPO status is required.

Technical Considerations

Although many different chemoembolization protocols have been used in the past, the combination of some chemotherapeutic agents and a vehicle such as lipiodol constitutes the basis of most procedures. Single drug therapies or combinations of agents have been used. The most widely used single chemotherapeutic agent is doxorubicin and the combination of cisplatin, doxorubicin, and mitomycin C is the most common drug combination infused. The issue of how selectively the catheter should be placed (lobar or segmental) during chemoembolization remains controversial. Nonocclusive and occlusive techniques have been described.²⁴ Improved tumor response has been shown when chemoembolization can be repeated multiple times with maintenance of long-term arterial patency.^{25,26} Several types of embolic agents have been utilized in conjunction with lipiodol for chemoembolization, including gelfoam powder and pledgets, polyvinyl alcohol, starch and glass microspheres, or embospheres.²⁴ The gelatin sponges cause only temporary thrombosis lasting about 2 weeks, whereas polyvinyl alcohol and embospheres create a more permanent effect.

Following, we describe the Johns Hopkins Hospital protocol, which consists of segmental or subsegmental chemoembolization with use of the triple chemotherapeutic cocktail of

doxorubicin, mytomicin, and cisplatin with lipiodol, followed by the injection of embospheres.

Technique

After a treatment plan is formulated and written, informed consent is obtained the patient is brought to the interventional radiology suite, placed on the fluoroscopy table supine and both groins are prepared in a sterile fashion. After volume loading with normal saline and administration of conscious sedation, the single-wall Seldinger technique with an 18-gauge needle is used to access the right common femoral artery. A 5-French vascular sheath is then placed into the artery over a 0.035 glide wire. Under fluoroscopic guidance, a 5-French catheter (Simmons-1 or Cobra) is then used to select the superior mesenteric artery (SMA) and the celiac axis.

A prolonged angiogram of the SMA is performed, which is carried well into the portal venous phase. This allows concurrent assessment of any variant vessels to the liver (acces-

sory or replaced hepatic artery), retrograde flow through the gastroduodenal artery (GDA), and visualization and identification of a patient portal vein (Fig 1A-C and 2A-C). A celiac angiogram adequately demonstrates hepatic branch anatomy, possible presence of replaced left hepatic artery, or other variant arteries. If possible, the right inferior phrenic artery should be interrogated to exclude malignant parasitization of blood flow. It is necessary that the injection rates used should balance adequate opacification of the targeted vessels without unnecessary reflux of contrast material into the aorta or other vessels proximal to the injection site. Over the guide wire, the 5-French catheter is next advanced into the desired hepatic artery branch. Depending on tumor location, a selective hepatic arteriogram demonstrates the tumor "blush" (Fig 3A-C). Special attention should be paid to the falciform, phrenic, right, or accessory gastric arteries, supraduodenal, retroduodenal, retroportal, and cystic arteries, to avoid nontarget embolization. The catheter should be advanced beyond the gastroduodenal artery. In difficult cases with complex vascular anatomy, the utilization of three-di-

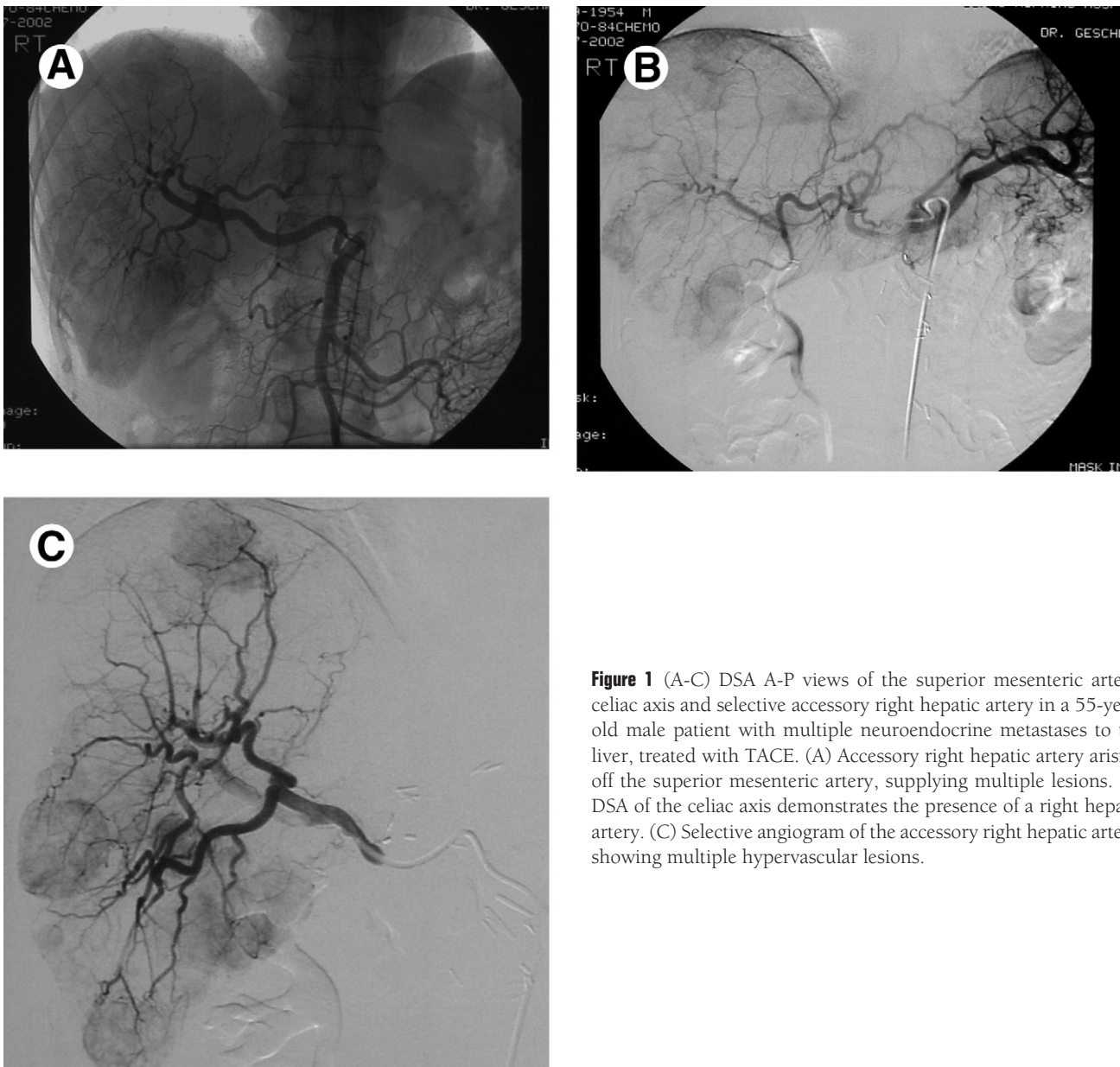


Figure 1 (A-C) DSA A-P views of the superior mesenteric artery, celiac axis and selective accessory right hepatic artery in a 55-year-old male patient with multiple neuroendocrine metastases to the liver, treated with TACE. (A) Accessory right hepatic artery arising off the superior mesenteric artery, supplying multiple lesions. (B) DSA of the celiac axis demonstrates the presence of a right hepatic artery. (C) Selective angiogram of the accessory right hepatic artery, showing multiple hypervascular lesions.

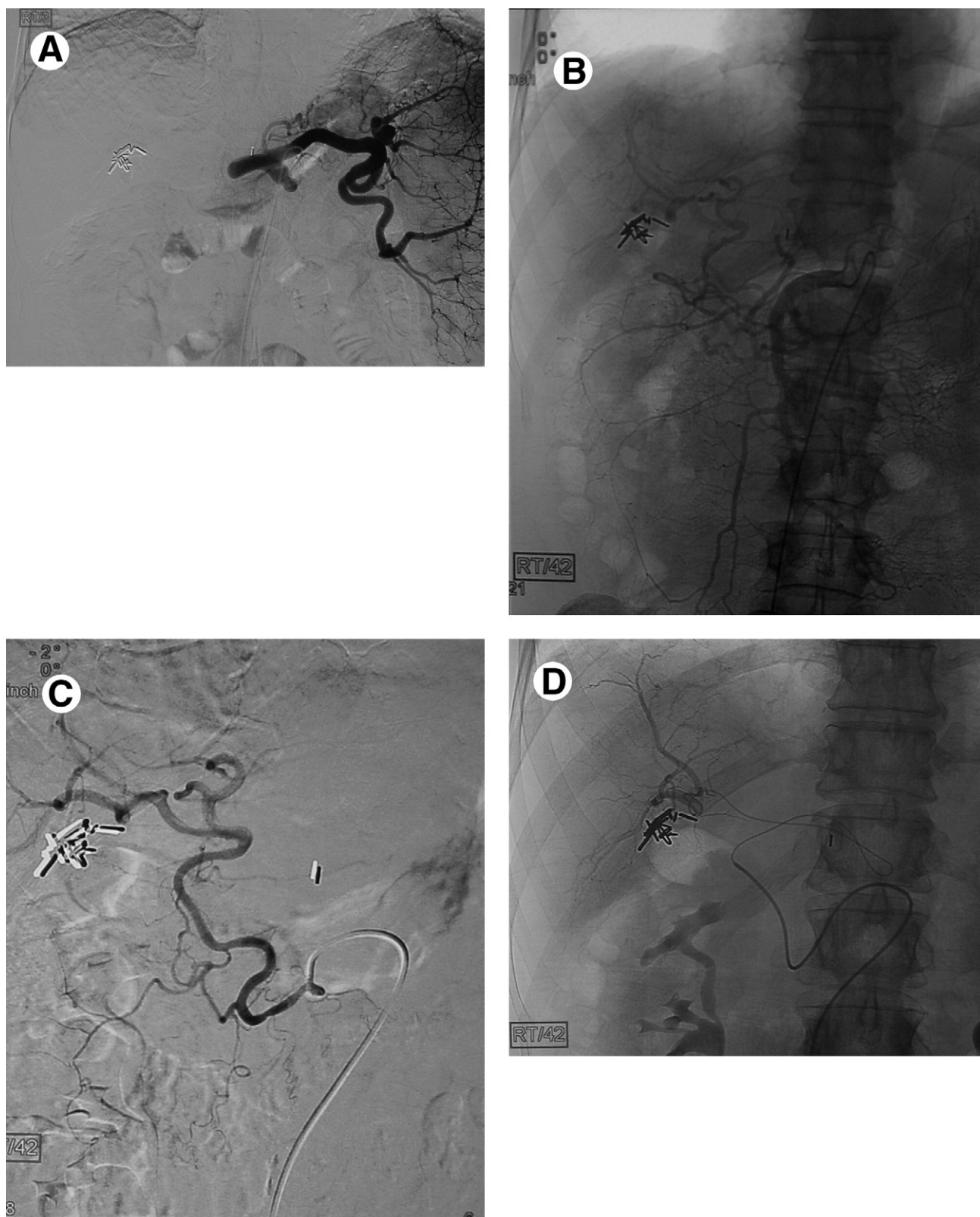


Figure 2 (A-D) DSA A-P views of the celiac axis, SMA, and right hepatic artery of 71-year-old male patient with HCC. (A) DSA view of the celiac axis, showing occlusion of the common hepatic artery. (B) DSA view of the SMA shows a hypertrophied pancreaticoduodenal arcade and GDA, communicating with the proper hepatic artery. (C) Selective DSA view of the pancreaticoduodenal arcade, GDA, and right hepatic artery. The tip of the 5 French glide Cobra catheter is in the SMA and secured at the origin of the inferior pancreaticoduodenal artery. (D) Successful engagement of the right hepatic artery with a 3 French microcatheter.

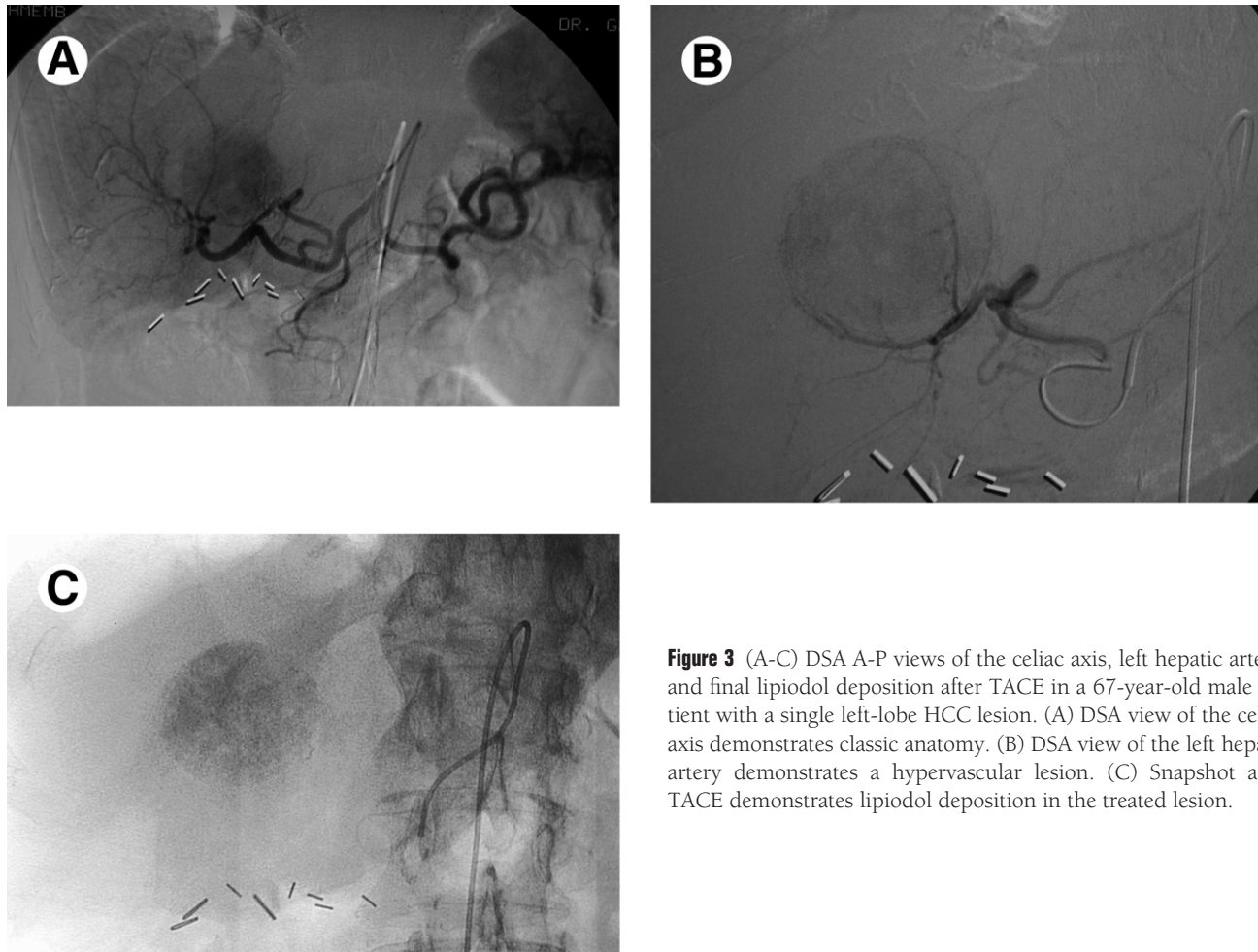


Figure 3 (A-C) DSA A-P views of the celiac axis, left hepatic artery, and final lipiodol deposition after TACE in a 67-year-old male patient with a single left-lobe HCC lesion. (A) DSA view of the celiac axis demonstrates classic anatomy. (B) DSA view of the left hepatic artery demonstrates a hypervascular lesion. (C) Snapshot after TACE demonstrates lipiodol deposition in the treated lesion.

mensional rotational angiography may help in minimizing procedure risks or complications and lead a more effective lesion targeting.²⁷

Visualization of reversal of flow can be demonstrated by a microcatheter injection with relatively high injection rates. It is also important to identify any arteriovenous shunting patterns, which have been reported to occur in 31 to 63% of cases between second-order branches.²⁸ In such cases, direct embolization of recognized shunts, even in the setting of portal vein thrombosis, followed by chemoembolization may prove effective (Figs 4A, B).

After this 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 to 2:1 mixture with ethiodol is subsequently injected, until stasis is achieved. Then, 5 to 10 mL of intra-arterial lidocaine is injected for immediate analgesia and to diminish postprocedural symptoms. This is followed by injection of 1 to 2 mL of mixture containing embosphere particles (100-500 μm in size), suspended in 1:1 ratio in contrast medium. The embolization endpoint is not artery occlusion, but reduction in arterial inflow, for prevention of quick chemotherapy washout. Closure of femoral artery access can be achieved with use of a closure device when no standard contraindication prevailed after the performance of common femoral arteriography. A recent study on patients treated with TACE, showed that repetitive use of a collagen plug closure device after each procedure, does not impose

patients to further risks.²⁹ Table 2 shows the list of items used in our angiography suites for each procedure.

Recovery

After proper hemostasis is achieved, the patient is placed on patient controlled analgesia (PCA) pump, intravenous hydration and sent to the floor. Frequent vital signs monitoring is only required for the 4-hour postprocedure period after which routine nursing checks are adequate. PRN medication should include (in addition to the morphine or fentanyl PCA), anti-nausea and additional pain medication for breakthrough pain. After the initial observation period, the patient is encouraged to ambulate under supervision. The use of a closure device can reduce the observation period to 2 hours. As soon as the patient ambulates, the Foley catheter (if one was placed) is removed and orally intake is advanced as tolerated. When the patient is ambulatory, a noncontrast CT of the abdomen is obtained to document the distribution of lipiodol and the degree of lipiodol uptake by the tumor.

Follow-up and Evaluation of Response to Treatment

For maximum benefit, patients should be advised to return for a follow-up clinical visit 4 to 6 weeks after treatment. During this visit, liver function tests, as well as a perfusion-

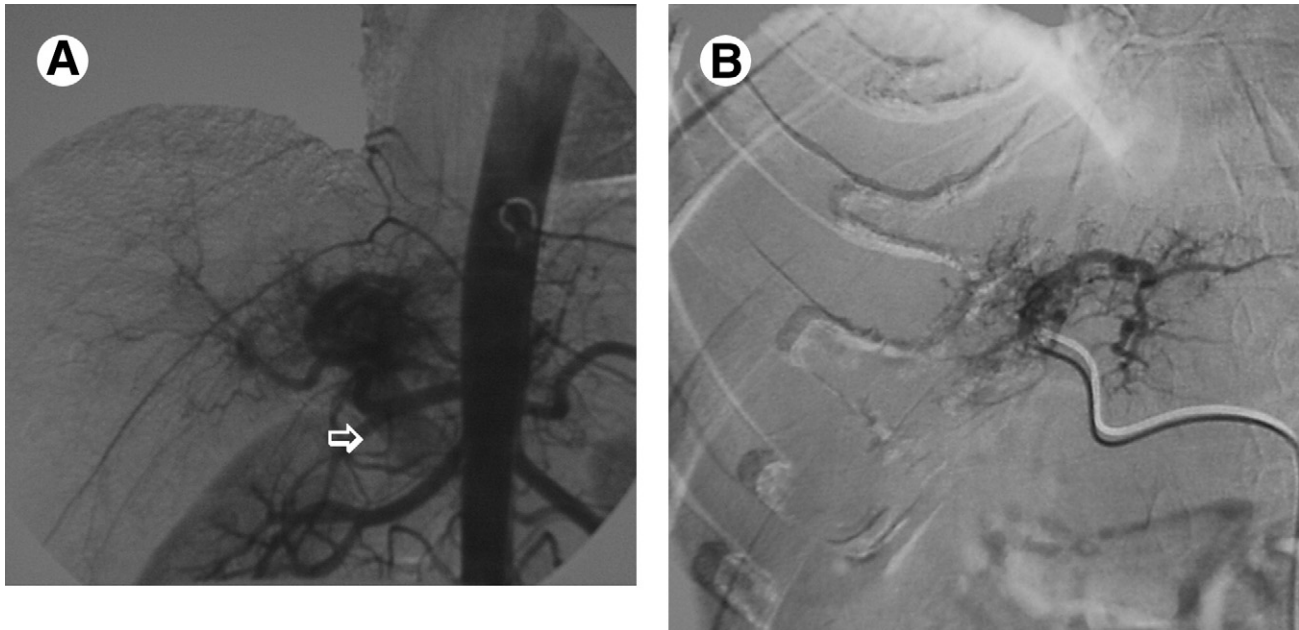


Figure 4 (A, B) DSA A-P views of the aorta and left hepatic artery in a 50-year-old male with history of multifocal HCC (left lobe lesion shown here) and intratumoral arterio-portal venous communication. (A) DSA view of the aorta, showing a hypervascular left lobe lesion, with early opacification of the portal vein, revealing an impressive arterio-portal venous shunting. (B) After successful gelfoam embolization of the arterio-portal venous shunting, selective engagement of the left hepatic artery shows no further communication. TACE was safely performed thereafter.

diffusion MRI scan of the liver is performed. The decision to retreat is based on the combination of imaging and laboratory findings as well as the patient's performance status.

According to the World Health Organization (WHO) and the Response Evaluation Criteria in Solid Tumors (RECIST), reduction in tumor size is the optimal outcome of every chemoembolization.^{30,31} Additionally, tumor enhancement on CT or MRI delineate viability, as enhancing portions of the tumor are presumed to be viable whereas the nonenhancing ones are presumed necrotic.³²⁻³⁴ However, the presence of lipiodol on CT scans after chemoembolization may obscure tumor enhancement and make image interpretation more difficult. Perfusion-diffusion MRI can successfully overcome this obstacle, as lipiodol does not obscure gadolinium enhancement and measurement of increased free water content within the tumor translates into cancerous cell death.²³ Furthermore, diffusion MRI may prove more useful in the early posttreatment period after TACE, when tumors are not expected to change in size despite the fact that they may be nonviable (Fig 5).^{35,36}

Lack of satisfactory response after one session of TACE

does not predict eventual response and repeated treatments targeting the same lesion are sometimes necessary to be performed. The emergence of any contraindications to TACE between consecutive procedures precludes re-treatment; thus, before each procedure, the relevant laboratory values should be obtained and the patient re-evaluated.

Complications and Side Effects

TACE has been reported to be frequently complicated by pain, fever, nausea, fatigue, and elevated transaminases, commonly referred to as the postembolization syndrome. These symptoms are usually self-limited, are more common in cases where large tumors are treated. In selected cases, careful postoperative monitoring is required to differentiate postembolization syndrome from other, more serious, complications, such as liver abscess, gallbladder infarction, and septicemia.

Complications resulting from nontarget embolization include necrosis in undesirable arterial beds, such as the cystic artery and gastrointestinal, cutaneous, and phrenic capillary beds. Hepatic arterial pseudoaneurysm formation or arterial stenosis may occur after difficult or inelegant catheter manipulations. Liver failure and hepatorenal syndrome are more likely to occur in debilitated patients with advanced disease and those with impaired liver function or compromised portal flow; in such individuals, it is important to weigh the possible complications of the procedure against its potential benefits. Other uncommon problems after TACE include ischemic cholecystitis, pulmonary or cerebral embolization, hypothyroidism, or the development of a pleural effusion. Table 3 summarizes a list of most commonly encountered side effects and complications of TACE.

Table 2 List of Materials Used in an Angiography Suite for a Chemoembolization Procedure

Items
5 Fr vascular sheath
Bentson wires
5 Fr pigtail catheters
5 Fr Simmons 1 catheters, glide
0.35 Terumo glide wires
3 Fr microcatheters (ie, Renegade)
Microcatheter wires (ie, Transcend)
Chemotherapy resistant three way stop cocks

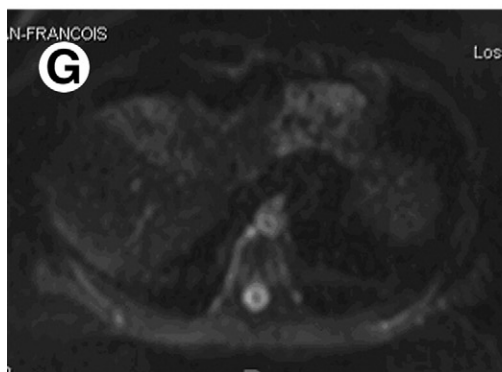
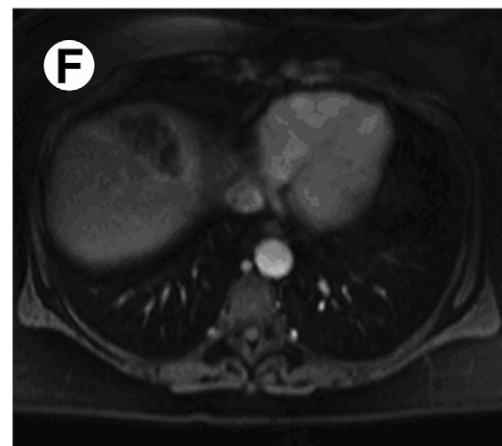
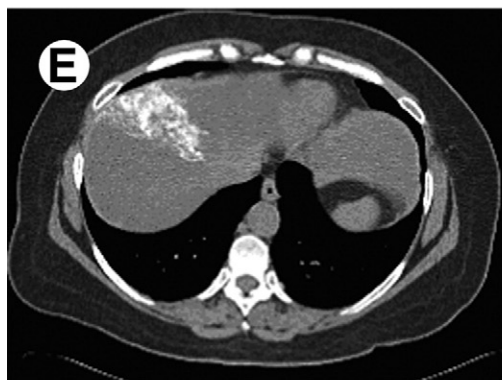
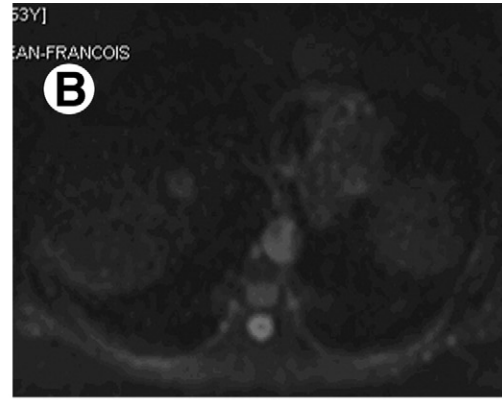
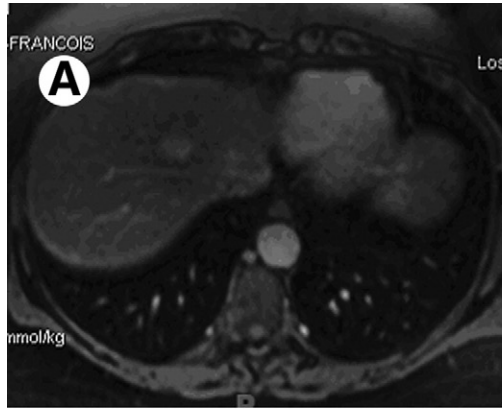


Table 3 Complications of TACE

Complication
Postembolization syndrome (pain, fever, nausea, fatigue, and leucocytosis)
Liver abscess
Gallbladder infarction
Septicemia
Irreversible liver failure
Hepatorenal syndrome
Pulmonary oil embolization
Cerebral embolization

Survival Benefit

The median survival of patients with inoperable HCC is 4 to 7 months (which can be extended with maximal supportive care to approximately 10 months). Despite that chemoembolization had early in its course proved to reduce tumor growth, initial large randomized trials failed to demonstrate a survival advantage.³⁷⁻³⁹ However, in 2002, two randomized controlled trials published showed a survival advantage for TACE in selected patients with preserved liver function and supportive maintenance.^{13,14} A meta-analysis that included seven randomized trials of arterial embolization for unresectable hepatocellular carcinoma provided further support of the efficacy of TACE.¹⁶ Compared with control (either conservative treatment or less favorable therapy, such as intravenous 5-fluorouracil), there was a statistically significant improvement in 2-year survival with arterial chemoembolization (odds ratio 0.53, 95% confidence interval 0.32-0.89).¹⁶ TACE showed a median survival of more than 2 years and, although rarely, converted some patients into operable candidates.

There is less experience with TACE in the treatment of hepatic metastases.⁴⁰ Several studies have an excellent symptomatic and biologic complete response rate of 70 to 73% of patients with metastatic carcinoid treated with chemoembolization.⁴¹ The efficacy of TACE in other groups, such as patients with colorectal metastasis, is less established.⁴²

Future Promise

Research activity on chemoembolization can be divided into three distinct areas that correspond to the three major elements of the procedure: advancements in chemotherapeutic agents, embolic agents, and embolization technique.

Advances in the knowledge of the molecular and hepatic

tumorigenesis have led to the development of novel cytostatic agents that may interact on some disrupted pathways, inhibit angiogenesis, and limit chemotherapeutic dose-related toxicity. Phase I/II/III studies are currently testing whether antiangiogenesis agents, inhibitors of growth-factor-signaling and cell cycle enzymes, nonspecific growth inhibitory agents, specific antagonists of HCC tumor markers, and anti-inflammatory agents, may have a potential impact on the treatment of liver cancer.⁴³ The combination of these emerging agents with chemoembolization seems challenging, as the reduction in the formation of new vessels may combined with the high-intratumoral cytotoxic chemotherapeutic concentrations that are achieved during TACE. Bevacizumab (Avastin, Genentech Inc, San Francisco, CA), a humanized monoclonal antibody that binds vascular endothelial growth factor (VEGF) and prevents its interaction to receptors on the surface of endothelial cells, has been recently added to the triple chemoembolization cocktail for patients with primary and metastatic liver cancer. A recent pilot study, in selected HCC patients undergoing TACE who additionally received intravenous bevacizumab, showed encouraging results with good drug tolerance and prolonged disease control.⁴⁴ Two phase II trials, evaluating the safety and efficacy of the combination of bevacizumab with TACE, are currently recruiting patients with primary and metastatic unresectable liver cancer.^{45,46} 3-Bromopyruvate (3-BrPa) is another example of a drug disrupting a metabolic pathway, which has been recently tested via transcatheter infusion. 3-BrPa is a hexokinase II specific inhibitor, which potently abolishes cell ATP production via the inhibition of glycolysis.³ Preliminary studies on the rabbit VX2 liver tumor model with direct intrarterial infusion of 3-BrPa showed complete tumor destruction, without affecting the surrounding normal liver parenchyma.^{3,43} The mechanism of resistance of normal cells against 3-BrPa has not yet been clarified, though it might be related to the different levels of hexokinase II expression between normal and malignant cells.⁴⁷ Recombinant adenoviral vectors, such as those expressing recombinant b-galactosidase or human hepatocyte growth factor, soaked in gelatin sponge pledgets, have been recently tested for transcatheter delivery in canines.⁴⁸

Despite that extensive research is available on hepatic embolization, the precise effect of embolization on tumor cells remains largely undefined. In fact, recent data suggest that hypoxia, generated by arterial embolization, may activate several genes, including vascular endothelial growth factor (VEGF) and hexokinase II, therefore leading to compensa-

Figure 5 (A-G) A 53-year-old female with a history of metastatic carcinoid to the liver. (A) Baseline MRI scan of the liver (portal venous phase) showing a hypervascular lesion measuring 1.8 cm in segment 8. (B) Baseline MRI scan of the liver (diffusion weighted imaging) corresponding to the lesion described in (A). (C) DSA A-P view of the right hepatic artery demonstrates hypervascularity in segments 7 and 8. (D) Single spot image after the injection of the chemoembolization mixture, showing good lipiodol deposition in the targeted area. (E) CT scan of the liver, 1 day after TACE, showing good lipiodol deposition in the targeted area. (F) MRI scan of the liver (portal venous phase), 1 month after TACE, showing a wedge-shaped area, corresponding to the targeted area, with a 75% decrease in enhancement of the targeted lesion (favorable response). Note that, according to the RECIST and WHO criteria, the targeted area has now increased in size, measuring 4.4 × 5.6 cm. (G) MRI scan of the liver (diffusion weighted imaging), 1 month after TACE, showing a predominantly hyperintense wedge-shaped area, with an increased apparent diffusion coefficient (ADC) value (favorable response), compared with the baseline ADC value of the targeted area.

tory angiogenesis and tumor growth.⁴⁹ Similar simple observations have also confirmed the angiogenesis theory by the formation of early revascularization after proximal and temporary embolization induced with gelfoam.⁵⁰ It seems that occlusion of more peripheral vessels generates a nearly complete tumor necrosis, favoring for distal embolization. Spherical embolic agents allow for accurate calibration, optimal and complete geometric vessel occlusion and therefore, may play an important role in achieving distal occlusion. Moreover, drug-loaded (doxorubicin or irinotecan-loaded) microspheres have recently been developed for intra-arterial injection.⁵¹ Doxorubicin-eluting beads (DC Bead for loading by the physician and PRECISION Bead preloaded with doxorubicin, Biocompatibles UK Ltd, Surrey, UK) were initially tested on the rabbit Vx-2 tumor model and demonstrated consistent drug release over time with excellent tumor control.⁵¹ Clinical studies are currently in progress and initial results seem to be rather encouraging. Irinotecan-eluting beads for metastatic colon cancer are also under development.⁵²

Currently, there is no consensus on how selective (lobar versus segmental) chemoembolization should be. Many interventional radiologists prefer to treat one lobe of the liver at each treatment session, regardless of the extent or number of tumors, whereas others may choose a more selective approach. Despite that longer survival seems to be related to multiple TACE sessions, further research is required to assess the effectiveness of long-term arterial patency.⁵³ Time-to-re-treat is also a subject of debate. Some centers prefer to treat patients at fixed timing, whereas others on disease progression after the initial response. In our institution, decision to re-treat is made based on imaging and clinical assessment of tumor response. Appointments for imaging and clinical evaluation though are scheduled within a fixed interval of time after each treatment.

Conclusion

Chemoembolization is currently routinely performed in many institutions throughout the world. Despite that, standardization of the technique is essential for the conduct of large prospective randomized trials and meta-analyses, this may prove difficult to achieve, as there is no consensus regarding the chemotherapeutic agents, embolic materials, and embolization technique or re-treatment approach. Although homogeneity and consistency may boost the effectiveness of the procedure, research in other areas, such as the application of combination therapies or further employment of gene and molecular therapies, may also give new dimensions to this locoregional therapy.

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