Chemoembolization of hepatic malignancy

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Abstract

Treatment of primary and secondary hepatic malignancies with transarterial chemoembolization represents an essential component of interventional oncology. This article discusses patient selection, procedure technique, results, and complications associated with transarterial chemoembolization.

Key words: Chemoembolization—Hepatic malignancy—Hepatocellular carcinoma—Cirrhosis—Liver metastases

Treatment of primary and secondary liver malignancies with transarterial chemoembolization (TACE) is the keystone of interventional oncology. Over 50 years ago, it was determined that liver tumors are predominantly supplied by the hepatic artery [1]. Given the dual blood supply of normal liver (75% from the portal vein/25% from the hepatic artery), TACE delivers localized treatment to tumors while limiting the toxicity to uninvolved adjacent parenchyma. TACE also delivers highly concentrated doses of chemotherapeutic agents to liver tumors compared to systemic administration. The embolization component prolongs dwell time of chemotherapeutic agents within the liver thereby, limiting systemic toxicity associated with these agents.

We review patient selection, indications, contraindications, technique, and complications of TACE. In addition, success rates for TACE will be discussed for both primary and secondary hepatic malignancies. Finally, newer agents being investigated will be reviewed.

Indications and patient selection

TACE is typically used to treat patients with unresectable primary malignancies such as hepatocellular carcinoma (HCC) and cholangiocarcinoma as well as secondary hepatic malignancies, including neuroendocrine tumors (NET), melanoma, breast, colorectal, and soft-tissue sarcomas. Contraindications to therapy occur most frequently in patients with cirrhosis and HCC. For that reason, patient selection will focus mostly on this patient group. The ideal candidates for TACE are patients with liver-dominant disease, adequate liver function, and no vascular invasion by tumor. Patients should have an east coast oncology group (ECOG) performance status of 0–1 with a performance status of 2 acceptable if it is thought that TACE will improve this score (Table 1). Absolute contraindications for TACE include extensive liver disease, severe infection, and jaundice [2]. Relative contraindications include compromised liver function, uncorrectable bleeding diathesis, poor performance status, significant intractable arteriovenous shunting, significant renal insufficiency, and encephalopathy [2]. Main portal vein thrombosis is also considered a relative contraindication; however, TACE may be performed if adequate hepatopedal collateral flow to the liver is identified prior to treatment. Patients with biliary abnormalities, including biliary obstruction and absence of a competent sphincter of Oddi from prior surgery (i.e. hepaticojejunostomy), sphincterotomy, or biliary stent placement are at significantly increased risk for hepatic abscess formation following TACE [3–5]. Patients with biliary obstruction, even with normal bilirubin levels, are at significant risk of biliary necrosis of obstructed bile ducts and therefore, biliary obstruction should be considered a contraindication for TACE. For patients with bilioenteric anastomoses or biliary stents, aggressive periprocedural intravenous antibiotics with bowel preparation may provide protection against hepatic abscess formation [4, 5].

Exclusion criteria based on laboratory values have not been definitively established. However, the constellation of greater than 50% tumor burden, bilirubin greater than 2 mg/dL, lactate dehydrogenase greater than 425 mg/dL, and aspartate aminotransferase lever greater than 100 IU/L may be associated with an

Table 1. East coast oncology group performance status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Table 2. Child-Pugh liver scoring system

Variable	1	2	3
Encephalopathy	None	Moderate	Severe
Ascites	None	Moderate	Severe
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	≥3.5	2.8–3.4	<2.8
Prothrombin time (seconds)	<14	15–17	≥18
Child-Pugh score: $A = 5–6$; $B = 7–9$; $C = 10–15$			

increased postprocedural mortality [6]. Individual abnormalities of these aforementioned parameters have not been shown to predict adverse outcomes related to TACE [7]. In practice, the synthetic dysfunction must be considered in combination with the volume of liver to be treated in a given treatment session.

Numerous liver staging systems have been employed to determine patient survival following TACE such as the Child-Pugh, Okuda, Barcelona Clinic Liver Cancer, Model for End-Stage Liver Disease (MELD), and the Cancer of the Liver Italian Program (CLIP) scoring systems. Each liver staging system uses a combination of different variables to predict patient survival following TACE including laboratory values (i.e. bilirubin, prothrombin time, albumin), liver function-related signs and symptoms (i.e. ascites, encephalopathy), tumor morphology (i.e. tumor size and number as well as vascular invasion), and overall performance status [8]. A recent study by Georgiadis et al. [8] evaluated 12 different liver staging systems to determine which scoring system provides the most accurate predictor of survival following TACE. Of all the staging systems evaluated, the Child-Pugh scoring system, which uses laboratory values and indirect indications of liver dysfunction, was determined to be the most accurate predictor of survival (Table 2). The authors concluded that the Child-Pugh scoring system should be adopted as the standard for liver staging of patients prior to TACE. In another study by Brown et al. [7], patients with Child-Pugh A disease were found to have significant longer survivals following TACE than patients with Child B/C disease (27.5 months vs. 10.3 months). In this same study, albumin levels were also found to be an important predictor of survival. Patients with albumin levels of at least 3.4 g/dL had improved survival (29.3 months) compared to patients with lower albumin levels (15.8 months). Therefore, based on these reports, the Child-Pugh scoring system and albumin levels are accurate predictors of survival and should be employed when counseling patients regarding expectations following TACE.

Procedural considerations

Premedication before chemoembolization is standard. Hydration is mandatory with intravenous administration of 150–300 mL/h of normal saline solution. Other premedications include antiemetics and steroids. Preprocedure antibiotics are not required and have not been proven beneficial patients without predisposing biliary pathology [4, 5, 9, 10]. For patients with carcinoid tumors, pretreatment with octreotide (150 μg) subcutaneously is important to limit carcinoid crisis caused by hormonal release as a result of tumor necrosis after embolization [11]. Supplemental therapy is essential even in patients with clinically asymptomatic tumors as these tumors may be producing serotonin or bradykinin at low levels. Following embolization, a relatively larger quantity of this hormone may be released in the bloodstream resulting in carcinoid crisis in unprotected patients.

Diagnostic angiography of the superior mesenteric and celiac arteries is essential to identify variant hepatic arterial anatomy, vascular supply to tumor, and origins of extrahepatic vessels to prevent nontarget embolization. Imaging should extend into the portal venous phase to assess for patency of the main portal vein or presence of collateral vessels with hepatopedal flow. Practice patterns for level of catheter selection range from superselective to lobar embolization depending on the type and number of tumors to be treated. Treatment of the entire liver in one session is associated with an increase in mortality [12]. When TACE leads to permanent occlusion of native hepatic arteries, several collateral pathways have been treated with clinical success, including the inferior phrenic, internal mammary, and intercostal arteries [13–15]. If these collateral arteries have potential communication with cutaneous vessels, HAE instead of TACE should be performed to limit the risk of cutaneous ischemic ulceration [15]. Treatment should avoid the cystic artery; however, if treatment of tumor is not feasible without including the cystic artery, TACE may still be performed. The main risk of treatment of the cystic artery is pain, which may potentially lengthen the post-treatment hospital stay but in a majority of cases does not cause significant risk to the gallbladder itself [16].

Lipiodol (Ethiodol; Savage Laboratories, Melville, NY), an iodinated ester derived from poppy-seed oil, is commonly mixed with chemotherapeutic agents during TACE. Studies have demonstrated selective up-take and

retention of Lipiodol within both primary and secondary tumors of the liver. Lipiodol acts as both an embolic agent and a carrier of chemotherapeutic agents to tumors, although it has relatively little cytotoxic effect by itself. Lipiodol enters small arteries and peritumoral sinusoids and blocks blood flow to tumors [17]. In general, 1 mL of Lipiodol is used for every centimeter of hypervascular tumor up to a maximum of 15 mL. Larger doses of Lipiodol may flow through sinusoids into portal vein branches and cause liver dysfunction or hepatic infarction [17]. Studies have reported improved patient survival and treatment response for tumors that retain >50% Lipiodol following treatment [18].

Embolic agents employed for TACE include both permanent (i.e. polyvinyl alcohol) and temporary (i.e. gelfoam) agents. Successful TACE results have been reported utilizing both agents and therefore the choice of embolic material is typically dependent on the preference of the interventional radiologist performing the procedure. Regardless of which embolic agent is used, the goal is the same, to render tumors ischemic. Ischemia causes the disruption of intracellular glycoprotein pumps, which inhibits tumor cells from expelling chemotherapeutic agents. The disruption of these pumps results in prolonged tumor exposure to chemotherapy drugs. In fact, a study by Sasaki et al. [19] reported a sixfold increase in cisplatin retention within resected tumors (mean of 55 days; range, 13–114 days) compared to adjacent liver parenchyma following TACE with gelfoam. A majority of the tumors evaluated (15/20) demonstrated complete necrosis and the remaining five tumors demonstrated 70%–90% necrosis postprocedure. Although the necessary duration of vascular occlusion to induce tumor necrosis is unknown, Sasaki et al. [20] demonstrated that temporary arterial occlusion with gelfoam was sufficient in producing tumor ischemia allowing for prolonged chemotherapy retention within tumor cells. In a recent study, survival rates following TACE were compared using different embolic material. Eighty-one patients with HCC were treated by TACE using gelfoam powder ($n = 41$) or polyvinyl alcohol ($n = 40$) [20]. Both groups were similar in liver function and tumor characteristics and procedure technique did not differ except for the type of embolic agent used for embolization. The overall survival was similar for patients treated with gelfoam powder (mean, 659 days $\pm$ 83) and polyvinyl alcohol (mean, 565 days $\pm$ 71) with a trend toward improved survival in the group treated with gelfoam powder. Given the similar survival results reported by this group, either embolic agent is a reasonable choice for TACE.

Following TACE, patients are admitted overnight for observation. Antiemetics and analgesics should be available to control symptoms of postembolization syndrome (PES). Postprocedural imaging should be obtained 4–6 weeks following treatment. If treatment of both hepatic lobes is necessary, imaging between sessions may be performed based on operator preference. Signs of tumor necrosis on CT include Lipiodol uptake and absence of arterial-phase enhancement, if this was present on imaging before TACE [20, 21]. Disappearance of arterial enhancement is the principal determinant of tumor necrosis on MR imaging [22]. There is a paucity of literature regarding follow-up of lesions after TACE without arterial-phase enhancement. Obvious tumor enlargement or nodular enhancement in portal vein or delayed-phase imaging has been described as evidence of residual or recurrent tumor following radiofrequency ablation (RFA) of lesions without initial arterial-phase enhancement [23]. Similar findings may be present in the setting of residual or recurrent tumor after TACE. Correlation with tumor markers should be performed as available. Patients without active disease at follow-up should undergo repeated imaging every 3–4 months.

Outcomes with specific tumor types

Hepatocellular carcinoma

Worldwide, HCC causes approximately 1 million deaths annually and approximately 6,000 new cases are diagnosed each year in the United States [24].

The incidence of HCC is increasing especially in the United States mainly due to the significant rise in incidence of hepatitis C virus [25]. Despite advances in diagnosis and treatment of HCC, the overall 5-year survival is a dismal 2% [26]. Surgical resection and liver transplantation are the only two treatments that offer the potential for cure, however, only 10%–15% of patients with HCC are candidates for either of these treatments [27]. Even if surgical resection is possible, 75% of patients will develop recurrence of HCC in the remaining cirrhotic liver within 18–24 months following tumor resection [26]. For patients who are transplant candidates, the waiting period for transplantation can be as long as 1–2 years due to the shortage of donor organs available for the growing number of patients on the transplant waiting list [26]. In addition, 25% of patients awaiting transplantation develop tumor progression within 6 months, which may eliminate transplantation as an option [26]. Other therapies for HCC include external beam radiation therapy, which is limited by significant toxicity to the liver [27]. Therefore, TACE is currently the most widely performed procedure for patients with unresectable or recurrent HCC and for those awaiting transplantation.

In 2002, two, well-designed, randomized, prospective trials were published in the literature evaluating the impact of TACE on patient survival. A study by Lo et al. [28] compared patients treated with TACE to those treated with supportive care alone. The 1-, 2-, and 3-year survival rates for patients treated with TACE and supportive care were 57%, 31%, and 26%; and 32%, 11%, and 3%, respectively. Another trial by Llovet et al. [29], reported results of HCC patients treated with TACE,

HAE, and supportive care alone. The 1- and 2-year survivals were 82% and 63% for the TACE group, 75% and 50% for the HAE group and 63% and 27% for the supportive care group, respectively. Both studies demonstrated a significant survival benefit for patients treated with TACE and concluded that TACE is an effective treatment for patients with HCC.

TACE in combination with RFA may hold even more promising results for patients with HCC. A recently published randomized controlled trial reported a significant survival benefit for patients with large HCC (>3 cm) tumors treated with TACE combined with RFA, compared to TACE-alone or RFA-alone [30]. The benefits of this combined treatment can be attributed to the complete tumor response achieved in patients treated with both TACE and RFA. Better tumor response can be ascribed to the reduction of arterial flow following TACE. The reduction in arterial flow decreases heat loss during RFA, which lowers the mean impedance values within tumors resulting in a larger thermal ablation zone [30]. In addition, TACE disrupts intratumoral septa allowing for better distribution of heat within the tumor during RFA. This combination of therapies results in a greater percentage of tumor necrosis than with either procedure alone. Therefore, TACE used in combination with RFA may improve long-term survival for patients with HCC.

Neuroendocrine tumors (NET)

NET, such as carcinoid and islet cell carcinomas (also known as pancreatic endocrine tumors) have a strong predilection for developing liver metastases with reports of up to 78% in surgical series [31, 32]. Hepatic resection is possible in less than 10% of patients at the time of diagnosis and systemic chemotherapy provides limited effectiveness particularly for patients with carcinoid tumors [33]. NET metastases rarely cause early liver dysfunction and typically have a long, indolent disease course often causing bulk-related symptoms due to significant tumor burden within the liver. Many of these tumors result in a variety of hormonal syndromes (i.e. carcinoid syndrome) due to their ability to synthesize and secrete hormonally active polypeptide products. Somatostatin analogues (i.e. octreotide) are often initially effective in controlling symptoms associated with NET and also have been shown to increase patient survival [34]. However, NET metastases eventually become refractory to medical treatment. Accepted indications for catheter-directed therapy in patients with NET liver metastases include symptoms related to hormonal excess, tumor bulk, and treatment of tumors refractory to medical therapy.

Although several studies have reported the beneficial therapeutic effect of TACE and TAE for patients with NET liver metastases, it is still unclear whether TACE offers a significant advantage over TAE [34]. Gupta et al.

[11] recently reported a clear tendency toward prolonged survival (31.5 months vs. 18.2 months) and a better imaging response rate (50% vs. 25%) in patients with islet cell tumors treated by TACE compared to those treated with TAE although this failed to reach statistical significance. However, there was no such difference, statistically or otherwise in overall survival or response rate for patients with carcinoid tumor treated with either TACE or TAE. The authors attributed this to the fact that islet cell tumors tend to respond better (30%–69% response rate) to systemic chemotherapy whereas carcinoid tumors tend to be resistant to systemic chemotherapy (<15% response rate). Therefore, a reasonable approach is to pursue TACE for patients with islet cell tumors as opposed to carcinoid tumors where treatment with TAE or TACE may be equally effective [11].

Colorectal carcinoma

Liver metastases can be found in up to 80% of patients with colorectal carcinoma [35]. Although the standard curative treatment is resection, only 20% of patients are candidates for resection at presentation with a high percentage of recurrences expected [35]. Recently, more promising systemic chemotherapeutic agents for treatment of colorectal metastases have become available which have improved overall survival and tumor response rate. Therefore, TACE is currently reserved for patients who fail systemic therapy [36].

A current area of research involves the use of irinotecan drug-eluting beads to treat colorectal liver metastases. The initial results of a Phase II clinical trial comprising 20 patients reported an 80% response rate with reduction of contrast enhancement of treated tumors following treatment with irinotecan drug-eluting beads [37]. This promising treatment for patients with colorectal metastases merits further study both as a salvage agent and potentially in combination with systemic chemotherapy.

Breast carcinoma

Limited data are available regarding TACE for liver metastases from breast carcinoma. However, in 2004, Giroux et al. [38] reported their results of a retrospective review of eight patients treated with TACE for pain (n = 4) and/or liver-dominant disease unresponsive to systemic chemotherapy (n = 7). Five of eight patients demonstrated radiographic regression of liver tumors, one patient demonstrated stable disease, and two patients showed disease progression. Two of four patients with pain experienced clinical improvement of their symptoms. Only one patient with radiographic response or disease stabilization subsequently had progression of liver disease 3 months following TACE. Five patients developed other metastasis (i.e. brain metastases), at a

mean of 4.6 months (range, 2–12 months) following the first TACE procedure. All patients expired within 13 months of treatment, with a mean survival of 49 months from primary diagnosis, 20 months from liver metastasis diagnosis, and 6 months from the first TACE procedure. The authors concluded that TACE stabilizes or improves liver tumor burden alleviating bulk-related symptoms. Unfortunately, development of additional metastases, particularly brain metastases is the cause of death in a majority of patients with breast carcinoma [38].

Melanoma

Approximately 50% of patients with uveal melanoma develop hepatic metastases and in up to 90% of patients, the liver is the only site of metastatic spread [39]. In general, uveal melanoma metastases do not respond to systemic chemotherapy and without treatment, patients have a life expectancy between 2–7 months, with a 1-year survival of 15% [40, 41]. Because the liver is the primary site of metastatic spread, control of hepatic metastases with TACE holds promise for metastatic uveal melanoma. A study by Malvigit et al. [42] reported a 46% objective response with a median survival of 11 months using carboplatin and polyvinyl alcohol particles. However, two subsequent studies using the same regimen failed to reproduce similar results [43, 44]. In a study by Patel et al. [45], 30 patients with uveal melanoma metastases were treated with 100 mg of BCNU (1,3-bis (2-chloroethyl)-1-nitrosourea) followed by gelfoam sponge. The overall survival ranged from 0.1–27.6 months (median survival of 7.8 months) with a 1–year survival of 33%. Immunoembolization with granulocyte–macrophage colony stimulating factor (GM-CSF) and gelfoam have produced significantly better results (1-year survival 61.4%) than those achieved with TACE; however, a direct comparison of the two treatments has not been reported [46].

Cholangiocarcinoma

Median survivals for unresectable cholangiocarcinoma range between 6–12 months from the time of diagnosis [47]. Burger et al. [47] recently evaluated the safety and efficacy of TACE for patients with unresectable cholangiocarcinoma. Seventeen patients were treated with one or more cycles of TACE. The median survival for this patient population was 23 months (range 15.4–30.6 months) and two patients previously defined as having unresectable cholangiocarcinoma underwent successful resection following TACE. The majority of patients (82%) tolerated the procedure well. Two (12%) patients had minor complications and one patient had a major complication that resulted in a fatal outcome shortly after treatment. In another study by Herber et al.

[48], 15 patients with unresectable cholangiocarcinoma were treated with TACE. The authors reported a mean survival of 21.1 months (range 9.4–32.5 months). The 1-, 2-, and 3-year survival rates were 51.3%, 27.5%, and 27.5%, respectively. The authors in both studies concluded that TACE offers a potential benefit and prolonged survival for patients with unresectable cholangiocarcinoma.

Complications and side effects

Reported rates and expected thresholds for complications and side-effects associated with TACE are listed in Table 3.

Postembolization syndrome

Postembolization syndrome (PES) is considered a side-effect of TACE rather than a complication. PES can occur in up to 90% of patients following TACE and is characterized by abdominal pain, fever, anorexia, nausea, vomiting, and fatigue [16]. The cause of PES is not completely understood but several theories have been hypothesized including distention of the liver capsule, tumor necrosis, ischemia of the liver parenchyma, and gallbladder infarction [16, 49]. These symptoms usually last a few days but may last as long as 10 days. PES syndrome requiring extended hospital stay or readmission has been reported in one series in up to 4.6% of patients [50].

In an attempt to predict who is at risk for developing PES for TACE, Patel et al. [49] evaluated several procedural variables (i.e. HAE vs. TACE, tumor location, and tumor burden) for an association with PES in 62 patients following 130 procedures, and failed to find any strong predictors of PES following TACE. In a subsequent study by Leung et al. [16], several procedural variables were examined for association with PES in 29 patients following 70 TACE procedures. This study

Table 3. Major complications of hepatic arterial chemoembolization[a]

Major complication	Reported rate (%)	Suggested threshold (%)
Liver failure	2.3	4
Post-embolization syndrome requiring extended stay or readmission	4.6	10
Abscess with functional sphincter of Oddi	1	2
Abscess with biliary–enteric anastomosis/ biliary stent/sphincterotomy	25	25
Surgical cholecystitis	1	1
Biloma requiring percutaneous drainage	1	2
Pulmonary arterial oil embolus	1	1
Gastrointestinal hemorrhage/ulceration	1	1
Iatrogenic dissection preventing treatment	1	1
Death	1	2

[a] Brown et al. Quality Improvement Guidelines for Transhepatic Arterial Chemoembolization, Embolization, and Chemotherapeutic Infusion for Hepatic Malignancy. J Vasc Interv Radiol 2006; 17:225–232

unlike the previous report also analyzed procedural variables (i.e. dose of chemoembolic emulsion and gallbladder embolization), which could potentially be adjusted to prevent toxicity. An increased risk of PES was found in cases of gallbladder embolization and with the use of higher doses of chemoembolic emulsion, typically at the first session of therapy in a given area. At follow-up, there is pruning of the previously treated arterial branches which likely limits the embolization effect as well as PES.

Nontarget embolization

Nontarget embolization is defined as inadvertent reflux of chemotherapeutic agents and/or embolic material into unintended territories. Diagnostic arteriography prior to TACE is essential to identify variant hepatic arterial anatomy and origins of extrahepatic vessels. Arteries, such as the hepatic falciform ligament, phrenic, right, or accessory gastric arteries, supraduodenal, retroduodenal, and retroportal arteries need to be identified by diagnostic arteriography prior to TACE to prevent complications associated with nontarget embolization (Fig. 1) [2]. Gastrointestinal ischemia due to nontarget embolization of gastroduodenal arteries has been reported in <1% of patients (Table 3) [51]. The hepatic falciform ligament artery typically originates from branches of the left hepatic artery and has been reported in 7.6%–51.6% of patients [52, 53]. Nontarget embolization of this artery may lead to supraumbilical skin irritation if unrecognized. Prophylactic embolization of hepatic falciform ligament artery prior to TACE may prevent this complication from occurring (Fig. 2). In 2% of patients, the left inferior phrenic artery can arise form the left hepatic artery [52]. Embolization of the inferior phrenic artery may result in shoulder pain, atelectasis, and pleural effusion. Superselective TACE can reduce unintentional infusion of chemotherapeutic agents into extrahepatic arteries. If TACE cannot be performed distal to extrahepatic arteries, embolization of nontarget vessels using coils or gelfoam can be effective in preventing complications related to nontarget embolization.

Hepatic failure and death

Hepatic failure is more likely to occur in patients with extensive tumor, impaired hepatic function (Child-Pugh C), or compromised portal flow. Acute liver failure has been reported in up to 2.6% of patients following TACE [36, 51]. Death within 30 days of TACE has been reported in up to 1% of patients mostly related to acute hepatic failure; however, other causes reported include sepsis and pulmonary oil embolism [36, 51]. The Society of Interventional Radiology put forth suggested guidelines for major complications associated with TACE
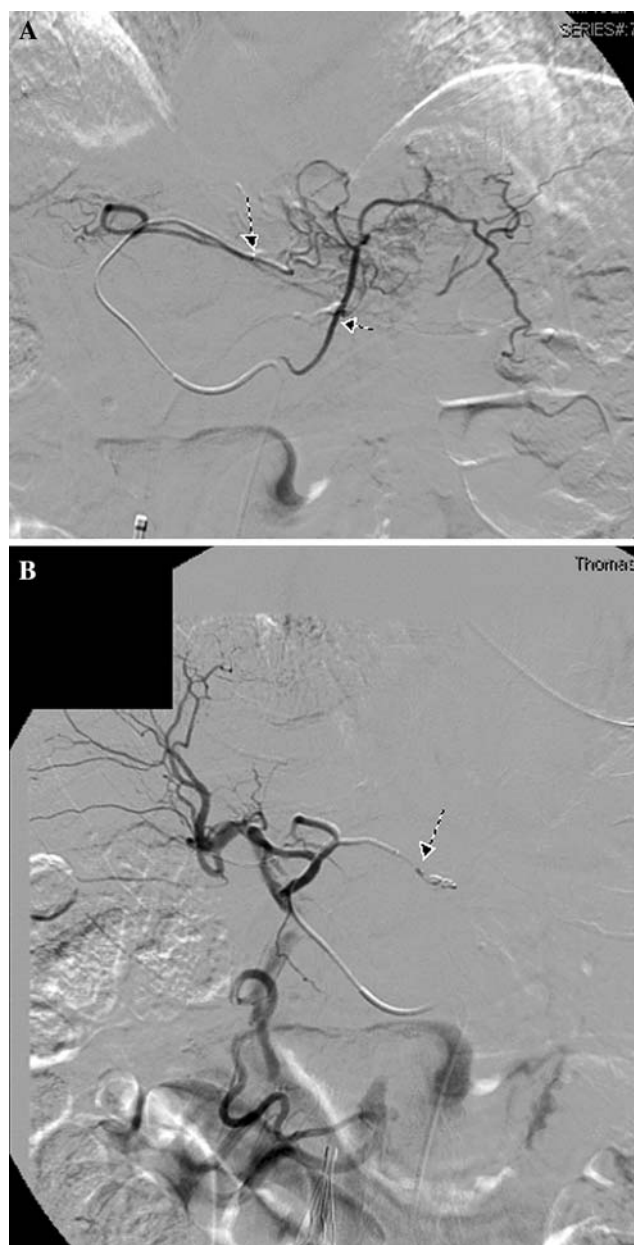

Fig. 1. (A) Left hepatic arteriography prior to TACE shows an accessory left gastric artery (*long arrow*) communicating with the main left gastric artery (*short arrow*). (B) Left hepatic arteriography following coil embolization of the accessory left gastric artery (*arrow*). TACE of the left hepatic artery was performed without complications.

including suggested thresholds of 2% and 4% for mortality and hepatic failure, respectively (Table 3) [36].

Tumor rupture

Tumor rupture after TACE is rare and occurs in less than 1% of cases [51]. Rupture following TACE is presumably due to tumor and capsular necrosis with secondary infection, arterial injury during TACE, or from
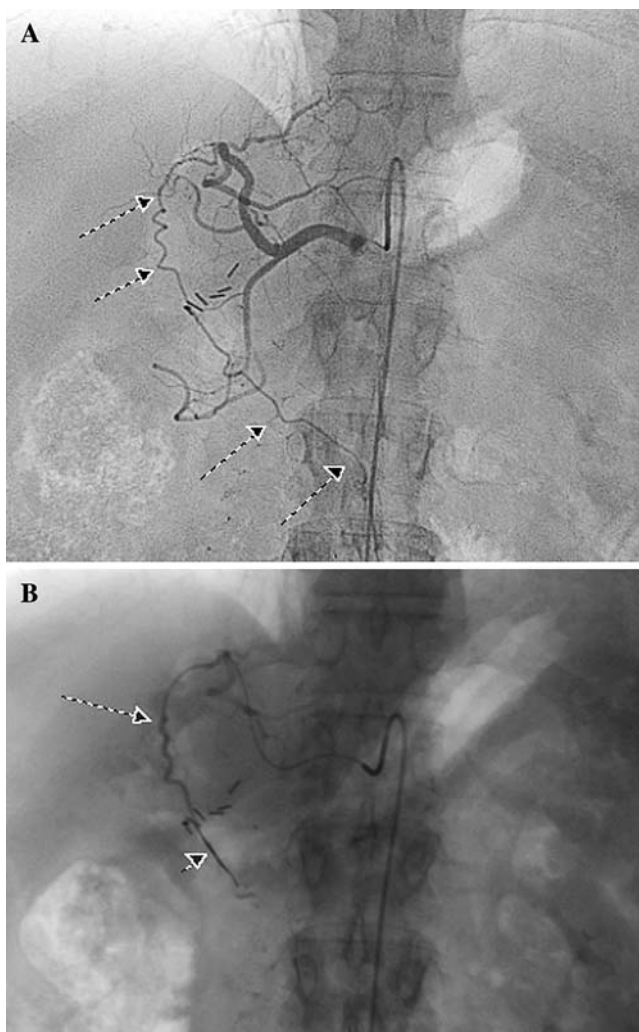
Fig. 2. (A) Left hepatic angiography prior to TACE demonstrates a hepatic falciform ligament artery (*arrow*). (B) Left hepatic arteriogram following coil embolization of the hepatic falciform ligament artery (*arrow*). TACE was performed without complications.
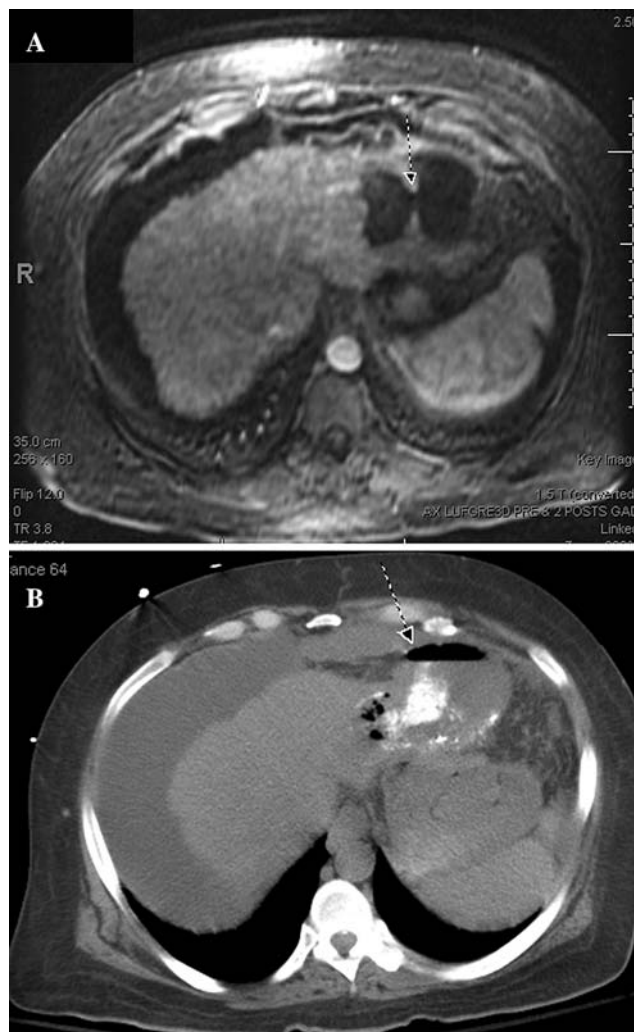

Fig. 3. (A) Gadolinium enhanced axial MRI of the liver demonstrates rupture of a left lobe HCC. The disruption of the hepatic capsule is evident (*arrow*) with an adjacent extrahepatic fluid collection. (B) CT scan a few weeks later demonstrates Lipiodol and air within an extrahepatic collection (*arrow*) representing superinfection of a perihepatic hematoma.

inflammation from chemotherapeutic agents [52, 53]. In a retrospective comparative study, Zhu et al. [54] showed that inflammatory mediators released due to vascular injury digest elastin and collagen fibrils. This inflammatory response may cause weakening of the arterial wall leading to aneurysm formation and rupture. Rupture following TACE is more common with large tumors and with exophytic tumors. Tumor necrosis caused by TACE may be exaggerated by infection. Necrosis and the presence of hematoma results in increased intratumoral pressure potentially leading to rupture. An alternative presentation is tumor rupture with hemoperitoneum which is fortunately uncommon (<1%) (Fig. 3) [51].

Bile duct injury

In contrast to normal hepatic parenchyma, intrahepatic bile ducts do not have a dual blood supply and are fed exclusively from hepatic arterial branches that give off a vascular plexus around the bile ducts, known as the peribiliary capillary plexus [55]. Therefore, ischemic bile duct injury can easily occur following TACE (Fig. 4). The mechanism of biloma formation following TACE results from bile duct necrosis caused by microvascular damage of the peribiliary capillary plexus [55].

In a study by Sakamoto et al. [55], 972 patients with HCC ($n = 920$) or metastatic tumor ($n = 52$) underwent TACE. The authors reported a significant higher incidence of bile duct injury, specifically intrahepatic biloma formation in patients with metastatic tumor (9.6%) compared to patients with HCC (3.3%). In a study by Yu et al. [56], 346 patients with various tumors underwent one or more sessions of TACE. The authors
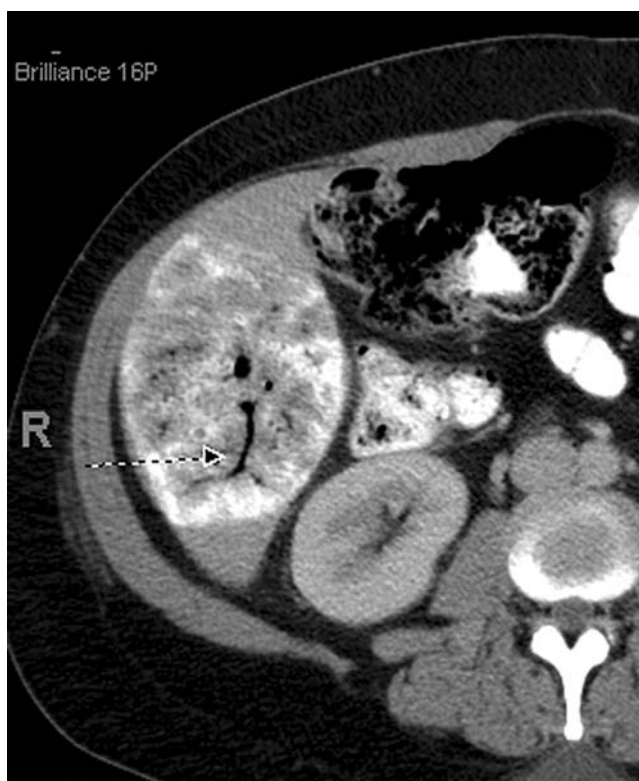
Fig. 4. Contrast enhanced CT scan of the abdomen shows air within dilated bile ducts in the posterior segment of the right lobe compatible with biliary necrosis (*arrow*).

found an 11.3% incidence of bile duct injury following TACE. The incidence of bile duct injury in this study was also more common in patients with metastatic tumors than in patients with HCC. In addition, the incidence of bile duct injury was significantly higher in patients with Child-Pugh class A (15.8%) disease compared to patients with more advanced cirrhosis (2.7% for Child-Pugh class B/C). These results imply that bile ducts in patients with cirrhosis are more resistant to ischemic injury following TACE than in patients without cirrhosis [57]. Demachi et al. [58] attributed this to hypertrophy of the peribiliary capillary plexus in cirrhotic livers which results in increased capacity for collateralization protecting bile ducts from ischemic injury. In noncirrhotic livers, however, even small amounts of embolic material may occlude the normal nonhypertrophied capillary plexus causing stasis of blood flow and ischemic injury to intrahepatic bile ducts [55, 58]. Based on these results, patients with metastatic tumors are at greater risk for bile duct complications than patients with HCC.

Conclusion

TACE is a safe and effective technique for treatment of primary and secondary hepatic malignancies. Current areas of research include drug-eluting beads, gene therapy, and the use of antiangiogenesis agents in combination with TACE. Preliminary trials have demonstrated the safety and efficacy of drug-eluting beads and radioactive microspheres [59]. Further investigation is needed to determine the safety and efficacy of antiangiogenesis agents and the clinical applicability of gene therapy.

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