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Complications Related to Transarterial Treatment of Hepatocellular Carcinoma: A Comprehensive Review

Hyoung Nam Lee[1], Dongho Hyun[2]

[1]Department of Radiology, Soonchunhyang University College of Medicine, Cheonan Hospital, Cheonan, Korea; [2]Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Currently, various types of transarterial treatments are performed for hepatocellular carcinoma from the early to advanced stages. Its indications and efficacy have been widely investigated. However, procedure-related complications have not been updated in the literature, although new types of transarterial treatments, such as drug-eluting bead transarterial chemoembolization and transarterial radioembolization, are common in daily practice. Herein, a comprehensive literature review was carried out, and complications were organized according to the organs affected and treatment modalities.
Keywords: *Transarterial treatment; Complication; Hepatocellular carcinoma; Chemoembolization; Radioembolization*

INTRODUCTION

Current guidelines recommend transarterial treatment as the first-line treatment for intermediate-stage hepatocellular carcinoma (HCC) [1-4]. However, in daily practice, transarterial treatment is often chosen as a second-line option at all stages via treatment stage migration [1,5]. Since transarterial embolization (TAE) was first reported in 1974, various types of transarterial treatments have emerged with the development of new devices and the introduction of new treatment concepts, including transarterial chemoembolization (TACE), drug-eluting bead (embolics) TACE (DEB-TACE), and transarterial radioembolization (TARE) [6-11].

Similar to other radiological procedures, transarterial treatments are safe but can result in adverse events (Fig. 1). The reported incidence varies widely according to the population, type of interventional procedure, and definition [12,13]. Although most of these complications are not serious, some lead to morbidity and mortality [14]. Some are specific to certain types of procedures, while others can occur regardless of modality (Tables 1, 2). Complications unfamiliar to both diagnostic and interventional radiologists can be encountered as newer techniques are introduced. Therefore, data from the current literature should be updated [12-15]. This study aimed to review and organize various complications related to currently available transarterial treatments for HCC.

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Corresponding author: Dongho Hyun, MD, Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
• E-mail: mesentery.hyun@samsung.com

Systemic Complications

PES

Postembolization syndrome (PES) is not considered a complication by itself but rather a predicted outcome after any type of embolotherapy [16]. Radiological findings specific to PES are unavailable since they are diagnosed solely based on clinical findings. PES is characterized by fever, abdominal pain, and/or leukocytosis within the first few days of transarterial treatment. PES is the most common adverse event (ranging from 15% to 90%) after TACE and is a frequent cause of prolonged hospital stays [17]. Although DEB-TACE is known to have a low incidence of PES since it has better pharmacokinetic features compared to TACE, recent studies show contradictory results [18-22].

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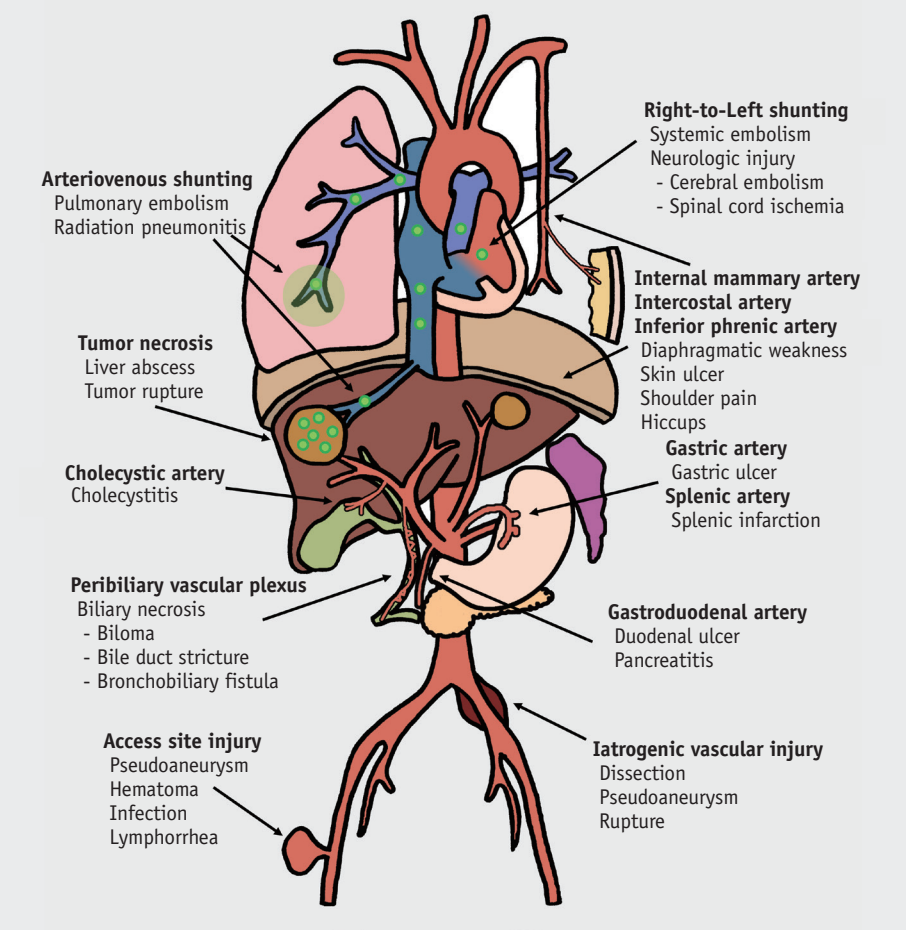

Fig. 1. Illustration of complications related to the transarterial treatment of hepatocellular carcinoma.

The minimal embolic effect of TARE is associated with a lower incidence of PES (20%–55%) [3]. A history of PES, tumor burden, number of treated nodules, presence of cirrhosis, and dose of embolic agents have been identified as predictive factors of PES [17,21,23]. Symptoms are usually self-limiting and subside within a few days. The treatment is supportive, including analgesics and antiemetics, as needed to control symptoms. The prophylactic use of anti-inflammatory agents (e.g., dexamethasone or parecoxib) to alleviate PES has been suggested in recent randomized controlled trials [24-26]. However, prophylactic agents should be used cautiously, particularly in patients with viral hepatitis or uncontrolled diabetes mellitus.

Lymphopenia

TARE is based on the local delivery of radionuclides bound to glass or resin microspheres, which minimizes systemic toxicity. A recent prospective study found that up to 1% of ^{90}Y administered via resin microspheres to the liver is eluted as free ^{90}Y in the blood [27]. After TARE, more than 95% of patients experience transient lymphopenia, which decreases by approximately 50% and recovers to approximately 60% of baseline at 6 months [28]. However, discernible clinical consequences have been reported to be rare, even after whole-liver radioembolization [29,30].

Hepatobiliary Complications

Liver Failure

Both conventional TACE and DEB-TACE can cause variable degrees of liver failure (Fig. 2). Liver failure was defined as an increase in serum bilirubin levels, increasing or newly developed ascites, or hepatic encephalopathy within 2 weeks of the procedure [31]. It is a serious complication that can lead to significant morbidity and mortality. TACE is mainly performed in patients with relatively preserved liver function (Child–Pugh stage ≤ B7) [32]; however, approximately 60% of patients experience at least one episode of liver failure during the course of treatment [33].

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TACE is based on a dual blood supply to the liver, and HCCs are supplied exclusively by the hepatic artery. Consequently, portal vein thrombosis has been recognized as a risk factor for postprocedural liver failure [34]. However, microcatheter systems allow TACE for HCCs with main portal vein tumor thrombosis [35]. Ascites, large tumors (> 5 cm), high aspartate aminotransferase, bilirubin, and alpha-fetoprotein levels, and low serum albumin and sodium levels have also been suggested as potential risk factors [36]. Non-selective bilobar chemoembolization is an important technical risk factor for liver failure.

REILD

Radioembolization-induced liver disease (REILD) is a specific type of liver injury caused by ^{90}Y microspheres. It typically manifests as jaundice and ascites that develop 4–8 weeks after treatment, without biliary obstruction or tumor progression. The overall incidence of REILD after TARE ranges from 4% to 9% [37,38]. Its severity ranges from minor changes in biochemical markers to severe liver failure [39]. Risk factors include whole liver treatment, sequential lobar treatment for < 6 weeks, tumor volume > 70% of the liver, radiation dose to the target liver ≥ 150 Gy,

Table 1. Complications according to Organs

Complications	Causes	Managements
Liver		
Failure (including REILD)	Main portal vein thrombosis, non-selective bilobar treatment	Conservative treatment
Infarction	Non-cirrhotic liver, large tumor, frequently repeated treatment	Observation
Abscess	History of bilioenteric anastomosis or biliary stent, grade 2 oily portogram	Antibiotics, drainage
Biliary tract	Ischemic cholangiopathy; cholangiopathy > biliopathy	
Ischemic biliopathy	TACE at the segment 1 and 4, non-cirrhotic liver, non-selective DEB-TACE	Biliary tree drainage, drainage of biloma, antibiotics
Bronchobiliary fistula	Post-TACE abscess near the diaphragm	Biliary tree drainage, fistula embolization or surgical repair
Cholecystitis	Reflux of embolics into the cystic artery	Observation, percutaneous cholecystostomy or cholecystectomy in refractory cases
Respiratory system		
Pulmonary infarction	Shunting of Lipiodol into pulmonary artery	Conservative treatment
Diaphragmatic injury	TACE at the inferior phrenic artery	Observation
Nervous system		
Cerebral embolism	Right-to-left shunt	Conservative treatment
Spinal cord ischemia	Reflux of embolics into the spinal artery	Conservative treatment
Skin		
Necrosis	Reflux of vesicant chemotherapeutic agent into the cutaneous branches	Conservative treatment, skin graft in refractory case

DEB = drug-eluting bead, REILD = radioembolization-induced liver disease, TACE = transarterial chemoembolization

Table 2. TARE-Specific Complications

Complications	Causes	Managements
REILD	Bilobar TARE with high liver dose	Conservative treatment
Radiation cholecystitis	Reflux of ^{90}Y into the cystic artery	Conservative treatment, cholecystectomy in refractory cases
Radiation pneumonitis	High lung shunt fraction with lung dose > 30 Gy/session (50 Gy/patient)	Corticosteroids
Gastrointestinal injury	Reflux of ^{90}Y into the arteries supplying the stomach, duodenum	Conservative treatment, surgery in refractory case
Radiation dermatitis	Reflux of ^{90}Y into the cutaneous branch	Conservative treatment, skin graft in refractory case

REILD = radioembolization-induced liver disease, TARE = transarterial radioembolization

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total bilirubin level > 1.2 mg/dL, young age (< 45 years), and concurrent use of chemotherapeutic agents (e.g., capecitabine) in the 2 months following TARE [40-42].

Imaging findings are nonspecific and include heterogeneous enhancement or poorly defined hypointense areas in the liver parenchyma and ascites (Fig. 3) [43]. Imaging

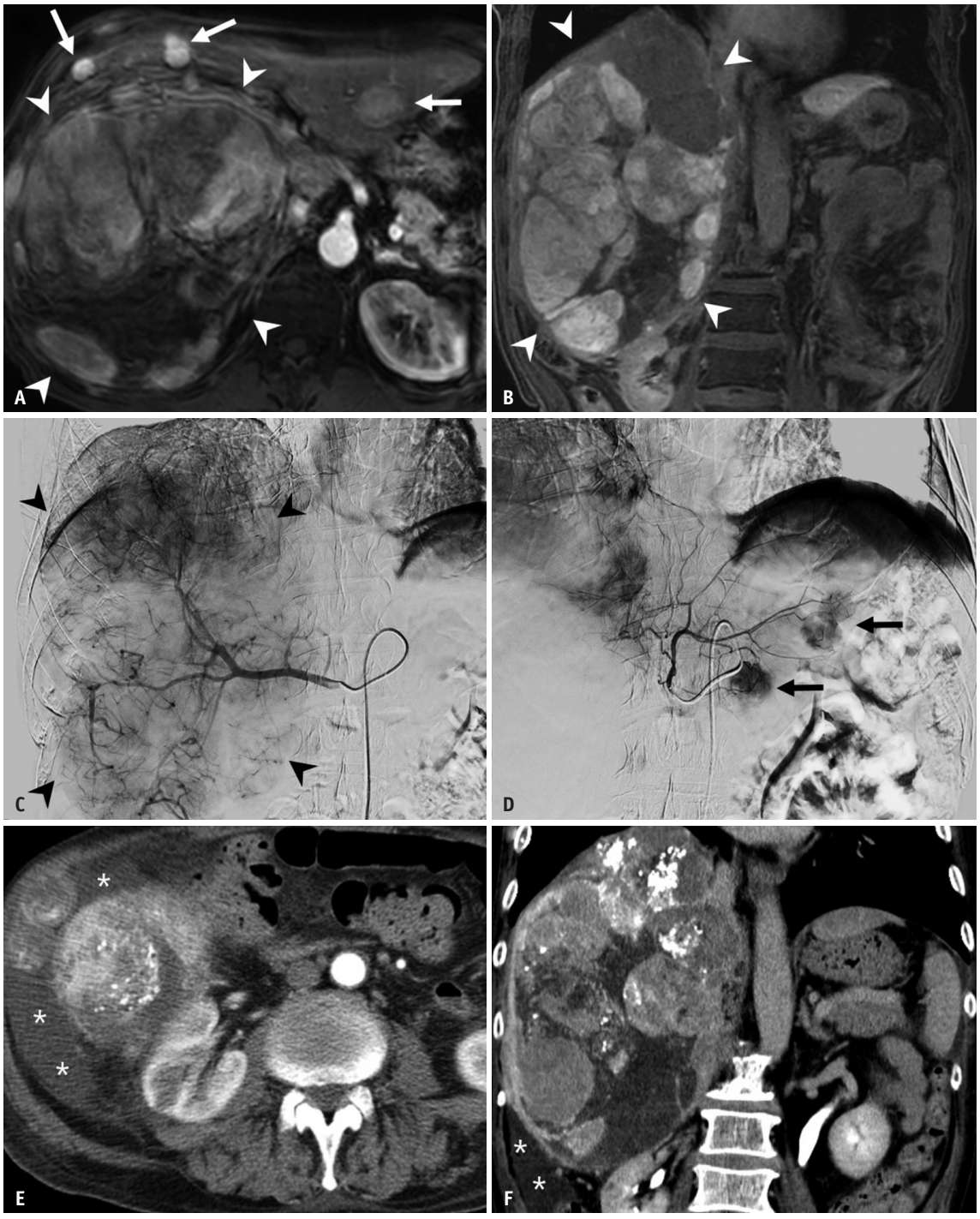

Fig. 2. A 73-year-old male patient with liver failure following transarterial chemoembolization.
A, B. Contrast-enhanced MR images in the arterial and hepatobiliary phase shows a 24.8 cm HCC (arrowheads) with mosaic architecture and multiple intrahepatic metastases (arrows). **C, D.** Proper and left hepatic angiograms shows huge tumor staining (arrowheads) in the right lobe and multiple small tumors (arrows) in the left lobe. Non-selective (lobar) chemoembolization is performed with a mixture of 10 mL of Lipiodol and 50 mg of doxorubicin, followed by gelatin sponge embolization. **E, F.** In the following weeks, the level of bilirubin increased from 1.0 mg/dL to 1.7 mg/dL. Two-week follow-up CT images in the arterial and portal phase revealed perihepatic ascites (asterisks) and partial Lipiodol uptake in HCC. HCC = hepatocellular carcinoma

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studies are important in excluding other causes, such as biliary obstruction or tumor progression [44]. Preventive measures include procedural principles to spare as many liver segments as appropriate and technically possible [45]. Recent studies have suggested emerging concerns regarding long-term (> 6 months) hepatotoxicity, which can limit

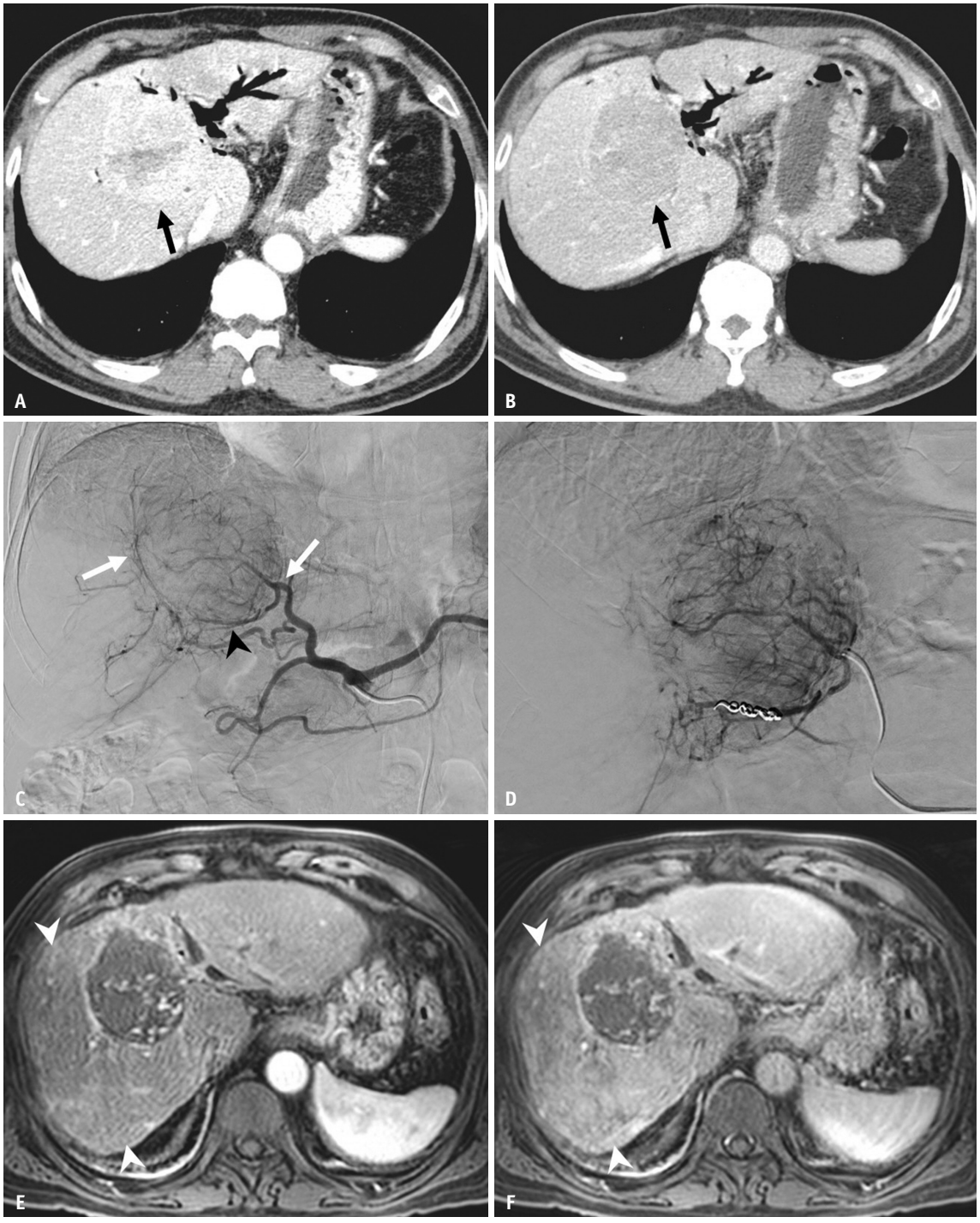

Fig. 3. Radioembolization-induced liver disease in a 73-year-old male patient.
A, B. Contrast-enhanced CT images in the arterial and portal venous phase shows a 6.4 cm HCC (arrows) in S4/8 of the liver. **C, D.** A celiac angiogram shows a hypervascular tumor supplied by the right anterior and middle hepatic arteries (arrows). A large intrahepatic collateral channel (arrowhead) is embolized with microcoils. Resin microspheres (SIR-Spheres; Sirtex Medical, Woburn, MA, USA) are administered with a total dose of 4 GBq (3 GBq at A8 and 1 GBq at A4). **E, F.** The bilirubin level increased from 0.6 mg/dL to 27.3 mg/dL in the following months. Three-month follow-up MRI in the arterial and portal venous phase shows the necrotic change of HCCs and diffuse ill-defined hypointense areas (arrowheads) in the right lobe of the liver. HCC = hepatocellular carcinoma

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subsequent therapeutic options in patients with a long life expectancy [46,47]. Known predisposing factors for long-term hepatotoxicity are tumor involvement in more than 50% of the liver and underlying cirrhosis [48].

Liver Infarction

Liver infarction is an uncommon complication due to a dual blood supply consisting of the hepatic artery and the portal vein. Although conservative management can be effective in most patients, secondary infections can result in serious complications, including abscess or sepsis [12]. It is more common with metastasis than HCC [49]. Non-cirrhotic patients appear to have a higher risk of developing locoregional complications than patients with liver cirrhosis. This may be due to the hypertrophied peribiliary plexus observed in patients with cirrhosis. Predisposing factors for liver infarction include non-selective embolization, large tumor burden, and frequently repeated treatments [50]. The imaging findings of liver infarction include hypodense areas without enhancement, air bubbles with Lipiodol on dynamic CT, and hypointensity on T1- and hyperintensity on T2-weighted images on MRI (Fig. 4) [51]. Clinical symptoms and signs can help discriminate between liver and liver infarctions.

Liver Abscess

Liver abscess has been reported as one of the serious side effects of TACE, with an incidence of 0.3%–1.3% [52,53]. Patients with bilioenteric anastomosis have a higher risk of liver abscess due to the lack of duodenal extensor muscle, which prevents bacterial flow from the intestines to the bile ducts [54]. Lv et al. [55] found that approximately 57.1% of patients who experienced a postprocedural liver abscess had a medical history of bilioenteric anastomosis or biliary stent implantation [55]. The mortality rate among these patients ranges from 13.3% to 50% [56,57]. Pathogenic mechanisms include 1) bacterial infection through ascending cholangitis, chronic biliary colonization, or portal pyemia, 2) infection during the procedure, and 3) decreased immunity due to chemotherapeutic treatment [58]. A grade 2 oily portogram, diabetes mellitus, hypoalbuminemia, portal venous tumor thrombus, non-cirrhotic liver, and

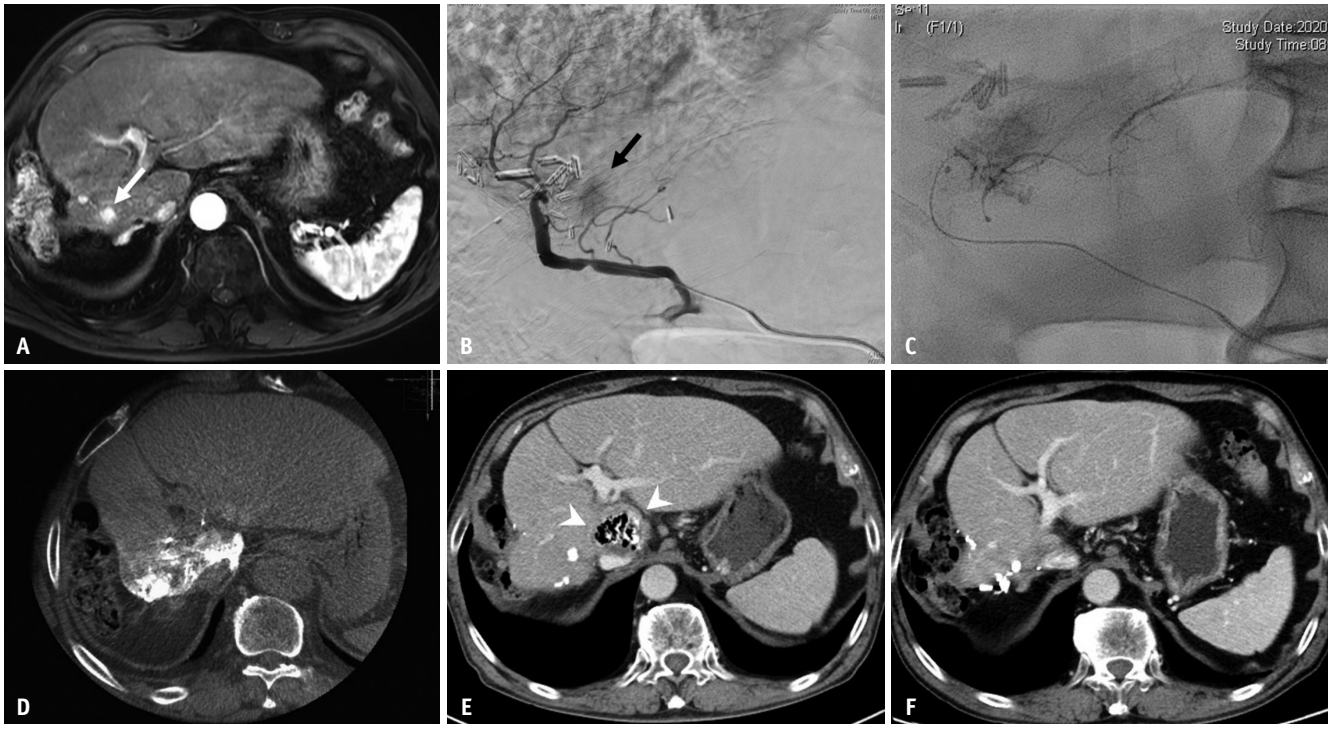

Fig. 4. Liver infarction following TACE in a 76-year-old female patient with recurrent HCC after hepatectomy.
A. A contrast-enhanced MR image in the arterial phase shows a 1.4 cm HCC (arrow) in the caudate lobe of the liver. **B.** A right hepatic angiogram shows the tumor-feeding A1 (arrow) arises from the proximal right hepatic artery. **C.** Selective TACE is performed using a mixture of Lipiodol and doxorubicin followed by gelatin sponge embolization. **D.** A C-arm cone-beam CT scan without contrast medium injection after TACE revealed extensive Lipiodol deposition in the target lesion and caudate lobe. **E.** One-month follow-up CT in the portal venous phase revealed a hypodense area in the caudate lobe with gas bubbles and Lipiodol within it (arrowheads). **F.** Five-month follow-up CT in the portal venous phase identified markedly atrophic changes in the caudate lobe. HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization

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DEBs have also been suggested as potential risk factors [52,54,57].

Fever, chills, and abdominal pain are the most frequently reported symptoms [43,54]. Imaging studies should be considered when patients with a high risk of liver abscess have high-grade fever for 2 weeks or longer after TACE. On contrast-enhanced CT, abscesses typically appear as low-attenuation lesions with or without scattered high-attenuation Lipiodol (Fig. 5). On ultrasound, they appear as circumscribed heterogeneously hypoechoic lesions. It may be difficult to differentiate liver abscesses from tumor necrosis or liver infarction immediately after TACE [53]. For early diagnosis, gas-containing focal lesions and clinical signs and symptoms may be useful features [59]. Percutaneous aspiration/catheter drainage and antibiotic treatment remain the mainstays of management [55,60]. Prophylactic antibiotics administered before and after treatment may reduce the risk of postembolization infection and should be considered [16,61].

HCC Rupture

HCC rupture after TACE is a rare but life-threatening

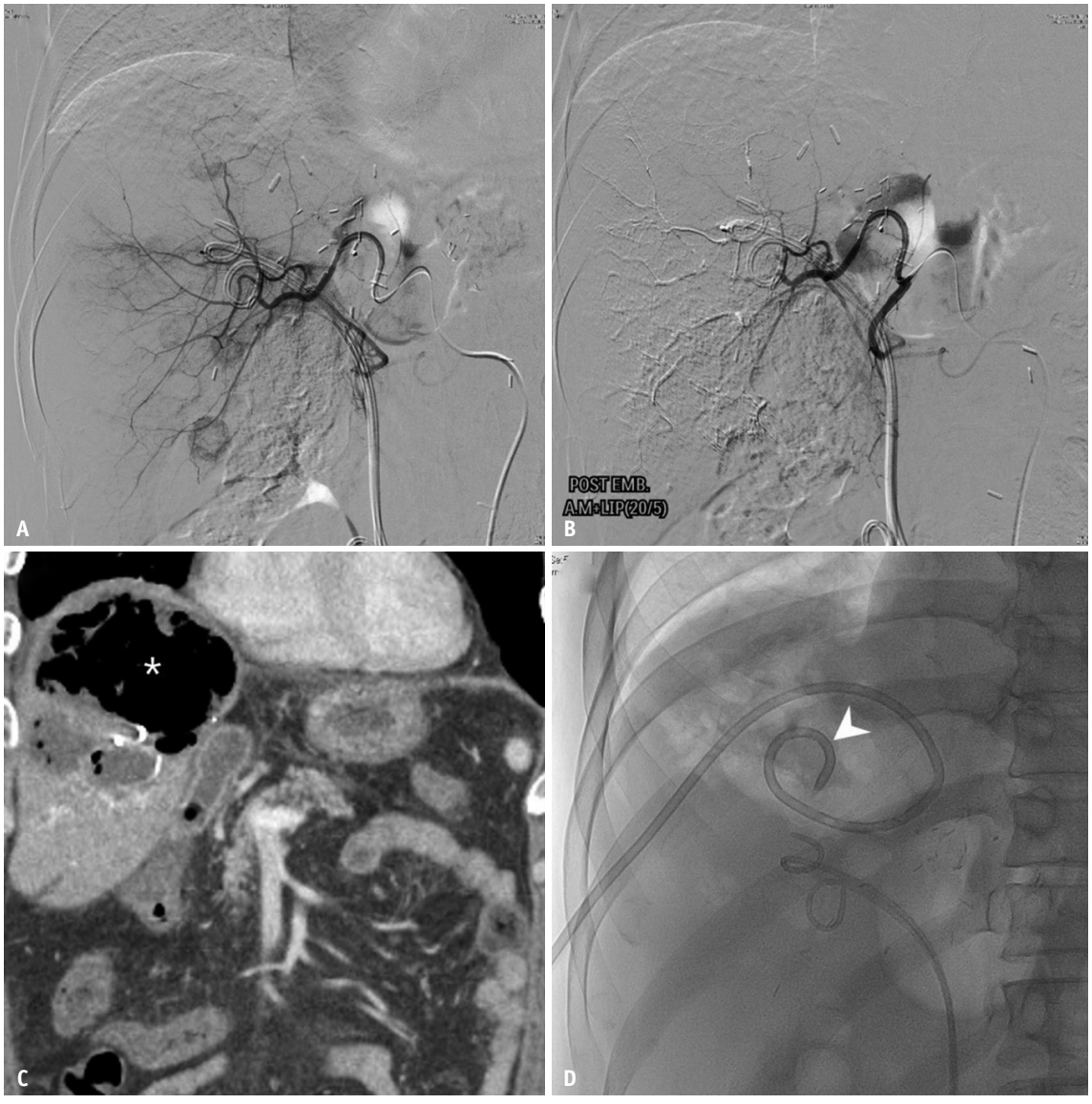

Fig. 5. Liver abscess after TACE in a 54-year-old male patient with recurrent HCC in the transplanted liver.
A. A hepatic angiogram shows multinodular tumor staining in the graft liver. Segmental TACE is performed with a mixture of 5 mL of Lipiodol and 20 mg of doxorubicin, followed by gelatin sponge embolization. **B.** A post-TACE angiogram shows the successful embolization of the vessels that supply the tumor. On the day after the procedure, the patient experienced nausea and chills. The fever lasted 3 days and the body temperature increased to 39°C. **C.** A follow-up coronal CT image revealed a large air-filled abscess (asterisk) in the graft liver. **D.** A percutaneous drainage catheter (arrowhead) was inserted into the abscess cavity. HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization

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complication with a high mortality rate (25%–75%) [62]. The mechanism underlying HCC rupture has not been fully elucidated. However, a combination of factors, including increased intratumoral pressure and local vasculopathy associated with malignancy, may be associated with the risk of rupture [63]. The vascular lake phenomenon during DEB-TACE is a common angiographic finding (incidence ranged from 12.1% to 25.5%), which may be caused by the rupture of the tumor microvasculature. It has been reported to be associated with HCC rupture in previous studies [64,65].

When HCC ruptures, CT can provide valuable information on the focus of bleeding to assist in treatment planning (Supplementary Fig. 1). The hemoperitoneum with the highest attenuation is usually closest to the sources of bleeding, while a hematoma located further from the bleeding site tends to be diluted by pre-existing ascites. Contour protrusion, discontinuity of the hepatic surface, and enucleation signs are additional important features to locate the source of the bleeding [66]. Contrast extravasation from a ruptured HCC is indicative of active bleeding.

Patients with active bleeding who are hemodynamically unstable require hemostatic intervention. TAE/TACE is a safe and effective treatment option to achieve immediate hemostasis [62,67]. Conservative management is recommended only for selected patients who are hemodynamically stable and have poor liver function. Compared with intervention or supportive care alone, a multimodal therapeutic approach in the form of embolization and staged hepatectomy could contribute to improved survival [68].

Ischemic Biliopathy

While the liver receives a dual blood supply from the hepatic artery and portal vein, the peribiliary capillary plexus receives blood supply exclusively from the hepatic artery. As bile duct branches commonly arise from the proximal portion of A1 and A4, TACE for HCC in segments 1 and 4 may be a risk factor for postprocedural bile duct injury (Supplementary Fig. 2) [69]. The risk of biliary complications is higher in non-cirrhotic patients than in cirrhotic patients with hypertrophy of the peribiliary capillary plexus. An increased risk of liver and biliary injury has also been reported following DEB-TACE [19,54]. To minimize hepatic locoregional complications, DEB-TACE should be performed in a super selective manner [20]. The recommended endpoint of embolization for DEB-TACE is near stasis (i.e., the contrast column should clear within two to five heartbeats) [70].

Imaging features of bile duct injury can be categorized as bile duct dilatation, biloma, or bile duct stricture (Fig. 6) [71]. Dilatation of bile ducts commonly occurs during the early stages of ischemic cholangiopathy. In more severe cases of ischemic insult, necrosis involving the full thickness of the bile ducts results in biloma. Chronic inflammation can eventually lead to fibrotic strictures in bile ducts. Endoscopic retrograde cholangiopancreatography or percutaneous transhepatic biliary drainage is required for bile duct strictures with dilatation. Percutaneous aspiration and catheter drainage should be performed in patients with infected bilomas.

Bronchobiliary Fistula

Bronchobiliary fistulas are characterized by abnormal communication between the bronchial and biliary trees. Pathogenic mechanisms include the following:

1) TACE-induced ischemia resulting in necrosis of the bile ducts and subsequent strictures and bilomas, 2) elevation of biliary system pressure, and 3) inflammatory reactions in the subdiaphragmatic space and subsequent rupture in the bronchial tree [72]. Early diagnosis and drainage of the biloma near the diaphragm may be a preventive measure. A bilious productive cough following TACE should raise suspicion of a bronchobiliary fistula. Diagnosis can be made based on sputum analysis and/or imaging studies (Fig. 7). Percutaneous transhepatic cholangiography and endoscopic retrograde cholangiopancreatography can be used to determine the exact anatomy of a fistulous tract. Endobronchial leakage of a high-density contrast agent from the intrahepatic bile ducts confirmed the presence of a bronchobiliary fistula.

The first-line treatment involves biliary decompression to decrease pressure gradients in the common bile duct and duodenum. If biliary decompression fails and the fistula remains patent on cholangiography, percutaneous or endobronchial embolization of the fistulous tract may be considered. According to a recent systematic review of 64 published articles, the success rate of percutaneous treatment is approximately 75% [73]. Surgical repair is the definitive treatment option for patients who do not respond to minimally invasive treatment.

Cholecystitis

Cholecystitis may be caused by obstruction of the cystic

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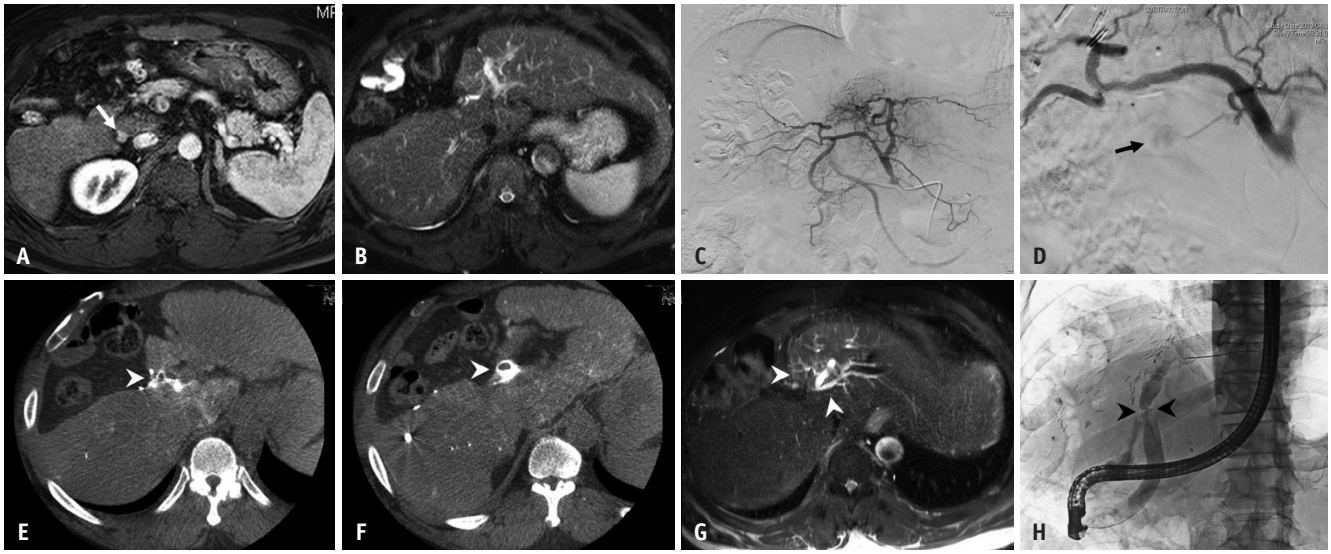

Fig. 6. Ischemic biliopathy following TACE in a 56-year-old male patient with recurrent HCC after hepatectomy.
A. Contrast-enhanced MR images in the arterial phase shows a 1.1 cm HCC (arrow) in S1 of the liver. **B.** A portal phase image showed no biliary dilatation before the procedure. **C.** There is no definite tumor staining on a proper hepatic angiogram. **D.** Selective angiogram of the caudate artery shows a tumor blush (arrow). **E, F.** Post-embolization cone-beam CT images show extensive Lipiodol deposition along the bile duct wall (arrowheads). **G.** A 4-month follow-up MR T2-weighted image identified biliary dilatation (arrowheads) in the left lobe of the liver.
H. Elevation of serum bilirubin (from 0.3 mg/dL to 2.3 mg/dL) and alkaline phosphatase from 56 U/L to 232 U/L is observed 5 months after the procedure. Endoscopic retrograde cholangiopancreatography shows dilatation of the common bile duct with focal narrowing (arrowheads). HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization

artery by embolic material or radiation injury from the accumulation of ^{90}Y particles (Supplementary Fig. 3) [44]. The cystic artery usually arises from the right hepatic artery, which divides into superficial and deep branches to supply the free peritoneal surface and gallbladder bed, respectively (Supplementary Fig. 2) [74]. The deep cystic artery can supply tumors located near the gallbladder. The superficial cystic artery may supply tumors via fine communication channels between the deep and superficial branches. During radioembolization, this complication can be prevented by identifying the cystic artery and positioning the catheter beyond its origin. When this method is not possible, the cystic artery is permanently or temporarily embolized using coils.

Superselective chemoembolization or chemoinfusion at the deep branch of the cystic artery is relatively safe [74]. Chu et al. [75] reported that transient or persistent gallbladder wall thickening was the most frequent CT finding following 340 sessions of intra-arterial therapy through the cystic artery. In their study, acute cholecystitis was observed in only two patients, who responded well to conservative management. Clinical presentation can range from asymptomatic to right upper quadrant pain and fever. Surgical interventions may be required in complicated cases, including cholecystectomy or percutaneous cholecystostomy [76].

Complications in the Gastrointestinal Tract, Pancreas, and Spleen

Gastrointestinal Ulcer and Pancreatitis

TARE has been associated with gastrointestinal complications such as gastroduodenal ulcers and pancreatitis [43]. Non-target embolization occurs due to the reflux of embolic material or ^{90}Y particles into the gastric/small intestinal vasculature or the presence of undetected anatomic variations. Accessory left gastric arteries arise from the left hepatic artery, and the right gastric artery arises from the proper hepatic artery is a relatively common anatomical variation. The supraduodenal artery supplies the horizontal portion of the first duodenal segment. The duodenal bulb and pancreatic uncinate process are supplied by the retroduodenal artery [77]. Therefore, a careful review of angiograms is recommended to prevent inadvertent reflux. Coil embolization is the most frequently performed preventive measure (Supplementary Fig. 4), and anti-reflux microcatheters or micro-balloon catheters have also been used recently. Prophylactic medications (H_2 receptor blockers or proton pump inhibitors) may be prescribed before the procedure [78]. Imaging findings are

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nonspecific and depend on the affected organ, which may include wall thickening and adjacent fat stranding. Clinical manifestations include gastritis/duodenitis, gastrointestinal ulceration, and bleeding [79]. Naymagon et al. [80] reported that abdominal pain, nausea, and vomiting are common symptoms that can appear several months after TARE. Chemotherapy or radiation-induced ulceration may be difficult to manage using conventional medical therapies [81]. Endoscopic evaluation is warranted in patients with gastrointestinal bleeding to rule out alternative causes of bleeding, such as varices.

Acute pancreatitis is a rare complication resulting from

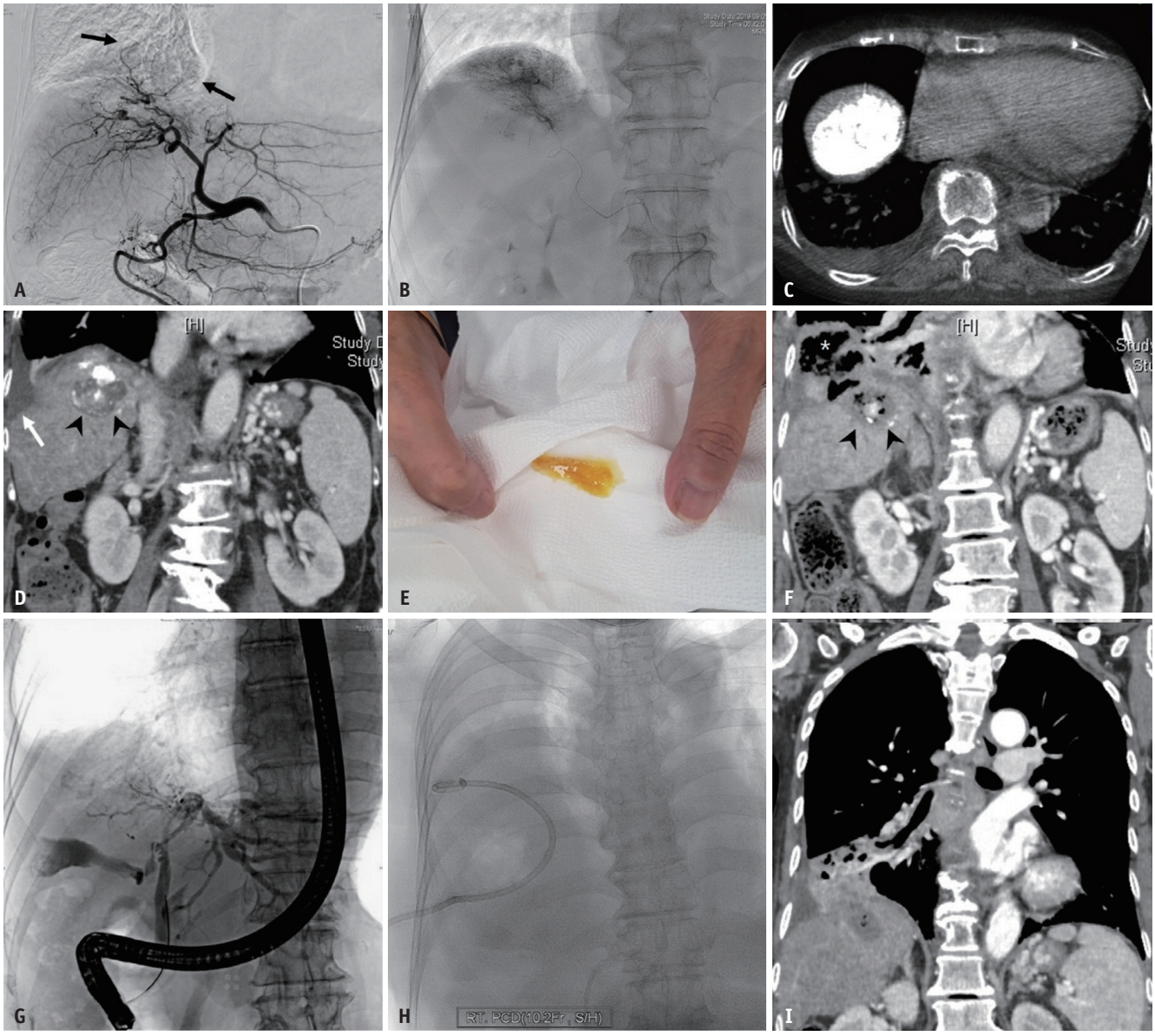

Fig. 7. A 69-year-old female patient with bronchobiliary fistula after TACE.
A. A common hepatic angiogram shows tumor staining (arrows) in the S8 region of the liver, just below the dome of the right diaphragm. **B.** A segmental feeder is selectively embolized using a microcatheter with a mixture of 4 mL of Lipiodol and 20 mg of doxorubicin, followed by gelatin sponge embolization. **C.** Unenhanced C-arm cone-beam CT shows dense iodized oil accumulation throughout the tumor and surrounding liver parenchyma. **D.** Coronal contrast-enhanced CT performed 2 months after TACE shows the necrotic change of the tumor (arrowheads) with internal Lipiodol retention. In addition, a right-sided pleural effusion is observed (arrow). **E.** Appoximatelly 3 months after the procedure, the patient had a greenish bilious sputum with a cough. **F.** Coronal contrast-enhanced CT shows right lower lobe pneumonia with air bubbles that indicate an abscess (asterisk) immediately adjacent to a hepatic tumor with abscess (arrowheads). **G.** The fistulous tract is not evident on endoscopic retrograde cholangiopancreatography. The patient underwent endoscopic retrograde biliary drainage. **H.** Percutaneous catheter drainage is performed for lung abscess. **I.** Around 10 months after the procedure, coronal contrast-enhanced CT shows that the lung abscess is present but decreased in size. The patient underwent primary repair of the diaphragm and revision of the bronchobiliary fistula. TACE = transarterial chemoembolization

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the regurgitation of embolic material from the hepatic artery into the dorsal pancreatic or gastroduodenal arteries. The pancreas has a rich vascular supply from the branches of the celiac trunk and the superior mesenteric artery. However, the pancreatic head and uncinate process are more prone to reflux embolization than the body or tail, as the gastroduodenal artery is one of the terminal branches of the common hepatic artery [82]. Most patients follow an uncomplicated or mild course of conservative treatment. Antibiotic treatment can be an effective strategy to prevent bacterial translocation from the gastrointestinal tract in patients with evident pancreatic necrosis on CT [83].

Splenic Infarction

Inadvertent embolization of the splenic artery is very rare but can lead to splenic infarction and/or abscess. Conditions that can increase the risk of embolic material reflux include celiac stenosis with hepatofugal blood flow in the common hepatic artery, increased blood flow through the splenic artery due to underlying liver cirrhosis and splenomegaly, and catheter-induced spasm of the proper hepatic artery [50]. Selective embolization with a microcatheter and meticulous procedures may prevent iatrogenic complications. The most typical clinical feature is acute left upper-quadrant abdominal pain, which subsides within 3–10 days [12]. Percutaneous drainage is indicated in rare cases of large splenic abscesses.

Pulmonary and Diaphragmatic Complications

Pulmonary Lipiodol Embolism, Acute Respiratory Failure, and Lung Infarction

Pulmonary Lipiodol embolism occurs when intrahepatic arteriovenous shunting between the hepatic artery and the hepatic vein or transpleural communication between the inferior phrenic artery and the pulmonary circulation. The azygoesophageal branch is the most common feeder of a systemic-to-pulmonary shunt, which may mimic tumor staining on inferior phrenic angiography (Supplementary Fig. 5) [84,85]. The use of cone-beam CT can help differentiate tumor staining from systemic-to-pulmonary shunt [86]. If tumor staining and systemic-to-pulmonary shunting are identified, selective embolization of the tumor feeder should be performed. If selective catheterization is not feasible, embolization of the shunt with particles or coils can be considered before TACE and TARE [74].

The incidence of pulmonary Lipiodol embolism ranges from 0.1% to 10% [87]. This could be underestimated, as many cases were asymptomatic and incidentally detected on CT. Respiratory symptoms can manifest hours to several days after TACE and include cough, dyspnea, hemoptysis, and tachypnea. The use of large amounts of Lipiodol may induce severe lung damage and life-threatening respiratory conditions, such as acute respiratory distress syndrome. The most likely cause of pulmonary toxicity is a chemical lung injury caused by free fatty acid components. Infusion of Lipiodol into the hepatic artery has been found to result in a dose-dependent increase in the incidence of pulmonary infarction [88].

To prevent fatal pulmonary Lipiodol embolism, Lipiodol at a dose of 14.5–20 mL has been recommended as the maximum safe dose in previous studies [50,87]. The use of DEBs may also be responsible for pulmonary infarction. The size threshold of these beads has not been established; however, fatal pulmonary infarction has been reported following the use of 40–120 μm beads [14]. The treatment of pulmonary infarction is essentially supportive and similar to that of fat embolism syndrome. In a previous study, hypoxemia and chest radiographic abnormalities gradually improved over 10–28 days [50].

Radiation Pneumonitis

A major concern of TARE is the shunting of ^{90}Y microspheres to the lungs. Pulmonary infarction manifests as radiation pneumonitis when excessive arteriovenous shunting is present. The incidence of radiation pneumonitis associated with TARE is < 1%. To prevent this serious complication, a lung shunt study should be performed, and dosimetry must be conducted before TARE. The recommended lung dose should be < 30 Gy per session and no more than 50 Gy per person [89]. Radiation pneumonitis typically occurs 1–6 months after treatment and is characterized by restrictive ventilatory dysfunction accompanied by exertional dyspnea and dry cough. Classic imaging findings are bilateral, symmetric patchy opacities, and ground-glass nodularity with relative hilar or perihilar sparing (bat-wing appearance) (Fig. 8). These findings may resolve or progress to fibrosis, traction bronchiectasis, or focal honeycombing [43]. Steroids are the mainstay of treatment for reducing inflammatory processes [90].

Ischemic Injury of the Diaphragm

The inferior phrenic artery is one of the most common extrahepatic collateral arteries supplying HCCs. TACE

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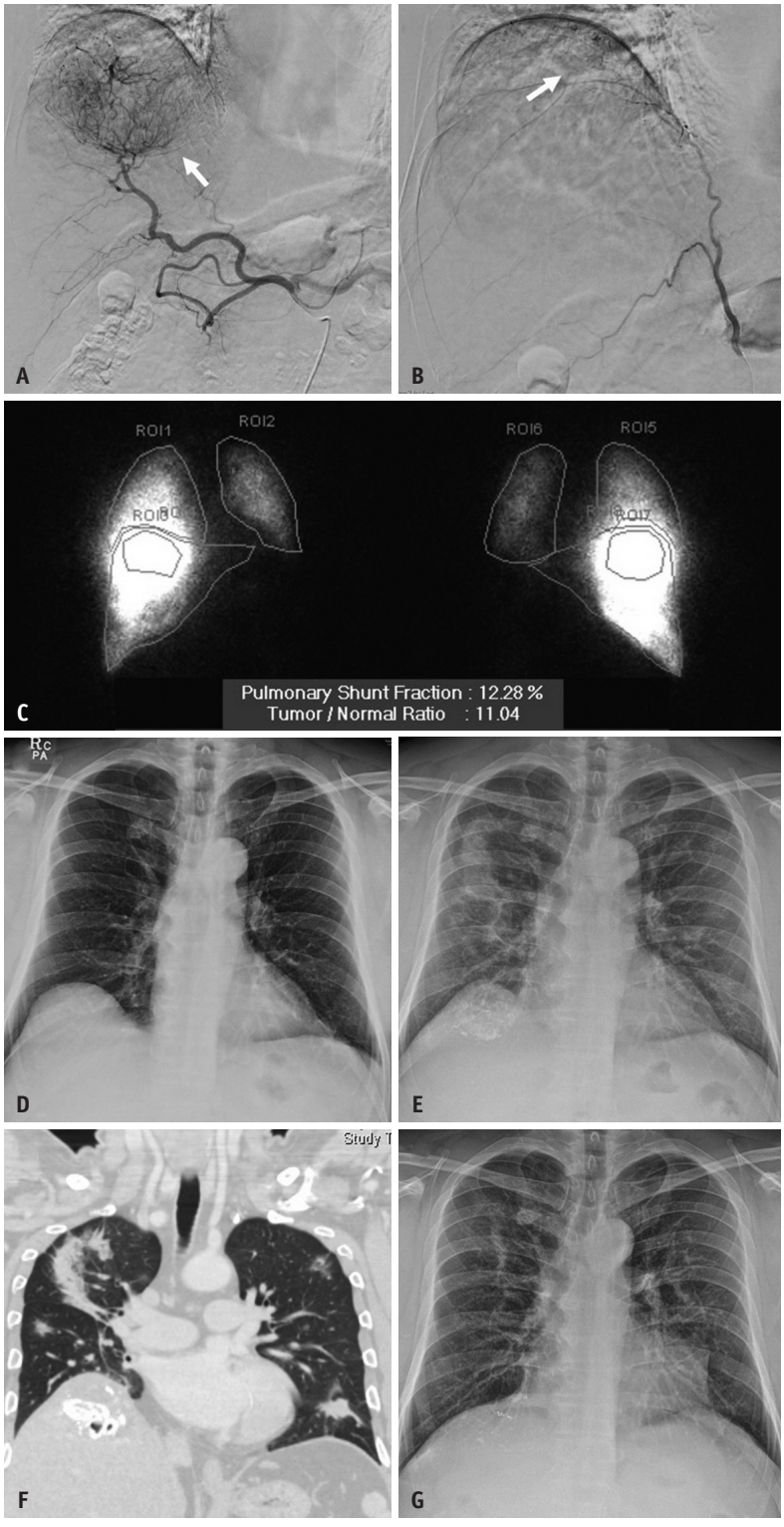

Fig. 8. Radiation pneumonitis after TARE in a 60-year-old male patient with hepatocellular carcinoma (Child A).
A, B. Common hepatic and right phrenic angiograms shows hypervascular tumors (arrows) in the right hepatic dome. **C.** A technetium-macroaggregated albumin scintigram shows a 12.3% lung shunt fraction. Resin microspheres (SIR-Spheres; Sirtex Medical, Woburn, MA, USA) are administered with a total dose of 3.9 GBq (3.2 GBq at A8 and 0.7 GBq at the right inferior phrenic artery). The posterior branch of the right inferior phrenic artery is first embolized with coils. The estimated lung dose is 29.74 Gy, and a prophylactic steroid is administered. **D.** The chest radiograph before the procedure is unremarkable. **E, F.** The patient developed progressive dyspnea and cough. Six-month follow-up chest radiography and CT revealed bilateral patchy areas of consolidation and ground-glass infiltration, more severe on the right than on the left. **G.** A 6-month follow-up chest radiograph shows the development of fibrotic sequelae.

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through the inferior phrenic artery is usually considered a safe procedure without serious complications. Potential minor complications include shoulder pain, hiccups, pleural effusion, and basal atelectasis [91]. However, the inferior phrenic artery is a major source of blood supply to the diaphragm, predominantly in the central region. Ischemic injuries may cause diffuse or focal diaphragmatic weakness and dysfunction. The incidence of diaphragmatic weakness after TACE through the inferior phrenic artery ranges from 18.7% to 40% [91]. Diaphragmatic weakness may resolve spontaneously or may be permanent in more than half of the patients [92]. Diaphragmatic perforation has been reported to be a rare but fatal complication of TACE through the inferior phrenic artery (Fig. 9) [93,94]. To reduce diaphragmatic injury, every effort should be made to selectively embolize the tumor feeders instead of sacrificing the entire inferior phrenic artery.

Neurological Complications

Cerebral Embolism

The frequency of TACE-related cerebral embolism has been reported to be 1.02 per 1000 procedures [95]. This condition usually results from right-to-left shunting, that is, communication between the right and left sides of the heart or between the systemic and pulmonary vessels. Pulmonary arteriovenous shunting, transpleural communication, or direct tumor invasion of the thoracic

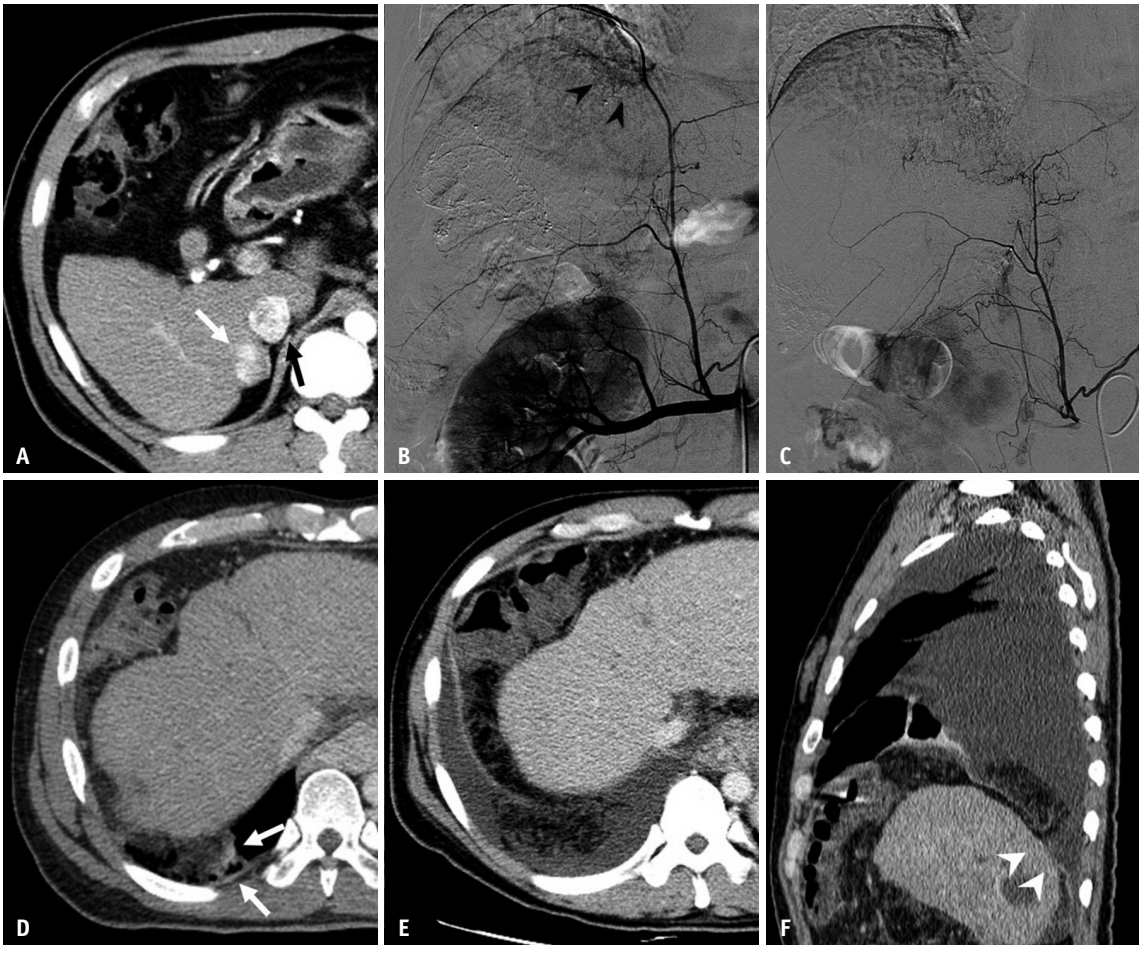

Fig. 9. A 43-year-old male patient with delayed diaphragmatic perforation after transarterial chemoembolization.
A. A contrast-enhanced CT image in the arterial phase shows an enhancement tumor (white arrow) in the right hepatic lobe and adjacent inferior phrenic artery (black arrow). **B.** A right inferior phrenic angiogram shows hypervascular staining (arrowheads). Note the inferior phrenic artery that originates in the right renal artery. **C.** Selective angiogram after three sessions of transarterial chemoembolization through the right inferior phrenic artery shows attenuation of the ascending branch. **D.** After 3 months, the patient complained of coughing and dyspnea. An axial CT scan at admission shows a mushroom-shaped diaphragmatic contour of the herniated omental fat (arrows). **E.** A 2-month follow-up CT image shows massive intrathoracic herniation of omental fat without organ entrapment and large pleural effusion. **F.** A reformatted sagittal CT image shows a direct discontinuity of the right hemidiaphragm (arrowheads).

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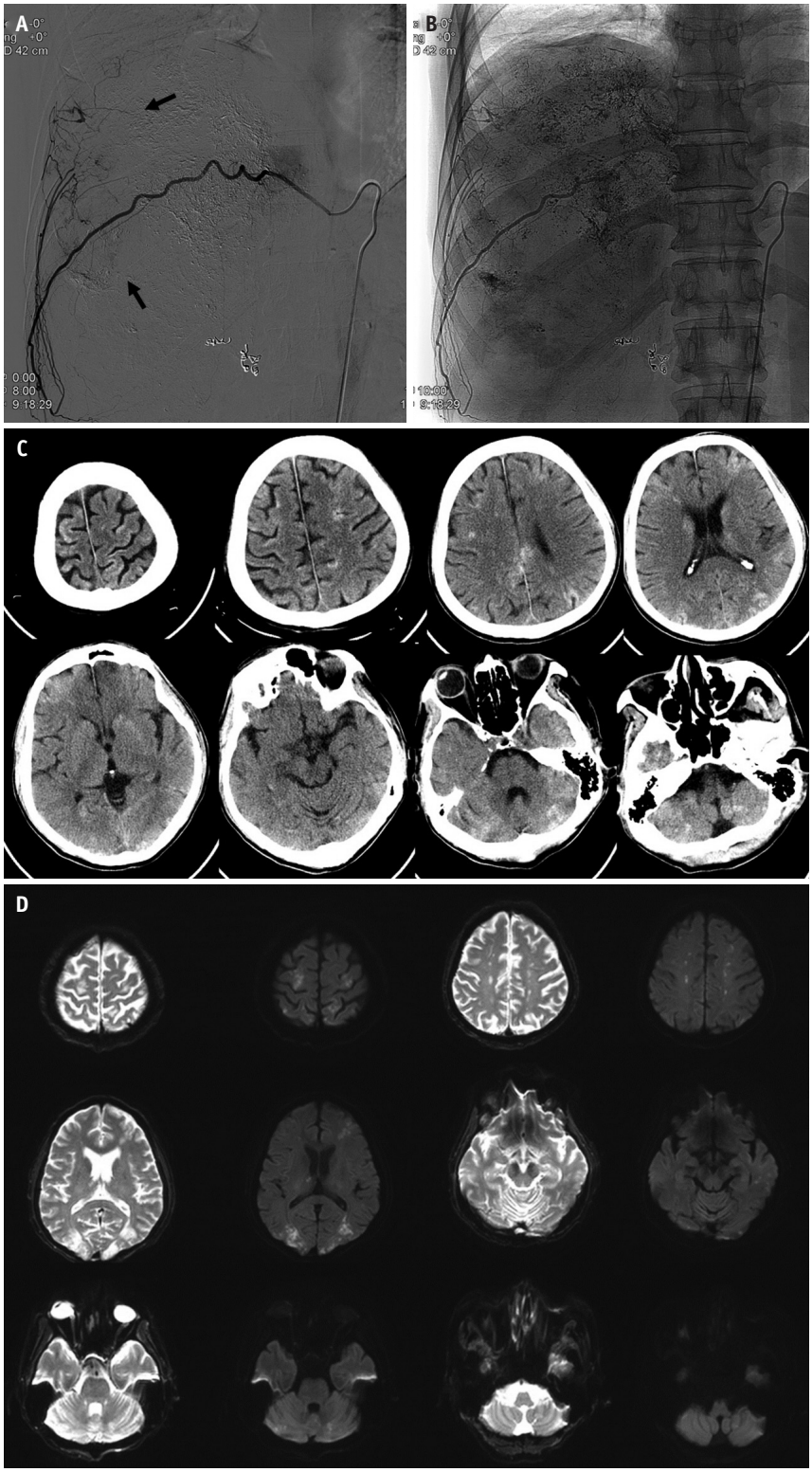

Fig. 10. A 58-year-old male patient with a large hepatocellular carcinoma and cerebral Lipiodol embolism after transarterial chemoembolization.

A. A right 10th intercostal angiogram shows a parasitized blood supply (arrows) to the large hypervascular tumor. **B.** A spot image obtained after selective embolization with an emulsion of Lipiodol and doxorubicin, and gelatin sponge shows the occlusion of the intercostal artery in the mid-portion. **C.** The day after the procedure, the patient experienced drowsiness and confusion. Non-contrast brain CT revealed disseminated punctate Lipiodol deposition in the bilateral cerebral and cerebellar hemispheres. **D.** Diffusion-weighted MRI detected disseminated acute ischemic lesions at the corresponding locations.

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cavity may increase the risk of paradoxical embolism. The most common presentations are acute disturbances of consciousness and respiratory distress. Disseminated punctate Lipiodol depositions involving both the anterior and posterior cerebral circulations on non-contrast brain CT are pathognomonic for cerebral embolism caused by Lipiodol (Fig. 10). Old age, female sex, and TACE through both the right inferior phrenic and right hepatic arteries may be associated with poor clinical outcomes [96]. Most of the causes are unavoidable, but a careful review of the medical history is needed.

Spinal Cord Ischemia

The main blood supply to the spinal cord originates from single anterior and paired posterior spinal arteries. The spinal arteries anastomose the segmental medullary and radicular arteries, derived from the cervical, lumbar, and intercostal arteries. These anatomical characteristics account for the association between spinal cord injury and TAE/TACE via extrahepatic collaterals. Therefore, the vertebral column should be included in the field of view of intercostal or lumbar angiograms. During TACE of the intercostal artery, the microcatheter should be advanced beyond the diaphragmatic insertion site (U-turn point) to prevent spinal infarction or skin necrosis [97,98]. Clinical symptoms usually appear 6–8 hours after the procedure as paresthesia, impaired sensory function, paraplegia, and urinary retention [99]. MRI findings are usually normal in the acute phase; however, spinal cord edema and T2 abnormalities may appear after 1–2 days (Fig. 11) [100].

Cutaneous Complications

Skin Necrosis, Radiation Dermatitis

Skin injury occurs due to non-target embolization of the cutaneous branches of the hepatic and extrahepatic feeders. The falciform ligament artery is known to be responsible for epigastric skin rash after TACE (Supplementary Fig. 6). It arises from the left or middle hepatic artery, runs through the falciform ligament and distributes around the umbilicus. Skin injury has also been reported following TACE via the internal mammary, intercostal, and lumbar arteries. Doxorubicin is a vesicant chemotherapeutic agent that binds to tissue DNA and may cause severe skin necrosis (Fig. 12) [101]. Radiation dermatitis is a specific form of skin injury associated with ^{90}Y microspheres. To avoid complications, prophylactic embolization of the cutaneous branches may be required. Wang et al. [102] reported that the topical application of ice decreased skin complications after TACE and TARE by causing vasoconstriction.

Vascular Injury

Common iatrogenic complications of transarterial treatment include vascular spasm, dissection, and occlusion, while puncture site problems such as hematoma, pseudoaneurysm, and lymphorrhea occur less frequently. Hepatic artery spasm is a transient, focal increase in vascular tone, which causes the lumen to narrow and blood flow to decrease (Supplementary Fig. 7). Nitroglycerine can be injected via a catheter to manage transient spasms during the procedure. Dissection of the hepatic artery may

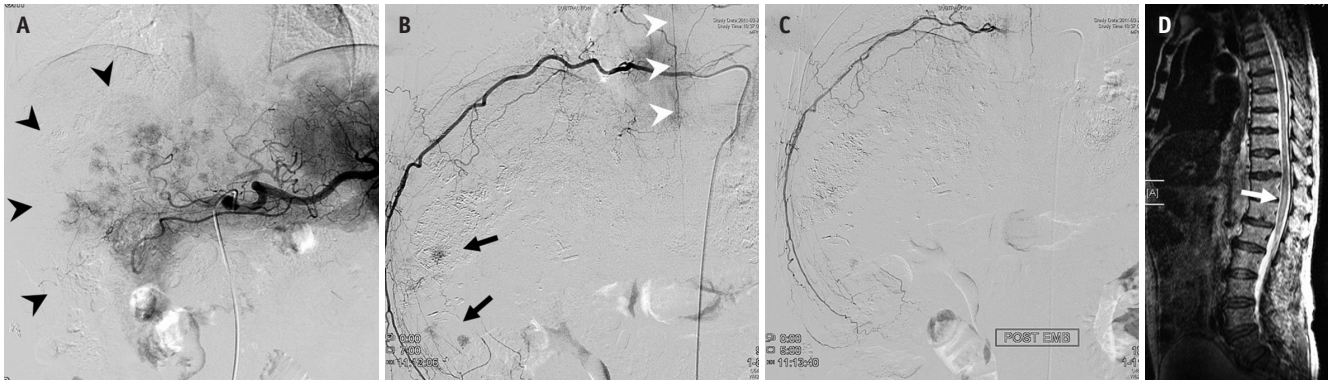

Fig. 11. A 65-year-old male patient with spinal cord infarction following transarterial chemoembolization.
A. A hepatic angiogram revealed multinodular tumor staining in the liver. Note the defect of hepatic parenchymal staining in the periphery of the right lobe (arrowheads). **B.** A right 9th intercostal angiogram shows the collateral supplies of hepatocellular carcinomas (arrows). Note the vertical midline course of the anterior spinal artery (arrowheads). **C.** An angiogram after chemoembolization showed no residual tumor enhancement. The anterior spinal artery is not visualized. The patient complained of weakness in the right leg during the procedure. Six hours after the procedure, left leg weakness developed. **D.** A T2-weighted sagittal image of the thoracic and lumbar spines showed an intramedullary high-signal intensity lesion from level T8 to L1 (arrow) and cord swelling.

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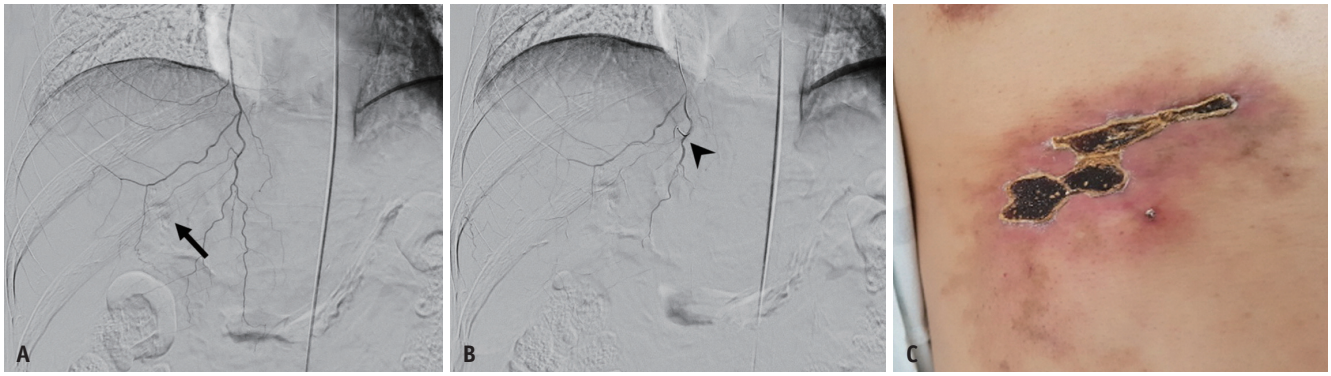

Fig. 12. Skin necrosis after TACE in a 66-year-old male patient.
A. A selective angiogram of the right internal mammary artery shows a small tumor blush (arrow). **B.** Chemoembolization is performed after advancing the microcatheter tip into the feeding artery (arrowhead). The patient complained of right upper abdominal pain soon after the procedure. **C.** After 3 days, the painful skin lesion progressed to necrosis. Supportive care improved the skin lesion over the following 6 months.
TACE = transarterial chemoembolization

resolve without treatment; however, it may cause significant stenosis and, eventually, obstruction [15]. Consequently, subsequent transarterial treatment or liver transplantation can be challenging. Iatrogenic aortic dissection is a rare but the most fatal complication associated with the procedure (Supplementary Fig. 8). To avoid complications, physicians should always gently manipulate the wires and catheters.

Summary

Transarterial treatment can cause various complications in the vessels and organs involved during the procedure. Non-target organs such as the skin, lungs, gastrointestinal tract, and even neurological systems can also be affected. Symptoms, signs, and postprocedural imaging findings play a key role in the evaluation and management of adverse events. Procedural details are also important when interpreting postprocedural imaging findings, as newer treatment modalities are frequently used. The type and location of a microcatheter, embolization extent, and presence of the cutaneous or spinal branches on angiograms are closely associated with complications for TACE. The lung shunt fraction, lung dose, and normal liver dose are critical values for TARE. Familiarity with various transarterial treatment procedures can help radiologists discriminate between treatment-related changes and complications, eventually leading to better patient management during the course of HCC treatment.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2022.0395.

Availability of Data and Material

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: all authors. Project administration: all authors. Resources: all authors. Supervision: Dongho Hyun. Writing—original draft: Hyoung Nam Lee. Writing—review & editing: all authors.

ORCID iDs

Hyoung Nam Lee
https://orcid.org/0000-0002-2135-9384
Dongho Hyun
https://orcid.org/0000-0002-2654-7202

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