Chemoembolization of Hepatic Neoplasms: Safety, Complications, and When to Worry[1]

Julia Gates, MD
George G. Hartnell, FRCR
Keith E. Stuart, MD
Melvin E. Clouse, MD

Chemoembolization of the liver for unresectable malignancy, although controversial, is being used with increasing frequency. Chemoembolization can be difficult, and there is great potential for causing complications. There are also findings after chemoembolization, particularly on computed tomographic scans, that may appear to indicate complications but are common and of no concern. Chemoembolization requires an understanding of the congenital and acquired variations of arterial anatomy that may be seen supplying the liver. Assessment of the patency of the portal vein is also required. An abnormal portal vein demands significant changes in technique to allow safe chemoembolization. Partial or complete occlusion of the portal vein is associated with significantly decreased survival but does not prevent a worthwhile response to chemoembolization and is not an absolute contraindication. The presence of chemoembolization material in the gallbladder is not uncommon; with the technique used by the authors, the chemoembolization material infrequently causes cholecystitis or gallbladder infarction. Extrahepatic chemoembolization material is commonly seen in other organs but usually does not cause problems, presumably because the dose deposited outside the liver is small compared with the dose delivered to the liver. Other complications include pseudocirrhosis, liver infarction and abscess formation, carcinoid crisis, hepatorenal syndrome, and liver rupture.

Abbreviation: HCC = hepatocellular carcinoma

Index terms: Arteries, chemotherapeutic embolization, 952.1264, 952.1266 • Hepatic arteries, chemotherapeutic infusion, 952.1264, 952.1266 • Liver, interventional procedure, 761.1264, 761.1266 • Liver neoplasms, chemotherapeutic infusion, 761.323, 761.33

RadioGraphics 1999; 19:399–414

[1]From the Departments of Radiology (J.G., G.G.H., M.E.C.) and Medical Oncology (K.E.S.), Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Mass. Presented as a scientific exhibit at the 1997 RSNA scientific assembly. Received February 26, 1998; revision requested April 6 and received June 10; accepted June 10. **Address reprint requests to** J.G., 6726 Bonnie Ridge, Apartment 102, Baltimore, MD 21209.

■ INTRODUCTION

Malignant liver tumors have a very poor prognosis. Primary hepatocellular carcinoma (HCC) is usually fatal with fewer than 5% of patients surviving 5 years after diagnosis. The median survival is 4–6 months for patients with unresectable tumors (1–3). Systemic chemotherapy is relatively ineffective with a low response rate (<20%) and a mortality rate of up to 25% (4). Liver metastases from colorectal tumors are common; the majority of cases of such metastases are inoperable and have a similarly poor prognosis. Liver metastases from neuroendocrine tumors have a better prognosis but can produce severe symptoms that require treatment.

Selective arterial treatment of liver tumors with chemotherapeutic and embolic agents (chemoembolization) has been used in Japan for almost 20 years (5,6) and has produced results superior to those of surgery in some series of patients with resectable HCC (7). Although the benefits of chemoembolization have been disputed (8,9), it has been reported to improve the prognosis of several groups of patients with unresectable liver tumors, including HCC and metastases from colorectal tumors (10–13). Chemoembolization can be hazardous with the potential for numerous procedural errors and complications such as liver failure, abscess or infarction, biloma, cholecystitis, and the effects of extrahepatic embolization (14). There are many changes seen on computed tomographic (CT) scans after chemoembolization that may cause concern for the uninitiated but do not require changes in management and do not affect the prognosis.

In this article, an approach to chemoembolization that has been found to be safe and effective is presented, anatomic factors that may alter the procedure are identified, abnormal CT findings that are often clinically unimportant but may cause concern for the uninitiated are described, and complications of chemoembolization and ways of avoiding them are discussed.

■ APPROACH TO CHEMOEMBOLIZATION

● Patient Selection

Chemoembolization is used in patients with suitable liver tumors who are not surgical candidates; usually, the reason why surgery is not feasible is advanced malignant disease involving both lobes of the liver, a complicating factor such as cirrhosis, or failure of systemic chemotherapy. All patients should have unresectable liver tumors of a type known to respond to chemoembolization, such as HCC, metastases from colorectal tumors, metastases from neuroendocrine tumors, and metastases from ocular melanoma and gastrointestinal sarcomas. Other tumor types have been treated with chemoembolization with little evidence of benefit. The techniques and experience described herein are based on clinical practice at Deaconess Hospital, where over 100 chemoembolization procedures are performed yearly, and on the results of an intensive review of 251 chemoembolization procedures performed between July 1994 and December 1996 (15).

A thorough patient history should be obtained, and a thorough physical examination should be performed. The portal vein should be completely or partially patent with hepatopetal flow, although chemoembolization can be performed safely in cases of portal vein occlusion if a modified, low-dose (30%–50% of the usual dose), superselective technique is used (16). There should be no extrahepatic tumors or other medical condition that is likely to be life threatening within 3 months. There should be an adequate amount of residual uninvolved liver and adequate liver function.

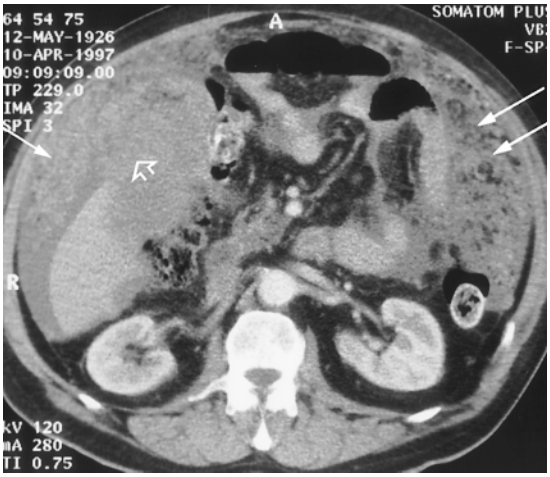


Figure 1. Contrast material–enhanced CT scan shows rupture of the liver (open arrow) with extensive omental tumor (solid arrows). The patient was referred for chemoembolization despite a similar appearance at CT a few weeks earlier. This patient is not suitable for chemoembolization because the risk of worsening liver rupture with potential for extravasation is very high.

Table 1
Inclusion and Exclusion Criteria for Chemoembolization of Liver Tumors

Inclusion criteria
Tumor responsive to chemoembolization
Unresectable tumor
Patent portal vein
Satisfactory liver function (normal alkaline phosphatase and aspartate transaminase levels)
Serum bilirubin level < 2 mg/dL (34 μmol/L)
No major contraindications to angiography (eg, normal coagulation and renal function)
Exclusion criteria
Clinically apparent jaundice
Hepatic encephalopathy
Occluded portal vein
Hepatofugal portal vein flow
Extrahepatic tumors or other medical condition likely to be life threatening within 3 months
Liver rupture or tumor penetration of liver capsule
Poor liver function (coagulopathy not correctable with vitamin K, lactate dehydrogenase level > three times institutional upper limit of normal, elevated alkaline phosphatase level) (12)
Serum bilirubin level > 5 mg/dL (85 μmol/L)
Biliary obstruction
Serum creatinine level > 2 mg/dL (177 μmol/L)
Hemoglobin level < 8 g/dL (80 g/L)
White blood cell count < 2.5×10^3/μL (2.5×10^9/L)
Platelet count < 60×10^3/μL (60×10^9/L)
Pregnancy

Note.—The following criteria alone indicate an increased risk but individually need not preclude selective chemoembolization with a reduced dose: partially occluded portal vein, mildly abnormal liver function (albumin level < 3 g/dL [30 g/L], aspartate transaminase level of 40–100 U/L, lactate dehydrogenase level one to three times institutional upper limit of normal) (12), serum bilirubin level greater than 2 mg/dL (34 μmol/L) but less than 5 mg/dL (85 μmol/L) (see discussion in text), and mild coagulopathy correctable with vitamin K. If several of these factors are combined, the risk of liver failure may be unacceptable.

What constitutes an adequate amount of residual uninvolved liver is not clear and may depend on the type of lesion being treated. In one series of patients treated for metastases from neuroendocrine tumors, the majority had more than 60% of the normal liver replaced (17). In other reports, replacement of more than 50% or 75% of the normal liver is regarded as a contraindication to chemoembolization (18). Estimating the percentage of replacement is difficult and may not be relevant when the liver is greatly enlarged. Of more significance is the residual function as indicated by biochemical markers of liver function.

More specific inclusion and exclusion criteria based on the literature are listed in Table 1. There is some variation in the recommended safe bilirubin level. Some suggest a maximum of 2 mg/dL (34 μmol/L) (18), whereas we usually use a maximum of 3 mg/dL (51 μmol/L); however, in one study patients with a bilirubin level of up to 5 mg/dL (85 μmol/L) were treated without any apparent increase in complications (12). Some patients will have indicators of increased risk, despite which it may be appropriate for an experienced operator to perform careful chemoembolization with a modified, low-dose technique (16).

All images obtained before chemoembolization should be reviewed. Prechemoembolization imaging must include at least ultrasonography or CT to ensure that there is no evidence of liver rupture (Fig 1) and that the portal vein is patent and to define the positions of the lesions to be treated.

• Technique

Patients are usually admitted the morning of the day chemoembolization is performed. They undergo vigorous intravenous hydration (500 mL 5% dextrose in normal saline solution before chemoembolization then continued at 100 mL/h) for at least 24 hours or longer if there is a delay in resuming full oral administration of fluids. Prophylactic antibiotics (ampicillin sodium and sulbactam sodium [Unasyn, Roerig, New York, NY]; 3 g every 6 hours for five doses) are used routinely. Premedication includes an analgesic such as hydromorphone hydrochloride (Dilaudid, Knoll Laboratories, Mount Olive, NJ; 1 mg subcutaneously) and a sedative and antiemetic such as hydroxyzine (Vistaril, Pfizer, New York, NY; 50 mg orally).

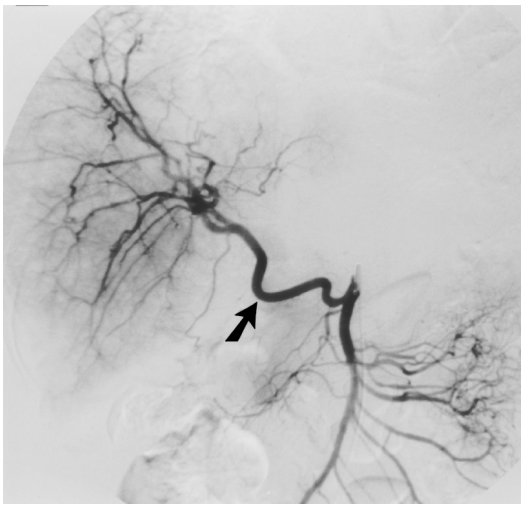
There is no consensus on the best chemoembolization protocol. Our protocol is based on the results of laboratory studies at our institution, which were followed by clinical studies with satisfactory results (9,12). Other protocols with similar results have been described (5,7, 13,17). We perform selective arterial chemoembolization with a mixture of 10 mL iopamidol (Isovue; Squibb Diagnostics, New Brunswick, NJ), 20 mL ethiodized oil (Ethiodol; Savage Laboratories, Melville, NY), and a cytotoxic agent. For HCC and metastases from neuroendocrine tumors, the chemotherapeutic agent is doxorubicin (60 mg) (9). For metastases from colorectal tumors, fluorouracil (1 g) and mitomycin (10 mg) are used (13). Chemotherapeutic material is injected into the right or left hepatic arteries or, more usually, the first- or second-order branches of these arteries. During chemoembolization, conscious sedation is achieved with a combination of intravenous midazolam hydrochloride (Versed; Hoffmann-LaRoche, Nutley, NJ) and fentanyl citrate (Sublimaze; Janssen, Titusville, NJ) and monitored by an experienced (intensive care–trained) radiology nurse. Metastases from neuroendocrine tumors are treated with chemoembolization with somatostatin analogue (octreotide) coverage (19,20).

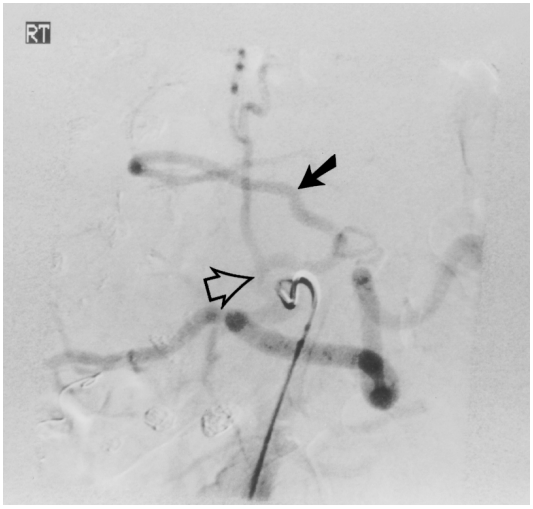
When necessary, feeding vessels arising from the superior mesenteric artery or phrenic arteries are also embolized. Less frequently (1%–2% of cases), other vessels such as intercostal arteries or the internal thoracic (internal mammary) artery require embolization (21). Administration of the chemotherapeutic material is followed by embolization with a slurry of gelatin sponge (Gelfoam; Upjohn, Kalamazoo, Mich) powder and absolute alcohol (typically 2–3 mL) to almost but not quite abolish flow in the treated artery (~90% flow reduction). Lidocaine is given intraarterially in 10-mg doses between 10-mL aliquots of chemoembolization material to reduce pain after chemoembolization (22). If there are lesions in both lobes, the lobe with the largest tumor load is embolized first.

The chemoembolization material must be delivered close to the tumor being treated but not so close that not all vessels are treated. The injection should be beyond the cystic and gastroduodenal arteries when injecting the proper hepatic artery. Coil embolization of the gastroduodenal artery may be required to prevent inadvertent chemoembolization of the pancreas and duodenum. Injection should be slow with continuous fluoroscopic monitoring to ensure that there is no reflux of chemoembolization material. There should be adequate blood flow past the catheter to ensure that the chemoembolization material is carried into the tumor. Microcatheters may be required to prevent occlusion of feeding vessels. A postembolization image is acquired to show the distribution of the ethiodized oil, but acquisition of a postprocedure angiogram is unnecessary.

After chemoembolization, the following medications are used routinely: (*a*) furosemide (20 mg intravenously) at the end of the procedure; (*b*) hydromorphone hydrochloride (Dilaudid; 0.5–2.0 mg subcutaneously every 3 hours as required) or acetaminophen (orally every 6 hours as required) for pain relief; (*c*) prochlorperazine maleate (Compazine, SmithKline Beecham Pharmaceuticals, Philadelphia, Pa; 10 mg orally or intramuscularly as required) for antiemesis; (*d*) famotidine (Pepcid, Merck, Whitehouse Station, NJ; 20 mg orally every 12 hours) for histamine$_2$-receptor blocking; and (*e*) lactulose (30 mL orally every 12 hours).

Multiple chemoembolization treatments may be required to treat all lesions as well as





2. **3.**

Figures 2, 3. **(2)** Selective superior mesenteric arteriogram shows filling of a replaced right hepatic artery (arrow) that supplies an HCC in the right lobe of the liver. **(3)** Selective celiac arteriogram shows a left hepatic artery (solid arrow) that arises from the origin of the left gastric artery (open arrow). To ensure safe chemoembolization without embolization of the left gastric artery, it was necessary to use a microcatheter to access the aberrant left hepatic artery to selectively deliver chemoembolization material.

recurrences. Nonenhanced CT scans are obtained 1 day, 1 month, 3 months, 6 months, and 1 year after chemoembolization and then as required. CT scans are assessed for changes in tumor morphology, changes in tumor size, the initial pattern of ethiodized oil uptake, changes in the pattern of ethiodized oil distribution, resorption of ethiodized oil, overall liver size, and development of new lesions or metastases. Although contrast-enhanced CT or magnetic resonance (MR) imaging may be used to identify all lesions before chemoembolization, we have found that nonenhanced CT scans suffice for follow-up. In this patient population, the dominant tumors are easily visible without contrast material. Although small new lesions may develop, no survival benefit has been shown for treating these. Other investigators recommend continuing follow-up with contrast-enhanced CT or gadolinium-enhanced MR imaging (23).

Levels of tumor markers (α-fetoprotein for HCC, carcinoembryonic antigen for metastases from colorectal tumors, 5-hydroxyindoleacetic acid for carcinoids) are measured routinely before and after chemoembolization at the same intervals as follow-up CT. A fall in tumor marker levels indicates a response to chemoembolization; a subsequent rise in tumor marker levels indicates tumor recurrence, which may lead to repeat chemoembolization.

■ ANATOMIC FACTORS

● Variant Vascular Anatomy

The anatomy of the arterial supply of the liver is prone to frequent congenital variations. A full understanding of the potential variations and the ability to achieve selective cannulation is required to allow complete treatment with chemoembolization (Figs 2, 3). For this reason, selective celiac and superior mesenteric arteriography should be performed with late-phase imaging of the portal venous anatomy. Knowledge of the patency of the portal vein is essential for safe chemoembolization.

● Selective Catheterization

Careful manipulation of catheters is required to prevent spasm in the target artery. Although it is usually possible to pass a conventional catheter far into the peripheral arteries close to the liver capsule, this maneuver is not necessarily desirable. Manipulation of conventional guide wires and catheters in small vessels frequently

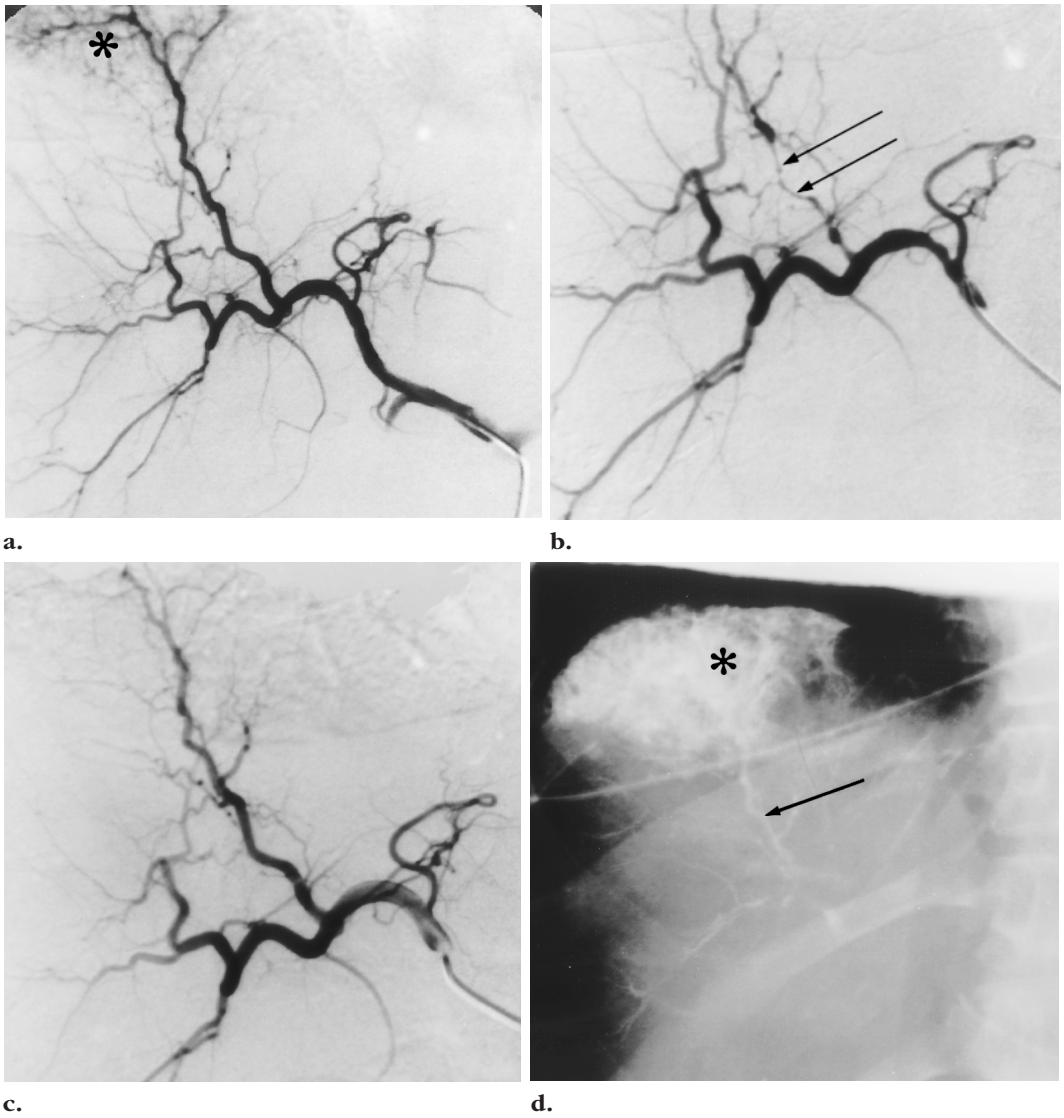
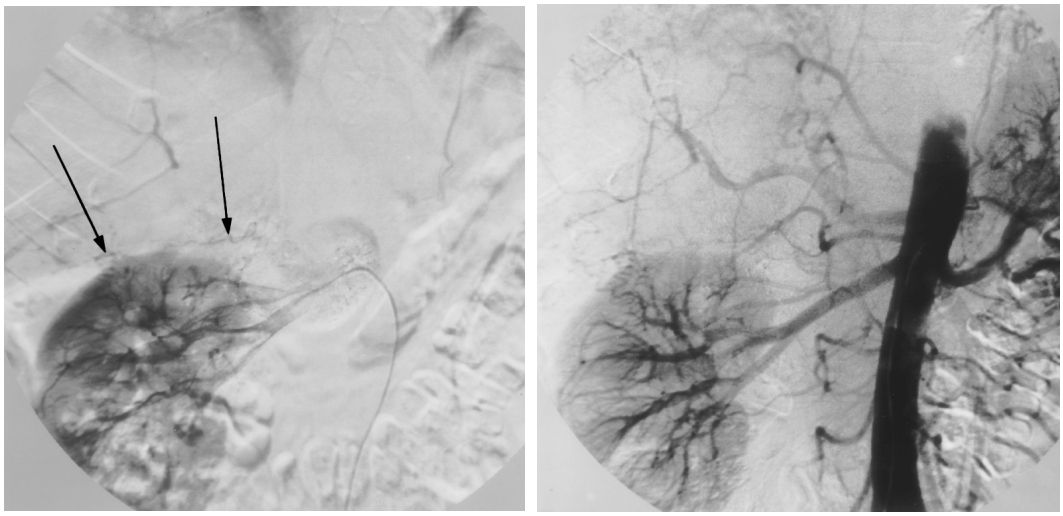


Figure 4. **(a)** Selective proper hepatic arteriogram shows a vascular blush (*), which represents an HCC close to the dome of the liver; the HCC is supplied by a branch of the right hepatic artery. An attempt to select this vessel by using a 5-F Cobra (C2) catheter and a hydrophilic guide wire was successful but produced intense spasm. **(b)** Selective proper hepatic arteriogram obtained after injection of vasodilators (papaverine hydrochloride and nitroglycerin) shows persistence of the spasm (arrows). **(c)** Selective proper hepatic arteriogram obtained after recannulation of the vessel affected by spasm with a microcatheter and injection of vasodilators shows resolution of the spasm. **(d)** Angiogram obtained at the end of the procedure shows chemoembolization material well distributed throughout the tumor (*) and gelatin sponge powder in the feeding artery (arrow).

causes spasm (Fig 4), which prevents adequate flow to carry the chemoembolization material into the lesion. In addition, if the catheter has a cross-sectional area close to that of the vessel being injected, the size similarity will also reduce flow and increase the risk of reflux of chemoembolization material into other arteries.

• Parasitic Arterial Supply

Some advanced or superficial tumors may parasitize arteries from the arterial blood supply of adjacent organs after multiple chemoembolization procedures (Figs 5, 6). Such parasitization



a. b.

Figure 5. **(a)** Selective renal arteriogram obtained after several chemoembolization treatments for metastases from a neuroendocrine tumor shows small parasitic arteries (arrows) arising from the right kidney and leading to hepatic artery branches in the right lobe of the liver. **(b)** Aortogram shows that it would be very difficult to embolize the small parasitic arteries without jeopardizing a large segment of the right kidney; hence, these arteries were not treated at this time.

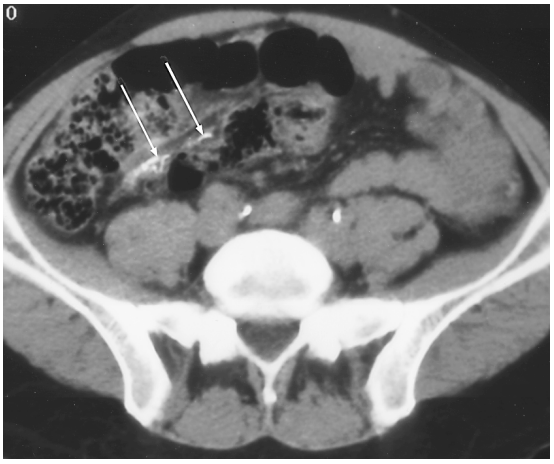


Figure 6. Nonenhanced CT scan of a patient with metastases from an islet cell tumor shows ethiodized oil (arrows) in the mesentery. The image was acquired 1 day after chemoembolization with one-third of the conventional dose of multiple parasitic arteries that arose from gastroepiploic and gastroduodenal artery branches. There were no adverse consequences of this procedure.

may require chemoembolization of branches from the right kidney, colon, stomach, and phrenic, internal thoracic, and intercostal arteries. It is important to recognize that not all such vessels can be safely treated without risk to other important organs and that not all need to be treated (Fig 5). The recommended indication for when to embolize these vessels is the "back of the room" rule, which means that tumor blood supply from these vessels is obvious (23). Depending on the vessel treated, there is potential to cause inadvertent damage such as skin necrosis (internal thoracic and intercostal arteries). However, it is possible to carefully embolize via parasitized arteries in cases in which there is an increased but acceptable risk (Fig 6). In these situations, it is usually necessary to use microcatheters positioned distal to any branches supplying the chest wall (21). The chemoembolization mixture consists of the usual dose of chemotherapeutic agent in a smaller volume (50% of the usual volume) of ethiodized oil and contrast material (21).

• Portal Vein Patency

It is essential to assess the patency of the portal vein and the direction of portal flow. The safety of conventional chemoembolization is dependent on normal liver tissue receiving an adequate blood supply from the portal vein. Portal vein occlusion or hepatofugal flow (Fig

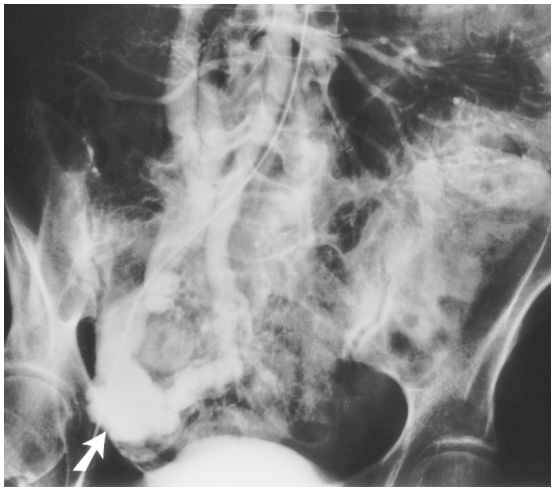


Figure 7. Venous-phase image from superior mesenteric arteriography in a patient with portal hypertension and HCC shows hepatofugal flow through a large pelvic portosystemic shunt (arrow).

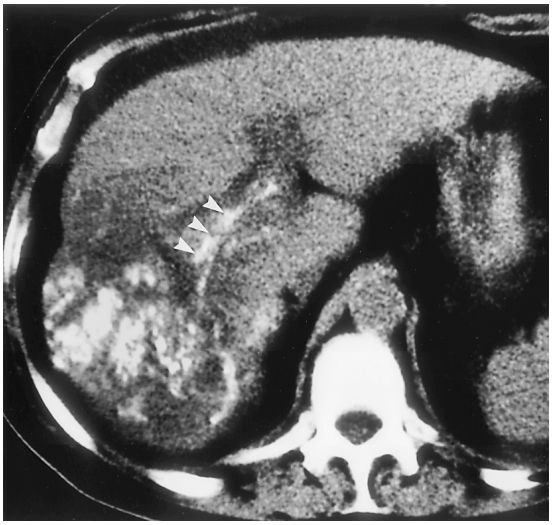


Figure 8. Nonenhanced CT scan shows occult portal vein invasion by the tumor as the thread and streak sign (arrowheads).

7) greatly increases the risk of liver necrosis due to chemoembolization, especially if a full dose of chemoembolization material and gelatin sponge powder is injected or if the injection is not selective. Portal vein occlusion is also predictive of a poor prognosis (24). A modified technique that involves superselective injection of reduced amounts of chemoembolization material (30%–50% of the usual dose) with little or no gelatin sponge powder can allow safe chemoembolization in patients with portal vein occlusion (16).

● Occult Portal Vein Occlusion

In patients with occult partial occlusion of the portal vein, ethiodized oil may be deposited in the portal vein; in this situation, the ethiodized oil appears as the "thread and streak" sign on nonenhanced CT scans (Fig 8). The cause of this finding has not been verified with autopsy in any of our patients, but the finding may represent the effects of embolization of the tumor invading the portal vein. Although there are limited data to indicate that this situation is safe, we have not seen liver necrosis complicating chemoembolization in the 5% of our patients with occult partial occlusion of the portal vein as indicated by this sign (15).

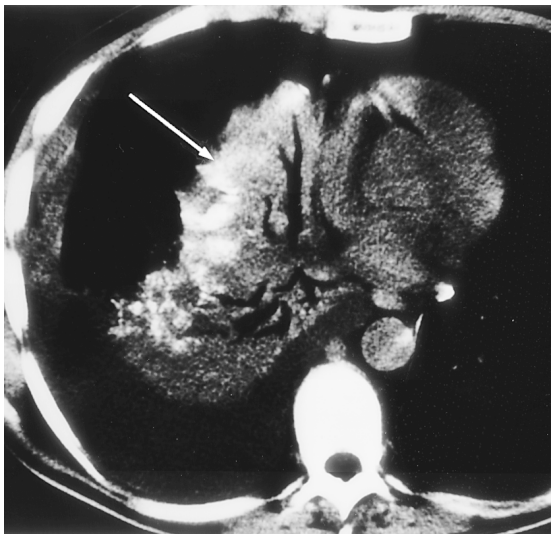


Figure 9. Nonenhanced CT scan obtained 1 day after chemoembolization shows hyperattenuating ethiodized oil (arrow) in the collapsed lower lobe of the right lung. This finding caused no significant problems.

■ ABNORMAL CT FINDINGS AND COMPLICATIONS

Extrahepatic uptake of chemoembolization material is relatively common. Although any extrahepatic chemoembolization material is undesirable and may cause complications, the frequency of significant complications due to such uptake is low. Asymptomatic deposition of chemoembolization material may be seen in the lung, stomach, pancreas, duodenum, gallbladder, diaphragm, and spleen.

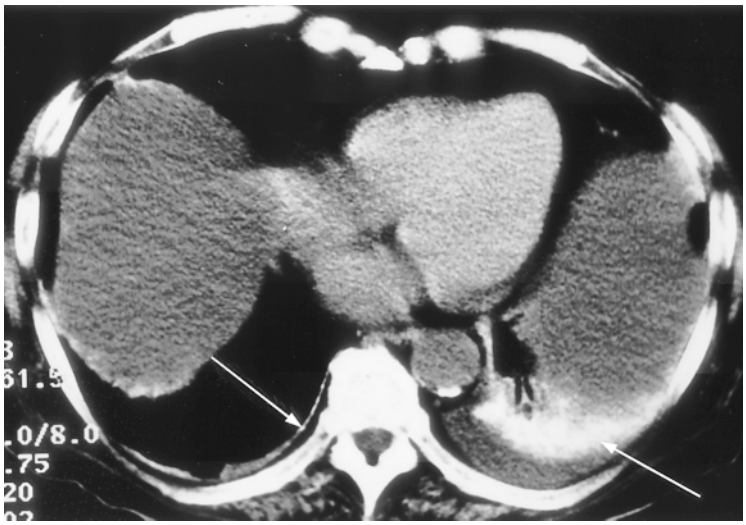


Figure 10. Nonenhanced CT scan obtained 1 day after chemoembolization shows bilateral deposition of ethiodized oil in the lung and pleura (arrows) with the most marked deposition in the left lung. There were no symptoms due to this finding.

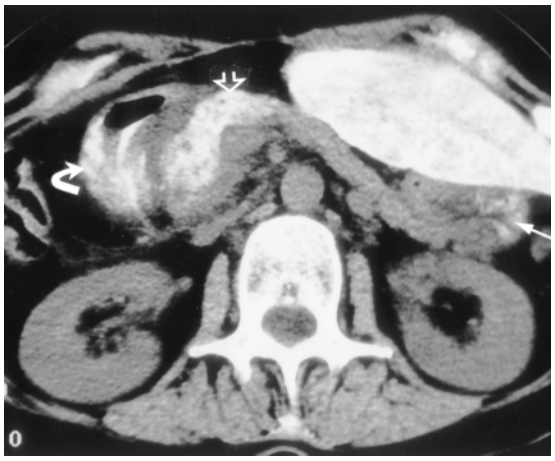


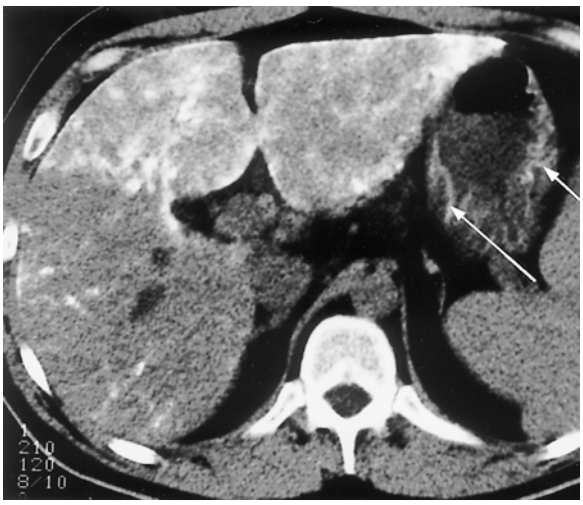
Figure 11. Nonenhanced CT scan obtained after chemoembolization shows ethiodized oil in the stomach (straight solid arrow), duodenum (curved arrow), and pancreas (open arrow). Nonenhanced CT performed 1 month later showed that the extrahepatic ethiodized oil had almost disappeared. There were no adverse consequences of this extrahepatic embolization.

• Lung Uptake

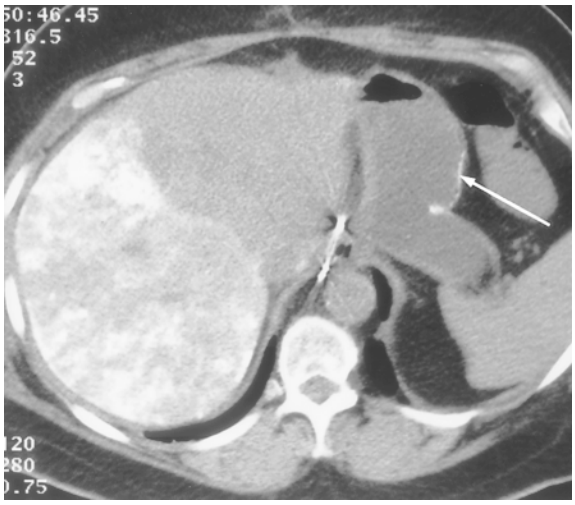
It is not uncommon for small arteriovenous shunts in tumors to allow chemoembolization material to pass into the hepatic veins and thence into the lungs (Fig 9). These shunts are usually not visible. Injection of the phrenic arteries may also cause lung or pleural uptake. In our experience, lung or pleural uptake is common, can be bilateral (Fig 10), and is seen on CT scans in up to 25% of cases (15), although it may be a subtle finding. Although ethiodized oil may cause inflammatory changes in experiments (25), the amount of ethiodized oil usually seen after chemoembolization is unlikely to cause significant problems. Larger amounts may cause significant pulmonary infarction (26). The lobar collapse commonly seen after chemoembolization is usually due to pain and resultant hypoventilation and resolves rapidly, even when ethiodized oil persists in the lung. We routinely use incentive spirometry to minimize this problem.

• Embolization of Celiac Artery Branches

Embolization affecting the organs supplied by the celiac trunk is not uncommon. Fortunately, such embolization is usually not a significant problem if it is due to mild reflux from a selective injection (Fig 11). Embolization of the pancreas after nonselective chemoembolization is common and is symptomatic; this fact is one of the reasons for performing selective chemoembolization. Pancreatic embolization is uncommonly of significance after selective chemoembolization (27). If injection of the common hepatic or proper hepatic artery is required close to the origin of the gastroduodenal artery, coil embolization of the gastroduodenal artery protects the pancreas and duodenum from inadvertent chemoembolization.

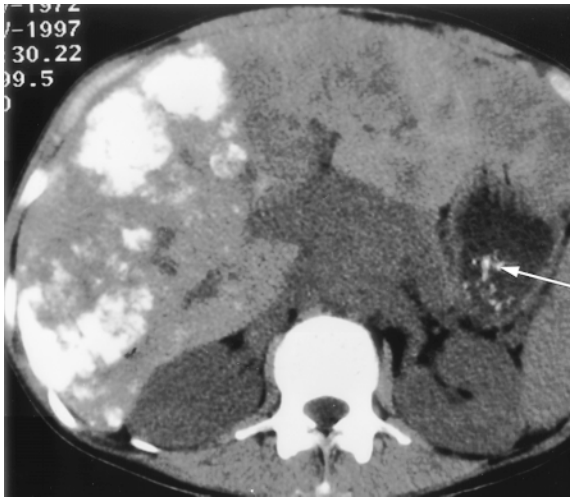


12.



13.

Figures 12–14. **(12)** Nonenhanced CT scan shows gastric deposition of chemoembolization material with ethiodized oil (arrows) following the line of the gastric mucosa. **(13)** Nonenhanced CT scan shows calcification of the gastric wall (arrow). The calcification was caused by radiation therapy for renal cell carcinoma many years earlier. **(14)** Nonenhanced CT scan shows hyperattenuating areas in the lumen of the stomach due to ingestion of milk of magnesia (arrow).



14.

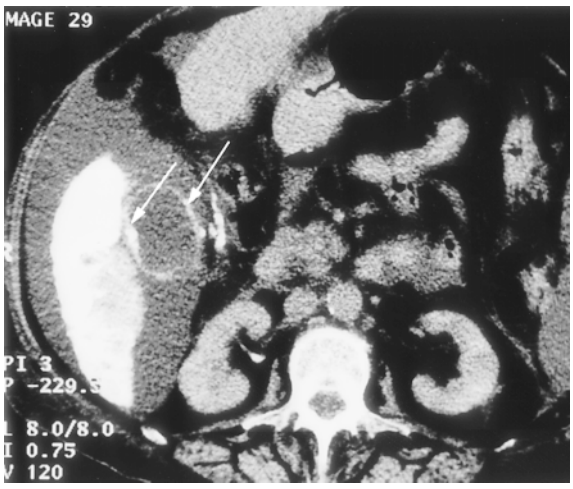
• Gastric Uptake

Gastric deposition of chemoembolization material is characterized by ethiodized oil following the line of the gastric mucosa (Fig 12). In our experience, gastric uptake is uncommon (1% of cases) and asymptomatic (15), although others report a high frequency of peptic ulceration (28). All of our patients receive prophylactic histamine$_2$-receptor blockers for 1 month after chemoembolization. Gastric uptake must be differentiated from gastric wall calcification (Fig 13) or ingested radiopaque material, which is intraluminal and should be obvious (Fig 14).

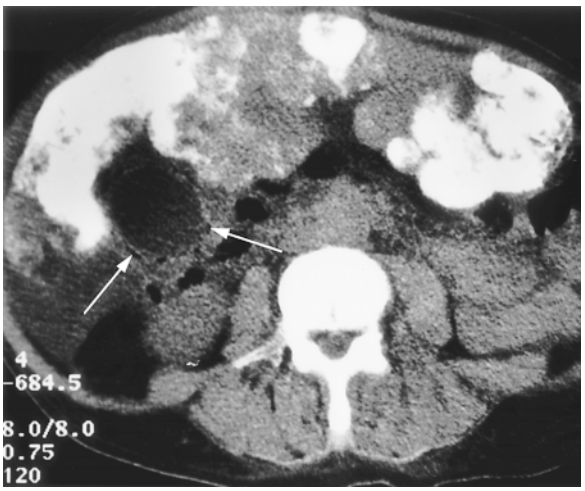
• Gallbladder Uptake and Infarction

Ethiodized oil is not uncommonly seen in the wall of the gallbladder after chemoembolization (14% of cases in our experience [15]) despite efforts to avoid injection proximal to the cystic artery. Even when the gallbladder does receive some chemoembolization material, there is usually no adverse outcome (29,30). The reason may be because gelatin sponge powder, which may be more likely to cause infarction, does not necessarily go to the area outlined by the ethiodized oil; also, this area already has reduced flow due to the oil embolization. Ethiodized oil uptake by the gallbladder may be focal or diffuse (Fig 15). Occasionally, chemoembolization of the gallbladder may cause emphysematous cholecystitis, even when little ethiodized oil is present (Fig 16), although cholecystectomy may not be required.

Because of the unfavorable anatomy, it may be impossible to deliver chemoembolization

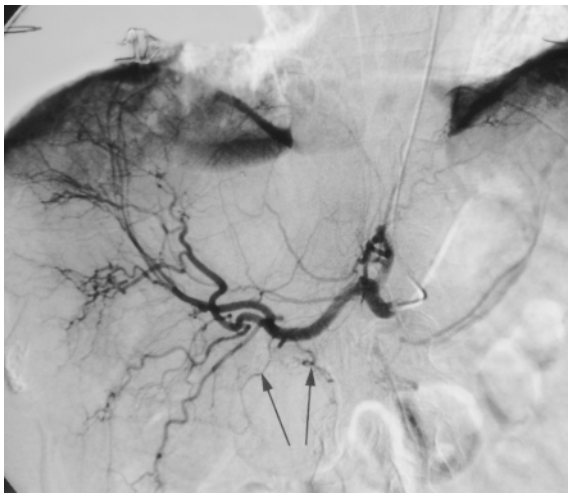


15.

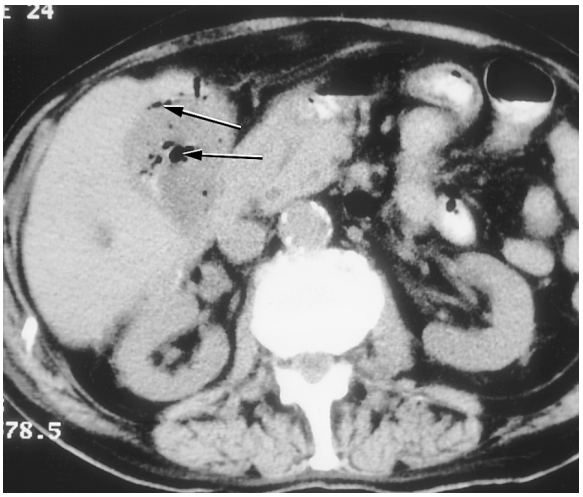


16.

Figures 15, 16. **(15)** Nonenhanced CT scan shows diffuse gallbladder uptake of chemoembolization material (arrows) in a patient with HCC. There were no symptoms from the gallbladder uptake. **(16)** Nonenhanced CT scan shows changes due to emphysematous cholecystitis (arrows indicate gas in the wall of the gallbladder). Only a little ethiodized oil is present. The patient had no symptoms beyond those normally expected after chemoembolization. He was treated with antibiotics, recovered, and did not require cholecystectomy.



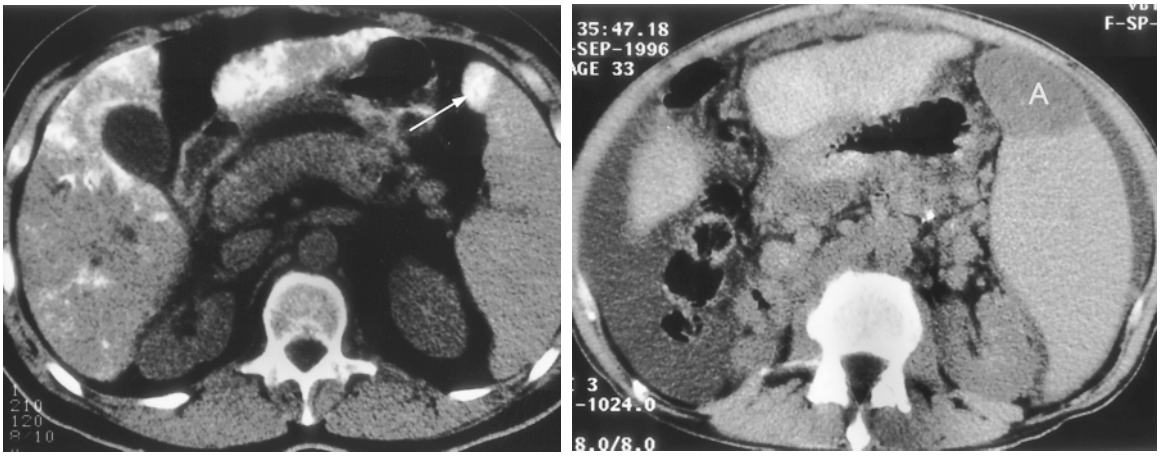
a.



b.

Figure 17. **(a)** Hepatic arteriogram obtained before chemoembolization shows two cystic arteries (arrows); the gallbladder is well demonstrated. A nonenhanced CT scan obtained 24 hours after chemoembolization (not shown) showed a normal gallbladder. **(b)** Nonenhanced CT scan obtained 3 weeks later, when the patient presented with right upper quadrant pain, fever, and general malaise, shows gas in the wall and lumen of the gallbladder (arrows). These changes of emphysematous cholecystitis were confirmed at cholecystectomy. Ethiodized oil was found at histologic analysis of the gallbladder.

material distally without some reflux into the cystic artery; such reflux may lead to gallbladder infarction (Fig 17). The infarction may be delayed for some time after the chemoembolization procedure. Fortunately, in our experience, only one of 251 patients who underwent chemoembolization in a 30-month period required cholecystectomy for gallbladder infarction (Table 2).



a. **b.**

Figure 18. **(a)** Nonenhanced CT scan obtained 1 day after chemoembolization shows ethiodized oil in an anterior segment of the spleen (arrow). There were no symptoms. **(b)** Nonenhanced CT scan obtained more than 1 year later shows a hypoattenuating area (*A*) that corresponds to a splenic infarction. The patient had no symptoms related to the spleen throughout this period. Interval development of ascites and varices adjacent to the spleen is also evident.

Table 2
Complications in 251 Chemoembolization Procedures

Complication	No. of Patients*
Puncture site hematoma	4 (1.6)
Peripheral arterial occlusion	1 (0.4)
Catheter-induced complications	1 (0.4)
Idiosyncratic reaction to contrast material	3 (1.2)
Nonidiosyncratic reaction to contrast material	9 (3.6)
Renal failure (>50% increase in creatinine level)	6 (2.4)
Prolonged fever	1 (0.4)
Liver abscess	1 (0.4)
Carcinoid crisis	1 (0.4)
Respiratory depression (due to sedation)	1 (0.4)
Procedure-related deaths	5 (2.0)
Total	33 (13.1)

Source.—Reference 15. The procedures were performed over 30 months (July 1994–December 1996).
*Numbers in parentheses are percentages.

● Splenic Uptake and Infarction

Reflux of chemoembolization material into the splenic artery is uncommon but may cause focal splenic infarction (Fig 18). Splenic artery reflux seldom causes symptoms.

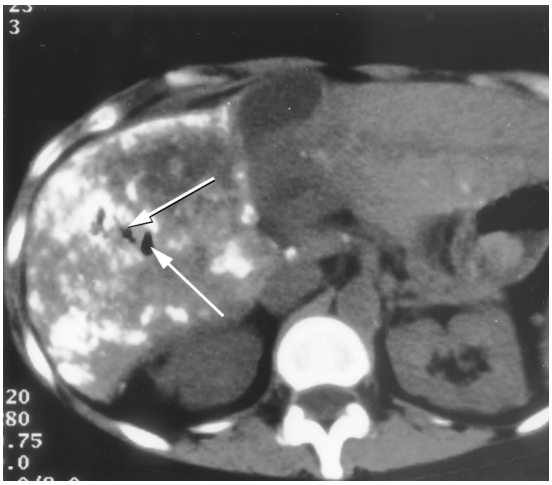


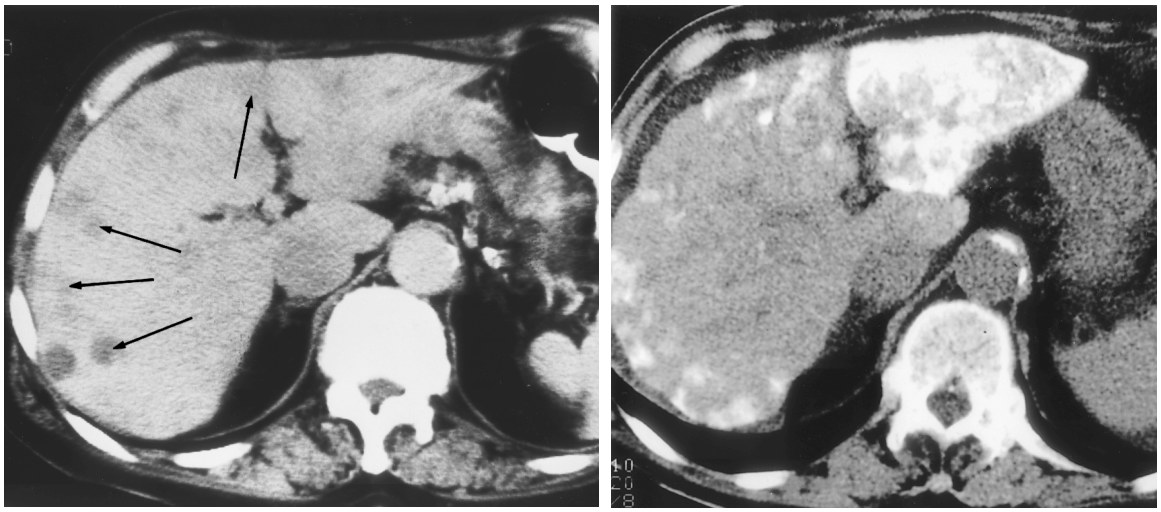
Figure 20. Nonenhanced CT scan obtained immediately after chemoembolization of the right hepatic lobe shows small collections of gas (arrows) surrounded by deposits of ethiodized oil.

● Pseudocirrhosis

The liver can respond to chemoembolization in several ways, including the development of pseudocirrhosis (Fig 19). At CT, pseudocirrhosis appears as irregularity of the hepatic surface, an appearance superficially similar to that of cirrhosis.

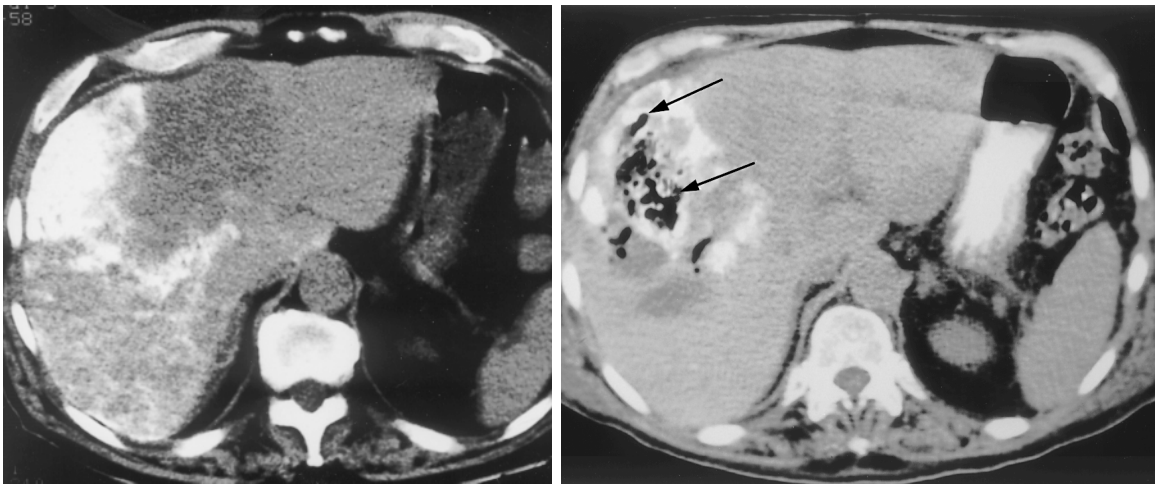
● Liver Infarction and Abscess Formation

A degree of tumor infarction after chemoembolization is probably inevitable; small amounts of gas are commonly seen and are usually of no



a. b.

Figure 19. **(a)** Contrast-enhanced CT scan obtained immediately before chemoembolization shows multiple hypoattenuating tumors (arrows) in a smooth right lobe of the liver. **(b)** Nonenhanced CT scan obtained 4 months after right lobe chemoembolization and immediately after left lobe chemoembolization shows that the right lobe has an irregular surface, which represents pseudocirrhosis.



a. b.

Figure 21. **(a)** Nonenhanced CT scan obtained immediately after chemoembolization of the right hepatic lobe shows no evidence of infarction. **(b)** Nonenhanced CT scan obtained 1 month later shows extensive gas (arrows) in the treated tumor due to liver infarction and abscess formation.

consequence (Fig 20). In our experience, more extensive infarction that leads to necrosis and abscess formation is rare (Fig 21). Other authors have reported abscess formation as a result of biliary infarction (20), but we have not encountered this problem. Excess gelatin sponge powder may contribute to infarction and resulting conditions, as may excessive chemoembolization in patients with portal vein occlusion.

● Carcinoid Crisis

Until the introduction of somatostatin analogues (eg, octreotide), exacerbation of the symptoms of carcinoid or frank carcinoid crisis was common with chemoembolization of metastases from carcinoids. Now, somatostatin analogues are used routinely, for hormonally

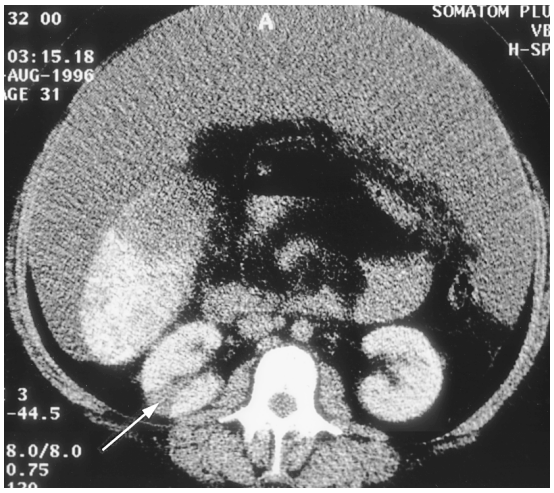


Figure 22. Nonenhanced CT scan obtained 1 day after chemoembolization of metastases from adenocarcinoma shows a huge amount of ascites (*A*) and contrast material in the liver and kidneys. The patient, who had moderate liver and renal dysfunction, underwent the procedure with a full understanding of the risks involved. There is no excretion of contrast material due to the severe renal failure resulting from worsening hepatorenal syndrome. Note the right renal infarction (arrow).

active tumors, during and after chemoembolization to prevent carcinoid crisis and can be used intravenously in emergencies (19). Carcinoid crisis now occurs in only a small percentage of patients. Treatment of these patients, who often have severe disease of the pulmonary and tricuspid valves, is difficult because there is little room for error when reducing preload to treat pulmonary edema. Right atrial pressure must be maintained to ensure adequate flow through the diseased tricuspid valve. Maintenance of right atrial pressure requires close collaboration with an experienced cardiologist.

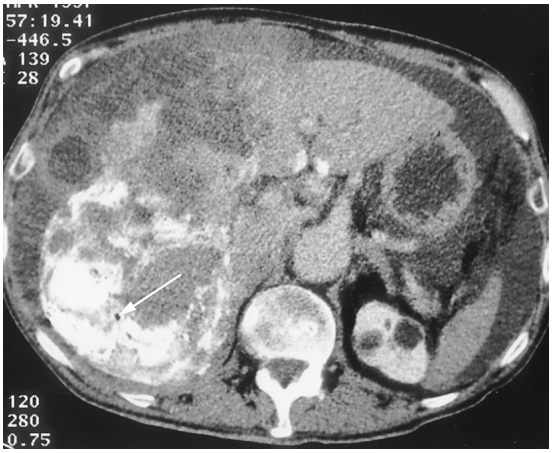


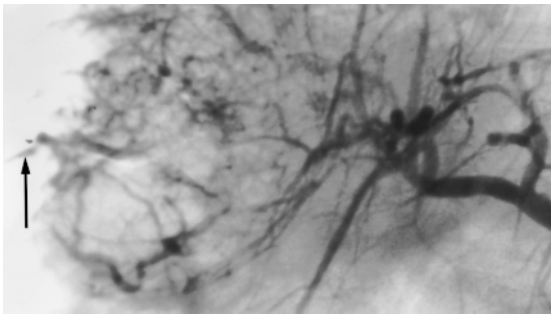
Figure 23. Nonenhanced CT scan obtained several days after chemoembolization for HCC shows liver rupture with liquefied liver spreading into the peritoneal space. It is unclear whether the rupture was directly due to chemoembolization because the rupture is adjacent to but not at the area treated. Note the small amount of gas in the treated tumor (arrow). The presence of this amount of gas is common and by itself should not cause concern.

● Hepatorenal Syndrome

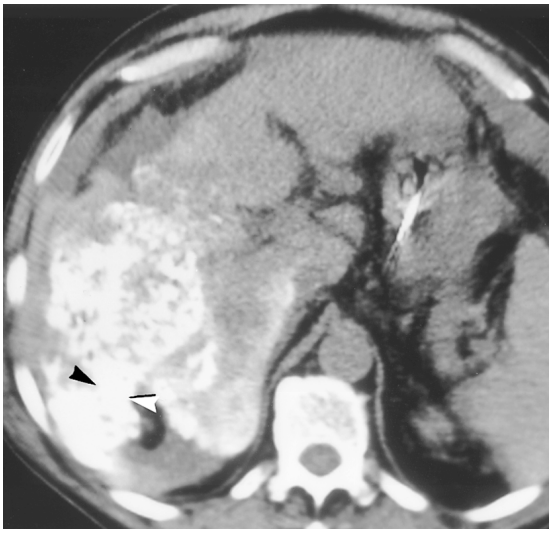
Advanced liver failure can lead to hepatorenal syndrome, which may be exacerbated by chemoembolization and the associated contrast material load. Severe liver dysfunction and renal dysfunction are relative contraindications to chemoembolization. On occasion, it may be appropriate to attempt chemoembolization under these circumstances, even though there is a substantial risk involved, because there is a greater risk to doing nothing (Fig 22).

● Liver Rupture

Large liver tumors adjacent to the liver capsule may rarely cause necrosis and lead to liver rupture (Fig 23). Liver rupture may also occur in the absence of chemoembolization (Fig 1). In addition, liver rupture may occur after chemoembolization if the liver capsule was breached before chemoembolization (Fig 24).



a.



b.

Figure 24. **(a)** Selective hepatic arteriogram shows extravasation of contrast material at the site of a recent liver biopsy (arrow). The extravasation was discovered only after chemoembolization. **(b)** Nonenhanced CT scan obtained later that day shows continuing leakage of ethiodized oil from the biopsy site (arrowheads).

■ CONCLUSIONS

There are numerous potential errors and complications associated with chemoembolization for unresectable liver tumors. A good understanding of the congenital and acquired variations of arterial anatomy that may be seen supplying the liver is required. A full assessment of portal vein patency is also required. An abnormal portal vein demands significant changes in technique to allow safe chemoembolization. Partial or complete portal vein occlusion is associated with significantly decreased survival but does not prevent a worthwhile response to chemoembolization and is not an absolute contraindication. The presence of chemoembolization material in the gallbladder is not uncommon; however, when the technique described herein is used, the chemoembolization material infrequently causes cholecystitis or gallbladder infarction. Our experience in this regard is unlike that of other investigators, who report that gallbladder complications are common (31). Extrahepatic chemoembolization material is commonly seen in other organs but usually does not cause problems, presumably because the dose deposited outside the liver is small compared with the dose delivered to the liver.

■ REFERENCES

1. DiBisceglie AM, Rustgi VK, Hoofnagle JH, et al. Hepatocellular carcinoma. Ann Intern Med 1988; 108:390–401.
2. Rustgi VK. Epidemiology of hepatocellular carcinoma. Gastroenterol Clin North Am 1987; 16:545–551.
3. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment: study of 850 patients. Cancer 1985; 56:918–928.
4. Nerenstone S, Friedman F. Medical treatment of hepatocellular carcinoma. Gastroenterol Clin North Am 1987; 16:603–612.
5. Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. Radiology 1983; 148:397–401.
6. Kakamura H, Mitani T, Murakami T, et al. Five-year survival after transcatheter chemoembolization for hepatocellular carcinoma. Cancer Chemother Pharmacol 1994; 33 (suppl):S89–S92.
7. Onodera H, Ukai K, Nakano N, et al. Outcomes of 116 patients with hepatocellular carcinoma. Cancer Chemother Pharmacol 1994; 33(suppl):S103–S108.

8. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. A comparison of Lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 1995; 332:1256–1261.
9. Miller DL. First, do no harm (editorial). Radiology 1996; 198:10–12.
10. Clouse ME, Stokes KR, Stuart KE, et al. Chemoembolization for hepatocellular carcinoma: epinephrine followed by a doxorubicin–ethiodized oil emulsion and gelatin sponge powder. JVIR 1993; 4:717–725.
11. Patt YZ, Chuang VP, Wallace S, et al. Hepatic arterial chemotherapy and occlusion for palliation of primary hepatocellular and unknown primary neoplasms in the liver. Cancer 1983; 51:1359–1363.
12. Sanz-Altamira PM, Spence LD, Huberman MS, et al. Selective chemoembolization in the management of hepatic metastases in refractory colorectal carcinoma: a phase II trial. Dis Colon Rectum 1997; 40:770–775.
13. Lang EK, Brown CL. Colorectal metastases to the liver. Radiology 1993; 189:417–422.
14. Sakamoto I, Aso N, Nagaoki K, et al. Complications associated with transcatheter arterial embolization for hepatic tumors. RadioGraphics 1998; 18:605–619.
15. Gates J, Hartnell GG, Stuart K, Perry LJ, Clouse ME. Differentiation of abnormal uptake from complications of chemoembolization of unresectable liver tumors. Presented at the 22nd Annual Scientific Meeting of the Society of Cardiovascular and Interventional Radiology, Washington, DC, March 8–13, 1997.
16. Pentecost MJ, Daniels JR, Teitelbaum GP, Stanley P. Hepatic chemoembolization: safety with portal vein thrombosis. JVIR 1993; 4:347–351.
17. Therasse E, Breittmayer F, Roche A, et al. Transcatheter chemoembolization of progressive carcinoid liver metastases. Radiology 1993; 189:541–547.
18. Soulen M. Tutorial 16: chemoembolization of hepatic malignancies. In: Haskal ZJ, Kerlan RK, eds. Thoracic and visceral vascular interventions. Fairfax, Va: Society of Cardiovascular and Interventional Radiology, 1996; 261–272.
19. Diaco DS, Hajarizadeh H, Mueller CR, Fletcher WS, Pommier RF, Woltering EA. Treatment of metastatic carcinoid tumors using multimodality therapy of octreotide acetate, intra-arterial chemotherapy, and hepatic arterial chemoembolization. Am J Surg 1995; 169:523–528.
20. Ruszniewski P, Rougier P, Roche A, et al. Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumors: a prospective phase II study in 24 patients. Cancer 1993; 71:2624–2630.
21. Kim JH, Chung JW, Han JK, Park JH, Choi BI, Han MC. Transcatheter arterial embolization of the internal mammary artery in hepatocellular carcinoma. JVIR 1995; 6:71–77.
22. Hartnell GG, Gates J, Brophy DP, Stuart K, Underhill J, McEniff JN. Reduction of pain and other complications of hepatic chemoembolization by adjunctive intra-arterial injection of lidocaine (abstr). Radiology 1997; 205(P):156–157.
23. Sullivan KL, Soulen M. Tutorial 17: advanced chemoembolization—anatomy, complications, and technique. In: Haskal ZJ, Kerlan RK, eds. Thoracic and visceral vascular interventions. Fairfax, Va: Society of Cardiovascular and Interventional Radiology, 1996; 273–288.
24. Stuart K, Stokes K, Jenkins R, Trey C, Clouse ME. Treatment of hepatocellular carcinoma using doxorubicin/ethiodized oil/gelatin powder chemoembolization. Cancer 1993; 72:3202–3209.
25. Kishi K, Sonomura T, Satoh M, et al. Acute toxicity of Lipiodol infusion into the hepatic arteries of dogs. Invest Radiol 1994; 29:882–889.
26. Chung JW, Park JH, Han JK, Han MC. Pulmonary oil embolism after transcatheter oily chemoembolization of hepatocellular carcinoma. Radiology 1993; 187:689–693.
27. Khan HN, Nakata K, Shima M, et al. Pancreatic tissue damage by transcatheter arterial embolization for hepatoma. Dig Dis Sci 1993; 38:65–70.
28. Hirakawa M, Iida M, Aoyagi K, Matsui T, Akagi K, Fujishima M. Gastroduodenal lesions after transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. Am J Gastroenterol 1988; 83:837–840.
29. Takayasu K, Moriyama N, Muramatsu Y, et al. Gallbladder infarction after hepatic artery embolization. AJR 1985; 144:135–138.
30. Kuroda C, Iwasaki M, Tanaka T, et al. Gallbladder infarction following hepatic arterial embolization. Radiology 1983; 149:85–89.
31. Makuuchi M, Sukigara M, Mori T, et al. Bile duct necrosis: complication of transcatheter hepatic arterial embolization. Radiology 1985; 156:331–334.