# Complications of chemoembolization for hepatic neoplasms

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## ABSTRACT

**Objective:** To present a safe and effective approach to chemoembolization for hepatic neoplasms, and to discuss the complications of chemoembolization and ways of avoiding them.

**Methods:** The techniques and experience described herein are based on clinical practice at Yichang Central People's Hospital, Yichang, Hubei, China, where over 200 chemoembolization procedures are performed yearly, and on the results of an intensive review of 1054 chemoembolization procedures performed between July 1997 and December 2005.

**Results:** There were complications as follow: 5 cases with celiac artery branch embolization, gastric uptake in 4, 6 with gallbladder uptake and infarction, splenic uptake and infarction in 8, liver infarction and abscess formation in 3, and hepatorenal syndrome in 4, liver rupture in 2, lung uptake in 6, and spinal cord injury in 2 cases.

**Conclusion:** 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.

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Most patients with hepatocellular carcinoma (HCC) are not candidates for surgical treatment at the time of referral to an interventional radiology department. Radiation therapy and systemic chemotherapy are ineffective at prolonging survival, and transplantation remains the only curative option. The demand for donated organs far outstrips supply. Many patients require some kind of image-guided therapy as a bridge to transplantation or as palliative therapy.[1-6] In this article, an approach to transarterial chemoembolization (TACE) 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 TACE and ways of avoiding them are discussed.

**Methods.** The techniques and experience described herein are based on clinical practice at Yichang Central People's Hospital, Yichang, Hubei, China, where over 200 chemoembolization procedures are performed yearly, and on the results of an intensive review of 1054 chemoembolization procedures performed in 568 patients between July 1997 and December 2005. We have gotten a ethical approval on this study from Ethics Committees of Three Gorges University.

***Patient selection.*** Transarterial chemo-embolization 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 gastrointestinal sarcomas. Other tumor types have been treated with chemoembolization with little evidence of benefit. 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. 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. What constitutes an adequate amount of residual uninvolved liver is not clear and may depend on the type of lesion being 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; 3 g every 6 hours for 5 doses) are used routinely. Premedication includes an analgesic such as hydromorphone hydrochloride and a sedative, and an antiemetic such as hydroxyzine. Our protocol is based on the results of laboratory studies at our institution, which were followed by clinical studies with satisfactory results. We perform selective arterial chemoembolization with a mixture of 10 mL iopamidol, and a cytotoxic agent. For HCC and metastases, the chemotherapeutic agent is doxorubicin (60 mg). For metastases from colorectal tumors, fluorouracil (1 g) and mitomycin (10 mg) are used. 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 and fentanyl citrate and monitored by an experienced (intensive care-trained) radiology nurse. Metastases from neuroendocrine tumors are treated with chemoembolization with somatostatin analogue (octreotide) coverage. 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. Administration of the chemotherapeutic material is followed by embolization with a slurry of gelatin sponge powder and absolute alcohol (typically 2-3 mL) to almost but not quite abolish flow in the treated artery (approximately 90% flow reduction). Lidocaine is given intra-arterially in 10 mg doses between 10 mL aliquots of chemoembolization material to reduce pain after chemoembolization. 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.[7,8] Multiple chemoembolization treatments may be required to treat all lesions as well as recurrences. Nonenhanced CT scans are obtained one month, 3 months, 6 months, and one year after chemoembolization, and then as required. Computerized tomography 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. Levels of tumor markers ($\alpha$-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.

***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 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. 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.

**Results.** In 1054 chemoembolization procedures, there were 5 cases with celiac artery branch embolization, gastric uptake in 4, **(Figure 1)**, 6 with gallbladder uptake and infarction **(Figure 2)**, splenic uptake and infarction in 8, liver infarction and abscess formation in 3, and hepatorenal syndrome in 4, liver rupture in 2, lung uptake in 6 **(Figure 3)**, and spinal cord injury in 2 cases **(Figure 4)**.

**Discussion.** ***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. 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. 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.[2-4]

***Gastric uptake.*** Gastric (**Figure 1**) deposition of chemoembolization material is characterized by ethiodized oil following the line of the gastric mucosa. In our experience, gastric uptake is uncommon and asymptomatic, although others report a high frequency of peptic ulceration. All of our patients receive prophylactic histamine 2-receptor blockers for one month after chemoembolization. Gastric uptake must be differentiated from gastric wall calcification or ingested radiopaque material, which is intraluminal and should be obvious.[5-8]

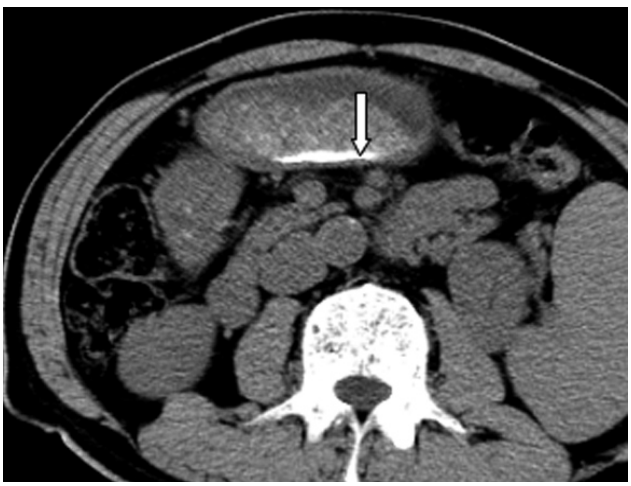

**Figure 1 -** Gastric uptake: nonenhanced CT scan obtained after chemoembolization shows ethiodized oil in the stomach (white arrow).

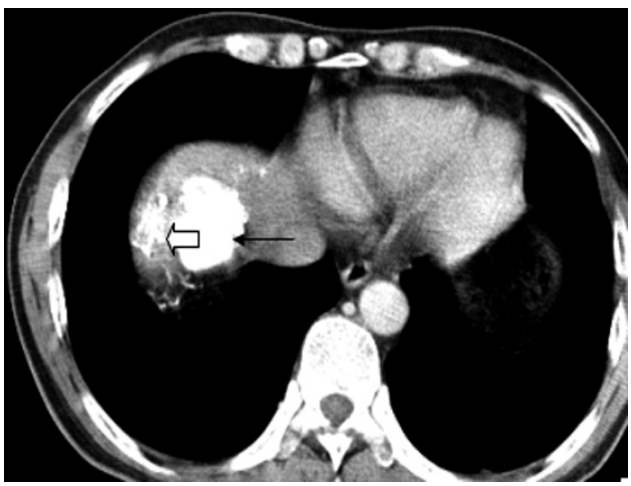

**Figure 3 -** Lung uptake: nonenhanced CT scan obtained 28 days after chemoembolization shows hyperattenuating ethiodized oil (white arrow) in the lower lobe of the right lung beside ethiodized oil in hepatocellular tumor (black arrow).

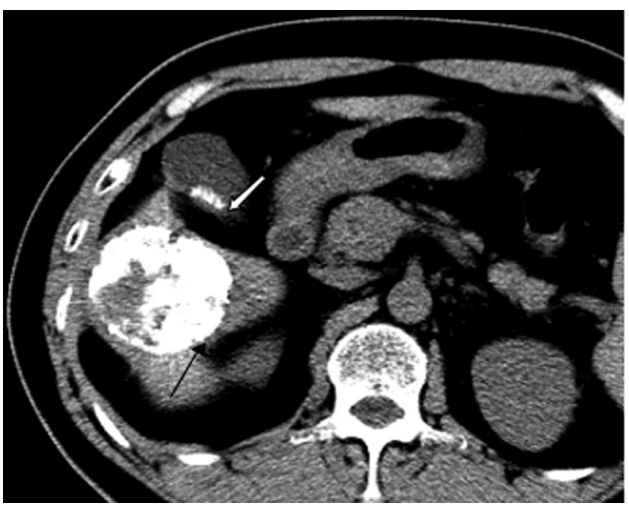

**Figure 2 -** Gallbladder uptake: Nonenhanced CT scan shows a small gallbladder uptake of chemoembolization material (white arrow) in a patient with hepatocellular carcinoma (black arrow).

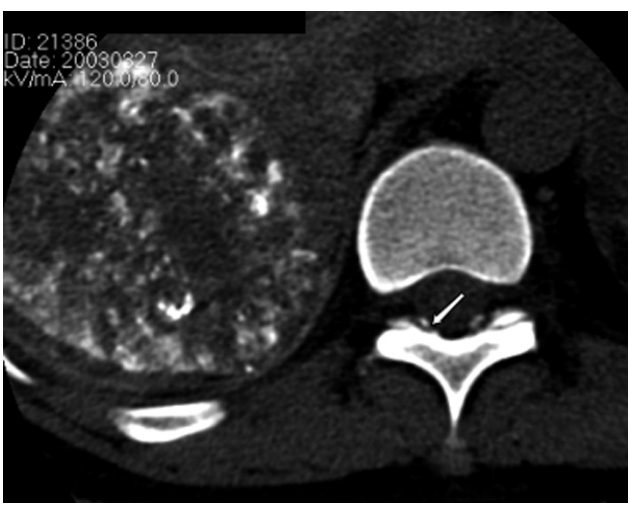


**Figure 4 -** Embolization in spinal artery: nonenhanced CT scan obtained one day after chemoembolization shows hyperattenuating ethiodized oil (white arrow) in the myelon.

***Gallbladder uptake and infarction***[6-10] **(Figure 2).** Ethiodized oil is not uncommonly seen in the wall of the gallbladder after chemoembolization (5% of cases in our experience) 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. 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. Occasionally, chemoembolization of the gallbladder may cause emphysematous cholecystitis, even when little ethiodized oil is present, although cholecystectomy may not be required. Because of the unfavorable anatomy, it may be impossible to deliver chemoembolization material distally without some reflux into the cystic artery; such reflux may lead to gallbladder infarction. The infarction may be delayed for some time after the chemoembolization procedure. Fortunately, in our experience, only 2 of 568 patients who underwent chemoembolization in a 30-month period required cholecystectomy for gallbladder infarction.

***Lung uptake*** **(Figure 3).** 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.

***Splenic uptake and infarction.*** Reflux of chemoembolization material into the splenic artery is uncommon but may cause focal splenic infarction). Splenic artery reflux seldom causes symptoms.

***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 consequence. In our experience, more extensive infarction that leads to necrosis and abscess formation is rare. Other authors have reported abscess formation as a result of biliary infarction, 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.

***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, although there is a substantial risk involved, because there is a greater risk to doing nothing.

***Liver rupture.*** Large liver tumors adjacent to the liver capsule may rarely cause necrosis and lead to liver rupture. Liver rupture may also occur in the absence of chemoembolization. In addition, liver rupture may occur after chemoembolization if the liver capsule were breached before chemoembolization.[6-13]

***Spinal cord injury or embolization in the spinal artery*** **(Figure 4).** Patients with HCC supplied by intercostal arteries may cause this severe complication.[9,10] The most disastrous complication of TACE is spinal cord ischemia due to the inadvertent occlusion of spinal arteries. Only 2 of 568 patients who underwent chemoembolization encountered this complication. The visualization of radicular branches on intercostal angiograms is not an absolute contraindication for TACE. However, when the anterior medullary artery (artery of Adamkiewicz) is visualized at angiography, embolization should not be performed. Or, it is usually necessary to use microcatheters positioned distal to any branches supplying the spine.

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. 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.

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