Preoperative Portal Venous and Hepatic Arterial Embolization of Tumor

Eric M. Walser, M.D.¹

ABSTRACT

Although the goal of embolization is usually to create therapeutic ischemia or hemostasis without surgery, the rationale for preoperative embolotherapy is different in several respects. First, the aim is to prepare patients for definitive surgical resection rather than cure or palliation, and, thus, the goals and expectations are limited and defined by close communication between the interventionalist and the surgeon. Second, when considering segmental resection, the normal liver should be protected from procedural damage. Third, the search for extrahepatic disease is crucial for these patients because resection is typically abandoned in favor of alternative therapies for patients with systemic disease. Finally, intraoperative ultrasound should always be considered to survey the future liver remnant for unsuspected small tumors and allow ablation of these lesions to maximize the success of partial hepatectomy. This article describes preoperative hepatic arterial and portal venous embolization in patients with or without cirrhosis complicated by tumors judged eligible for surgical resection or orthotopic liver transplantation (OLT). Each type of embolization will be reviewed in terms of indications and contraindications, technique, and complications. Finally, the outcomes will be evaluated in terms of morbidity, mortality, and tumor recurrence rates.

KEYWORDS: Liver surgery, liver cancer, liver metastases, transcatheter arterial chemoembolization, portal vein embolization

Objectives: On completion of this article, the reader should realize the indications, contraindications, techniques, and long-term success of hepatic arterial and portal venous embolization in preparation for major hepatic resection or liver transplantation.

Accreditation: Tufts University School of Medicine (TUSM) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit: TUSM designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*TM. Physicians should only claim credit commensurate with the extent of their participation in the activity.

PREOPERATIVE HEPATIC ARTERIAL EMBOLIZATION

Background and Indications

Cirrhotic patients develop complicating hepatocellular carcinoma (HCC) at a rate of 3 to 4% per year.^{1,2} Due to the frequent advanced stage of disease at presentation

and the tenuous hepatic synthetic reserve in most of these patients, curative hepatic resection is considered in only 20% of patients. Patients with preserved liver function and normal portal pressures occasionally present with primary hepatic neoplasms confined to a single lobe; these patients are the rare candidates for hepatic resection for whom preoperative transarterial

¹Mayo Clinic, Jacksonville, Florida.

Address for correspondence and reprint requests: Eric M. Walser, M.D., Professor of Radiology, Mayo Clinic, Davis Bldg 2N, 4500 San Pablo Road, Jacksonville, Florida 32224 (e-mail: Walser.eric@mayo.edu).

Embolization 2008; Guest Editor, Thomas R. Burdick, M.D.

Semin Intervent Radiol 2008;25:242–251. Copyright © 2008 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1 (212) 584-4662.

DOI 10.1055/s-0028-1085926. ISSN 0739-9529.

chemoembolization (TACE) might be considered (Fig. 1).

A far more common scenario is HCC on a background of cirrhosis, for which the current preferred treatment is orthotopic liver transplantation (OLT). Early results of OLT for HCC were disappointing but have improved considerably with more stringent patient selection criteria. Hepatocellular carcinoma was the indication for OLT in ~3% of transplant surgeries according to a United Network for Organ Sharing (UNOS) report in 2003, and it is becoming a more frequent indication as liver transplant centers multiply and selection criteria produce improved clinical outcomes.³ Currently, liver transplantation leads to a reasonable 70% 5-year survival rate and 15% recurrence rate in patients satisfying the Milan criteria (one lesion < 5 cm, or up to three lesions with none > 3 cm and no regional or distant metastases or vascular invasion).⁴⁻⁶ A recent expansion of the Milan criteria by the University of California, San Francisco (UCSF) group (one lesion < 6.5 cm or 2 to 3 lesions with none > 4.5 cm and total tumor diameter < 8 cm) yields similar results and expands the pool of HCC candidates eligible for OLT.⁷ While waiting for a suitable organ, transplant physicians will frequently refer patients for TACE with the intent of confining tumor to the liver, shrinking tumors, and thwarting progression to vascular invasion, or to reduce the chances of embolizing viable tumor systemically during hepatic manipulation at transplant hepatectomy⁸⁻¹⁰ (Fig. 2).

Contraindications for preoperative TACE are similar to TACE in general and are predominantly relative. Absolute contraindications are few and include active systemic infection or encephalopathy. Synthetic parameters warranting caution include a serum bilirubin > 3 mg/dL, significantly elevated liver enzymes, and

creatinine > 2mg/dL. Anatomic warning signs include tumor occupying the majority of a hepatic lobe, significant arteriovenous tumor shunting, and portal thrombosis or hepatofugal portal venous flow. When these factors are present, TACE is performed more carefully by reducing chemotherapy dosages and using super-selective embolization techniques to spare as much normal hepatic parenchyma as possible.

Techniques

Transarterial chemoembolization is a procedure typically performed with intravenous moderate sedation. Broad-spectrum antibiotics are administered before the procedure, especially in patients with bilioenteric anastomoses because they have a greater incidence of hepatic abscess postembolization.¹¹ The arterial anatomy of the liver is mapped after the superior mesenteric and celiac arteries are catheterized with a Cobra or other visceral selective 5F catheter. Replaced or accessory right and left hepatic arteries are noted, and venous phase imaging will enable evaluation of the portal vein. Selection of the inferior phrenic arteries is occasionally helpful for dome lesions, which may parasitize flow from these vessels. Chemoembolization involves some combination of three common chemotherapeutic agents (mitomycin C, doxorubicin, and cisplatin) and iodized oil. Metastatic lesions are sometimes treated with cancer-specific agents, such as 5-fluorouracil for colon cancer metastasis. On the other hand, neuroendocrine tumors are generally treated with bland particle embolization alone. A potentially new chemotherapeutic component of TACE for HCC is bevacizumab (Avastin, Genentech Inc., San Francisco, CA), which acts as an inhibitor of vascular endothelial growth factor (VEGF) and tumor angiogenesis.^{12,13}

Figure 1 A 60-year-old man with left lobe liver lesion discovered incidentally on (A) chest computed tomography performed to evaluate bronchiectasis. The patient was immediately referred to surgery. (B) Intraoperative ultrasound shows a single left-lobe lesion without vascular invasion (arrow shows left hepatic vein). Because no lesions were visible in the right lobe, only a left hepatectomy was performed.

Figure 2 Right lobe hepatocellular carcinoma (HCC) is shown in a patient awaiting orthotopic liver transplantation (OLT). (CT scan in A, hepatic arteriogram in B). Transarterial chemoembolization (C) was performed via the right hepatic artery with subsequent marked decrease in tumor diameter at follow-up computed tomography 3 months later (arrow in D).

Usually, a microcatheter is required to select the second-order arteries feeding the hepatic tumor while avoiding nontarget embolization in the vascular territories of the gastric arteries, gastroduodenal artery, phrenic arteries, and cystic artery. After injecting ~5 cc lidocaine in the tumor arterial bed, the oily chemoembolic mixture is injected under fluoroscopic guidance until arterial flow slows and contrast fills the tumor vessels, often refluxing slightly into portal venules around the index lesion. At this point, 150 to 500 μ m polyvinyl alcohol (PVA) particles or Embospheres mixed with contrast are used to conclude the embolization, adhering to the endpoint of sluggish forward flow rather than complete occlusion. Completely occluding the tumor blood flow may be detrimental because upregulated “shock” proteins may stimulate growth of residual tumor and because tumor response to TACE appears optimal when TACE is performed repeatedly via hepatic arteries with preserved patency.^{14,15}

Our practice, similar to others, involves reevaluating these patients with cross-sectional imaging at 8- to

12-week intervals, and repeating TACE as necessary before OLT.

Complications

Some degree of postembolization syndrome occurs after most TACE procedures, with nausea/vomiting, low-grade fevers, elevated liver enzymes, and upper abdominal pain constituting the bulk of patient complaints. Most patients respond to conservative measures, such as patient-controlled analgesia (PCA) administration, antiemetic therapy, and hydration, although high spiking fevers ($>100^{\circ}\text{F}$) warrant the institution of broad-spectrum antibiotics and imaging to rule out liver abscess formation, especially in patients with prior biliary surgery or anastomosis creation. Air bubbles within recently embolized tumors (<3 to 5 days) are a common finding and not representative of abscess in the absence of clinical findings or intra-tumoral fluid accumulation. In questionable cases, ultrasound or computed tomography (CT)-guided

aspiration and drainage are appropriate measures to institute (Fig. 3).

Other less-common complications include those of nontarget embolization such as gastric or duodenal ulceration or ischemic cholecystitis. Liver failure, encephalopathy, and/or hepatorenal syndrome can occur in patients who are marginal candidates for TACE. These complications should be discussed early with the patient and family to give them an appropriate assessment of the risk/benefit ratio.

Outcome

Although some investigators claim that repeated TACE before resection improves disease-free survival,¹⁶ others remain skeptical and report no differences in resected tumor size or in disease-free survival between embolized and nonembolized lesions.¹⁷ Because TACE seems to have little clinical impact in candidates for primary resection, when confronted with a noncirrhotic patient with truly confined disease, it seems prudent to forego neoadjuvant TACE and proceed directly to surgery with careful intraoperative ultrasound inspection of the liver remnant to exclude multilobar disease. Transarterial chemoembolization in the setting of HCC and hepa-

tectomy is perhaps better applied to patients with postoperative recurrences, estimated to occur in up to 50% of cases at 2 years¹⁸ and occurring after the hepatectomy option has expired.

Similarly, the validity of some assumptions regarding TACE before OLT remains questionable. Although some reports indicate a reduction of tumor recurrence rates after transplantation in patients treated with TACE preoperatively, other studies—notably two large studies from European investigators—refute this claim and assert that preoperative TACE has no bearing on survival or recurrence rates after OLT for liver cancer.^{19,20} In fact, a recent article involving a small series of transplant patients suggests that TACE and the resulting partial necrosis of liver tumors actually predisposes patients to higher recurrence rates after transplantation, presumably due to induced ischemic changes, which reduce the adhesion between tumor cells and allow easier systemic spread during surgery.²¹ This situation was also described by Adachi et al, who claimed that TACE-induced complete necrosis led to improved survival post-OLT, whereas patients with only partial necrosis suffered an increased recurrence rate.²² Indeed, recent studies investigating the mechanisms of chemoembolization effects found that TACE-induced ischemia upregulates several humoral factors (VEGF and hypoxia-inducible factor 1 [HIF-1]), which actually promote tumor growth and retard cell apoptosis.^{23,24} Given this controversy, TACE in the setting of OLT is best viewed as a treatment to halt tumor progression and macroscopic vascular invasion while awaiting transplant, especially if this wait is expected to be a long one. Given the available data, the select use of TACE before OLT seems prudent, with the primary focus aimed at downstaging patients who exceed Milan (or other) criteria. In fact, recent reports show the utility of locoregional therapy to drive HCC into Milan compliance, finding that these patients then enjoy the survival and recurrence rates of patients who meet such criteria from the beginning.²⁵

Figure 3 Computed tomography of abdomen in a patient 2 days after transarterial chemoembolization (TACE) for right lobe hepatocellular carcinoma shows multiple tiny air bubbles (arrows). The patient was asymptomatic, which can be a normal finding after TACE. In the presence of high fever or pain, these lesions can undergo image-guided sampling to rule out abscess formation.

PREOPERATIVE PORTAL VEIN EMBOLIZATION

Rationale and Indications

Portal vein embolization (PVE) is performed before partial hepatectomy to eliminate the devastating complication of postoperative liver failure in patients with reduced hepatic reserve or with large tumors that require extensive liver resection. Quite simply, PVE induces hypertrophy of the nonembolized hepatic segments, probably by ischemia and inflammation-induced production of hepatocyte growth factor (HGF), which, working in concert with other substances such as insulin, glucagon, and tumor growth factor (TGF), promotes liver regeneration.^{26,27} When the predicted residual

volume of liver parenchyma after resection falls below 20% of the total preoperative liver volume (excluding tumor volume), inadequate liver function will likely occur; these patients are candidates for PVE. Thus, cross-sectional imaging and liver volumetry are vital components of PVE planning, with the size of the future remnant liver (FRL), as described previously, determining the need for—or the adequacy of—PVE. Future remnant liver requirements increase in patients with compromised hepatic synthetic function; those with significant chemotherapy history need >30% FRL, whereas patients with chronic cirrhosis need even more (>40%) FRL.^{26–29}

Techniques

Successful PVE requires knowledge of the surgical resection plan, which, in turn, determines the hepatic

segments to be embolized 4 to 6 weeks before surgery. Additional procedural planning involves selection of ipsilateral versus contralateral transhepatic access routes and choice of embolic agents. Computed tomography or magnetic resonance imaging (MRI) scans with contrast are used to formulate the FRL by drawing regions of interest around the remnant liver segments and dividing this by the total estimated liver volume (TELV), which is calculated by the following formula:

$$\text{TELV} = -794.41 + (1267 \times \text{body surface area}[\text{BSA}])$$

This FRL, termed the “standardized FRL,” is considered a better method than the actual patient’s total liver volume because it presumes larger patients will need a larger FRL than smaller patients to survive major hepatic resection.³⁰ If the FRL is deemed inadequate, PVE is indicated (Fig. 4). Before the procedure, the transhepatic

Figure 4 (A) Enhancing liver mass (arrow) involves right lobe and medial left lobe. In preparation for extended right hepatectomy (right lobe + segment 4), portal vein embolization (PVE) was performed with an ipsilateral approach. Embolization of segments 4–8 was performed with Gelfoam slurry and coils, sparing the portal perfusion of segments 2 and 3 (lateral left lobe) (B). One month later, the lateral left lobe (i.e., future remnant liver [FRL]) has hypertrophied to 28% from 17.5% in preparation for PVE (C). Postoperative computed tomography shows FRL after extended right hepatectomy (D). Diagnosis was focal nodular hyperplasia.

access site is chosen and the surgical resection plan reviewed so that the appropriate hepatic segments are embolized to induce maximal FRL hypertrophy. Although ipsilateral lobar access (catheter through tumor-bearing liver) spares the FRL from possible complications of transhepatic punctures (rare), portal branch catheterization is more difficult, often requiring "hooked" catheters such as a Simmons catheter. Also, final portography and pressure measurements are not possible because access to the main portal vein is lost after embolization. Contralateral access (via the FRL) requires great care to avoid damage of the remnant liver but has the advantage of allowing easier catheterization of portal branches and also enables postembolization assessment of FRL portal flow and hemodynamics. Identification of a peripheral portal branch for puncture can be done with ultrasound or "blindly," by advancing a 20- to 22-gauge, 15-cm needle into the liver and injecting contrast while slowly withdrawing (similar to transhepatic cholangiography). When an adequate portal vein branch is accessed peripherally, a wire and then a 6F sheath is advanced into the main portal

vein, and portography is performed in at least two projections. If the patient has underlying cirrhosis, a portal pressure is obtained and compared with the central venous pressure. If the calculated portosystemic gradient is > 12 mm Hg, PVE and hepatectomy should be reconsidered carefully as these patients have an increased risk of posthepatectomy complications.³¹ Segment 4 portal branches should be embolized if an extended right or a total left hepatectomy is planned. These vessels extend anteriorly from the left portal vein (less commonly from the right) and may be small and difficult to catheterize. Segment 4 branches are usually embolized first because they originate near the portal bifurcation, and embolizing them last would require catheter exchanges and manipulation through freshly occluded peripheral portal branches, increasing the risks of dislodging material into the FRL. Occasionally, segment 4 branches are embolized last because they do not initially opacify during portography in a supine patient due to their anterior location. After occluding many of the right or left peripheral portal branches, however, the segment 4 veins will become

Figure 5 (A) Patient with large right lobe tumor undergoing ipsilateral right portal vein embolization (PVE). Small compressed right lobe segment 8 or segment 4 medial left lobe branches (arrow) are very close to left portal vein inflow to future remnant liver (FRL) (double arrows). (B) Gentle particulate embolization of these portal branches was done. Subsequently, the remaining right lobe portal supply was embolized and portal flow to left FRL preserved (C).

visible on portogram and can be selectively embolized. In this case, one must embolize carefully to avoid reflux into the FRL³² (Fig. 5).

A myriad of embolic materials are available for PVE. The technique used by Madoff's group at MD Anderson Cancer Center uses particulates (PVA or spherical particles) to occlude the peripheral portal branches and then large coils or other occluders to embolize the more central portal veins.²⁸ The newer spherical particles seem to induce better FRL hypertrophy than the traditional nonspherical particles (i.e., PVA).^{28,33} The Europeans tend to use n-butyl-2 cyanoacrylate (NBCA) due to its ability to occlude large and small portal branches with a single, quick application.^{27,34} Due to the cost of NBCA in the United States, it has not been widely accepted here for PVE. Other disadvantages of NBCA include its tendency to cause significant periportal inflammation and fibrosis (possibly adversely affecting subsequent surgery) and its relative difficulty of use, which increases the risk of accidental FRL embolization, especially for operators inexperienced in the use of liquid embolic agents or patients with reduced portal flow (cirrhosis).^{27,35} On the other hand, NBCA proponents suggest that PVE with glue leads to better FRL hypertrophy.^{34,36} Other PVE practitioners claim excellent results using absolute ethanol via custom balloon occlusion catheters,³⁷ fibrin glue and ethiodized oil,^{38,39} and gelatin sponge and sclerosants or coils.⁴⁰ Whatever the ingredients, a failed PVE will result if only the more central portal veins are occluded (coils only) or only the peripheral portal venules are occluded (particles only) because the occlusion will be short lived due to intrahepatic collateral formation or recanalization, respectively (Fig. 6). The proximal occlusions should be performed so as to

Figure 6 Two weeks after portal vein embolization (PVE) with particulates only (polyvinyl alcohol particles), this portal-enhanced computed tomography of patient's liver shows irregular enhancing channels in the thrombosed right portal veins (arrows) consistent with early recanalization. More proximal portal vein occlusive devices (such as coils) can thwart this event if used in conjunction with particulates.

leave 1 to 2 cm of portal vein at the bifurcation to facilitate clamp placement and ligation at surgery.⁴¹ We have found, as have others, that Amplatzer Vascular Plugs (AGA Medical Corp, Golden Valley, MN) enable adequate proximal occlusion after distal particulate embolization and can be done more quickly and accurately than multiple coils, because of its configuration and ability to be repositioned (Fig. 7).⁴² At the conclusion of the procedure, we place coils in the hepatic parenchymal sheath tract to avoid postprocedure peritoneal or subcapsular hepatic hemorrhage.

Figure 7 (A) Patient referred for right portal vein embolization due to right lobe liver metastasis from colon cancer. Intraoperative radiofrequency ablation was planned for the left lateral lobe lesion (arrow). (B) After particulate embolization of the right lobe branches from an ipsilateral approach, an Amplatzer occlusion device (arrow) was deployed more centrally, ~1 cm downstream from the right portal vein origin.

Japanese interventionalists tend to re-image the liver in 2 weeks with surgery closely following, whereas American groups tend to wait 4 to 6 weeks, believing that hypertrophy occurs throughout this period.

Complications

The complications of PVE are similar to those of any transhepatic procedure. In two series, the complication rate was 6 to 15% but only 1% of complications prompted cancellation of surgical resection. Pneumothoraces, ascites, subcapsular hemorrhages, hemobilia, hepatic artery pseudoaneurysms, and portal venous thrombosis made up the majority of listed complications.^{43,44} For this reason, many practitioners prefer the contralateral approach for PVE because it spares the FRL from these potential incidents. The use of liquid embolics (alcohol, NBCA) increases the risks of unintended portal branch or main portal vein occlusion, especially for those less familiar with these agents.

Outcome

Future remnant liver hypertrophy is maximal 4 weeks after PVE and ranges from 50 to 90% in otherwise normal patients.²⁷ Those with chronic liver disease or diabetes will experience a more protracted and reduced hepatocyte growth response, averaging 30 to 50% hypertrophy over 6 to 8 weeks.^{37,39}

Numerous studies confirm the reduced morbidity and mortality in patients receiving PVE before liver resection versus those patients who do not. The smoother postoperative course and shorter hospital stays benefit patients with cirrhosis or with normal hepatic function.^{29,45-47} More controversial is how tumor recurrence and survival rates differ after resection in PVE versus no-PVE patients. Although many believe that survival and disease-free survival is not affected by PVE,^{33,48} some claim that there exists an overall survival enhancement in PVE patients after surgery.⁴⁷

COMBINATION THERAPIES

Transarterial chemoembolization or hepatic arterial chemotherapy before PVE improves FRL hypertrophy and controls tumor growth before hepatic resection, with some reports of > 100% FRL hypertrophy in the setting of combined arterial and portal embolotherapy.^{27,49,50} There is some evidence of increased tumor growth in the FRL after PVE, which might be expected due to the influence of various hypertrophic factors on neoplastic cells, as well as the FRL hepatocytes.⁵¹ However, others dispute this claim.²⁸ Nevertheless, it seems prudent to treat any FRL tumors, usually with radiofrequency ablation (RFA), at the time of PVE

rather than later in the operating room because of these potential "growth spurts" of FRL lesions after PVE. The patency of the portal system should be confirmed after RFA in the FRL because PVE is contraindicated in the setting of compromised portal circulation in the FRL due to the heightened risk of global portal thrombosis.³²

REFERENCES

- Colombo M, de Franchis R, Del Ninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med* 1991;325(10):675-680
- Tsukuma H, Hiyama T, Tanaka S, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med* 1993;328(25):1797-1801
- Yoo HY, Patt CH, Geschwind JF, et al. The outcome of liver transplantation in patients with hepatocellular carcinoma in the United States between 1988 and 2001: 5-year survival has improved significantly with time. *J Clin Oncol* 2003; 21(23): 4329-4335 (Epub 2003 Oct 27)
- Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334: 693-699
- Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999;30: 1434-1440
- Bismuth H, Majno PE, Adam R. Liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 1999;19:311-322
- Yao FY, Xiao L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. *Am J Transplant* 2007;7(11):2587-2596
- Roayaie S, Frisher JS, Emre SH, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. *Ann Surg* 2002;235:533-539
- Harnois DM, Steers J, Andrews JC, et al. Preoperative hepatic artery chemoembolization followed by orthotopic liver transplantation for hepatocellular carcinoma. *Liver Transpl Surg* 1999;5:192-199
- Graziadei IW, Sandmueller H, Waldenberger P, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transpl* 2003;9:557-563
- Patel S, Tuite CM, Mondschein JI, et al. Effectiveness of an aggressive antibiotic regimen for chemoembolization in patients with previous biliary intervention. *J Vasc Interv Radiol* 2006;17(12):1931-1934
- Zhu AX, Blaszkowsky LS, Ryan DP, et al. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006;24(12):1898-1903
- Pang RW, Poon RT. From molecular biology to targeted therapies for hepatocellular carcinoma: the future is now. *Oncology* 2007;72(Suppl 1):30-44
- Jaeger HJ, Mehring UM, Castaneda F, et al. Sequential transarterial chemoembolization for unresectable advanced

- hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 1996; 19:388–396
15. Geschwind JF, Ramsey DE, van der Wal BC, et al. Transcatheter arterial chemoembolization of liver tumors: effects of embolization protocol on injectable volume of chemotherapy and subsequent arterial patency. *Cardiovasc Intervent Radiol* 2003;26:111–117
16. Zhang Z, Liu Q, He J, et al. The effect of preoperative transcatheter hepatic arterial chemoembolization on disease-free survival after hepatectomy for hepatocellular carcinoma. *Cancer* 2000;89:2606–2612
17. Paye F, Jagot P, Vilgrain V, et al. Preoperative chemoembolization of hepatocellular carcinoma: a comparative study. *Arch Surg* 1998;133:767–772
18. Muto Y, Moriwaki H, Ninomiya M, et al. Prevention of second primary tumors by an acyclic retinoid, polyphenolic acid, in patients with hepatocellular carcinoma. *N Engl J Med* 1996;334:1561–1567
19. Decaens T, Roudot-Thoraval F, Bresson-Hadni S, et al. Impact of pretransplantation transarterial chemoembolization on survival and recurrence after liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2005;11:767–775
20. Pérez Saborido B, Meneu JC, Moreno E, et al. Is transarterial chemoembolization necessary before liver transplantation for hepatocellular carcinoma? *Am J Surg* 2005; 190(3):383–387
21. Ravaioli M, Grazi GL, Ercolani G, et al. Partial necrosis on hepatocellular carcinoma nodules facilitates tumor recurrence after liver transplantation. *Transplantation* 2004;78: 1780–1786
22. Adachi E, Matsumata T, Nishizaki T, et al. Effects of preoperative trans-catheter hepatic arterial chemoembolization for hepatocellular carcinoma. The relationship between postoperative course and tumor necrosis. *Cancer* 1993;72: 3593–3598
23. Xiong ZP, Yang SR, Liang ZY, et al. Association between vascular endothelial growth factor and metastasis after transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2004;3:386–390
24. Kobayashi N, Ishii M, Ueno Y, et al. Co-expression of Bcl-2 protein and vascular endothelial growth factor in hepatocellular carcinomas treated by chemoembolization. *Liver* 1999; 19:25–31
25. Otto G, Herber S, Heise M, et al. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. *Liver Transpl* 2006;12:1260–1267
26. Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 1997;26:1176–1181
27. de Baere T, Roche A, Elias D, et al. Preoperative portal vein embolization for extension of hepatectomy indications. *Hepatology* 1996;24:1386–1391
28. Madoff DC, Abdalla EK, Vauthey JN. Portal vein embolization in preparation for major liver resection: Evolution of a new standard of care. *J Vasc Interv Radiol* 2005;16:779–790
29. Azoulay D, Castaing D, Krissat J, et al. Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. *Ann Surg* 2000;232:665–672
30. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 2000;127:512–519
31. Farges O, Malassagne B, Flejou JF, et al. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. *Ann Surg* 1999;229:210–215
32. de Baere T, Denys A, Madoff DC. Preoperative portal vein embolization: indications and technical considerations. *Tech Vasc Interv Radiol* 2007;10(1):67–78
33. Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg* 2003;237:208–217
34. de Baere T, Roche A, Vasseur D, et al. Portal vein embolization: utility for inducing left lobe hypertrophy before surgery. *Radiology* 1993;188:73–77
35. Imamura H, Shimada R, Kubota M, et al. Preoperative portal vein embolization: An audit of 84 patients. *Hepatology* 1999;29:1099–1105
36. Denys A. Portal vein embolisation. 2007 Annual Meeting of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE); Athens, Greece, September 8–12
37. Shimamura T, Nakajima Y, Une Y, et al. Efficacy and safety of preoperative percutaneous transhepatic portal embolization with absolute ethanol: a clinical study. *Surgery* 1997;121: 135–141
38. Nagino M, Nimura Y, Kamiya J, et al. Right or left trisegment portal vein embolization before hepatic trisegmentectomy for hilar bile duct carcinoma. *Surgery* 1995;117: 677–681
39. Nagino M, Nimura Y, Kamiya J, et al. Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. *Hepatology* 1995;21:434–439
40. Kaneko T, Nakao A, Takagi H. Experimental studies of new embolizing material for portal vein embolization. *Hepato-gastroenterology* 2000;47:790–794
41. Nagino M, Nimura Y, Kamiya J, et al. Selective percutaneous transhepatic embolization of the portal vein in preparation for extensive liver resection: the ipsilateral approach. *Radiology* 1996;200:559–563
42. Ringe KI, Weidemann J, Rosenthal H, et al. Transhepatic preoperative portal vein embolization using the Amplatzer Vascular Plug: report of four cases. *Cardiovasc Intervent Radiol* 2007;30(6):1245–1247
43. Di Stefano DR, de Baere T, Denys A, et al. Preoperative percutaneous portal vein embolization: evaluation of adverse events in 188 patients. *Radiology* 2005;234:625–630
44. Kodama Y, Shimizu T, Endo H, et al. Complications of percutaneous transhepatic portal vein embolization. *J Vasc Interv Radiol* 2002;13:1233–1237
45. Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg* 2003;7:325–330
46. Wakabayashi H, Yachida S, Maeba T, et al. Indications for portal vein embolization combined with major hepatic resection for advanced-stage hepatocellular carcinoma: a preliminary clinical study. *Dig Surg* 2000;17: 587–594

47. Tanaka H, Hirohashi K, Kubo S, et al. Preoperative portal vein embolization improves prognosis after right hepatectomy for hepatocellular carcinoma in patients with impaired hepatic function. *Br J Surg* 2000;87:879–882
48. Azoulay D, Castaing D, Smail A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. *Ann Surg* 2000;231:480–486
49. Ogata S, Belghiti J, Farges O, et al. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. *Br J Surg* 2006;93:1091–1098
50. Aoki T, Imamura H, Hasegawa K, et al. Sequential preoperative arterial and portal venous embolizations in patients with hepatocellular carcinoma. *Arch Surg* 2004;139:766–774
51. Elias D, De Baere T, Roche A, et al. During liver regeneration following right portal embolization, the growth rate of liver metastases is more rapid than that of the liver parenchyma. *Br J Surg* 1999;86:784–788