Strategies for Resection Using Portal Vein Embolization: Hepatocellular Carcinoma and Hilar Cholangiocarcinoma

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ABSTRACT

Preoperative portal vein embolization (PVE) is increasingly used to optimize the volume and function of the future liver remnant (FLR) and to reduce the risk for complications of major hepatectomy for hepatocellular carcinoma (HCC) or hilar cholangiocarcinoma (CCA). In patients with HCC who are candidates for extended hepatectomy and in patients with HCC and well-compensated cirrhosis who are being considered for major hepatectomy, FLR volumetry is routinely performed, and PVE is employed in selected cases to optimize the volume and function of the FLR prior to surgery. Similarly, in patients with hilar CCA who are candidates for extended hepatectomy, careful preoperative preparation using biliary drainage, FLR volumetry, and PVE optimizes the volume and function of the FLR prior to surgery. Appropriate use of PVE has led to improved postoperative outcomes after major hepatectomy for these diseases and oncological outcomes similar to those in patients who undergo resection without PVE. Specific indications for PVE are being clarified. FLR volumetry is necessary for proper selection of patients for PVE. Analysis of the degree of hypertrophy of the FLR after PVE (a dynamic test of liver regeneration) complements analysis of the pre-PVE FLR volume (a static test). Together, FLR degree of hypertrophy and FLR volume are the best predictors of outcome after major hepatectomy in an individual patient, regardless of the degree of underlying liver disease. This article synthesizes the literature on the approach to patients with HCC and CCA who are candidates for major hepatectomy. The rationale and indications for FLR volumetry and PVE and outcomes following PVE and major hepatectomy for HCC and CCA are discussed.

KEYWORDS: Portal vein embolization, liver volumetry, future liver remnant, hepatocellular carcinoma, hilar cholangiocarcinoma

Objectives: Upon completion of this article, the reader should understand the indications for preoperative portal vein embolization (PVE) before major hepatectomy in patients with hepatocellular carcinoma and hilar cholangiocarcinoma.

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Hepatocellular carcinoma (HCC) and hilar cholangiocarcinoma (CCA) are primary tumors involving the liver that are treated by major hepatectomy. The prognosis of patients with HCC who are not candidates for treatment is dismal—median survival time is ~6 to 9 months—and the prognosis of patients with untreated CCA is similarly poor.[1,2] Whereas HCC is a common cancer and a leading cause of death worldwide, CCA is relatively rare, although death rates from the disease nearly parallel incidence rates.[3,4] These two types of cancer are associated with different combinations of problems that significantly impact surgical management: HCC is commonly associated with hepatitis and cirrhosis, whereas CCA causes bile duct obstruction. Common to the majority of patients with HCC or CCA is the finding of advanced disease at presentation—even patients with liver-only disease at diagnosis tend to have significant hepatic involvement.

For patients with localized HCC or CCA, partial hepatectomy is the primary treatment modality. Chemotherapy is largely ineffective for treatment of primary liver cancer but for relatively exceptional cases[5–7] or for palliation. Chemoembolization is generally reserved for selected patients with unresectable HCC,[8,9] and radiotherapy is generally reserved for palliation or adjuvant treatment of CCA.[10] Liver transplantation can be an effective treatment for early HCC in patients with advanced liver disease because this approach completely removes the tumor and replaces the diseased liver with a normal liver, but liver transplantation has not been an effective approach for the majority of patients with HCC who present with more advanced disease, and it has not been useful for treatment of CCA.

Despite oncological differences among primary liver cancers, outcomes after major hepatic resection, regardless of cancer type, are linked to two critical factors: the volume and the function of the portion of the liver that will remain after resection, which is known as the future liver remnant (FLR). An inadequate FLR can be an unsalvageable problem (except by salvage liver transplantation, generally not appropriate in this setting). Patients with a marginal FLR develop cholestasis and impaired synthetic function and frequently suffer a cascade of complications (jaundice, fluid retention, pulmonary complications, and multiorgan dysfunction). Whereas marginal FLRs in patients with normal underlying liver may be associated with prolonged hospitalization, a prolonged intensive care unit stay, and multiple complications,[11,12] marginal FLRs in patients with diseased livers more often lead to progressive liver failure and death.[13] The critical link between FLR volume and posthepatectomy liver function is gradually being clarified.[11–16]

Portal vein embolization (PVE) is used to increase the volume and function of the FLR before resection. The use of PVE has enabled more patients with HCC and CCA to undergo major hepatectomy and has improved the safety of such procedure.[17] This article details modern approaches to assessment of the underlying liver and the predicted FLR volume and integration of preoperative PVE into the multidisciplinary individualized treatment plan for patients with HCC and CCA.

PVE: HISTORY, RATIONALE, AND INDICATIONS

Kinoshita et al initially used PVE to prevent portal extension of HCC, and they observed that the contralateral liver grew in response to ipsilateral PVE.[18] Makuuchi et al subsequently used PVE deliberately to induce FLR hypertrophy in preparation for extended hepatectomy for CCA.[19] Since that time, the critical link between FLR volume and hepatic function after major hepatectomy has been clarified. The increase in FLR volume following PVE correlates with increased function of the FLR with respect to increase in bile flow, shift in indocyanine green excretion,[20] increased uptake of technetium-labeled albumin,[21] and improved postoperative liver function tests.[12]

FLR volumes required for safe resection in patients with normal livers, mildly diseased livers, and severely diseased (cirrhotic) livers have been slowly refined.[22] Based on essential work in patients with CCA,[19,23–25] on our work, primarily in patients with normal underlying livers,[11,12,14,17,26,27] and on analysis of patients with HCC and cirrhosis,[28–30] PVE has come to be considered by some experts as the standard of care before major hepatectomy for patients with appropriate indications.[26] Whether PVE is indicated depends both on the degree of underlying liver disease and the extent of planned resection, determined not by what will be removed but by what will remain (FLR) after resection. In patients with normal underlying livers, complications are more common when the FLR is $\leq$20% of the standardized total liver volume.[11,15,27] In patients with well-compensated cirrhosis, complications and death increase when the FLR is $\leq$40% of the standardized total liver volume (TLV).[13,29] Thus the indications for PVE fall along a continuum from normal to severely abnormal underlying liver based on these FLR volume guidelines. In patients with normal underlying liver, PVE is indicated when the FLR is $\leq$20% of the standardized TLV.[11,27] In patients with intermediate liver disease, PVE is considered when the FLR is $\leq$30% of the TLV.[28] In patients with cirrhosis, PVE is considered when the FLR is $\leq$40% of the TLV (Fig. 1).[13,15,22,29]

Another potential benefit of preoperative PVE is that the sudden change in portal flow that results from removal of a large portion of the liver is temporally dissociated from the surgical manipulation of the small liver remnant. PVE leads to increased portal flow and pressure in the nonembolized liver, but these return to near pre-PVE values over a period of weeks. Thus the

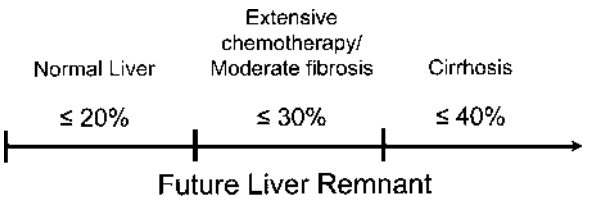

Figure 1 Indications for portal vein embolization (PVE) before major hepatectomy in terms of underlying liver disease and the volume of the expected future liver remnant (FLR) expressed as a percentage of the standardized total liver volume (TLV). In patients with normal liver, PVE is indicated when the FLR volume is $\leq 20\%$ of the standardized TLV. In patients with well-compensated cirrhosis, PVE is indicated when the FLR volume is $\leq 40\%$ of the standardized TLV. Although fewer data are available for patients with intermediate liver disease, there is consensus that those with significant fibrosis and those treated with aggressive preoperative chemotherapy should undergo PVE when the FLR volume is $\leq 30\%$ of the standardized TLV. (Adapted with permission from Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 2007;94:274–286. © British Journal of Surgery Society Ltd. Reproduced with permission. Permission is granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.)

patient's liver is not subjected to extensive portal flow changes at the same time as the surgical trauma, edema, and other changes associated with anesthesia and hepatectomy.[31–33]

In this way, PVE induces three presurgical preparatory effects—increased liver mass, shift in liver function to the FLR, and preoperative adjustment to portal pressure changes—that together help minimize the impact of major hepatectomy in patients with and without underlying liver disease.

PATTERNS OF LIVER HYPERTROPHY AFTER PVE

Animal and clinical studies have confirmed that both normal and some cirrhotic livers have the capacity to regenerate in response to portal flow diversion due to hepatic resection or portal occlusion. Cirrhotic livers regenerate at a slower rate and to a lesser extent than normal livers; other clinical factors, including diabetes and steatohepatitis, also negatively affect the rate and possibly degree of liver hypertrophy.[14,27] In a study that specifically evaluated the dynamics of liver regeneration in normal and injured livers, Yamanaka et al showed that in patients with cirrhosis, liver regeneration did occur, but at half the rate seen in patients with normal livers; further, plateau levels of regeneration were reached after 3 to 5 months versus 1 to 2 months in patients without underlying liver injury.[34] We recently confirmed that the plateau in regeneration in patients with normal liver occurs ~4 weeks after PVE.[27] Similarly, in a clinical study that evaluated the effect of PVE on normal and cirrhotic livers before right hepatectomy, Farges et al found that the median volume increase of the FLR was 16% in normal livers and 9% in cirrhotic livers. Further, they found that in 14% of cirrhotic livers, regeneration did not occur to a significant degree despite technically successful PVE.[29] The clinical significance of the degree or failure to hypertrophy is described later.

The pattern of liver regeneration after PVE has three major phases: an initial phase of rapid increase of liver volume during the first month, a second phase of slower regeneration during the second month, and a final phase of even slower regeneration extending up to 1 year.[34,35] In patients with normal liver, the plateau in regeneration occurs ~1 month after PVE, thus measurement of post-PVE volume before 4 weeks may underestimate the actual regeneration capacity.[27] In patients with cirrhosis and possibly in patients with diabetes, post-PVE volume may need to be assessed even later (e.g., 6 to 8 weeks after PVE) to provide a more accurate estimate of the true growth capacity, although specific kinetics data are not available in these populations.

The relationship between the magnitude of the stimulus for liver growth (PVE or resection) and the volume increase of the FLR has been well described. Yamakado et al evaluated the effect of extent of PVE in a group of 30 patients and demonstrated that the relative increases in FLR volume were 36.4% after right PVE, 15.2% after segmental PVE, and 2.4% after subsegmental PVE ($p = 0.002$).[36] Other groups have further stressed the importance of completely embolizing the liver to be resected to maximize the stimulus for FLR growth, minimize hypertrophy of segments that will be resected, and avoid the potential for tumor growth in nonembolized segments. Specifically, when extended right hepatectomy is indicated, the right liver plus segment IV should be embolized to optimize outcome.[37,38]

RELATIONSHIP BETWEEN RESULTS OF PVE AND CLINICAL OUTCOMES

PVE permits dynamic assessment of the FLR's capacity for hypertrophy. This may be particularly important in patients with underlying liver disease in whom the capacity for hypertrophy is difficult to predict (e.g., patients with prolonged biliary obstruction, those who have undergone chemotherapy, or those with compensated cirrhosis).

The degree of hypertrophy after PVE (measured as the percentage change in FLR volume) has been shown in two studies to predict outcome from subsequent hepatectomy.[27,29] Farges et al showed that cirrhotic patients with little or no hypertrophy after PVE suffered from liver insufficiency or death after resection,[29] confirming a finding suggested by prior work.[39] Recently, we found that the degree of hypertrophy $> 5\%$ of the TLV and achievement of the target FLR volume

($\geq$ 20% for patients with normal liver, for example) together provide the highest sensitivity and specificity in the prediction of outcome after hepatectomy.[27] Thus the combination of the static test (measurement of FLR volume after PVE) and the dynamic test (measurement of percentage change in FLR volume in response to PVE) together provide the most complete volumetric information available to predict outcome after a planned major hepatectomy.[27]

The method of volume measurement may also be important.[12,16] Three-dimensional computed tomography (CT) volumetry is a highly accurate method of measuring the FLR.[14] However, given the known association between body size (specifically, body weight or body surface area) and liver size, FLR is standardized to the patient's size to provide a better estimate of functional liver volume.[12,40,41] Many formulas have been calculated to describe the association between patient size and liver size, but a meta-analysis in 2005 found that the formula from Vauthey et al was "the most accurate, least biased formula."[42] Using this method the FLR is measured directly by CT volumetry (numerator), and the TLV (denominator) is estimated using a formula that relates liver volume to body surface area: standardized FLR volume (%) = FLR volume (from 3D CT) $\div$ estimated TLV (where estimated TLV = $-794.41 + 1{,}267.28 \times$ body surface area [m^2]). This method overcomes errors related to measurement of the diseased portion of the liver. CT measurement of the TLV may be a less useful index to standardize the FLR, especially in patients with primary liver cancer, because underlying liver disease may lead to an increase in liver volume due to tumor or biliary obstruction or a decrease in liver volume due to advanced cirrhosis or atrophy from long-term biliary obstruction or vascular compromise.

CLINICAL OUTCOMES AFTER PVE

PVE is a safe procedure with a technical success rate $>$ 90%.[29,43,44] We recently reported a $>$ 99% technical success rate for PVE (success in 111 of 112 consecutive patients).[27] Clinical success—that is, the resection rate after PVE—ranges from 60 to 100% and is generally reported to be ~70%.[26,27,39,45,46] The degree of hypertrophy after PVE ranges from 8 to 12% depending on the extent of PVE (right PVE only versus right PVE plus segment IV embolization) and degree of underlying liver disease (Table 1). Often, technical factors can be identified that explain poor regeneration (e.g., occult portal hypertension, decompression of diverted portal flow through unexpected collaterals, or incomplete PVE). However, when liver regeneration is inadequate and PVE was technically successful, subsequent resection is generally contraindicated.[27,29]

Complications of PVE are uncommon. Kodama et al[47] were the first specifically to evaluate complications in patients undergoing percutaneous PVE. They reported a 14.9% rate of complications, although the rate of complications requiring treatment—including pneumothorax, subcapsular hematoma, arterial puncture, pseudoaneurysm, hemobilia, and portal vein thrombosis—was only 8.5%. Importantly, the incidence of complications was similar for the ipsilateral and contralateral approaches, but most complications occurred in the punctured lobe. This important issue led Kodama et al and others to advocate ipsilateral PVE to protect the

Table 1 Selected Series of Patients with and without Underlying Liver Disease in Whom the Effect of PVE was Measured by CT Volumetry

Author (year)	Underlying Liver	PVE (n)	FLR pre (%)	FLR post (%)	Interval PVE to FLR Assessment (wk)	DH (%)
Portal vein embolization						
Vauthey (2000)[12]	Normal	12	26%	36%	4–6	10%
Azoulay (2000)[28]	Mild or moderate fibrosis	3	36%	52%	—	16%
	Cirrhosis	7				
Abdalla (2002)[11]	Normal	18	18%	25%	3–6	8%
Sugawara (2002)[54]	Cirrhosis	40	35%	48%	3	13%
Wakabayashi (2002)[39]	Normal	17	27%	36%	2	9%
	Hepatitis	25	33%	40%		7%
Farges (2003)[29]	Normal	13	31%	47%	4–8	16%
	Cirrhosis	14	35%	44%		9%
Ribero (2007)[27]	Normal, fibrosis, cirrhosis	120	—	—	4–8	9–11%
Transarterial chemoembolization followed by portal vein embolization						
Aoki (2004)[51]	ICGR15 $<$ 10%	8	40%	51%	2	11%
	ICGR15 $>$ 10%	9				
Ogata (2006)[50]	Cirrhosis (PVE)	18	29%	37%	4–8	8%
	Cirrhosis (TACE/PVE)	18	30%	42%		12%

PVE, portal vein embolization; CT, computed tomography; n, number of patients; FLR, future liver remnant; DH, degree of hypertrophy; —, not reported; ICGR15, indocyanine green retention at 15 minutes.

FLR from PVE-related complications.[38,47] Others have shown that the rate of major complications (e.g., portal vein thrombosis and liver insufficiency) after PVE may be increased in patients with cirrhosis, although in most instances even major complications were temporary and did not preclude resection.[27,28,43,48,49]

Serum transaminase levels have been reported to increase shortly after PVE and return to baseline values within the first week after the procedure. The peak transaminase level is higher in patients undergoing sequential transarterial chemoembolization (TACE) and PVE, although levels in such patients also return to baseline values prior to resection.[50,51] Similar trends are observed with white blood cell count; serum bilirubin rarely changes after PVE.[43,52]

OUTCOMES OF MAJOR HEPATECTOMY AFTER PVE

Complication and mortality rates following resection after PVE are consistently low (Table 2). In 2004, Takayama et al published their experience with 161 patients who underwent major hepatectomy after PVE in Japan. Their series included patients with different liver tumors, including a significant proportion with underlying liver disease. The complication and mortality rates of 19% and 1.2%, respectively, were remarkably low given the extent of resection, most likely because of the careful use of preoperative PVE.[44]

The role of PVE in patients undergoing extended hepatectomy (five or more segments) is well described. Hemming et al compared postoperative outcomes after extended hepatectomy in 31 patients who had PVE and 21 patients who did not have PVE.[49] Despite the fact that the groups were similar in terms of patient, tumor, and operative characteristics, rates of postoperative liver failure and length of hospital stay were higher in the no-PVE group. Similarly, Vauthey et al reported a 30% complication rate and a $<1\%$ mortality rate in 127 consecutive patients after extended hepatectomy[17] in which systematic use of volumetry led to use of PVE in 24% of patients. More recently, we updated our experience at the M. D. Anderson Cancer Center with 112 consecutive patients who underwent PVE. Complications occurred in 21% of patients, postoperative hepatic insufficiency occurred in 5.3% of patients, and the 90-day mortality rate was only 3% after major hepatectomy.[27]

PVE IN PATIENTS WITH HCC

Disease Staging and Patient Selection

In patients with HCC, after the general assessment of whether the patient is a candidate for major surgery (physical examination, cardiopulmonary and renal risk assessments, evaluation for stigmata of advanced liver disease), evaluation with multiphasic, thin-cut CT and/or magnetic resonance imaging (MRI) is done. CT is useful for analysis of the liver tumor(s), intrahepatic vascular anatomy, and extrahepatic sites (chest, peritoneum, lymph nodes, adrenal glands, and spleen). MRI is effective for staging the liver and evaluating intrahepatic vascular anatomy and may have particular utility for

Table 2 Selected Series of Patients Who Underwent PVE and Major Hepatectomy (resection of ≥ 4 segments) with Postoperative Outcomes and Mortality Rates

Author (year)	Cancer Type(s)	Underlying Liver	PVE (n)	Major Hepatectomy	Postoperative Complications*	Hepatic Insufficiency*	Mortality†
Imamura (1999)[55]	Mixed‡	Combined§	57	100%	1.8%	1.8%	1.8% (30 d)
Tanaka (2000)[45]	HCC	Cirrhosis	33	100%	—	—	3% (30 d)
Vauthey (2000)[12]	Mixed‡	Normal	12	100%	—	—	0% (30 d)
Azoulay (2000)[28]	HCC	Mild to moderate fibrosis	3	90%	45%	0%	0% (ND)
		Cirrhosis	7				
Wakabayashi (2001)[56]	HCC	Cirrhosis	26	100%	—	15.4%	12% (30 d)
Sugawara (2002)[54]	HCC	Chronic hepatitis	50	64%	19.7%	0%	0% (ND)
		Cirrhosis	16				
Abdalla (2002)[11]	Mixed‡	Normal	18	100%	38%	—	0% (90 d)
Hemming (2003)[49]	Mixed‡	Combined§	39	100%	—	10%	0% (30 d)
Farges (2003)[29]	Mixed‡	Combined§	27	100%	37%	4%	4% (in hospital)
Vauthey (2004)[17]	Mixed‡	Normal	31	100%	—	—	0% (30 d)
Takayama (2004)[44]	Mixed‡	Combined§	161	81%	19%	—	1.2% (ND)
Ribero (2007)[27]	Mixed‡	Combined§	78	100%	21%	5.3%	3% (90 d)

*Definitions of ''Complications'' and ''Hepatic insufficiency'' vary from study to study.
†Mortality was variably defined as 30 days, 90 days, in hospital, or not defined (ND).
‡Studies included HCC, hilar cholangiocarcinoma, and/or metastatic disease.
§Studies included patients with normal, fibrotic, and cirrhotic livers.
PVE, portal vein embolization; HCC, hepatocellular carcinoma; —, not reported.

problem solving in patients with small hypervascular lesions in the liver and for some patients with disease at extrahepatic sites (e.g., adrenal). However, MRI is less useful for determining the extent of disease in the peritoneum and has no role in determining whether disease has spread to the chest. Careful attention is given to exclude splenomegaly, varices (perisplenic or esophageal), and other radiographic signs of portal hypertension that would exclude patients from consideration for major hepatectomy.

Patients with HCC and normal underlying liver may be candidates for major hepatectomy. Patients with HCC and cirrhosis are generally assessed using the Child-Pugh-Turcotte scoring system;[53] only those with Child's classification A cirrhosis are considered for major hepatectomy. In addition to Child's classification A, a platelet count $>100{,}000$/mL is generally considered a requirement for safe major resection: A platelet count lower than this benchmark is considered a sign of occult portal hypertension.

When underlying liver disease necessitates further assessment, percutaneous biopsy can be considered to assess the degree of fibrosis, steatosis, inflammation, or other pathology of the liver that would affect surgical planning. In some cases, laparoscopy may be useful to visualize the gross appearance of the liver and guide targeted liver biopsy before other diagnostic or treatment decisions are made.

Following these analyses, and generally after multidisciplinary discussion, major hepatectomy may be considered. In all patients who will undergo extended right hepatectomy, volumetric measurement of the FLR should be considered.[22] Those who will undergo extended left hepatectomy rarely require PVE because of the consistently large volume ($\sim$30% of the TLV) of the right posterior sector.[40] In patients with significant underlying liver disease, especially those with well-compensated cirrhosis who will undergo right hepatectomy, FLR volumetry is recommended.[14,22] PVE is indicated based on the assessment of underlying liver disease and systematic FLR volumetry as described earlier. Some authors propose PVE for all patients with cirrhosis who will undergo right hepatectomy,[29] although the described selective approach based on volumetry is recommended.

An additional consideration in patients with HCC and cirrhosis is whether to employ TACE of the liver tumor followed by PVE of the liver to be resected. Recent studies have shown that this sequential strategy is associated with increased atrophy of the embolized liver and a greater degree of hypertrophy of the FLR than PVE alone.[50,51] Furthermore, TACE plus PVE may become the definitive treatment for patients initially considered to be candidates for resection whose disease becomes unresectable as therapy proceeds. This approach is discussed in detail in Imamura et al's article in this issue.

Reassessment after PVE and Outcomes following Resection

Reassessment with volumetry is critical after PVE in all cases (Fig. 2). Repeat imaging 4 weeks after PVE (for normal liver) to 8 weeks after PVE (in cirrhotic patients) permits not only volume measurement but also restaging of disease. Whether the target liver volume was achieved and the degree of hypertrophy allow risk assessment for liver insufficiency after resection, as discussed earlier.[27]

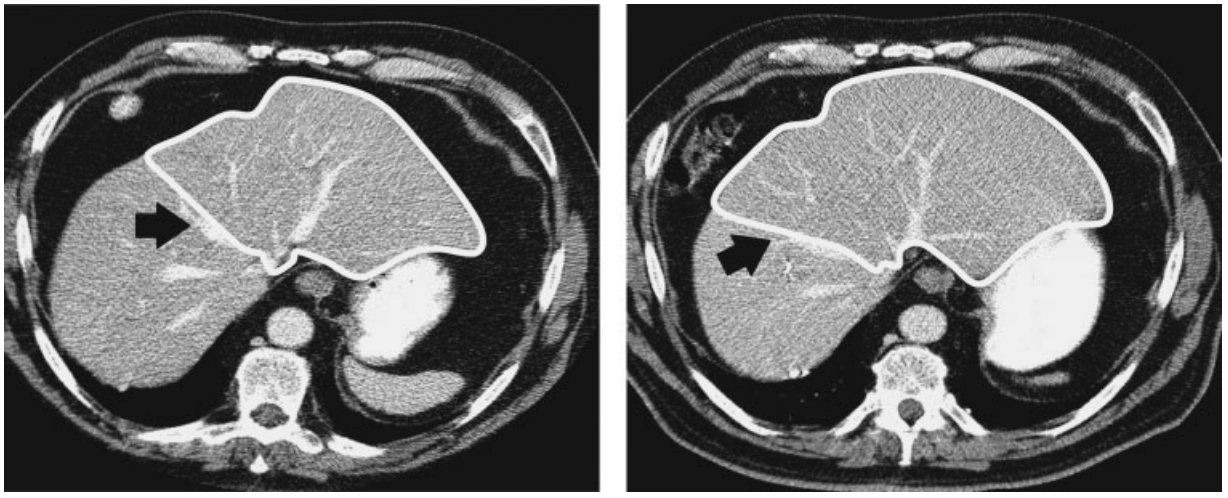

Figure 2 Hepatic venous phase of computed tomography in a patient with multifocal hepatocellular carcinoma involving the right liver before (left panel) and after (right panel) right portal vein embolization (PVE). The outlined left liver (with the main plane marked by the middle hepatic vein, arrow) increased from 36 to 46% of the standardized total liver volume as a result of PVE. Six days after an uneventful right hepatectomy, the patient was discharged from the hospital. The patient did not experience ascites, fluid retention, or cholestasis at any time during the postoperative course.

Failure to achieve the target volume or less than optimal hypertrophy indicate increased risk, which is then assessed in the context of the disease, comorbidity, and extent of planned surgery. The decision whether to proceed to hepatectomy is then made on the basis of the particular risk for the particular patient.

Long-term oncological outcomes in patients with HCC who undergo major hepatectomy are similar in patients who undergo preoperative PVE and those who do not. However, the postoperative course and operative mortality differ substantially for these two groups. These are the fundamental reasons why PVE is advocated before major hepatectomy for appropriately selected patients with HCC.

As indicated earlier, rates of hepatectomy after PVE in patients with HCC are reported to be ~70%;[12,27,28,39,45,46,49,54,55] series that report a very high rate of hepatectomy after PVE (> 90%) are either very small (< 15 patients) or include patients who underwent less extensive PVE (e.g., embolization of only the right anterior or right posterior sector).

Good outcomes following major hepatectomy after PVE in patients with HCC are consistently reported. Azoulay et al reported that 9 of 10 patients with fibrosis or cirrhosis and a predicted pre-PVE FLR < 40% underwent successful resection after PVE and none died despite major resection in all patients. All 9 patients who underwent resection were considered to have unresectable disease until PVE led to adequate volume increase. Compared with 19 patients with similar liver disease and HCC who underwent resection without PVE, patients who underwent resection with PVE had similar 5-year overall survival rates (44% PVE versus 53% no PVE), disease-free survival rates (21% PVE versus 17% no PVE), and complication rates (56% PVE versus 57% no PVE).[28] Importantly, overall and disease-free survival rates remain similar between the groups even after adjustment for HCC stage (overall, 40% PVE versus 46% no PVE; disease-free, 28% PVE versus 13% no PVE; both p = not significant).[56]

Some data suggest not only that PVE provides an outcome benefit in patients with cirrhosis but that the largest outcome benefit may occur in the subset of patients with worse liver function. In one study, multivariate analysis revealed that preoperative PVE was an independent predictor of survival following resection in patients with preoperative indocyanine green retention ≥ 13 (5-year overall survival rate, 52% PVE versus 20% no PVE; $p = 0.002$).[45]

Finally, TACE followed by PVE before hepatectomy may further improve long-term outcomes after major resection for HCC. Aoki et al reported on their experience with this strategy in 17 patients and found 5-year overall and disease-free survival rates of 56% and 47%, respectively.[51] In a similar retrospective study, Ogata et al found that TACE followed by PVE led to complete necrosis of the tumor in > 80% of patients, compared with 5% with PVE alone. They also found that TACE followed by PVE was associated with better 5-year disease-free survival rates than PVE alone (37% versus 19%; $p = 0.04$), primarily due to lower rates of early recurrence in the liver.[50]

The surgical approach may significantly affect outcome in patients with HCC undergoing major hepatectomy, especially in patients with right-sided tumors. A randomized study showed that for HCC ≥ 5 cm, resection using an anterior approach, which minimizes tumor manipulation, is associated not only with lower blood loss but also with longer overall survival.[57] We and others find this approach (with the "hanging maneuver") useful for most major hepatectomy cases.[58–61]

PVE IN PATIENTS WITH CCA

Staging and Preoperative Biliary Drainage

In patients with CCA, selection for major resection involves an initial surgical evaluation similar to that described earlier for HCC. However, for CCA, biliary anatomy rather than liver disease is the main focus of the evaluation. The staging workup is performed with multiphasic thin-cut CT or MRI. Cholangiography has traditionally been performed to assess the biliary extent of tumor and is done at the time of biliary drainage (see the next paragraph). However, cross-sectional imaging with CT or MRI has the advantage over cholangiography because the relation between the biliary tumor, the hepatic artery, and the portal vein can be assessed to predict resectability accurately.[62] Special attention is paid to determining the proximal extent of tumor within the intrahepatic biliary ducts and whether surrounding structures are involved by tangential tumor extension. Patients with distant metastatic disease (including hepatic parenchymal or peritoneal metastases and N2 disease—celiac, pancreaticoduodenal, retropancreatic, or para-aortic lymph node involvement) are not considered for resection. Further, cross-sectional imaging enables evaluation of liver atrophy or hypertrophy and can be used for liver volumetry, providing the information needed for all elements of surgical planning in a single study.

Hilar obstruction of the biliary tree with resulting hyperbilirubinemia is virtually always present at the time of initial evaluation for CCA. Liver resection in this setting is associated with increased postoperative complications due to both decreased liver function and impaired regeneration.[63–65] To avoid these problems, a systematic approach to drain the FLR preoperatively to achieve total bilirubin levels < 2 mg/dL is generally advised. Biliary drainage of the diseased liver is performed if the total bilirubin levels remain high or if there is evidence of cholangitis or sepsis originating from the

portion of the liver to be resected.[66] Preoperative biliary drainage is usually achieved through a percutaneous approach, which provides optimal and complete drainage of all obstructed sectors without the need to pass tight hilar strictures. Although endoscopic retrograde cholangiography can be considered, it is often difficult to stent tight strictures, and opacification of isolated sectors that cannot be fully drained can lead to cholangitis.[67]

In patients without normalization of the liver function tests after biliary drainage, extensive resection is not considered, and biliary drains are internalized. Metallic internal stents can be placed using either an endoscopic or a percutaneous approach, although bilateral metal stents can be placed more efficiently from a percutaneous approach when palliation is needed.

Anatomical Considerations

For patients with successful biliary decompression, the extent of resection is determined on the basis of preoperative imaging, and CT volumetry is performed. Inaccurate volume determination due to biliary dilatation in the FLR can be avoided by performing volumetry after biliary drainage.

Biliary anatomy defines the operation required to remove hilar cancers. Two key anatomical considerations require mention. First, 97% of all reported cases of variations of biliary anatomy include a long left hepatic duct (Fig. 3). Thus, for hilar tumors, whether type I, type II, or right sided (Bismuth-Corlette type IIIa), extended right hepatectomy allows resection in which the left duct is divided far enough away from the tumor to maximize the probability of a margin-negative resection. The right hepatic duct is consistently short; thus, when left hepatectomy is performed for type I or II tumors, the right duct must be cut close to the tumor. Left or extended left hepatectomy is indicated for left-sided tumors (type IIIb).

The second anatomical consideration that requires mention is that caudate anatomy is highly variable.[68] The dominant caudate bile duct generally drains to within 1 cm of the hilum, but of the described variations in caudate duct anatomy, most involve drainage to the hilum or right posterior bile duct. Thus caudate lobectomy is usually necessary to enable complete resection of involved bile ducts. En bloc resection of the extrahepatic bile duct with reconstruction with Roux-en-Y hepaticojejunostomy is performed.

Bile duct resection without hepatic resection is not considered appropriate for CCA: Because the tumor resides at the base of Couinaud segment IV, the liver must be resected with the bile duct to enable a good outcome. Portal lymphadenectomy is included as part of the procedure and functions probably as a staging rather than a therapeutic procedure.

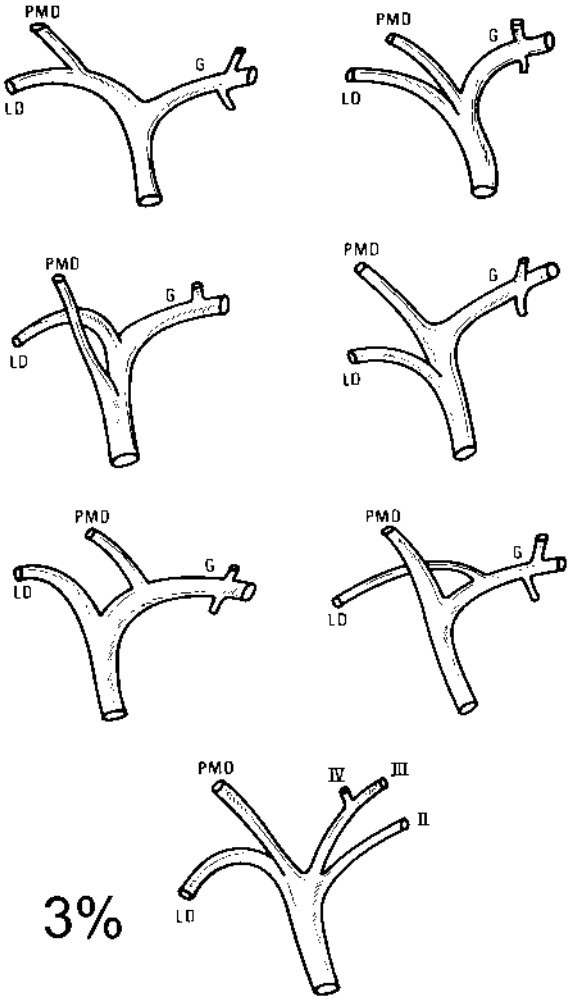

Figure 3 Described variations of biliary anatomy. A long left hepatic duct is present in 97% of all reported cases of variations in biliary anatomy. Thus, for cancer of the biliary confluence (hilar cholangiocarcinoma), whether it involves the right liver and confluence or the confluence only, extended right hepatectomy permits division of the left duct far enough away from the tumor to maximize the probability of a margin-negative resection. The right hepatic duct is consistently short; therefore, left or extended left hepatectomy is reserved for left-sided tumors. (Reprinted with permission from Couinaud C. Le Foie: Etudes Anatomiques et Chirurgicales. Paris: Masson; 1957:469–479.)

Volumetry and Surgical Strategy

Given the anatomical considerations outlined in the previous section, most patients with CCA who undergo resection undergo extensive hepatectomy. About 75% of patients with CCA without atrophy or hypertrophy are found to have a segment 2/3 volume $< 20\%$ of the standardized TLV,[40,69] and hence volumetry is a critical element of preoperative planning in most patients with CCA. In patients with an anticipated standardized FLR $\leq 20\%$ of the TLV, PVE is recommended (Fig. 1). Response to PVE is assessed with repeat CT volumetry 4 to 6 weeks after

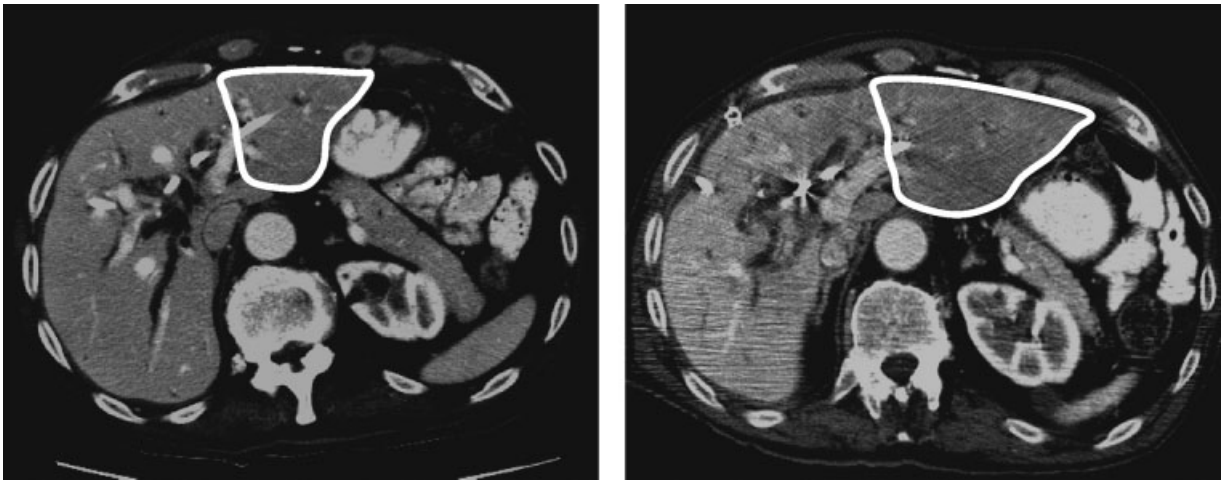

Figure 4 Portal phase of thin-cut computed tomograms in a patient with hilar cholangiocarcinoma before (left panel) and after (right panel) right trisectoral portal vein embolization (PVE) (embolization of segment IV and the right liver). Outlined is the future liver remnant, which increased in volume from 11 to 26% of the standardized total liver volume. Atrophy and arterialization of the right liver are apparent after PVE. Extended right hepatectomy with total caudate lobectomy was performed with negative margins and no postoperative hepatic dysfunction. The patient was discharged from the hospital on postoperative day 9.

embolization (Fig. 4). If regeneration is adequate, resection is planned.

Hepatectomy frequently begins with laparoscopy to exclude peritoneal and liver-surface metastases.[70] Exploratory laparotomy follows, and a more thorough evaluation of the extent of disease is performed including frozen section assessment of N2 lymph nodes when indicated. Intraoperative ultrasound is routinely used. Resection of portal vein due to involvement of the branch contralateral to the main tumor is generally considered based on operative findings of abutment/encasement of this branch from the tumor.[25,71] Some centers advocate systematic portal vein resection as a part of a "no touch" technique; however, their data suggest high mortality and do not indicate a sufficient prevalence of portal invasion to make routine portal vein resection a standard.[72,73]

Outcomes

Margin-negative resection is essential for the best survival in patients with CCA. Recent reports continue to stress that an operative approach including hepatectomy—rather than bile duct resection without hepatectomy—is more likely to result in negative margins.[73–77] A comparison of the 15-year experience at the Lahey Clinic with the experience at Nagoya University in Japan[74] is illustrative of the impact of margin status. Although the Nagoya patients had overall higher disease stage, the rate of R0 resection (microscopic, margin-negative resection) in patients who underwent exploratory surgery was higher in the Nagoya patients (79% versus only 28% at the Lahey Clinic). The Nagoya patients had 5-year and 10-year overall survival rates of 16% and 12%, respectively, versus 7% and 0%, respectively, for the Lahey Clinic patients. These higher margin-negative resections and survival rates in Japan appear to be directly related to resection technique: 89% of the Nagoya patients underwent hepatic resection with en bloc resection of the tumor and caudate lobe, versus only 8% of the Lahey Clinic patients; 39 portal vein resections and 18 pancreaticoduodenectomies were performed in Nagoya. The more extensive surgery performed in Japan was not associated with a significant increase in operative mortality.

Extrahepatic procedures and preoperative biliary obstruction increase the morbidity of major hepatic resection in patients with CCA, which further emphasizes the importance of preoperative preparation before resection of this disease. A shift in practice to include systematic biliary drainage and PVE decreases blood loss, transfusion requirements, intensive care unit stay, hospital stay, and postoperative mortality[78] despite a simultaneous shift to more extensive resections. The shift in practice resulted in a higher resectability rate (45% after the shift versus 16% before; $p < 0.001$), unchanged rates of perioperative complications and mortality, and better oncological outcomes—the 5-year overall survival rate was significantly higher for patients treated with the new strategy (41% versus 8%; $p < 0.001$).[78] Similar approaches have led to similar results from other groups.[71,75,79,80]

The largest published series of hepatic resection for CCA come from Nimura's group in Nagoya, Japan. They are strong advocates for PVE and extended hepatectomy for CCA, and their results are noteworthy. Following PVE in 240 patients with biliary cancer that required extended hepatectomy (150 CCAs, 90 gallbladder carcinomas), the overall resection rate was 80% (88% for CCA), the overall operative mortality rate was

only 8.8% (4.5% for CCA), and the 5-year overall survival rate was 27% for CCA. These results—in patients with more advanced CCA who required PVE (100%) and underwent extrahepatic bile duct resection (97%), pancreaticoduodenectomy (22%), or portal vein resection (33%)—compare favorably with results in patients at their own institution who underwent < 50% hepatectomy (operative mortality rate, 3.7%; 5-year overall survival rate, 28%).[75]

CONCLUSIONS

PVE is a safe, effective method for increasing the volume and function of the FLR prior to major hepatectomy. Indications for PVE are being clarified, and they are based on a systematic approach including FLR volumetry. In patients with normal underlying liver, PVE is indicated when the FLR volume is $\leq$ 20% of the standardized TLV. Indications for PVE in patients with liver disease fall on a continuum; for patients with treatment-related liver injury or moderate fibrosis, PVE is indicated when the FLR volume is $\leq$ 30% of the TLV, and for patients with well-compensated cirrhosis, PVE is indicated when the FLR volume is $\leq$ 40% of the TLV.

PVE functions not only to increase the volume and function of the FLR but also to dissociate the impact of portal flow diversion from the impact of surgical stress to the small liver remnant. Both normal and diseased livers can grow in response to PVE, and the degree of hypertrophy appears to be an important predictor of outcome after hepatectomy performed after PVE. Patients who do not have at least a 5% increase in FLR volume after PVE are more likely to develop hepatic insufficiency or liver failure after resection. Patients whose FLR volumes increase to the target volume and experience a degree of hypertrophy > 5% appear to have the lowest risk for posthepatectomy complications. Tumor growth after PVE is not seen when the entire tumor-bearing liver is embolized, and oncological outcomes after hepatectomy are similar in patients who undergo preoperative PVE and those who do not. Further, a proportion of patients who would otherwise be considered to have unresectable disease experience long-term survival following resection with PVE.

Patients with HCC and normal underlying liver who will require extended hepatectomy should undergo volumetry and be considered for PVE if the FLR volume is $\leq$ 20% of the standardized TLV. Patients with HCC and well-compensated cirrhosis, normal liver function, platelet count > 100,000/mL, and no evidence of splenomegaly or varices can be considered for major hepatectomy (such as right hepatectomy). In these patients, volumetry with PVE is recommended if the FLR is $\leq$ 40% of the standardized TLV. For many patients with HCC, TACE followed by PVE is recommended. For patients who will undergo right hepatectomy, resection using the anterior approach with hanging maneuver is advocated.

Patients with CCA generally require biliary drainage of the FLR before extensive hepatectomy can be considered. FLR volumetry is recommended, with PVE as indicated earlier. Adequate liver growth (degree of hypertrophy > 5%) and achievement of the target liver volume allow for extended hepatectomy, bile duct resection, and caudate resection when indicated, with low morbidity and excellent oncological outcomes.

The integrated approach to the treatment of HCC and CCA is by nature multidisciplinary. After a patient is deemed to be a candidate for major resection, the oncological extent of disease is carefully assessed, and the quality, volume, and function of the liver that will remain after surgery are determined. The combination of the static test (volume) and dynamic test (degree of hypertrophy) allows the surgeon to understand the capacity of the individual patient's liver to grow. This information, liver growth in response to PVE, may be the best way to predict outcome because data suggest that patients do well when the liver grows adequately after major resection. This dynamic test overcomes variability in degrees of underlying liver disease. Understanding the evolution of liver volume in response to PVE marks a major advance in patient selection for major hepatectomy and has enabled a small but growing proportion of patients with HCC and CCA to undergo potentially curative therapy.

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REFERENCES

1. Barbara L, Benzi G, Gaiani S, et al. Natural history of small untreated hepatocellular carcinoma in cirrhosis: a multivariate analysis of prognostic factors of tumor growth rate and patient survival. Hepatology 1992;16(1):132–137
2. Ribero D, Abdalla EK, Thomas MB, Vauthey JN. Liver resection in the treatment of hepatocellular carcinoma. Expert Rev Anticancer Ther 2006;6(4):567–579
3. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340(10): 745–750
4. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57(1): 43–66
5. Lau WY, Ho SK, Yu SC, Lai EC, Liew CT, Leung TW. Salvage surgery following downstaging of unresectable hepatocellular carcinoma. Ann Surg 2004;240(2):299–305

6. Charoentum C, Thongprasert S, Chewaskulyong B, Munprakan S. Experience with gemcitabine and cisplatin in the therapy of inoperable and metastatic cholangiocarcinoma. World J Gastroenterol 2007;13(20):2852–2854
7. Lee J, Kim TY, Lee MA, et al. Phase II trial of gemcitabine combined with cisplatin in patients with inoperable biliary tract carcinomas. Cancer Chemother Pharmacol 2008;61(1): 47–52
8. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359(9319):1734–1739
9. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35(5): 1164–1171
10. Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11(4):941–954
11. Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002;137(6):675–680; discussion 680–671
12. 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(5):512–519
13. Shirabe K, Shimada M, Gion T, et al. Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. J Am Coll Surg 1999;188(3):304–309
14. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. Br J Surg 2001;88(2):165–175
15. 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(5):1176–1181
16. Ribero D, Chun YS, Vauthey J-N. Standardized liver volumetry for portal vein embolization. Semin Intervent Radiol 2008;25:104–109
17. Vauthey JN, Pawlik TM, Abdalla EK, et al. Is extended hepatectomy for hepatobiliary malignancy justified? Ann Surg 2004;239(5):722–730; discussion 730–722
18. Kinoshita H, Sakai K, Hirohashi K, Igawa S, Yamasaki O, Kubo S. Preoperative portal vein embolization for hepatocellular carcinoma. World J Surg 1986;10(5):803–808
19. Makuuchi M, Thai BL, Takayasu K, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 1990;107(5):521–527
20. Uesaka K, Nimura Y, Nagino M. Changes in hepatic lobar function after right portal vein embolization: an appraisal by biliary indocyanine green excretion. Ann Surg 1996;223(1): 77–83
21. Hirai I, Kimura W, Fuse A, Suto K, Urayama M. Evaluation of preoperative portal embolization for safe hepatectomy, with special reference to assessment of nonembolized lobe function with 99mTc-GSA SPECT scintigraphy. Surgery 2003;133(5):495–506
22. Madoff DC, Hicks ME, Vauthey JN, et al. Transhepatic portal vein embolization: anatomy, indications, and technical considerations. Radiographics 2002;22(5):1063–1076
23. 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(2):434–439
24. Nagino M, Kanai M, Morioka A, et al. Portal and arterial embolization before extensive liver resection in patients with markedly poor functional reserve. J Vasc Interv Radiol 2000; 11(8):1063–1068
25. Ebata T, Nagino M, Kamiya J, Uesaka K, Nagasaka T, Nimura Y. Hepatectomy with portal vein resection for hilar cholangiocarcinoma: audit of 52 consecutive cases. Ann Surg 2003;238(5):720–727
26. Madoff DC, Abdalla EK, Vauthey JN. Portal vein embolization in preparation for major hepatic resection: evolution of a new standard of care. J Vasc Interv Radiol 2005;16(6):779–790
27. Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg 2007;94(11):1386–1394
28. 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(5):665–672
29. Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 2003;237(2):208–217
30. Denys A, Lacombe C, Schneider F, et al. Portal vein embolization with N-butyl cyanoacrylate before partial hepatectomy in patients with hepatocellular carcinoma and underlying cirrhosis or advanced fibrosis. J Vasc Interv Radiol 2005;16(12):1667–1674
31. Goto Y, Nagino M, Nimura Y. Doppler estimation of portal blood flow after percutaneous transhepatic portal vein embolization. Ann Surg 1998;228(2):209–213
32. Shimada R, Imamura H, Nakayama A, Miyagawa S, Kawasaki S. Changes in blood flow and function of the liver after right portal vein embolization. Arch Surg 2002;137(12): 1384–1388
33. Makuuchi M, Kosuge T, Lygidakis NJ. New possibilities for major liver surgery in patients with Klatskin tumors or primary hepatocellular carcinoma: an old problem revisited. Hepatogastroenterology 1991;38(4):329–336
34. Yamanaka N, Okamoto E, Kawamura E, et al. Dynamics of normal and injured human liver regeneration after hepatectomy as assessed on the basis of computed tomography and liver function. Hepatology 1993;18(1):79–85
35. Nagino M, Ando M, Kamiya J, Uesaka K, Sano T, Nimura Y. Liver regeneration after major hepatectomy for biliary cancer. Br J Surg 2001;88(8):1084–1091
36. Yamakado K, Takeda K, Matsumura K, et al. Regeneration of the un-embolized liver parenchyma following portal vein embolization. J Hepatol 1997;27(5):871–880
37. Nagino M, Kamiya J, Kanai M, et al. Right trisegment portal vein embolization for biliary tract carcinoma: technique and clinical utility. Surgery 2000;127(2):155–160
38. Madoff DC, Abdalla EK, Gupta S, et al. Transhepatic ipsilateral right portal vein embolization extended to segment IV: improving hypertrophy and resection outcomes with spherical particles and coils. J Vasc Interv Radiol 2005;16(2): 215–225

39. Wakabayashi H, Ishimura K, Okano K, et al. Application of preoperative portal vein embolization before major hepatic resection in patients with normal or abnormal liver parenchyma. Surgery 2002;131(1):26–33
40. Abdalla EK, Denys A, Chevalier P, Nemr RA, Vauthey JN. Total and segmental liver volume variations: implications for liver surgery. Surgery 2004;135(4):404–410
41. Urata K, Kawasaki S, Matsunami H, et al. Calculation of child and adult standard liver volume for liver transplantation. Hepatology 1995;21(5):1317–1321
42. Johnson TN, Tucker GT, Tanner MS, Rostami-Hodjegan A. Changes in liver volume from birth to adulthood: a meta-analysis. Liver Transpl 2005;11(12):1481–1493
43. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138(11):1198–1206; discussion 1206
44. Takayama T, Makuuchi M. Preoperative portal vein embolization: is it useful? J Hepatobiliary Pancreat Surg 2004;11(1):17–20
45. Tanaka H, Hirohashi K, Kubo S, Shuto T, Higaki I, Kinoshita H. Preoperative portal vein embolization improves prognosis after right hepatectomy for hepatocellular carcinoma in patients with impaired hepatic function. Br J Surg 2000;87(7):879–882
46. Lee KC, Kinoshita H, Hirohashi K, Kubo S, Iwasa R. Extension of surgical indications for hepatocellular carcinoma by portal vein embolization. World J Surg 1993;17(1):109–115
47. Kodama Y, Shimizu T, Endo H, Miyamoto N, Miyasaka K. Complications of percutaneous transhepatic portal vein embolization. J Vasc Interv Radiol 2002;13(12):1233–1237
48. 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(2):625–630
49. Hemming AW, Reed AI, Howard RJ, et al. Preoperative portal vein embolization for extended hepatectomy. Ann Surg 2003;237(5):686–691; discussion 691–683
50. Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. Br J Surg 2006;93(9):1091–1098
51. Aoki T, Imamura H, Hasegawa K, et al. Sequential preoperative arterial and portal venous embolizations in patients with hepatocellular carcinoma. Arch Surg 2004;139(7):766–774
52. Makuuchi M. Remodeling the surgical approach to hepatocellular carcinoma. Hepatogastroenterology 2002;49(43):36–40
53. Christensen E. Prognostic models including the Child-Pugh, MELD and Mayo risk scores: where are we and where should we go? J Hepatol 2004;41(2):344–350
54. Sugawara Y, Yamamoto J, Higashi H, et al. Preoperative portal embolization in patients with hepatocellular carcinoma. World J Surg 2002;26(1):105–110
55. Imamura H, Shimada R, Kubota M, et al. Preoperative portal vein embolization: an audit of 84 patients. Hepatology 1999;29(4):1099–1105
56. Wakabayashi H, Ishimura K, Okano K, et al. Is preoperative portal vein embolization effective in improving prognosis after major hepatic resection in patients with advanced-stage hepatocellular carcinoma? Cancer 2001;92(9):2384–2390
57. Liu CL, Fan ST, Cheung ST, Lo CM, Ng IO, Wong J. Anterior approach versus conventional approach right hepatic resection for large hepatocellular carcinoma: a prospective randomized controlled study. Ann Surg 2006;244(2):194–203
58. Ogata S, Belghiti J, Varma D, et al. Two hundred liver hanging maneuvers for major hepatectomy: a single-center experience. Ann Surg 2007;245(1):31–35
59. Donadon M, Abdalla EK, Vauthey JN. Liver hanging maneuver for large or recurrent right upper quadrant tumors. J Am Coll Surg 2007;204(2):329–333
60. Belghiti J, Guevara OA, Noun R, Saldinger PF, Kianmanesh R. Liver hanging maneuver: a safe approach to right hepatectomy without liver mobilization. J Am Coll Surg 2001;193(1):109–111
61. Kim SH, Park SJ, Lee SA, et al. Various liver resections using hanging maneuver by three glisson's pedicles and three hepatic veins. Ann Surg 2007;245(2):201–205
62. Aloia TA, Charnsangavej C, Faria S, et al. High-resolution computed tomography accurately predicts resectability in hilar cholangiocarcinoma. Am J Surg 2007;193(6):702–706
63. Kawasaki S, Makuuchi M, Miyagawa S, Kakazu T. Radical operation after portal embolization for tumor of hilar bile duct. J Am Coll Surg 1994;178(5):480–486
64. Kanai M, Nimura Y, Kamiya J, et al. Preoperative intrahepatic segmental cholangitis in patients with advanced carcinoma involving the hepatic hilus. Surgery 1996;119(5):498–504
65. Miyagawa S, Makuuchi M, Kawasaki S. Outcome of extended right hepatectomy after biliary drainage in hilar bile duct cancer. Arch Surg 1995;130(7):759–763
66. Ishizawa T, Hasegawa K, Sano K, Imamura H, Kokudo N, Makuuchi M. Selective versus total biliary drainage for obstructive jaundice caused by a hepatobiliary malignancy. Am J Surg 2007;193(2):149–154
67. Chang WH, Kortan P, Haber GB. Outcome in patients with bifurcation tumors who undergo unilateral versus bilateral hepatic duct drainage. Gastrointest Endosc 1998;47(5):354–362
68. Abdalla EK, Vauthey JN, Couinaud C. The caudate lobe of the liver: implications of embryology and anatomy for surgery. Surg Oncol Clin N Am 2002;11(4):835–848
69. Leelaudomlipi S, Sugawara Y, Kaneko J, Matsui Y, Ohkubo T, Makuuchi M. Volumetric analysis of liver segments in 155 living donors. Liver Transpl 2002;8(7):612–614
70. Jarnagin WR, Conlon K, Bodniewicz J, et al. A clinical scoring system predicts the yield of diagnostic laparoscopy in patients with potentially resectable hepatic colorectal metastases. Cancer 2001;91(6):1121–1128
71. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. Ann Surg 2006;243(3):364–372
72. Neuhaus P, Jonas S, Bechstein WO, et al. Extended resections for hilar cholangiocarcinoma. Ann Surg 1999;230(6):808–818; discussion 819
73. Neuhaus P, Jonas S, Settmacher U, et al. Surgical management of proximal bile duct cancer: extended right lobe resection increases resectability and radicality. Langenbecks Arch Surg 2003;388(3):194–200

74. Tsao JI, Nimura Y, Kamiya J, et al. Management of hilar cholangiocarcinoma: comparison of an American and a Japanese experience. Ann Surg 2000;232(2):166–174
75. Nimura Y, Kamiya J, Kondo S, et al. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. J Hepatobiliary Pancreat Surg 2000; 7(2):155–162
76. Saldinger PF, Blumgart LH. Resection of hilar cholangiocarcinoma: a European and United States experience. J Hepatobiliary Pancreat Surg 2000;7(2):111–114
77. Tabata M, Kawarada Y, Yokoi H, Higashiguchi T, Isaji S. Surgical treatment for hilar cholangiocarcinoma. J Hepatobiliary Pancreat Surg 2000;7(2):148–154
78. Liu CL, Fan ST, Lo CM, Tso WK, Lam CM, Wong J. Improved operative and survival outcomes of surgical treatment for hilar cholangiocarcinoma. Br J Surg 2006;93(12):1488–1494
79. Seyama Y, Kubota K, Sano K, et al. Long-term outcome of extended hemihepatectomy for hilar bile duct cancer with no mortality and high survival rate. Ann Surg 2003;238(1):73–83
80. Kawasaki S, Imamura H, Kobayashi A, Noike T, Miwa S, Miyagawa S. Results of surgical resection for patients with hilar bile duct cancer: application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. Ann Surg 2003;238(1):84–92