Extended Hepatectomy in Patients With Hepatobiliary Malignancies With and Without Preoperative Portal Vein Embolization

Eddie K. Abdalla, MD; Carlton C. Barnett, MD; Dorota Doherty, PhD; Steven A. Curley, MD; Jean-Nicolas Vauthey, MD

Hypothesis: Preoperative portal vein embolization (PVE) allows potentially curative hepatic resection without additional morbidity or mortality in patients with hepatobiliary malignancies who are marginal candidates for resection based on small liver remnant size.

Design: A retrospective review of a consecutive series of patients in a multi-institutional database who underwent extended hepatectomy.

Setting: University-based referral centers.

Patients: Forty-two patients underwent preoperative determination of the future liver remnant (FLR) volume before extended hepatectomy (≥5 segments) for hepatobiliary malignancy without chronic underlying liver disease. Patients were stratified by treatment with or without preoperative PVE.

Intervention: Preoperative percutaneous PVE.

Main Outcome Measures: Clinical characteristics, FLR volume, operative morbidity, and survival.

Results: There was no difference between the groups that did and did not undergo PVE for the number of tumors, tumor size, estimated blood loss, duration of the operation, complexity of resection, or surgical margins. The FLR at presentation was significantly smaller in patients who underwent PVE than in patients who did not undergo PVE (18% vs 23%; P<.001). After PVE, FLR volumes increased significantly (P=.003); preoperative FLR volumes were similar in both groups (patients who underwent PVE, 25%; and patients who did not undergo PVE, 23%). There was no perioperative mortality and no statistical difference in the incidence of perioperative complications between those who did and those who did not undergo PVE (5 [28%] of 18 patients vs 5 [21%] of 24 patients). The overall 3-year survival was 65% and the median survival duration was equivalent in the 2 groups (40 vs 52 months for those who did vs those who did not undergo PVE).

Conclusion: Portal vein embolization enables safe and potentially curative extended hepatectomy in a subset of patients who would otherwise be marginal candidates for resection based on a small liver remnant size.

Arch Surg. 2002;137:675-681
underlying liver was demonstrated. In the same study, the
subset of patients in whom the standardized FLR volume
was 25% or less of the TLV had a longer hospital stay and
more frequent complications compared with the patients
with an FLR volume greater than 25% of the TLV.

The present study was designed to compare pa-
tients with a normal underlying liver who underwent
extended hepatic resection (≥5 segments) with or without
PVE. The FLR volume was measured preoperatively
in all patients to aid in the selection for PVE. Clinical char-
acteristics, FLR volume, morbidity, and survival were ex-
amined.

RESULTS

Forty-two patients who underwent extended heptec-
tomy for hepatobiliary malignancies were studied. The
overall patient characteristics are summarized in Table 1.
Table 2. Among 42 patients studied, 18 (43%) underwent PVE before surgery based on the criteria de-
scribed in the “Patients and Methods” section. Patients
underwent PVE were more likely to be men and to have

40 years. All of the patients underwent extended right
hepatectomy. Thirteen patients (31%) also underwent
complex procedures with associated resection of the com-
mon bile duct (n=7), caudate lobe (n=3), portal vein and
common bile duct (n=1), inferior vena cava (n=1), and
inferior vena cava and caudate lobe (n=1). Most pa-
tients in this series had negative margins of resection, and
10 had major postoperative complications that included
hepatic insufficiency (bilirubin level >12 mg/dL [>205.2 µmol/L]) (n=3), ascites or fluid retention
(n=2), biliary fistula or peripancreatic fluid collection (n=3), partial mesenteric portal venous thrombosis (n=1), and
enteric fistula (n=1). Of 12 patients with a standardized
FLR of 20% or less, 6 (50%) sustained complications; only
4 (13%) of 30 patients with a standardized FLR greater
than 20% had complications (P=.02) (Figure 1).

Patient, tumor, standardized FLR, operative, and post-
operative variables stratified by PVE treatment are pre-

PATIENTS AND METHODS

An original patient series comprising 55 consecutive pa-
tients who underwent extended hepatectomy between Oc-
tober 1, 1993, and March 30, 2001, was reviewed. Two sur-
geons (S.A.C. and J.-N.V.) performed all of the resections
at The University of Texas MD Anderson Cancer Center,
Houston, or the University of Florida, Gainesville. Thir-
ten patients were excluded because of the absence of mea-
surement data, inclusion in a previously published PVE pro-
tocol,14 or chronic underlying liver disease. The group of patients retained for analysis included 18 who underwent
preoperative PVE and 24 who did not undergo PVE. Over-
all survival duration in patients who did and did not un-
dergo PVE were compared and examined in the context of
existing survival data for each tumor type treated.

Portal vein embolization was performed at the discre-
tion of the operating surgeon when volumetric measure-
ment revealed that the FLR volume would be 23% or less
of the estimated TLV; the 25% cut point was determined in
a previous study.12 Portal vein embolization was system-
atically performed in patients with cholangiocar-
cinoma and nearly all patients who required associated pro-
cedures. Two patients with an FLR volume greater than 25% (27% and 29%) underwent PVE as well, because of esti-
mation of an associated increased perioperative risk based
on greater complexity of the procedure.16

The standardized FLR was calculated as a ratio using
the following equation: standardized FLR=FLR volume/
TLV (reported previously15). The FLR volume was mea-
sured directly using computed tomography, while the TLV
was calculated from the patient’s body surface area using a
mathematical formula recently described.17 The 3-dimen-
sional method of reconstruction based on computed to-
mography is accurate because the error associated with
computed tomographic volumetric measurement is ap-
proximately 5%,18-20 and this translates into a 1% error in
percentage FLR because the FLR is divided by the
calculated TLV (eg, measured FLR=300 mL±15 mL [5%]
in a patient with TLV equal to 1500 mL yields a standard-
ized FLR of 19%-21%)

Percutaneous transhepatic PVE was performed using
an ipsilateral approach. The details of this technique were
recently reported.12 Briefly, percutaneous access to the
ipsilateral portal vein was gained under light, monitored
anesthesia and fluoroscopic control. Following portogra-
phy, selected portal vein segments were embolized using
polyvinyl alcohol and microcoils. Attention was paid to com-
plete occlusion of the entire tumor-bearing liver, includ-
ing segment 4 branches, to maximize hypertrophy of the
FLR and prevent PVE-induced accelerated tumor growth
during the interval before surgery.22

All patients underwent extended right hepatectomy with
or without caudate lobe resection (resection of Couinaud seg-
ments 4 to 8 ±1).23 The general principles of the technique
of extended resection have been published previously.9,10 All
of the operations were performed under low central venous
pressure conditions. Inflow and outflow control were usu-
ally obtained before parenchymal transection was per-
formed. Complete vascular exclusion with venovenous by-
pass was used in 1 patient who underwent en bloc vena cava
resection. Perioperative complications and perioperative mor-
tality were defined as events occurring during the same hos-
pital stay or within 3 months following resection.

The preoperative clinical characteristics of the pa-
tients who did and did not undergo PVE were compared
using the Mann-Whitney test for continuous variables and
the Fisher exact or the χ² test for categorical data. For pa-
tients who underwent PVE, a comparison of the FLR be-
fore and after PVE was performed using the Wilcoxon signed
rank test. The overall survival probability was estimated us-
ing the Kaplan-Meier method.24 The overall survival du-
ration was compared using the log-rank test. Exact infer-
ence was used in all of the statistical tests because of the
small sample size. All statistical analyses were performed
using statistical software programs (S-Plus25 and StatXact26).
Statistical significance was determined at P<.05.
COMMENT

Among factors that impact outcome after hepatic resection, the extent of resection contributes significantly to operative morbidity 27 and mortality. 31 In our study, all 42 patients underwent hepatic volumetric measurement before extended right hepatectomy. Portal vein embolization was performed in 18 patients with a median estimated standardized FLR of 18% at presentation. This systematic measurement was performed to avoid leaving an inadequate liver remnant after resection and was based on the reported variability in hepatic volumetric distribution 20 and operative standardized FLR for this group compared with the group that did not undergo PVE. There was no difference in the occurrence of major postoperative complications or length of hospital stay between groups.

The median survival duration in the entire cohort of patients was 52 months (Figure 4). The median follow-up time was 11 months (range, 3-85 months). The survival after resection was 82% at 12 months (95% confidence interval, 74.0%-99.8%), 71% at 24 months (95% confidence interval, 54.6%-92.5%), and 65% at 36 months (95% confidence interval, 46.8%-89.3%). The median survival duration in patients who did not undergo PVE (52 months) was not significantly different from that in patients who did undergo PVE (40 months) (P = .70).
Patients who are considered for PVE are most often those who present with multiple metastases and left lateral bisegmental sparing or patients with hilar cholangiocarcinoma without the atrophy/hyper trophy complex. Portal vein embolization enables the possibility of extended resections for patients who would have otherwise been marginal candidates for resection or would have undergone less extensive procedures with greater potential for compromised margins of resection. The overall margin-positive resection rate in this series (17%), and that in patients who underwent preoperative PVE (11%), compares favorably with the recently reported margin-positive rate in patients who underwent extended hepatectomy for multiple hepatic colorectal metastases (25%) or resection for hilar cholangiocarcinoma (17%).

It is increasingly evident that the volume of residual liver rather than the volume of liver resected may more accurately predict the risk of complications after extended hepatic resection. The present study confirms the association between a small liver volume and an increase in complications after an extended hepatic resection that leaves a small liver remnant. Specifically, while all patients underwent similar extended resections (of Couinaud segments 4 to 8 ±1), 6 of the 12 patients with a standardized FLR of 20% or less had major complications while only 4 of the 30 patients with a standardized FLR greater than 20% FLR will be shown to have a (low)

Figure 2. Standardized future liver remnant (% FLR) volume in patients who did and did not undergo portal vein embolization (PVE). There was a significant increase in the % FLR after PVE compared with before PVE ($P= .003$). Data are given as medians. The lower and upper end of bars indicate first and third quartiles, respectively; lower and upper brackets, minimum and maximum, respectively.

Figure 3. Survival duration in 42 patients who underwent extended hepatectomy (with or without portal vein embolization before resection).

Figure 4. Survival duration in patients who underwent extended hepatectomy, stratified by portal vein embolization (PVE) before surgery. The difference between the 2 groups is not significant ($P= .70$).
complication rate similar to patients presenting with greater than 20% FLR up front. Small numbers preclude a definite answer.

Portal vein embolization is used to minimize the risk of nontechnical complications and death associated with a small FLR. The absence of perioperative mortality within 3 months of surgery in this series compares favorably with previous studies reporting the results of extended resections. However, a randomized trial designed to test the efficacy of PVE cannot yet be recommended, for the decision to perform PVE must be individualized and prospective data must be collected to clarify the subsets of patients who can benefit most from the procedure. Systematic measurement of the FLR allows the surgeon to integrate the predicted FLR size with other procedure-related risks (such as the complexity of the procedure and associated underlying liver disease) to determine the need for PVE on an individual patient basis.

Several patients with a small FLR who underwent resection in this series likely would not have been considered to be candidates for extended resection without PVE. Such patients who do not undergo resection have an expected survival duration of 11 to 12 months—the median survival duration of unresected patients with colorectal cancer liver metastases is about 12 months, while that of unresected patients with cholangiocarcinoma is about 11 months. The overall 3-year survival rate in the present study (65%) compares favorably with reported 3-year survival rates for resection of metastatic colorectal carcinoma (30%-58%) and the rate after resection of hilar cholangiocarcinoma (60%). Finally, our results are validated by 2 reports that provide survival data with longer follow-up for patients with colorectal metastases who were considered to be unresectable without PVE, but who underwent successful resection following PVE. A subgroup of 27 patients described by Elias et al achieved an overall 5-year survival of 29%. Similarly, Azoulay et al reported a 40% 5-year actuarial survival for resection following PVE compared with a 38% 5-year survival for a similar extent of resection without PVE.

Thus, the selective use of PVE enables safe and potentially curative extended hepatectomy in a subset of patients with advanced hepatobiliary malignancies who would have otherwise been marginal candidates for resection.

This paper was presented at the 109th Scientific Session of the Western Surgical Association, San Antonio, Tex, November 13, 2001.

Corresponding author and reprints: Jean-Nicolas Vauthey, MD, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Box 444, Houston, TX 77030 (e-mail: jvauchy@mdanderson.org).

REFERENCES
The determination of the minimum size of the remnant liver after liver resection to prevent hepatic failure is a difficult number to be certain, but I think it is generally accepted to be in the 20% to 30% range. Since most surgeons are reluctant to leave less than approximately 25% of normal nondonated liver parenchyma in place following liver resection, this factor alone can often determine whether a patient undergoes attempted liver resection. This becomes even more critical for patients with hepatitis, hepatic steatosis, or fibrosis, where a larger volume cutoff of functioning remnant liver must be left in place depending on the patient’s individual circumstances.

In this report, Dr Vauthey’s group demonstrates that this technique can be performed safely and in a timely manner 3 to 6 weeks prior to planned liver resection. In the group of patients undergoing portal vein embolization, the volume of future remnant liver increased from 18% to 25% on average and, as we heard, no patient was excluded from treatment because of suspected insufficient hepatic synthetic functional reserve. As we have heard, this technique performed 3 to 6 weeks prior to planned liver resection induces atrophy in the intended site of resection, with compensatory hypertrophy in the remnant liver that will remain following resection. Their reported clinical results are excellent, with no mortality amongst 42 patients undergoing major resection, all extended right hepatic lobectomy with and without major vascular resections. Now this is an area of major clinical significance, since hepatic insufficiency in the period following liver resection is associated with a high rate of complications and increased mortality. Despite ongoing trials of liver-assist devices, there are currently no proven means to support patients during periods of significant hepatic insufficiency.

How did you factor in the response to portal vein embolization for your planned procedure? While the mean remnant volume rose to 25%, there were still patients who did not have an increase to that level. In fact, some had quite low remnant liver volumes but underwent resection in any event. From this point of view, did the patients need to show some evidence of hypertrophy before you performed the resection? Would waiting a longer period of time or considering repeat embolization have helped in this group?

Finally, while the authors have demonstrated that this technique can be performed safely and will on average increase the liver volume, I am not sure that this study proves that this technique actually makes a difference clinically. The primary measure of success was that there was a significant difference in the percentage of major complications following resection in these patients with remnant volumes less than 25% compared to those with remnant volumes greater than 25%.

In looking at the specific complications reported, 3 out of the 10 were biliary fistulas and/or intra-abdominal abscesses. One out of 10 was mesenteric vein thrombosis, 1 out of 10 an enteric fistula, 2 out of 10 ascites or fluid retention, and only 3 or 30% representing cholestasis or hyperbilirubinemia. I guess I am a little uncertain as to how the remnant liver volume would affect the development of fistulas, bile leak, and mesenteric vein thrombosis.

What may have been helpful would have been more specific assessment of measures of hepatic insufficiency, like comparisons of coagulation profiles, development of encephalopathy, and the presence of hyperbilirubinemia, to be convinced that the remnant liver volume itself was a major determinant in outcome after major liver resection.

Richard Ramos Lopez, Jr, MD, Los Angeles, Calif: The liver transplant community and particularly those centers that perform living donor liver transplants have provided us with a lot of information about the consequences of major hepatic resections in patients with limited liver volume. It is becoming clearer that one of the consequences is excessive inflow and limited outflow in these small remnants. Thus, I want to ask the authors if they used any pharmacologic treatment in the patients following liver major resection? Specifically, I am referring to the use of nitroglycerin to diminish right heart and central venous pressures and the use of somatostatin in an effort to diminish portal inflow.

Dr Barnett, I spent a good number of years in the laboratory studying hepatotrophic factors in the portal blood and it is exciting and rewarding to see clinical applications coming from that work.

One of the effects in experimental animals of augmenting portal venous flow is an increase in hepatocyte size rather than the induction of hyperplasia, as one sees in regeneration. Thus, I wonder whether, as one might expect, the same effect was seen in the “future liver remnant,” namely, an increase in hepatocyte size, or in fact whether regeneration was “jump-started” by the portal embolization.

This leads to my second question. Was there an influence on the rate of regeneration after resection? In other words, was remnant size at 3 or 6 months postoperatively affected? Did portal embolization affect either the extent or rate of subsequent remnant regeneration?

Philip D. Schneider, MD, Sacramento, Calif: About 2½ years ago, we started doing combined preoperative hepatic artery embolization and portal vein occlusion for patients with early cirrhosis in the Pugh 5 to 6 range of Child’s A. The best way to view this procedure is that it potentially improves liver...
functional reserve in a population that largely has impaired liver function. Most of these patients with hepatocellular carcinoma, in fact, have cirrhosis.

The questions I have are: (1) Have the authors done any routine liver function studies, like ICG [indocyanine green] retention or some similar functional analysis for their patients? (2) Have you added hepatic artery embolization for any of your patients whose remnant volumes did not increase with portal vein occlusion, and, finally, as a follow-up to the authors’ data and as noted in a recent paper in Cancer, if survival is not being improved in this patient population with this procedure, other than the fact that we are making surgery available, why are we doing this if they are not living longer?

Michael B. Farnell, MD, Rochester, Minn: Dr Chapman alluded to the 3- to 6-week interval between embolization and operation in his discussion, and I wonder if the authors could comment regarding the optimal time interval to achieve maximum volumetric enlargement of the future liver remnant?

A second question regarding timing is with regard to postembolization inflammatory reaction around the embolized portion of liver. Did the authors note the development of perihepatic inflammation and adherence to the diaphragm resulting in any technical challenges for them?

Thomas Biehl, MD, Seattle, Wash: Could you mention something about the technical aspects of doing the portal venous embolization and whether or not any patients had complications of the procedure? Specifically, did you injure any of the contralateral lobe (or what you wanted to leave behind) vessels and then make a patient nonoperable based on that?

Also, it is very difficult to tell how many of these patients really needed the procedure. I am not really sure how to get a handle on that. You gave the example of one patient who had a hilar cholangiocarcinoma. I have noticed with that disease, frequently you get atrophy of the lobe that you plan to resect and the lobe you are going to leave behind is already hypertrophic, so the disease itself has done to some degree what you are planning on doing with the portal vein embolization.

Dr Vauthey: Regarding the determinant of treatment for PVE, as asked by Dr Chapman, there were several patients who had less than 25% liver remnant volume who indeed did not get portal vein embolization. These were patients that were operated on at the onset of this retrospective study. They were younger, they had colorectal metastases, and had excellent performance status. Indeed, there were 12 patients with less than 25% liver volume. Notably, 7 had a volume of less than 20%, and 4 out of these 7 had complications.

Regarding the factors affecting response to portal vein embolization: As you noticed, 18 patients got portal vein embolization and, while 2 of 3 increased their remnant volume above 20%, 1 of 3 did not increase and remained in the group with a volume of less than 20%. What are the factors affecting the response to portal vein embolization? I think the numbers are too small. Other series have mentioned diabetes as a reason for lack of regeneration. Again, no patient in this series had underlying liver disease, which impacts regeneration rates.

We have not waited longer than 6 weeks in most patients; however, with the addition of chemotherapy in some of these patients, we are keen on waiting longer and remeasuring volume before embarking on an extended resection, given the results that we have presented here.

The difference that this makes clinically is that many patients present to us as unresectable and we can resect these patients in spite of a very small volume. Some have suggested a randomized study for portal vein embolization. It is too early to propose such a study and to deny the benefit of portal vein embolization to patients with a small remnant liver volume. The response to portal vein embolization corresponds not only to an increase in volume but also to an increase in function, and this has been demonstrated experimentally and also clinically by Makuch’s group in Japan.

Dr Chapman mentioned that only 3 patients had liver failure or cholestasis. I think we should look at the complications as a whole in these patients. We are not looking only at reducing the incidence of transient liver failure or cholestasis, but we are looking at reducing other complications with this procedure. Certainly, we have been pleased not to see the cascade of multiple complications occur in patients who had significant technical complications. These patients did not go into multiple organ failure or liver failure, and we had no deaths in the series.

Dr Lopez asked about nitroglycerin and other agents to reduce the portal pressure. Perioperatively, we have used nitroglycerin. We have no experience with somatostatin.

Are there histological changes in the lobes that undergo atrophy? We have seen mild histological changes. As a rule, most of the changes that occur after portal vein embolization are mild changes because hepatocytes in the lobe that atrophy undergo apoptosis.

Dr Putnam asked about the histology of the changes in the lobe that hypertrophies. There is true DNA synthesis and clonal expansion of the hepatocytes.

Dr Schneider asked about functional analysis of the remnant volume. We have not done this, although we rely on our IRB [Institutional Review Board]–approved preliminary study that we published 3 years ago, in which we showed an improvement in the liver function tests postoperatively in patients who have undergone portal vein embolization. Should we add hepatic artery embolization to our procedure? There is little evidence that additional hypertrophy is affected by arterial occlusion as the 3 main factors contributing to maintenance of liver volume are patent portal and hepatic veins and free biliary flow.

Dr Farnell asked about the difficulty encountered during surgery in these patients. The mobilization of the right lobe is usually easier because of the reduction in size of the right lobe as a result of the atrophy. The hilar resection might be slightly more difficult, but there is no significant development of collaterals.

Dr Biehl asked about the technique of portal vein embolization. We used a percutaneous, transhepatic, ipsilateral approach. In our series of 40 patients who have undergone portal vein embolization, 30 patients had resection and we have encountered 2 complications that did not preclude subsequent surgery. This is consistent with the reported complication rate for portal vein embolization in the literature, about 5% to 7%.