

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

EXTENDED HEPATECTOMY (resection of ≥ 5 hepatic segments) is increasingly used to achieve margin-negative resection of hepatobiliary malignancies. Prolonged survival has been reported after complete hepatic resection of colorectal metastases,^{1,2} hilar cholangiocarcinoma,^{3,4} and hepatocellular carcinoma.⁵⁻⁷ Although the surgical mortality rate has been minimized as a result of improved patient selection and safer technique, complications associated with postoperative hepatic insufficiency, such as cholestasis, bleeding, fluid retention, and impaired hepatic synthetic function, still contribute to an extended hospital stay and protracted recovery.⁸⁻¹¹ In the process of preoperative selection for extended hepatectomy, a subset of patients may be ex-

cluded from consideration for potentially curative resection because of limitations associated with an anticipated small liver remnant.

In 1990, Makuuchi et al¹² proposed the use of portal vein embolization (PVE) to induce preoperative hypertrophy of the future liver remnant (FLR) in an attempt to increase the safety of major hepatectomy for hilar bile duct carcinoma. Since then, this procedure has been used before major hepatic resection (defined as resection of a hepatic lobe or more) in selected patients when the remaining liver was 40% or less of the total liver volume (TLV) and deemed to be compromised by hepatitis, cirrhosis, or chemotherapy.^{13,14} In a preliminary investigation,¹⁵ the safety and efficacy of PVE before extended hepatectomy in patients without a compromised

From the Departments of Surgical Oncology (Drs Abdalla, Barnett, Curley, and Vauthey) and Biostatistics (Dr Doherty), The University of Texas MD Anderson Cancer Center, Houston.

PATIENTS AND METHODS

An original patient series comprising 55 consecutive patients who underwent extended hepatectomy between October 1, 1993, and March 30, 2001, was reviewed. Two surgeons (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. Thirteen patients were excluded because of the absence of measurement data, inclusion in a previously published PVE protocol,¹⁵ 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. Overall survival duration in patients who did and did not undergo PVE were compared and examined in the context of existing survival data for each tumor type treated.

Portal vein embolization was performed at the discretion of the operating surgeon when volumetric measurement revealed that the FLR volume would be 25% or less of the estimated TLV; the 25% cut point was determined in a previous study.¹⁵ Portal vein embolization was systematically performed in patients with cholangiocarcinoma and nearly all patients who required associated procedures. Two patients with an FLR volume greater than 25% (27% and 29%) underwent PVE as well, because of estimation 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 measured 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-dimensional method of reconstruction based on computed tomography is accurate because the error associated with computed tomographic volumetric measurement is approximately 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 \pm 15 mL [5%] in a patient with TLV equal to 1500 mL yields a standardized FLR of 19%-21%).

Percutaneous transhepatic PVE was performed using an ipsilateral approach. The details of this technique were recently reported.^{15,21} Briefly, percutaneous access to the ipsilateral portal vein was gained under light, monitored anesthesia and fluoroscopic control. Following portography, selected portal vein segments were embolized using polyvinyl alcohol and microcoils. Attention was paid to complete occlusion of the entire tumor-bearing liver, including 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 segments 4 to 8 \pm 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 usually obtained before parenchymal transection was performed. Complete vascular exclusion with venovenous bypass was used in 1 patient who underwent en bloc vena cava resection. Perioperative complications and perioperative mortality were defined as events occurring during the same hospital stay or within 3 months following resection.

The preoperative clinical characteristics of the patients who did and did not undergo PVE were compared using the Mann-Whitney test for continuous variables and the Fisher exact or the χ^2 test for categorical data. For patients who underwent PVE, a comparison of the FLR before and after PVE was performed using the Wilcoxon signed rank test. The overall survival probability was estimated using the Kaplan-Meier method.²⁴ The overall survival duration was compared using the log-rank test. Exact inference 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 $P < .05$.

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 patients 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 characteristics, FLR volume, morbidity, and survival were examined.

RESULTS

Forty-two patients who underwent extended hepatectomy for hepatobiliary malignancies were studied. The overall patient characteristics are summarized in **Table 1**. Twenty-three patients presented with metastatic colorectal cancer, 8 with cholangiocarcinoma, 5 with hepatocellular cancer, and the remaining 6 with other diagnoses. The median age of the patients at resection was

60 years. All of the patients underwent extended right hepatectomy. Thirteen patients (31%) also underwent complex procedures with associated resection of the common 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 patients 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 $\mu\text{mol/L}$]) ($n = 3$), ascites or fluid retention ($n = 2$), biliary fistula or perihepatic 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 postoperative variables stratified by PVE treatment are presented in **Table 2**. Among 42 patients studied, 18 (43%) underwent PVE before surgery based on the criteria described in the "Patients and Methods" section. Patients treated with PVE were more likely to be men and to have

Table 1. Summary of Characteristics for the 42 Patients Studied*

Characteristic	Value
Sex	
Female	22 (52)
Male	20 (48)
Age, y†	60 (33-79)
Diagnosis	
Metastatic colorectal cancer	23 (55)
Cholangiocarcinoma	8 (19)
Hepatocellular carcinoma	5 (12)
Other	6 (14)
No. of tumors†	2 (1-20)
Size of the largest tumor, mm†	60 (7-190)
Underwent preoperative PVE	18 (43)
Duration of the operation, min†	385 (164-645)
Blood loss, mL†	675 (200-2500)
Transfusion, U†	0 (0-8)
Complex resection	
No	29 (69)
Yes	13 (31)
Margin of clearance	
Negative	35 (83)
Positive	7 (17)
Major complications	
No	32 (76)
Yes	10 (24)
Length of hospital stay, d†	8 (5-52)

*Data are given as number (percentage) of patients unless otherwise indicated. There were no perioperative deaths. PVE indicates portal vein embolization.

†Data are given as median (range).

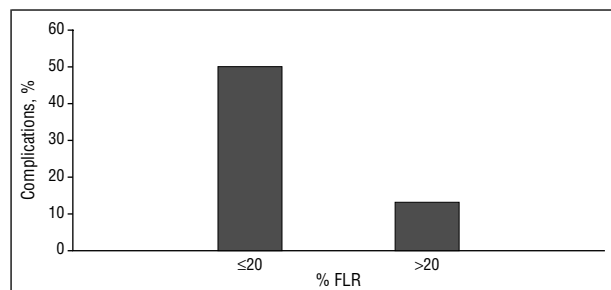


Figure 1. Complication rate stratified by standardized future liver remnant (% FLR) volume. Of 12 patients with a % FLR of 20% or less, 6 had complications; of 30 patients with a % FLR of greater than 20%, 4 had complications ($P=.02$). The % FLR was calculated according to the formula given in the "Patients and Methods" section.

primary hepatobiliary malignancies, whereas patients not treated with PVE were more likely to have metastatic disease. There were no differences in tumor characteristics (number of tumors or size of the largest tumor) or perioperative characteristics (estimated blood loss, duration of the operation, transfusion requirements, and complexity of the resection) between the groups. The median increase in standardized FLR was 8% (range, 1%-22%; first quartile, 4%; and third quartile, 10%); this change in standardized FLR was statistically significant ($P=.003$) (**Figure 2**). The standardized FLR at presentation was smaller in the group that underwent PVE than in the group that did not undergo PVE. However, as a result of the increase in the standardized FLR in the group that underwent PVE, there was no difference in the immediate pre-

Table 2. Patients Characteristics Stratified by PVE Status*

Characteristic	PVE Performed		P Value
	No (n = 24)	Yes (n = 18)	
Sex			
Female	19	3	.001
Male	5	15	
Age, y†	57 (33-79)	63 (37-76)	.43
Diagnosis			
Metastatic disease	20	9	.04
Hepatobiliary primary tumor	4	9	
No. of tumors†	2 (1-20)	2 (1-8)	.81
Size of the largest tumor, mm†	65 (17-170)	57 (7-190)	.72
% FLR† at presentation	23 (15-55)	18 (11-29)	<.001
Preoperatively	23 (15-55)	25 (14-42)	.86
Duration of the operation, min†	385 (164-578)	420 (205-645)	.50
Blood loss, mL†	625 (200-2000)	850 (250-2500)	.22
Transfusion, U†	0 (0-8)	2 (0-8)	.22
Complex resection			
No	18	11	.51
Yes	6	7	
Margin of clearance			
Negative	19	16	.68
Positive	5	2	
Major complications			
No	19	13	.72
Yes	5	5	
Length of hospital stay, d†	8 (5-25)	8 (6-52)	.67

*Data are given as number of patients unless otherwise indicated. PVE indicates portal vein embolization; FLR, future liver remnant. †Data are given as median (range).

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 3**). 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) ($P=.70$) (**Figure 4**).

COMMENT

Among factors that impact outcome after hepatic resection, the extent of resection contributes significantly to operative morbidity²⁷ and mortality.¹¹ 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 distribution²⁰ and

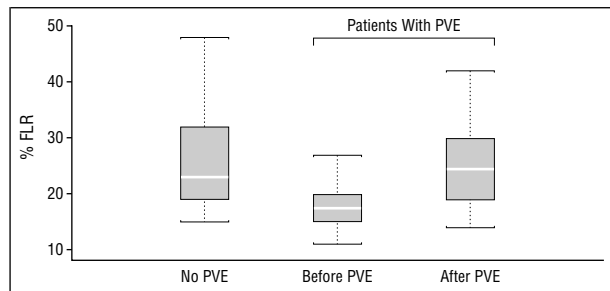


Figure 2. Standardized future liver remnant (% FLR) volume in patients who did and did not undergo portal vein embolization (PVE). There was a significant increase in the % FLR after PVE compared with before PVE ($P=.003$). Data are given as medians. The lower and upper end of bars indicate first and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

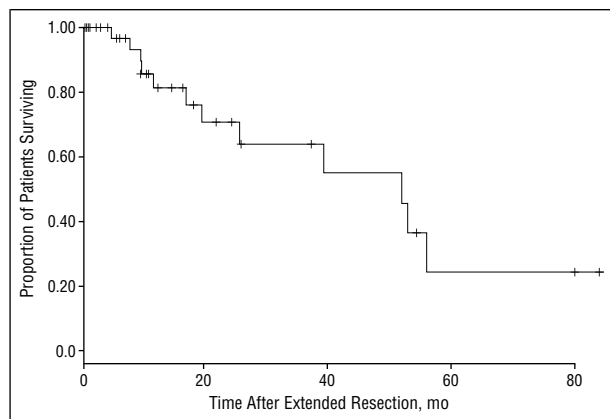


Figure 3. Survival duration in 42 patients who underwent extended hepatectomy (with or without portal vein embolization before resection).

known relatively small size of segments 2 and 3 in the absence of compensatory hypertrophy.²⁸

At our institutions, PVE is performed percutaneously in the interventional radiology suite using conscious sedation 3 to 6 weeks before hepatic resection. The median hospital stay after the procedure is 1 day, as the postembolization syndrome of pain, nausea, and fever associated with transarterial embolization is uncommon after PVE.²¹ Specifically, arterial embolization causes tumor necrosis and systemic cytokine release, which leads to the clinical postembolization syndrome, while PVE leads mostly to apoptosis of the embolized liver, which does not create this clinical effect.¹⁶ The reported complication rate of PVE is 3% to 10%; to our knowledge, procedure-related mortality has not been reported.¹⁶ Our experience is similar, and no PVE-related complication has precluded planned resection in any of our patients.²¹

In the present study, PVE resulted in an 8% increase in the standardized FLR. Eighteen extended resections were performed following PVE without an increase in the perioperative complication rate compared with that in patients having similar preoperative FLR volumes who did not undergo PVE. The rationale for PVE is based on existing data indicating that the increase in FLR volume is associated with improvement in function. For example, biliary excretion of the postembolization FLR increases^{29,30} and the natural history of postoperative liver function tests improves after PVE.¹⁵

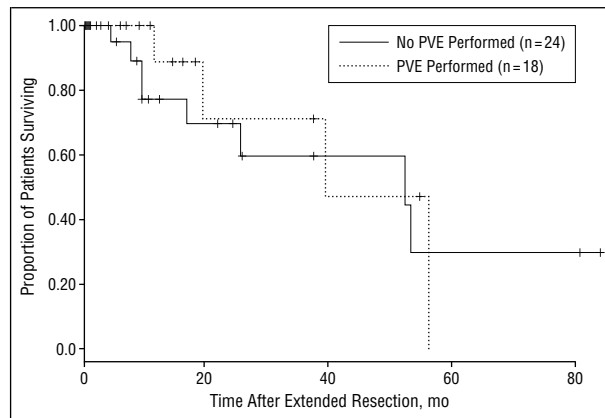


Figure 4. Survival duration in patients who underwent extended hepatectomy, stratified by portal vein embolization (PVE) before surgery. The difference between the 2 groups is not significant ($P=.70$).

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/hypertrophy 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%)³¹ or resection for hilar cholangiocarcinoma (17%).³

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.³² 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 \pm 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% had complications ($P=.02$), which emphasizes the importance of residual volume over resected volume.

An important limitation of our study was the absence of randomization. Twelve highly selected patients did not undergo PVE for a standardized FLR of 25% or less (young, with excellent performance status) in the early part of the study. Resections in these patients were performed mainly for hepatic colorectal metastases ($n=9$) in patients who did not require associated procedures ($n=10$). Consistent with our other findings, many of these patients with a standardized FLR of 20% or less and no PVE sustained major complications (4 of 7 patients). In the absence of a randomized study on PVE, the best presumptive evidence of efficacy of PVE will be demonstrated when patients who have undergone PVE resulting in greater than 20% FLR will be shown to have a (low)

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^{9,11} 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,³³ while that of unresected patients with cholangiocarcinoma is about 11 months.³⁴ 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%)³⁵ and the rate after resection of hilar cholangiocarcinoma (60%).³ 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 al³⁶ achieved an overall 5-year survival of 29%. Similarly, Azoulay et al¹⁴ 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: jvauthey@mdanderson.org).

REFERENCES

1. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg.* 1995;19:59-71.
2. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg.* 1999;230:309-318.
3. Burke EC, Jarnagin WR, Hochwald SN, et al. Hilar cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a pre-surgical clinical staging system. *Ann Surg.* 1998;228:385-394.
4. Neuhaus P, Jonas S, Bechstein WO, et al. Extended resections for hilar cholangiocarcinoma. *Ann Surg.* 1999;230:808-819.
5. Bilimoria MM, Lauwers GY, Doherty DA, et al. Underlying liver disease, not tumor factors, predicts long-term survival after resection of hepatocellular carcinoma. *Arch Surg.* 2001;136:528-535.
6. Vauthey JN, Klimstra D, Franceschi D, et al. Factors affecting long-term outcome after hepatic resection for hepatocellular carcinoma. *Am J Surg.* 1995;169:28-35.
7. Fan ST, Ng IO, Poon RT, et al. Hepatectomy for hepatocellular carcinoma: the surgeon's role in long-term survival. *Arch Surg.* 1999;134:1124-1130.
8. Tsao JI, Loftus JP, Nagorney DM, Adson MA, Ilstrup DM. Trends in morbidity and mortality of hepatic resection for malignancy: a matched comparative analysis. *Ann Surg.* 1994;220:199-205.
9. Vauthey JN, Baer HU, Guastella T, Blumgart LH. Comparison of outcome between extended and nonextended liver resections for neoplasms. *Surgery.* 1993;114:968-975.
10. Cunningham JD, Fong Y, Shriver C, et al. One hundred consecutive hepatic resections: blood loss, transfusion, and operative technique. *Arch Surg.* 1994;129:1050-1056.
11. Melendez J, Ferri E, Zwillman M, et al. Extended hepatic resection: a 6-year retrospective study of risk factors for perioperative mortality. *J Am Coll Surg.* 2001;192:47-53.
12. 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;107:521-527.
13. 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.
14. Azoulay E, 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.
15. 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.
16. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. *Br J Surg.* 2001;88:165-175.
17. Vauthey JN, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in Western adults. *Liver Transpl.* 2002;8:233-240.
18. Heymsfield SB, Fulenwider T, Nordlinger B, et al. Accurate measurement of liver, kidney, and spleen volume and mass by computerized axial tomography. *Ann Intern Med.* 1979;90:185-187.
19. Henderson JM, Heymsfield SB, Horowitz J, Kutner MH. Measurement of liver and spleen volume by computed tomography: assessment of reproducibility and changes found following a selective distal splenorenal shunt. *Radiology.* 1981;141:525-527.
20. Soyer P, Roche A, Elias D, Levesque M. Hepatic metastases from colorectal cancer: influence of hepatic volumetric analysis on surgical decision making. *Radiology.* 1992;184:695-697.
21. Madoff DC, Hicks ME, Abdalla EK, Vauthey JN. Portal vein embolization using polyvinyl alcohol and coils in preparation for major liver resection for hepatobiliary malignancy. *Radiology.* In press.
22. 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.
23. Strasberg SM, for the International Hepato-Pancreato-Biliary Association Terminology Committee Survey. The Brisbane 2000 Terminology of Liver Anatomy and Resections. *HPB.* 2000;2:333-339.
24. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
25. *S-Plus 5 for Unix Guide to Statistics.* Seattle, Wash: Data Analysis Products Division; 1998.
26. *StatXact for Windows User Manual.* Cambridge, Mass: Cytel Software Corp; 1997.
27. Belghiti J, Hiramatsu K, Benoist S, et al. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg.* 2000;191:38-46.
28. 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.
29. Ijichi M, Makuuchi M, Imamura H, Takayama T. Portal embolization relieves persistent jaundice after complete biliary drainage. *Surgery.* 2001;130:116-118.
30. 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;223:77-83.

31. Weber SM, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y. Survival after resection of multiple hepatic colorectal metastases. *Ann Surg Oncol*. 2000;7:643-650.
32. 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;188:304-309.
33. Vauthey JN, Marsh Rde W, Cendan JC, Chu NM, Copeland EM. Arterial therapy of hepatic colorectal metastases. *Br J Surg*. 1996;83:447-455.
34. Farley DR, Weaver AL, Nagorney DM. "Natural history" of unresected cholangiocarcinoma: patient outcome after noncurative intervention. *Mayo Clin Proc*. 1995;70:425-429.
35. Strasberg SM, Dehdashti F, Siegel BA, Drebin JA, Linehan D. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. *Ann Surg*. 2001;233:293-299.
36. Elias D, Cavalcanti A, de Baere T, Roche A, Lasser P. Résultats carcinologiques à long terme des hépatectomies réalisées après embolisation portale sélective. *Ann Chir*. 1999;53:559-564.

DISCUSSION

William C. Chapman, MD, Nashville, Tenn: Dr Vauthey and his group of expert hepatobiliary surgeons, including Dr Steve Curley, Dr Abdalla, and others, examined the technique of preoperative portal vein embolization to extend standard liver resection techniques in patients who might otherwise be deemed unresectable because of suspect 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.

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 nondiseased 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 cut-off 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 hepatic 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 the technical aspects of the procedure.

I have several questions for Dr Abdalla and Dr Vauthey. What were your specific determinants for treatment with portal vein embolization? While the study appears to suggest that 25% remnant liver volume was the trigger point for portal vein embolization, there was significant overlap in patient groups in this study, such that patients with remnant livers less than 25% underwent resection without portal vein embolization and other patients with remnant volumes greater than 25% received portal vein embolization. So, perhaps you can tell us about the specific indications that you now employ when considering this technique in patients for planned resection.

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.

Second, did they compare the histologic changes in the lobes that were resected to the remnants that remained? It is important to see if there were actually histologic changes in the segments that were embolized.

Charles W. Putnam, MD, Tucson, Ariz: 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 Makuuchi'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%.