Surgical Management of Hilar Cholangiocarcinoma

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Objective: To assess the surgical management of hilar cholangiocarcinoma over a time period when liver resection was considered standard management.

Summary Background Data: Hilar cholangiocarcinoma remains a difficult challenge for surgeons. An advance in surgical treatment is the addition of liver resection to the procedure. However, liver resection in the setting of liver dysfunction caused by biliary obstruction can be associated with increased mortality.

Methods: Between 1997 and 2004, 80 patients with hilar cholangiocarcinoma having surgery were reviewed. Fifty-three patients had attempted curative resections, 14 patients had palliative bypasses, while 13 patients had findings that precluded any further intervention. Twenty-three patients required portal vein resection and reconstruction to achieve negative margins, 3 of which also required reconstruction of the hepatic artery.

Results: Patients undergoing resection had a 9% operative mortality, with morbidity of 40%. Patients who demonstrated lobar hypertrophy preoperatively due to tumor involvement of the contralateral liver or induced with portal vein embolization (PVE) had a significantly lower operative mortality than those patients without hypertrophy. Median overall survival in patients resected was 40 months, with 5-year survival of 35%. Negative margins were achieved in 80% of cases and were associated with improved survival. Five-year survival in patients undergoing resection with negative margins was 45%.

Conclusion: Combined liver and bile-duct resection can be performed for hilar cholangiocarcinoma with acceptable mortality, though higher than that for liver resections performed for other indications. The use of PVE in cases where hypertrophy of the remnant liver has not occurred preoperatively may reduce the risk of operative mortality.

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Cholangiocarcinoma is a relatively rare tumor with an estimated incidence of 3000 cases in the United States in 2002.[1] A review of 294 patients with cholangiocarcinoma by Nakeeb et al[2] demonstrated that two thirds of patients had hilar tumors, 27% of tumors were in the distal bile duct, and 6% were intrahepatic. It is difficult to accurately estimate the proportion of patients with hilar cholangiocarcinoma (HCCA) that are amenable to surgical resection. This is because the majority of series published reflect only patients that are referred for surgical management and do not include patients that present with unresectable disease that are never seen by a surgeon. Perhaps the best current estimate is presented in a series by Jarnagin et al;[3] approximately 30% of patients with HCCA seen at their multidisciplinary hepatobiliary cancer center presented with unresectable disease, while 70% went on to some attempt at surgical management. Of those patients managed surgically, only 50% had an attempted curative resection. The low number of patients amenable to curative resection results in few surgeons outside of specialized centers gaining experience in the management of this formidable disease.

Early reports of resection of HCAA consisted mainly of resections of the biliary tree and bilioenteric anastomosis to the intrahepatic ducts.[4,5] Blumgart and Launois, pioneers of modern hepatobiliary surgery, were early proponents of the addition of liver resection to bile duct resection for this disease;[6,7] however, the concept was greeted with little enthusiasm by surgeons at the time that had a relatively nihilistic view of any surgical treatment of HCAA. Advances in liver surgery over the last 2 decades have led to a more aggressive approach to HCAA. Partial liver resection was added to biliary resection to manage those tumors with direct hepatic invasion, as well as to obtain oncologic margins on tumors that frequently extend longitudinally out the hepatic ducts.[3,8–10] However, major liver resection in the setting of liver dysfunction caused by biliary obstruction can be associated with increased mortality.[11]

With relatively few exceptions, reports to date by necessity include case series that extend over a prolonged time period. These reports incorporate patients that underwent bile duct resection alone who would currently be managed with the addition of liver resection. This study examines

the results of surgical management of HCAA during a time period when liver resection in addition to bile duct resection was considered the standard management for curative resection of HCAA.

PATIENTS AND METHODS

Patients

The University of Florida institutional review board approved this study. Eighty consecutive patients with HCCA undergoing surgical intervention with curative intent between July 1997 and July 2004 at the University of Florida by the hepatobiliary/transplant service were reviewed. Patients were classified as HCCA if there was an adenocarcinoma originating from the biliary confluence or the left or right hepatic duct. Tumors that arose from the proximal hepatic duct were included only if they extended to involve the right or left hepatic duct. All patients had HCCA confirmed by pathology after resection or by biopsy if palliative surgery was performed. Forty-nine patients were male (61%; male to female ratio of 1.6:1). Mean patient age was 63 ± 12 years (range 24–85).

Preoperative Assessment

The standard preoperative workup consisted of triphasic computed tomography (CT) to assess biliary, portal venous, and hepatic arterial involvement. Ideally, imaging was performed prior to any interventions on the biliary tree. Stents had been placed prior to referral to our center, however, in 69 of the 80 patients. Chest and abdominal CTs were also performed to assess for the presence of extrahepatic disease. After an assessment of the CT scan, resectability was determined. Further imaging with magnetic resonance cholangiopancreatography was obtained in 41 patients and allowed more precise determination of the degree of biliary tree involvement than could be obtained with CT in some cases. If patients were already stented but the biliary tree on side of the liver to be left in was not drained, then percutaneous transhepatic stents were placed to decompress the biliary tree of the future liver remnant (FLR) regardless of the patient's bilirubin level. Patients that presented with a bilirubin >5.0 mg/dL and had not been stented previously underwent percutaneous transhepatic stenting of the biliary tree of the FLR. Only 1 patient presented with a bilirubin level of <5 mg/dL that had not been stented prior to referral and subsequently underwent left trisegmentectomy without preoperative biliary intervention.

Patients were staged preoperatively (Table 1) according to both the Bismuth-Corlette[5] staging system and the proposed T-staging system of Jarnagin et al.[3] Postoperative staging was performed according to American Joint Committee on Cancer 2002 guidelines.[12]

In 14 cases where there was no preexisting lobar hypertrophy and it could be definitively determined which side of the liver was to be resected, preoperative portal vein embolization (PVE) was performed on the side of the liver that was to be resected 4 to 6 weeks prior to surgery.[13] Twelve patients had embolization of the right portal vein for subsequent right trisegmentectomy, and 2 patients had embolization of the left portal vein for subsequent left trisegmentectomy.

TABLE 1. Patients as Classified by the Bismuth-Corlette Staging System[12] and by the Proposed Staging System of Jarnagin and Blumgart[3]

Bismuth-Corlette Stage	Number of Patients	Blumgart T1 Stage	Number of Patients
2	10	T	37
3a	42	T2	40
3b	24	T3	3
4	4		

Surgical Technique and Procedures

An initial exploration to detect disseminated-intra-abdominal-disease patients was performed. Patients without disseminated disease underwent a standardized assessment of resectability. Intraoperative ultrasound was used in all cases. If the tumor was predominantly right-sided, then a dissection of the left hepatic duct and left portal vein at the base of the falciform ligament was performed. The presence of an uninvolved hepatic duct at the segment 2–3 junction, along with a patent left portal vein, would allow us to proceed with curative right resection, though this did not preclude the necessity of reconstructing the left portal vein due to more proximal involvement by tumor. If the tumor was predominantly left sided and a left trisegmentectomy was contemplated, then ultrasound examination of the right liver became more important. In most cases, it could be determined that tumor clearly did not extend to the posterior division of the right hepatic duct using a combination of dissection along the posterior aspect of the right portal pedicle, manual palpation, and intraoperative ultrasound. The division into segments 6 and 7 ducts occurs relatively intrahepatically, however, and without lowering the hilar plate, a definite identification of tumor at the segment 6–7 takeoffs without dividing the liver is difficult. We did not lower the hilar plate due to concerns of broaching tumor planes.

Once a decision regarding resectability within the liver was made, dissection of the hepatic artery was performed, ensuring arterial supply to the planned liver remnant. The common bile duct was divided at the level of the pancreas and reflected superiorly. Lymph nodes of the celiac axis, common hepatic artery, and all lymphatic structures in the hepatoduodenal ligament were resected. Caudate lobectomy was per-

formed routinely. Frozen-section analysis of margins was used to guide resection; additional resection was performed, if possible, when margins were initially positive. In suitable candidates who had initial positive margins of the distal bile duct or those with disease that clearly extended into the intrapancreatic portion of the bile duct, pancreaticoduodenectomy was also performed (Fig. 1). Roux-en-Y biliary enteric reconstruction was performed using a 60-cm-long segment of jejunum. Patients received postoperative chemoradiotherapy if clear margins (R0 resection) were not obtained. In the last 3 years of the study, patients with positive lymph nodes also received adjuvant chemoradiotherapy.

Patients with clearly disseminated disease had no further surgical intervention and were managed with stents, chemotherapy, and/or radiotherapy, depending on patient-specific factors. Patients with localized disease that were felt to be unresectable had either a segment 3 or segment 6 bypass performed. In both situations, cholecystectomy was generally performed.

Fifty-three patients had attempted curative resections, 14 patients had palliative segment 3 or segment 6 bypasses, and 13 patients had findings at surgery that precluded any further intervention. Of the 14 patients that had palliative bypasses, 9 had unreconstructable vascular involvement by tumor, while 5 had extensive biliary involvement by tumor and underlying patient status that precluded curative resection. The 13 patients in whom no further intervention was attempted had metastatic disease within the liver in 4 cases and peritoneal implants in 9 cases. Liver resections performed with biliary resection included 44 trisegmentectomies (34 right, 10 left) and 8 lobectomies (6 left, 2 right). One elderly patient had only the bile duct resected as it was felt that his physical status would not allow extended hepatectomy. Four patients also had simultaneous pancreaticoduodenectomy performed for extension of disease into the intrapancreatic portion of the bile duct. Twenty-three patients required portal-vein resection to achieve negative margins. Portal-vein reconstructions were from main portal vein to left portal vein in 19 cases (Fig. 2), main portal vein to right portal vein in 3 cases, and from main portal vein to the posterior branch of the right portal vein in 1 case. Three patients required arterial resection and reconstruction; 2, reconstructions of the right hepatic artery; and 1, of the main hepatic artery.

Parametric statistical analysis was performed using Student *t* tests, while nonparametric analysis of data was performed using Kendall's τ, χ^2, or Fisher exact test, when appropriate. Survival was calculated using the Kaplan-Meier method, with differences in survival assessed using the log-rank test. Cox regression analysis was used on variables that were suggested by univariate analysis to be significant. Statistical analysis was performed using SPSS 10.0 software. Operative mortality was defined as death within 30 days or within the same hospital admission. Operative blood use was defined as intraoperative transfusion or blood received within 48 hours of surgery. Results are reported as mean ± 1 standard deviation unless otherwise specified.

RESULTS

An assessment of the 2 preoperative staging systems used demonstrated no correlation between the Bismuth-

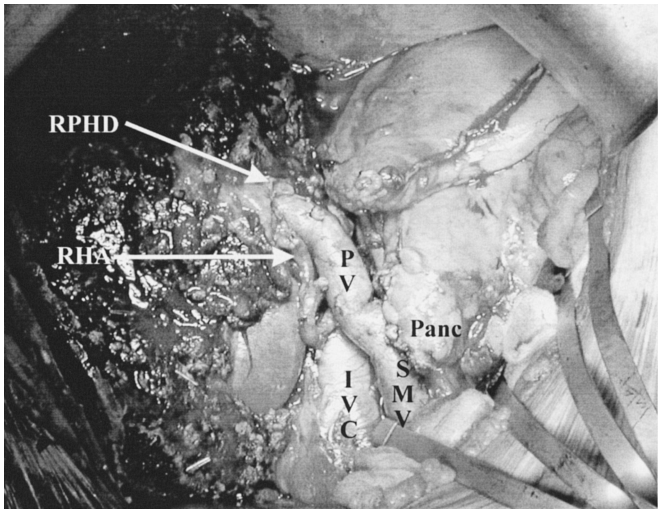

FIGURE 1. Left trisegmentectomy with pancreaticoduodenectomy. IVC indicates inferior vena cava; panc, pancreas; PV, portal vein; RHA, right hepatic artery; and RPHD, right posterior hepatic duct.

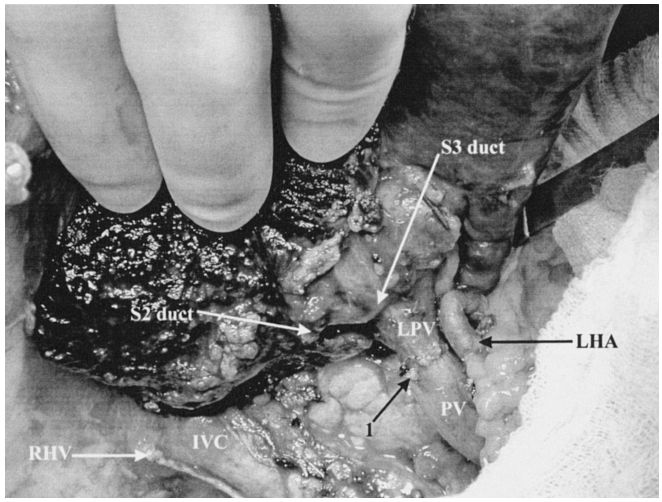

FIGURE 2. Right trisegmentectomy with reconstruction of the main portal vein to left portal vein. IVC indicates inferior vena cava; LHA, left hepatic artery; LPV, left portal vein; PV, main portal vein; RHV, stapled end of right hepatic vein; S2 duct, segment 2 hepatic duct; S3 duct, segment 3 hepatic duct; and 1, portal venous anastomosis.

Corlette staging system[5] and eventual resectability. The staging system proposed by Jarnagin et al,[3] however, showed a significant correlation to resectability, with no Blumgart T3 lesions, 55% of Blumgart T2 lesions, and 84% of Blumgart T1 lesions undergoing resection ($P < 0.01$, Kendall's τ). All 3 Blumgart T3 lesions had involvement of the main portal vein that was thought to be reconstructable preoperatively but had more extensive unresectable disease identified at operation.

The median blood loss in patients undergoing resection was 700 ± 310 mL (range 100–1800 mL). Forty-five percent of patients received no blood, but the median number of transfused units was 2 (range 0–8 units). Hospital stay was 14 ± 6 days (range 7–32 days).

Complications occurred in 21 of the 53 patients (40%) that underwent attempted curative resection. Some patients had more than 1 complication. There were 5 bile leaks managed conservatively, 2 cases of pleural effusions large enough to require drainage, and 6 intraabdominal abscesses that required drainage. Wound infections occurred in 8 patients. One patient developed renal failure requiring temporary dialysis, and 2 patients developed pneumonia. Liver failure not related to an infectious complication occurred in 2 patients, neither of whom had the FLR's biliary tree drained preoperatively. One had a preoperatively placed biliary drain and underwent a left trisegmentectomy; however, the biliary drain had been placed in the right anterior sector, which did not communicate with the posterior sectoral ducts. The other was a patient that had a right trisegmentectomy without preoperative drainage of the left biliary tree. There were 5 perioperative deaths (9% operative mortality). Two patients died of liver failure, and 3 patients had an initial infectious complication (pneumonia $n = 2$, subphrenic abscess, $n = 1$) leading to liver failure. Patients who demonstrated lobar hypertrophy preoperatively due to tumor involvement of the contralateral liver or induced with PVE had a significantly lower operative mortality than those patients without hypertrophy (3% versus 21%, $P = 0.01$).

Forty-two of 53 patients resected (80%) had histologically negative margins (R0). The remaining 11 patients had microscopically positive margins. Nine of these were initially called negative by frozen section analysis but were found to be positive on permanent section. In 2 cases, it was known that the margins were microscopically positive at surgery; however, further extension of the biliary resection margin was not technically possible. In 1 left trisegmentectomy, the segment 6 and segment 7 ducts were already widely separate, while in 1 right trisegmentectomy, resection had already been performed back to separate segment 2 and 3 ducts.

Papillary tumors occurred in 8% of resected patients. Twenty-three percent of patients had well-differentiated tumors, with the remainder either moderately or poorly differentiated. Mean tumor size was 3.3 ± 1.8 cm. Twenty-one percent of patients had positive nodes in the hepatoduodenal ligament.

Median survival for all patients was 22 months, with median follow-up time of 16 months. Five-year actuarial survival for patients undergoing resection was 35%. Not surprisingly, patients that were resected had a better survival than patients that were not (median survival 40 months, 95% CI 27–55 months, versus 9 months, 95% CI 7–11 months; $P < 0.0001$; Fig. 3). Patients that had an R0 resection survived longer than patients resected with microscopically positive margins (median survival, 53 months, 95% CI 43–62 months, versus 24 months, 95% CI 14–38 months; $P < 0.01$; Fig. 4). There were no long-term survivors that had positive-resection margins.

Patients who were resected with microscopically positive margins (R1 resection) did show some benefit in survival compared with patients with locally advanced, unresectable disease who were bypassed (median survival 24 months, 95% CI 14–38 months, versus 12 months, 95% CI 9–13 months; $P < 0.05$).

Factors not associated with an effect on survival by univariate analysis in patients that were resected included age >70, sex, preoperative Bismuth-Corlette and Blumgart stage, tumor size >2.5 cm, type of resection, and postoperative AJCC stage. There was no difference in survival between patients that had portal vein resections and those that did not. Patients with lymph node involvement by tumor appeared to have a worse 5-year survival than patients with node negative status; however, this difference was not statistically signifi-

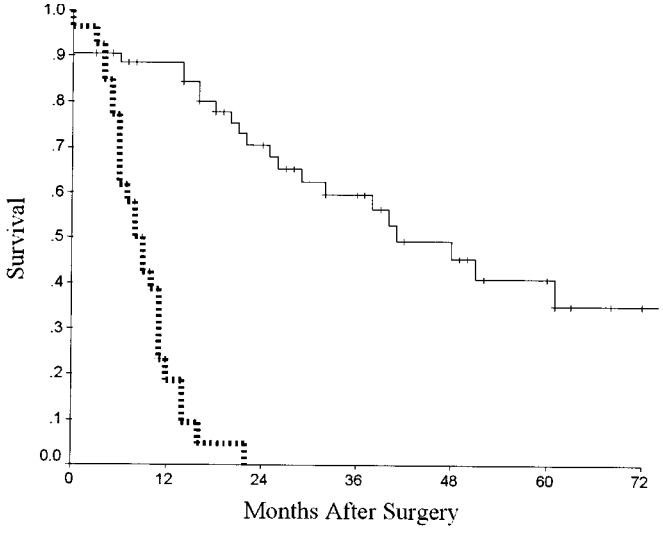

FIGURE 3. Actuarial survival of patients who underwent resection (solid line) versus those patients who were not resected (dotted line). Patients resected had better overall 5-year survival (35%) than patients that were not resected. No unresected patient survived to 24 months ($P < 0.0001$ log rank).

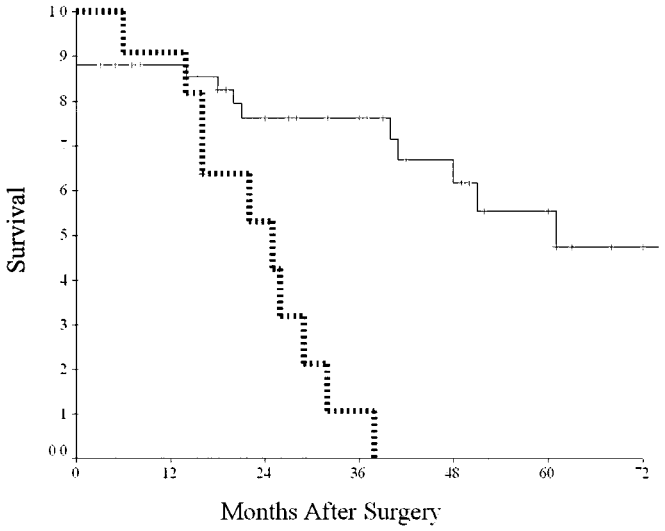

FIGURE 4. Actuarial survival of patients that were resected with negative margins (solid line) versus those who were resected with positive margins. Patients resected with negative margins had a better 5-year survival of 45% than patients resected with positive margins, with no patient resected with positive margins surviving longer than 40 months ($P < 0.01$ log rank).

cant (21% versus 45%; $P = 0.06$; Fig. 5). Patients with well-differentiated tumors showed a trend toward improved survival compared with patients with moderately or poorly differentiated tumors; however, this trend was not significant

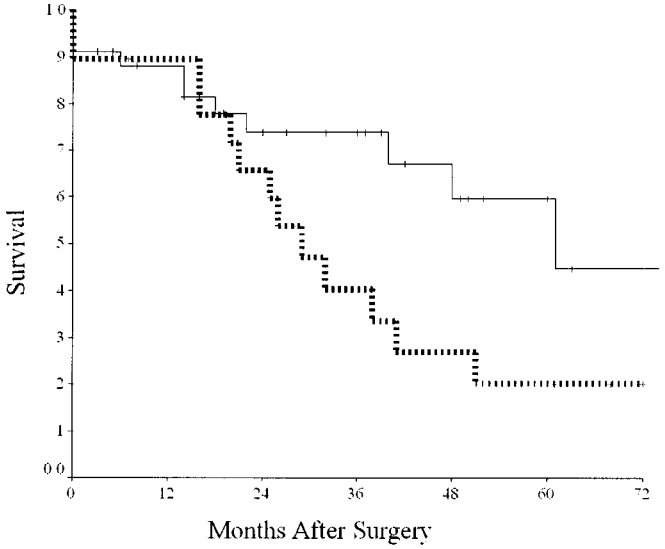

FIGURE 5. Actuarial survival of patients resected with negative nodes (solid line) versus those resected with positive nodes (dotted line). Patients resected with negative nodes appeared to have an improved survival over those with positive nodes; however, this difference did not prove to be significant ($P = 0.06$ log rank).

($P = 0.08$). Only R0 status demonstrated an effect on survival at a level of significance of <0.05 by univariate analysis. A Cox regression analysis was performed on variables, with $P < 0.10$, including R0 status, lymph node status, and tumor differentiation. This confirmed that only R0 status remained a significant predictor of survival.

DISCUSSION

HCAA remains a difficult challenge for the surgeon. Achieving negative surgical margins when resecting this relatively uncommon tumor is technically demanding due to the close proximity of the bile duct bifurcation to the vascular inflow of the liver. A recent advance in surgical treatment is the addition of liver resection to the procedure, both to increase the number of patients who can be offered potentially margin-free resection and to increase the oncologic clearance of the procedure in patients that would previously have been treated with bile-duct resection only. Extended hepatectomy in the setting of biliary obstruction and elevated bilirubin can be associated with increased risk, however.[11,14,15] Attempts to reduce the risks associated with biliary obstruction by preoperative biliary drainage remain controversial. There is little doubt that the presence of preoperative biliary drainage increases the rate of bacterial colonization of the biliary tree and can increase the rate of perioperative infectious complications.[3,16] Conversely, several recent series of hepatic resections for HCAA demonstrate a reduced incidence of liver failure when preoperative biliary drainage was used, although PVE was also used in those series.[17,18] Unfortunately, from the practical point of view, it would appear that biliary drainage is a fait accompli in the majority of cases seen by the hepatobiliary surgeon. In our series, 69 of 80 patients already had biliary stents placed prior to surgical referral. In many cases, the stents were placed without consideration of subsequent surgery and were placed into the side of the liver that would be removed rather than the side of the planned remnant liver after resection. Ideally, patients should undergo early referral with the need for and planning of preoperative biliary drainage done in concert with the surgeon.

HCAA has traditionally been staged preoperatively using the Bismuth-Corlette staging system.[5] Although the Bismuth-Corlette system provides some information as to anatomic location of the tumor, it was not shown to be predictive of subsequent resectability in this study. The Blumgart T-staging system,[3] which incorporates the degree of biliary involvement, as well as portal venous involvement and hepatic lobar atrophy, demonstrated a strong correlation with eventual resectability. The importance of the concept of lobar atrophy and subsequent contralateral lobar hypertrophy also became apparent when assessing perioperative mortality. Patients that had lobar hypertrophy induced either by contralateral portal vein involvement by tumor (Blumgart T2) or

by preoperative PVE were less likely to die in the perioperative period. This underscores the importance of the role of remnant liver function after extended hepatectomy. Only 2 of the 5 deaths in this series were from isolated liver failure without initial infectious complication. However, the 3 other patients that died initially had infection that led to the development of liver failure as a component of their demise. In a recent series of 58 patients undergoing major hepatectomy for HCAA, Seyama et al[18] used preoperative PVE in all patients undergoing resection of >50% of initial liver volume and reported a 0% operative mortality, although there was a 43% morbidity which is similar to our series. While speculative, it may be that the improved remnant liver function provided by preoperative lobar hypertrophy not only prevents primary liver failure but also provides a degree of hepatic functional reserve that allows patients to better tolerate a subsequent insult such as an infectious complication. Complication rates for extended hepatectomy for HCAA range from 40% to 52% in recent series.[3,18–20] It would appear reasonable to use preoperative PVE in all patients that are undergoing planned extended hepatectomy for HCAA that do not have preexisting lobar hypertrophy of the remnant liver from contralateral tumor involvement.

Only the presence of an R0 resection proved to be predictive of an improvement in survival. Patients resected with negative margins had a 45%, 5-year actuarial survival while no patients with positive margins were alive past 40 months. Patients that had lymph node involvement showed a trend toward having worse survival that did not reach statistical significance. The power of this study was not sufficient to determine whether there was a true difference in survival associated with lymph node involvement, and the possibility of a type II error is relatively high. The literature provides conflicting results regarding the association of lymph node status on survival, with some authors showing a clear effect[18,21] and some showing none.[3,20] It is clear that positive lymph nodes in the porta hepatis, while probably not a good thing, do not preclude a curative procedure if negative margins can be obtained.

A somewhat surprising finding in this series was that patients undergoing an R1 resection fared better than patients undergoing biliary bypass for locally advanced disease. Others have demonstrated no benefit for resections performed with positive margins.[3,20] There is a possible explanation for this finding. All patients with R1 resections received adjuvant chemoradiotherapy as standard therapy, while less than 50% of patients that underwent biliary bypass for locally advanced disease received either chemotherapy or radiotherapy. This may have prolonged survival of patients receiving an R1 resection. We certainly would not advocate performing resections for HCAA with anything other than the intent to perform an R0 resection.

In even some of the earliest reports of combined liver and bile-duct resection for HCAA, it was apparent that portal-vein resection and reconstruction would be required in some cases to completely resect the tumor.[22] Portal-vein resection with reconstruction was employed in 43% of cases in this series and did not increase operative morbidity or mortality. In the last several years, we have adopted many of the "no-touch" principles espoused by Neuhaus et al[23] and, when performing extended right hepatectomies, will more often than not resect the portal-vein bifurcation. Resecting the portal-vein bifurcation when performing a left trisegmentectomy is substantially more difficult due to the relatively short course of the right portal vein prior to branching and was uncommonly performed in the current series. We could show neither a survival advantage nor disadvantage associated with en bloc resection of the portal vein. The results suggest that, while portal-vein resection should not necessarily be a standard part of every resection, the need for portal-vein resection should not be a contraindication to resection for cure.

In summary, the current study confirms that an aggressive surgical approach to HCAA that includes hepatic resection as standard therapy is warranted. Although the operative mortality was 9%, which is higher than for extended hepatectomies performed for other indications at our institution, a 45% 5-year survival can be expected if negative margins can be obtained, even if this requires resection and reconstruction of the hepatic vasculature. Obtaining negative resection margins is the single most important factor in achieving prolonged survival. The use of strategies to optimize the functional liver remnant prior to resection may allow more aggressive resections in pursuit of negative margins and reduce operative mortality.

REFERENCES

1. Olnes MJ, Erlich R. A review and update on cholangiocarcinoma. *Oncology*. 2004;66:167–179.
2. Nakeeb A, Pitt HA, Sohn TA, et al. Cholangiocarcinoma: a spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg*. 1996;224:463–473.
3. Jarnagin WR, Fong Y, DeMatteo RP, Blumgart L, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg*. 2001;234:507–517.
4. Tompkins RK, Thomas D, Wile A, et al. Prognostic factors in bile duct carcinoma: analysis of 96 cases. *Ann Surg*. 1981;194:447–457.
5. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. *Surg Gynecol Obstet*. 1975;140:170–178.
6. Launois B, Campion JP, Brissot P, et al. Carcinoma of the hepatic hilus: surgical management and the case for resection. *Ann Surg*. 1979;190: 151–157.
7. Beazley RM, Hadjis N, Benjamin IS, et al. Clinicopathological aspects of high bile duct cancer: experience with resection and bypass surgical treatments. *Ann Surg*. 1984;199:623–636.
8. Kosuge T, Yamamoto J, Shimada K, et al. Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. *Ann Surg*. 1999;230:663–671.
9. Neuhaus P, Jonas S, Bechstein WO, et al. Extended resections for hilar cholangiocarcinoma. *Ann Surg*. 1999;230:808–818.
10. Launois B, Reding R, Lebeau G, et al. Surgery for hilar cholangiocarcinoma: French experience in a collective survey of 552 extrahepatic bile duct cancers. *J Hepatobiliary Pancreat Surg*. 2000;7:128–134.

11. Su CH, Tsay SH, Wu CC, et al. Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. *Ann Surg*. 1996;223:384–394.
12. American Joint Committee on Cancer. Extrahepatic bile ducts. In: Greene FL, eds. *American Joint Committee on Cancer: AJCC Cancer Staging Handbook*. New York: Springer; 2002:163–169.
13. Hemming AW, Reed AI, Howard RJ, et al. Preoperative portal vein embolization for extended hepatectomy. *Ann Surg*. 2003;237:686–691.
14. 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.
15. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg*. 2003;138:1198–1206.
16. Hochwald SN, Burke EC, Jarnagin WR, et al. Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangiocarcinoma. *Arch Surg*. 1999;134:261–266.
17. Kawasaki S, Imamura H, Kobayashi A, et al. 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;238:84–92.
18. 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;238:73–83.
19. Lee SG, Lee YJ, Park KM, et al. One hundred and eleven liver resections for hilar bile duct cancer. *J Hepatobiliary Pancreat Surg*. 2000;7:135–141.
20. Rea DJ, Munoz-Juarez M, Farnell MB, et al. Major hepatic resection for hilar cholangiocarcinoma: analysis of 46 patients. *Arch Surg*. 2004;139:514–523.
21. Nimura Y, Kamiya J, Kondo S, et al. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. *J Hepatobiliary Pancreat Surg*. 2000;7:155–162.
22. Hadjis NS, Blenkharn JI, Alexander N, et al. Outcome of radical surgery in hilar cholangiocarcinoma. *Surgery*. 1990;107:597–604.
23. 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;388:194–200.

Discussion

DR. LESLIE H. BLUMGART (NEW YORK, NEW YORK): I much enjoyed listening to your presentation. Your abstract states that "achieving negative margins in resection of hilar cholangiocarcinoma is difficult due to the close proximity of the biliary confluence to the vascular inflow." In addition, you have shown that hepatic resection is important in achieving this goal. I am absolutely delighted to see this affirmation of the stance that I and others took and for which we were at one time vigorously criticized, particularly in a presentation to this Society 20 years ago and published in the *Annals of Surgery* in June 1984. The core of the criticism at that time revolved around the performance of liver resection as part of the procedure.

I would like to quote 2 statements from that discussion. The first stated that the operation had use only "for the surgeon's capacity or need for rationalization." The second, a subjective statement that "when Les Blumgart does [that operation], he feels good—[but it] makes this reviewer feel bad." Perhaps I should say that at this time and in my past experience it just makes me feel tired.

You can see why I am so pleased that attitudes have turned full cycle and why I welcome this fine contribution to the surgical understanding of this disease. And, in particular to the most significant point, namely, that hepatic resection is important in achieving R/O resection.

I am also delighted to see your use of the classification proposed by Jarnagin and myself; that is, the preoperative clinical classification of these patients, taking into account the importance of lobar atrophy and portal vein involvement.

However, having complimented you, there are some questions which should be addressed. First, could you please tell us what the true denominator is of the number of patients that you saw with this disease? Eighty were operated upon, of whom 53 had an attempted curative resection. How many patients did you see overall and how does this relate to operability and resectability?

Second, 27 patients were submitted to laparotomy and not resected. Thirteen of these had metastatic disease and might have been spared a laparotomy by preliminary laparoscopy. Do you use this at all, even in advanced cases? (That is, T2 and T3?) As you know, this has been shown by others (including ourselves) to spare patients unnecessary laparotomy, especially in the era of effective percutaneous transhepatic intubation. Your surgical bypass rate approximates the rate which we had years ago and which has now fallen to a small number with the use of interventional radiology.

Third, you make no mention of preoperative biliary drainage, which is lauded by some as being absolutely essential in preoperative management of the jaundiced patient. As you know, the Japanese carry this out to a fine degree. What is your practice in relation to preoperative drainage? Infective complications appear to be directly related to the presence of preoperative biliary drainage.

Fourth, you suggest that portal veinous embolization might be important in reducing operative mortality, but I doubt that you have evidence of that in the data you have produced. You have certainly used it quite freely in this study. Before it can be accepted that portal venous embolization is responsible for an improvement in results, it must be related to infective complications due to drains and the necessity or otherwise for vascular resection in such cases. In our studies, only 1 patient died of liver failure not related to infection. It can be argued that portal venous embolization allows the patient better resistance to infection, but it could also be argued that increasing experience has resulted in the improvement of results, neither biliary drainage nor portal vein embolization. Thus, in our studies, mortality has now fallen to approximately 3% in the most recently treated patients, with no operative deaths in the last 30 or so cases despite no use of elective preoperative drainage or portal veinous embolization.

So, the questions are first, is preoperative drainage or, particularly, portal venous embolization essential?

Second, is it possible that in selective patients for portal venous embolization, you are selecting the clearly resectable at preoperative study with clearly unilateral disease? Otherwise, might you be portal venous embolizing the wrong side of the liver?

Finally, are the results of portal venous embolization part of a self-fulfilling prophecy?

Having asked these questions, may I once again emphasize the quality of this presentation, clearly demonstrating a high degree of technical ability with excellent results. It has taken the best part of 20 years to see an affirmation of the importance of hepatic resection. In another 20 years you may be at this meeting, demonstrating the importance of portal vein embolization and percutaneous drainage and reflecting upon my remarks just as I have on the comments made in 1983.

DR. WILLIAM CHAPMAN (ST. LOUIS, MISSOURI): I, too, wish to congratulate Dr. Hemming and his colleagues from Gainesville on their impressive experience performing complex hepatic resection in 80 patients analyzed over a 7-year period.

In this series, 53 out of 80 patients had attempted curative resection for hilar cholangiocarcinoma, the majority of which included complex hepatic resection in combination with biliary tract resection. In addition, vascular resection and reconstruction was performed in over half the patients undergoing attempted curative resection and preoperative portal vein embolization was utilized in 14 of these patients, or 26%.

So essentially almost all of these patients required complex, extensive hepatic resection, and, not surprisingly, the overall complication rates were high at 40%, with a perioperative mortality rate of 9%. However, using this aggressive, complicated approach, these authors were able to achieve a margin negative or R(0) resection rate of 80%, with an impressive 5-year actuarial survival result of 35%.

I have 3 general question areas for the authors. I, too, would like to ask about the use of portal vein embolization which was stressed in this manuscript and suggested for consideration. And as I understand your suggestion, presently you would consider portal vein embolization in any patient who did not have evidence of atrophy/hypertrophy complex.

So is this something that we should be using in every patient who has not yet had spontaneous hypertrophy? And what is this based on? Does the size of the potential remnant liver play a role? And what target hypertrophy are you looking for?

There are other reports that have shown that not all patients respond to portal-vein embolization. What do you do if there is no response after a 4- to 6-week period? Do you decline to reoperate, consider reembolization, or use some other strategy?

Have you had any patients in whom tumor progression occurred during this period and/or have you had any technical complications of the embolization; for example, embolizing the side that you had planned to leave in place that made a patient unresectable?

Second, is there a role for in situ preservation or ex vivo preservation techniques to allow for completion of resection in these complex patients?

Finally, do you have data beyond 5 years in this series? With hilar carcinoma, there are reports suggesting that tumor progression or recurrence continues even beyond 5 years, so the 5-year survival may not be equivalent to long-term cure.

I congratulate the authors on yet another excellent hepatobiliary series.

DR. HENRY A. PITT (INDIANAPOLIS, INDIANA): I would also like to congratulate Dr. Hemming and his colleagues from Florida on their excellent results. These results are 2 to 3 times better than most of us were achieving 1 or 2 decades ago, and now general consensus exists that being aggressive with respect to liver resection is the way to achieve an R0 resection and improve survival in biliary malignancies.

A question remains, however, as to how aggressive we should be. Liver resection can be done even in these obstructed patients with an acceptable mortality, usually less than 5%. When we add a portal vein or hepatic artery resection to the liver resection, or add a Whipple to the liver resection, however, oftentimes the mortality is not additive, it becomes much higher. So my first question is: What were your mortalities in patients with vascular resection and in the 4 patients who had a Whipple?

The other question that many of us have been asking for a long time is: What is the role of adjutant therapy in these patients? I presume from your presentation that most of your patients did not receive adjuvant therapy. We have taken a slightly different approach 6 or 7 years ago when we decided to be aggressive with the liver resection but not to resect the vascular structures or the pancreas; however, we routinely added adjuvant chemoradiation with infusional 5 FU and gemcitabine. With this approach, we have reported a 70% 4-year survival in patients with resected biliary malignancies. So there may be a tradeoff here where we are a little less aggressive, add some adjuvant therapy, and perhaps we will get the best results.

DR. JEAN-NICOLAS VAUTHEY (HOUSTON, TEXAS): The most important aspect of this report is the combined resection of the portal vein in 23 out of 53 patients and the absence of survival difference between those who had and those who didn't have portal vein resection. In the paper, the authors report that they have mostly endorsed the no-touch technique of Professor Neuhaus in Germany. In contrast, Professor

Nimura in Japan performs portal-vein resection only when the tumor is inseparable from the portal vein.

Do the authors recommend portal-vein resection based upon stage, macroscopic intraoperative criteria, or simply endorse the no-touch technique? What was the rate of microscopic vascular invasion of the portal vein? Analyzing portal-vein resection within the context of stage might be important in understanding whether and when we should perform portal-vein resection.

At our institution, we prefer to approach type 1, 2, and 3A Bismuth-Corlette hilar cholangiocarcinomas with extended right hepatectomy. We use portal-vein embolization and we take advantage of the long extrahepatic course of the left hepatic duct for reconstruction, similar to the long transverse course of the left portal vein. Can the authors comment on the side-specific constraints as it relates to resectability and curability? Was the RO resection rate higher with extended right hepatectomy in your series?

DR. REID B. ADAMS (CHARLOTTESVILLE, VIRGINIA): I just have a few additional questions to add. The first is: In our practice we are seeing an increasing number of endoprostheses versus a PTC. How do you deal with those? Are you taking those out and putting in the PTC in the liver remnant or are you leaving the endoprosthesis in? The reason I ask is because I think that we are seeing a higher rate of complications with the endoprosthesis versus the PTC because they are not getting adequate drainage in the remnant. I would be interested in how you deal with that issue.

I also have a question about what your target volume or percentage is for your portal vein embolization. Finally, you didn't comment on this and your numbers are probably too small, but do you see a difference in outcomes in those patients that had hepatic artery resection versus those that had no hepatic artery resection?

DR. ALAN W. HEMMING (GAINESVILLE, FLORIDA): I thank the discussants for their comments and I will try to get through all of the questions.

In particular I would like to thank Dr. Blumgart for his comments since this paper is in many ways the application of principles that he has advocated for the past 20 years. I would note, as Dr. Blumgart pointed out, that at the 1983 meeting of the Southern Surgical Association he gave one of the earliest papers on combined liver and bile-duct resection for hilar cholangiocarcinoma and was essentially condemned by one of the discussants for doing heroic procedures that offered no chance for cure at the cost of high operative mortality. I am glad that Dr. Blumgart, along with others such as Drs. Bernard Langois and Bernard Langer, the latter from whom I received much of my training, persisted in their efforts. Liver resection is considered a standard part of surgery for this disease by the majority of specialized hepatobiliary surgeons today.

One of the questions was about the true denominator. We don't know. I see only the patients sent to me for possible surgery. I have no real idea the numbers of patients sent to the institution or failed to be sent to the institution who may have been considered unresectable and not referred to surgery. Dr. Blumgart's paper from 2001 in *Annals of Surgery* suggests that about a third of patients present with unresectable disease. I think that is the best evaluation of a true denominator that I have seen.

In terms of laparoscopy, I would like to say that we use laparoscopy in every patient, since I think that is a reasonable option to avoid unnecessary laparotomy; however, we only performed it in about half of the patients. Currently, we perform laparoscopy in any patient that we can see an initial mass on preoperative imaging or if there appears to be any lymphadenopathy.

Of the 27 patients that were not resected at laparotomy, 14 had bypass and I don't think would have been detected by laparoscopy because it was mainly due to local invasion. Of the 13 that had disseminated disease, I think 5 of them had laparoscopy and we missed the disease at laparoscopy anyway.

In terms of the role of preoperative biliary drainage, it is controversial. There is little prospective evidence that preoperative biliary drainage improves outcome. However, many studies looking at the role of preoperative biliary drainage include distal common bile duct lesions. I have little doubt that there is small if any benefit in any but the most jaundiced or malnourished patients with preoperative drainage prior to pancreaticoduodenectomy.

When dealing with extended hepatectomy, I think the situation is somewhat different, since frequently 75% of the liver volume is removed, and if remaining 25% is not functioning well there is the risk of liver failure. Draining the biliary tree of the future liver remnant is an attempt to optimize remnant liver function. There is no doubt, however, that biliary drainage does cause bacterial colonization and, in some cases, infection of the biliary tree.

Portal venous embolization is also an attempt to optimize remnant liver function by increasing the volume of the remnant liver preoperatively. It takes 4 to 6 weeks to get such hypertrophy after portal vein embolization. I think it can't be a good thing for the liver to have the biliary tree obstructed for an additional 6 weeks, so PVE is another reason to preoperatively drain the biliary tree. I am also not sure that you can induce preoperative hypertrophy if you don't drain the segment that you are trying to cause hypertrophy of.

Currently—and this answers some of the other questions at the same time—currently we drain the biliary tree liver remnant if the bilirubin is above 5 mg/dL. If patients come undrained with a bilirubin under 5 mg/dL, we will

operate on them right away. So I don't believe in draining everybody. But if the bilirubin is over 5—and that to a certain extent comes from a paper also from Dr. Blumgart's group that demonstrated that a bilirubin of over 6 has an increased risk of mortality during liver resection. Some Japanese groups use a cutoff of 5. So we picked the lower number and used 5.

We use portal-vein embolization in any patient who doesn't have preexisting hypertrophy of the remnant liver due to contralateral tumor involvement, and where I can definitely determine which side of the liver is to be resected. That is not always possible. Sometimes we will start a procedure thinking, for example, that a left trisegmentectomy is required, but the right hepatic artery is found to be involved. So we adjust and end up doing a right trisegmentectomy. So I don't always know which side is to be resected.

Dr. Chapman, you asked about the cutoff for remnant liver volume we use to utilize portal vein embolization. With these, we don't use volume so much because I think that what you are looking at is remnant function in an obstructed liver. I don't think volume and function necessarily correlate in this setting, although I have no proof that that is true. That is just me thinking, which may be dangerous.

The question about whether there is a role for ex vivo or cold preservation in these, if you are doing either portal vein resection or hepatic artery resection. When you are doing portal vein resection, you still have arterial flow, so the liver is being perfused. I don't think you need cold perfusion to do the portal vein. If you are doing an arterial reconstruction, the portal vein flow is maintained. I don't think you need cold preservation for that. In fact, in Pichlmayr's original series on ex vivo liver resection, the one group that did terribly with cold preservation was the group that had biliary obstruction. So we tend not to use it, at least for Klatskin tumors.

Regarding data beyond 5 years. As the series is 7 years long, most of the patients have really been done in the past 5 years. So, no, we don't have any data really much past 5 years. There are a few patients alive at 7 years in the series. Cholangiocarcinoma certainly can recur late. But if we have patients alive at 5 years, we are impacting positively on their disease. If they are not resected, they don't survive 18 months. So I think we are benefiting patients with these resections.

To clarify our approach to portal vein resection: When we resect the portal vein when performing a right trisegmentectomy, we resect the vein if it appears there is even slight adherence of the tumor to the portal vein. The majority of the time, there will not be true invasion of the portal vein at all. And that is largely a technical issue. As you know, when you are performing a right trisegmentectomy, it is easier to resect the vein; you have more length to work with on the left portal vein. So right or wrong, when we are doing a right trisegmentectomy, I choose to believe in the principles espoused by Neohaus: I resect the right portal vein liberally.

When performing a left trisegmentectomy, I more closely follow Nimura. I say that because it is quite hard to resect the right portal vein when doing a left trisegmentectomy since it branches quickly. So on the right side, I only take the vein if I have to; in other words, if I cannot separate the tumor from the portal vein. I think that answers the difference between right-sided and left-sided hepatectomies.

Dr. Adams, regarding the endoprosthesis, we have a huge problem. I would prefer never to see one again, at least in a patient that is undergoing resection. How we deal with them? I have not been able to get them removed preoperatively, so we just have to deal with them at the time of surgery. They create a tremendous amount of inflammation in the porta hepatis and make dissection very difficult. In fact, 2 out of the 3 hepatic artery reconstructions were done in patients who had endoprosthesis. And as I said, we don't have a target liver volume for PVE.

Dr. Pitt asked about relative complication rates with portal-vein reconstruction, artery reconstruction. Interestingly, with the portal-vein reconstructions, I think we only had 1 death. And that was, if you look at how it breaks out, slightly better than without vein resection. The reason they did slightly better may be because they had a hypertrophic remnant liver from portal vein involvement, essentially a form of autoembolization of the portal vein. Dr. Blumgart may disagree, but we are allowed to disagree sometimes.

Adjuvant chemotherapy. Strictly speaking, it wasn't used consistently through the whole study. In the last 3 years of the study, if the patients had positive nodal disease, they received adjuvant chemoradiotherapy. If patients had R-1 resections, they received adjuvant chemoradiotherapy throughout the whole time period. I think some of the major advances in therapy of this tumor will be adjuvant therapies. Extending the limits of surgery has its limits and at best deals with local disease.