PAPER

Major Hepatic Resection for Hilar Cholangiocarcinoma

Analysis of 46 Patients

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Hypothesis: Major hepatectomy, bile duct resection, and regional lymphadenectomy for hilar cholangiocarcinoma are associated with actual long-term (>5 years) survival.

Design: Retrospective outcome study.

Setting: Single tertiary referral institution.

Patients: Between 1979 and 1997, 46 consecutive patients had resection of hilar cholangiocarcinoma by major hepatectomy, bile duct resection, and regional lymphadenectomy.

Main Outcome Measures: Overall survival and tumor recurrence were correlated to clinicopathological factors, operative morbidity, and mortality.

Results: Twenty-five patients underwent left hepatectomy, 17 underwent right hepatectomy, and 4 had extended right hepatectomy. Eighteen patients underwent resection of segment 1. Negative (R0) resection margins were achieved in 37 patients (80%). The operative mortality rate was 9%, and the surgical morbidity rate was 52%. Actual 1-year, 3-year, and 5-year survival rates were 80%, 39%, and 26%, respectively. Factors adversely associated with patient survival rates included: male sex, lymph node metastases, tumor grade 3 or 4, elevated direct serum bilirubin level at diagnosis, elevated preoperative activated partial thromboplastin time, and more than 4 U of red blood cells transfused perioperatively. Tumor size and R0 resection approached significance for survival. Factors associated with tumor recurrence included: male sex, tumor grade 3 or 4, a low hemoglobin level both at diagnosis and preoperatively, and a low preoperative prothrombin time and low alkaline phosphatase level at diagnosis and preoperatively. Median time to recurrence was 3.6 years. Tumor recurrence was predominantly local and regional.

Conclusions: The actual 5-year survival rate of 26% justifies major partial hepatectomy, bile duct resection, and regional lymphadenectomy for hilar cholangiocarcinoma. The high frequency of local and regional recurrence warrants investigation of adjuvant therapy.

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SINCE THE REPORTED RESECTION of a primary cancer originating at the hepatic duct confluence by Brown and Myers[1] in 1954, hilar cholangiocarcinoma (HC) has remained a formidable challenge. Early independent descriptions of the major clinical and pathological features of HC highlighted the management problems posed by this malignancy.[2,3] These clinical and pathological features, along with more recent molecular aspects of biliary tract cancers, have recently been reviewed by our institution.[4] Despite a reputed slow tumor growth rate and uncommon hematogenous metastases, the propensity for extensive local invasion of the hepatic hilum and the limited resolution of hepatic hilar imaging initially accounted for the low overall resectability. As a consequence of limited resectability of HC, prognosis was poor and surgical management was primarily palliative. In fact, early attempts at complete resection were noteworthy.[5]

In 1979, the first substantive experience of patients undergoing resection for HC was reported.[6] With improved resolution of hepatic hilar imaging and further recognition of the patterns of HC growth, operative approaches for resection of HC have evolved. The inclusion of partial hepatectomy of variable extent to address both direct hepatic invasion and the intrahepatic intraductal extension of HC has been the major advance in the surgical management of HC during the last 2 decades.[7,8] Subsequently, numerous investigators have demonstrated that complete resection of HC inclusive of partial hepatectomy and regional lymphadenectomy may be the operative treatment of

choice for select patients.[9-13] Despite promising survival outcomes, perioperative mortality and morbidity remain formidable. Although recent single and multiinstitutional reports have endorsed major partial hepatectomy, bile duct resection, regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy for HC, actual 5-year follow-up is sparse.[14,15] These considerations prompted our review of this operative approach for HC at the Mayo Clinic, Rochester, Minn, during the last 2 decades. Our aims were to reexamine the clinical and pathological features of HC, to correlate these factors with patient survival rates and tumor recurrence, and to define the actual long-term (5-year) survival associated with this operative approach.

METHODS

This study was performed with approval by the Mayo Foundation institutional review board. We reviewed the records of consecutive patients with HC who underwent major partial hepatic resection, resection of the extrahepatic bile duct to the head of the pancreas, removal of the gallbladder (if present), regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy at the Mayo Clinic from 1979 to 1997. We limited our study through 1997 to obtain a minimum potential follow-up interval of 5 years. Data were abstracted from institutional medical, surgical, and pathological records and from available extrainstitutional records. Clinical features at initial examination and comorbid conditions were recorded. The Eastern Cooperative Oncology Group scale[16] was used to categorize patient performance status before and after surgery. The assessment of proximal and distal tumor extent in the biliary tree was estimated preoperatively with endoscopic retrograde cholangiography and/or percutaneous transhepatic cholangiography. Preoperative biliary decompression, whether endoscopic or transhepatic, was recorded. Ultrasonography and computed tomography were used preoperatively to evaluate local and distant tumor involvement. Visceral angiography was used selectively to define regional vascular invasion. Laboratory data at diagnosis and immediately prior to operation (preoperative) included the following: platelet count; levels of hemoglobin, serum calcium, serum phosphorus, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, total protein, and albumin; prothrombin time; and activated partial thromboplastin time. Adenocarcinoma of bile duct origin was confirmed histopathologically in each patient. Pathological factors examined included: tumor size, tumor grade, lymph node metastases, and margins of resection. Tumor grading was according to the method of Broder. The American Joint Committee on Cancer 2002[17] was used for tumor staging. The anatomical extent of bile duct involvement was typed by the classification of Bismuth and Corlette.[18] Resection was considered as curative in intent if all gross cancer was excised and microscopic margins of resection were tumor free. Major partial hepatic resection was defined as resection of 3 or more anatomical hepatic segments. Regional lymphadenectomy was defined as excision of hilar, cystic, pericholedochal, posterior-superior pancreaticoduodenal, portal, and hepatic arterial lymph nodes. Portal venous resection was either segmental or tangential. Operative mortality was defined as death within 30 days of surgery or during hospitalization of the index operation. Any events prolonging or complicating patient recovery were classified as operative morbidity.

All continuous variables are reported as the mean ± standard deviation. Survival and recurrence rates were calculated using the Kaplan-Meier method.[19] Comparisons of discrete variables in the Kaplan-Meier analyses were made using log-rank tests.[20] The effects of continuous variables on these outcomes were evaluated using Cox proportional hazards models.[21] Potential predictors of survival and tumor recurrence were evaluated in multivariable Cox proportional hazards models. Beginning with a pool of clinically important factors and statistically significant predictors identified in the univariate analyses, variables were selected using stepwise regression. The resulting models were validated using a bootstrap resampling technique with 500 iterations.[22] Variables that were significant in at least 60% of the 500 bootstrap samples were included in the final models. P values $<.05$ were considered statistically significant. All analysis was conducted using SAS version 8.2 (SAS Institute Inc, Cary, NC) on a Sun Ultra II computer (Sun Microsystems Inc, Palo Alto, Calif).

Table 1. Demographics, Clinical Features, Functional Status, and Comorbidities of Patients Undergoing Major Hepatic Resection for Hilar Cholangiocarcinoma*

Men:Women	25:21
Age, mean ± SD, y	59.7 ± 11.3
Duration symptoms, mean ± SD, mo	2.9 ± 4.6 (range, 0-24)
Symptoms	
Weight loss	29 (63)
Pruritis	27 (59)
Anorexia	22 (48)
Pain	21 (46)
Fatigue	19 (41)
Signs	
Jaundice	37 (80)
Hepatomegaly	14 (30)
Fever	5 (11)
Cachexia	3 (7)
Weight loss at diagnosis, mean ± SD, kg	4.2 ± 4.1 (range, 0-15)
Preoperative ECOG[16] status	
0	35 (76)
1	6 (13)
2	5 (11)
Medical comorbidities	
Hypertension	10 (22)
Liver or biliary tract disease	10 (22)
Hepatitis	6 (13)
History of other malignancy	5 (11)
Diabetes mellitus	3 (7)
Preoperative biliary decompression	35 (76)

Abbreviation: ECOG, Eastern Cooperative Oncology Group Scale.
*Values are expressed in number (percentage) of patients unless otherwise indicated.

RESULTS

Forty-six consecutive patients underwent major partial hepatic resection, resection of the extrahepatic bile duct to the head of the pancreas, removal of the gallbladder (if present), regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy for HC during the study period. Demographics and clinical findings of our patients are presented in **Table 1**. There were 25 men and 21 women with a mean ± SD age of 59.7 ± 11.3 years (range, 36-86 years). The mean ± SD duration of symptoms was 2.9 ± 4.6 months (range, 0-24 months). Symptoms included weight loss (29 patients [63%]), pruritis (27 patients [59%]), anorexia (22 patients [48%]), pain (21 patients [46%]), and fatigue (19 patients [41%]). The mean ± SD weight loss at diagnosis was 4.2 ± 4.1 kg (range, 0-15 kg). Physical signs

Table 2. Pathological Findings and TMN Stage of Hilar Cholangiocarcinoma in Patients Undergoing Major Hepatic Resection*

Tumor size, mean ± SD, cm	2.9 ± 1.8
Tumor grade	
1	6 (13)
2	16 (35)
3	17 (37)
4	7 (15)
Lymph node metastases	
No	38 (83)
Yes	8 (17)
Local invasion	
Liver	20 (43)
Portal vein	15 (33)
Hepatic artery	5 (11)
Resection margin	
Negative (R0)	37 (80)
Microscopically positive (R1)	5 (11)
Grossly positive (R2)	4 (9)
Tumor stage (AJCC 2002[17])	
Tis/N0/M0	1 (2)
T1-2/N0/M0	17 (38)
T1-2/N1/M0	0 (0)
T3/N0/M0	20 (43)
T3/N1/M0	8 (17)

Abbreviation: AJCC, American Joint Committee on Cancer.
*Values are expressed as number (percentage) of patients unless otherwise indicated.

at the time of diagnosis included jaundice (37 patients [80%]), hepatomegaly (14 patients [30%]), fever (5 patients [11%]), and cachexia (3 patients [7%]). Only 1 patient had an abdominal mass. Despite these symptoms, the preoperative Eastern Cooperative Oncology Group scale status of patients was 0 in 35 patients (76%), 1 in 6 (13%), and 2 in 5 (11%). Medical history of our patients included the following: a history of liver or biliary tract disease in 10 patients (22%), hypertension in 10 (22%), hepatitis in 6 (13%), other malignancy in 5 (11%), and diabetes mellitus in 3 (7%). Prior biliary tract disease consisted of a prior cholecystectomy for acute or chronic cholecystitis (with or without cholelithiasis) in nearly all patients. Two patients had primary sclerosing cholangitis. Prior malignancies included either squamous cell cancer of the skin or breast cancer.

Diagnostic imaging was not standardized across the study period because of the duration of the study period and both the evolution of imaging modalities and the sequence of imaging obtained. The biliary tract was evaluated by percutaneous transhepatic cholangiography in 37 patients (80%) and by endoscopic retrograde cholangiography in 38 patients (83%). All patients had cholangiographic findings consistent with malignancy. Ninety-six percent of patients (44 of 46) underwent computed tomography. Five patients (11%) had their scan results interpreted as normal. Ultrasonography was used in 37 patients (80%), and results were interpreted as negative for tumor in 6 patients (16%). Visceral angiography was used preoperatively in 37 patients (80%), and results were interpreted as normal in 16 patients (43%). More recently, visceral angiography has been supplanted by computed tomographic angiography and high-resolution Doppler ultrasonography of the hilar vasculature. Preoperative biliary drainage was performed in 35 patients (76%). Biliary tract decompression was performed at the discretion of the interventional radiologist, endoscopist, or surgeon and was not standardized preoperatively.

We classified HC cholangiographically as Bismuth type II in 7 patients (15%), type IIIa in 18 patients (39%), and type IIIb in 21 patients (46%). Patients with Bismuth type II HC required lobectomy because of direct parenchymal invasion or invasion of the lobar vasculature. Seventeen patients (37%) underwent right hepatic lobectomy (segments 5-8), 25 patients (54%) underwent left lobectomy (segments 2-4), and 4 (9%) underwent extended right lobectomy (segments 4-8). Of the 46 patients undergoing resection, 18 (39%) had concomitant caudate lobe (segment 1) resection. The pathological data from our series are shown in **Table 2**. Margins of resection were negative (R0 resection) in 37 patients (80%); microscopically positive (R1 resection) in 5 patients (11%); and grossly positive (R2 resection) in 4 patients (9%). All patients with caudate lobe resections had negative surgical margins. Direct tumor extension into the liver occurred in 20 patients (43%). Extension of HC into the ducts of the caudate lobe was documented pathologically in 9 (50%) of 18 patients. Portal vein invasion was documented pathologically in 15 patients (33%). Hepatic artery involvement was less common, occurring in only 5 patients (11%). Vascular involvement was always ipsilateral to the resected liver.

The mean±SD operative time was 5.8±1.3 hours. The hepaticojejunostomy was intubated intraoperatively in 44 patients (96%) and intubation was transhepatic in 39 (85%) of these patients. Thirty-three patients required intraoperative red blood cell transfusions, with a mean±SD transfusion requirement of 4±5 U. The mean±SD number of red blood cell units transfused during the hospitalization was 6±7 (range, 0-33 units). The patient operative mortality rate was 9% (4/46). The causes of death were gastrointestinal tract hemorrhage from a postoperative pancreatic abscess, ischemic liver failure in 2 patients (1 from a hepatic arterial thrombosis and 1 from a portal vein thrombosis), and multiorgan failure from sepsis.

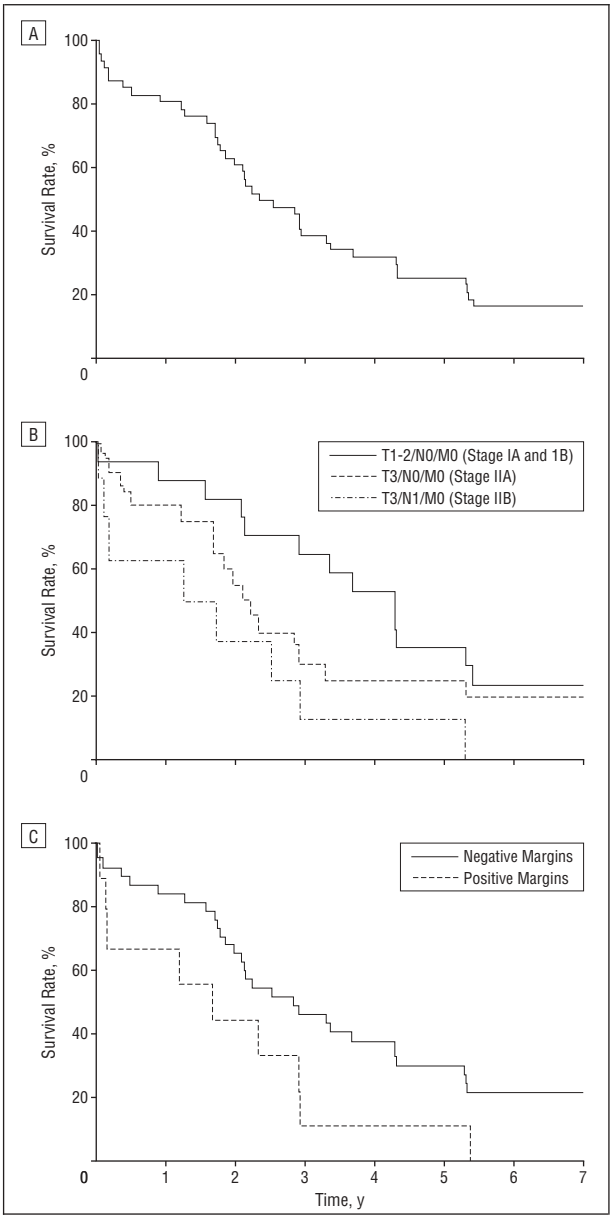
Serious operative morbidity occurred in 24 patients (52%). Complications included transient liver failure in 5 patients (11%), perihepatic abscess in 5 (11%), cholangitis in 3 (7%), wound infection in 3 (7%), biliary leak in 2 (4%), gastric outlet obstruction in 2 (4%), respiratory failure in 2 (4%), and upper gastrointestinal tract bleeding in 2 (4%). A hepatic abscess, pancreatitis, congestive heart failure exacerbation, myocardial infarction, aspiration pneumonia, leakage from the hepaticojejunostomy, vocal cord paralysis, and *Clostridium difficile* colitis each occurred in 1 patient. Some patients had multiple complications. Infectious complications did not differ between patients who had or did not have preoperative biliary decompression.

The overall median survival was 2.3 years and the actual 5-year survival rate was 26% (**Figure**, A). Currently 7 (15%) of 46 patients are alive. Median time from the date of operation to last follow-up for the actual survivors was 6.4 years with the longest follow-up 14.0 years.

The 1-year and 5-year survival rates for patients with curative (R0) resections were 84% and 30%, respectively. The correlation of clinical and pathological factors to survival is presented in **Table 3**. Male sex ($P=.003$), lymph node metastases ($P=.04$), tumor grade 3 or 4 ($P=.03$), elevated direct bilirubin level at diagnosis ($P=.001$), elevated activated partial thromboplastin time value ($P=.04$), and more than 6 U of red blood cells transfused perioperatively ($P=.001$) were statistically significant for poor overall survival. Survival of patients by TNM stage (American Joint Committee on Cancer 2002) was also significant ($P=.04$) (Figure, B). The most robust difference in survival was noted between patients with American Joint Committee on Cancer 2002 stage IA and IB HC and those with stage IIB HC ($P=.009$). R0 resections (Figure, C) and tumor size less than 3 cm approached significance for improved survival ($P=.06$ and $P=.10$, respectively). Adjuvant treatment with chemotherapy, irradiation, or both and resection of the caudate lobe did not affect overall survival.

We documented HC recurrence in 19 (50%) of 38 patients with a median recurrence time of 3.6 years. The longest interval to recurrence was 5.3 years. The primary site of recurrence was the liver in 10 (53%) of 19 patients, the peritoneum in 5 (26%), biliary tract in 4 (21%), retroperitoneum in 3 (17%), and lungs in 1 (5%). Recurrence in the liver was typically adjacent to the resection interface. Some patients had multiple sites of recurrence. No recurrence was considered operable with intent for cure. We performed an analysis of variables associated with tumor recurrence, which is presented in **Table 4**. By univariate analysis, an increased rate of tumor recurrence was associated with male sex ($P=.02$), tumor grade 3 or 4 ($P=.005$), a low hemoglobin level at diagnosis and preoperatively ($P=.01$ and $P=.03$, respectively), a low preoperative prothrombin time ($P=.01$), and a low alkaline phosphatase level at diagnosis and preoperatively ($P=.004$ and $P=.03$, respectively). R0 resection and the absence of lymph node metastases approached significance for recurrence-free survival ($P=.19$ and $P=.16$, respectively). Adjuvant chemotherapy and caudate lobe resection were not associated with the frequency of recurrence.

A stepwise regression model was used to further correlate significant univariate factors to survival and tumor recurrence. In the multivariable analysis for survival, we included age, sex, a history of hepatitis, tumor grade, lymph node metastases, margin status, tumor size, TNM stage, direct bilirubin level at diagnosis, and number of units of red blood cells transfused perioperatively. Identical variables, including the prothrombin time, were used in the multivariable analysis for recurrence. The results of the multivariable analysis for survival and recurrence are presented in **Table 5**. By the multivariable analysis, history of hepatitis, male sex, a high direct bilirubin level at diagnosis, and more than 4 U of red blood cells transfused perioperatively were significantly associated with poorer survival. In contrast, only high tumor grade was significantly associated with increased recurrence rate. When these models were validated using the bootstrap technique, the variables that were validated in our model included only male sex and the number of units of red blood cells transfused perioperatively for overall survival and tumor grade for recurrence.



A, Overall Kaplan-Meier[19] survival rate for all patients undergoing major hepatectomy, bile duct resection, and regional lymphadenectomy. The median survival is 2.3 years, and the 5-year survival rate is 26%. B, Kaplan-Meier survival rate by American Joint Committee on Cancer 2002 stage[17]. The survival difference among all groups is statistically significant ($P=.04$). C, Kaplan-Meier survival rate for patients undergoing R0 resection (negative margins) vs R1 and R2 resections (positive margins). The difference in survival approached statistical significance ($P=.058$).

COMMENT

The major findings of our study of patients with HC undergoing hepatic and biliary tract resection and regional lymphadenectomy with Roux-en-Y hepaticojejunostomy were that the actual survival rate of patients at 5 years was 26% and that few clinicopathological factors were associated with survival. Our findings provide further support for this operative approach for HC recommended by others based on actuarial 5-year outcome.[23-27] Although few

Table 3. Correlation of Clinical and Pathological Factors to Survival in Patients With Hilar Cholangiocarcinoma Undergoing Major Hepatic Resection

Variable*	No. of Patients	Median Survival, mo	Actuarial Survival, %			*P* Value†
			1 y	3 y	5 y	
Sex						
Men	25	23	80	20	8	.003
Women	21	51	81	62	48	
Age, y						
<60	23	39	87	52	26	.29
≥60	23	25	74	26	26	
ECOG status at surgery						
0	35	25	74	34	26	.52
1 or 2	11	39	100	54	27	
History of hypertension						
No	36	34	78	42	25	.89
Yes	10	25	90	30	30	
History of other malignancy						
No	41	26	80	37	22	.13
Yes	5	65	80	60	60	
History of diabetes						
No	43	28	79	40	26	.57
Yes	3	35	100	33	33	
History of PSC						
No	44	28	82	39	25	.51
Yes	2	NA	50	50	50	
History of hepatitis						
No	40	34	82	42	28	.08
Yes	6	14	67	17	17	
Resection margin						
Negative	37	34	84	46	30	.058
Positive	9	20	67	11	11	
Lymph node metastasis						
No	37	34	84	43	27	.04
Yes	8	15	62	12	12	
Caudate lobe resection						
No	28	21	71	29	25	.40
Yes	18	39	94	56	28	
Tumor grade						
1-2	22	35	91	50	36	.03
3-4	24	22	71	29	17	
Maximum tumor size, cm						
≤3.0	33	34	79	42	30	.10
>3.0	13	22	85	31	15	
AJCC tumor stage						
T1-2/N0/M0	17	51	88	65	35	.04
T3/N0/M0	20	25	80	30	25	
T3/N1/M0	8	15	62	12	12	
Chemotherapy given						
Yes	19	35	95	42	16	.91
No	27	26	70	37	33	
AST level at diagnosis, U/L						
≤100	23	34	91	39	22	.27
>100	23	28	70	39	30	
ALT level at diagnosis, U/L						
≤110	35	34	80	40	26	.86
>110	11	25	82	36	27	
Alkaline phosphatase level, U/L at diagnosis						
≤781	23	34	87	35	13	.16
>781	23	28	74	44	39	
Direct bilirubin level at diagnosis, mg/dL						
≤6.4	25	44	92	56	44	.001
>6.4	21	21	67	19	5	
Total bilirubin level at diagnosis, mg/dL						
≤9.9	24	35	88	50	38	.06
>9.9	22	21	73	27	14	

(continued)

Table 3. Correlation of Clinical and Pathological Factors to Survival in Patients With Hilar Cholangiocarcinoma Undergoing Major Hepatic Resection (cont)

Variable*	No. of Patients	Median Survival, mo	Actuarial Survival, %			*P* Value†
			1 y	3 y	5 y	
Albumin level at diagnosis, g/dL						
≤3.6	27	28	78	37	22	.58
>3.6	19	30	84	42	32	
Total protein level at diagnosis, mg/dL						
≤6.75	26	26	81	38	23	.61
>6.75	20	30	80	40	30	
Hemoglobin level at diagnosis, g/dL						
≤13.2	23	34	87	44	39	.06
>13.2	23	26	74	35	13	
Platelet count at diagnosis, $\times 10^3/\mu L$						
≤298	23	35	91	44	30	.21
>298	23	25	70	35	22	
Prothrombin time at diagnosis, s						
≤11.7	26	28	81	38	31	.82
>11.7	20	26	80	40	20	
Preoperative AST level, U/L						
≤91	23	35	91	39	26	.87
>91	23	23	70	39	26	
Preoperative ALT level, U/L						
≤80	37	35	81	43	27	.78
>80	9	23	78	22	22	
Preoperative alkaline phosphatase level, U/L						
≤693	23	25	83	30	13	.08
>693	23	35	78	48	39	
Preoperative direct bilirubin level, mg/dL						
≤4.1	24	39	92	54	29	.13
>4.1	22	22	68	23	23	
Preoperative total bilirubin level, mg/dL						
≤5.7	24	40	92	58	38	.009
>5.7	22	21	68	18	14	
Preoperative albumin level, g/dL						
≤3.4	26	26	77	35	23	.69
>3.4	20	30	85	45	30	
Preoperative total protein level, g/dL						
≤6.5	29	28	83	34	21	.43
>6.5	17	30	76	47	35	
Preoperative hemoglobin level, g/dL						
≤12.9	23	34	87	44	30	.10
>12.9	23	26	74	35	22	
Preoperative platelet count, $\times 10^3/\mu L$						
≤286	23	35	91	44	30	.42
>286	23	25	70	35	22	
Preoperative prothrombin time, s						
≤11.7	25	28	84	32	24	.51
>11.7	21	35	76	48	29	
Preoperative APTT, s						
≤27.9	34	35	82	47	32	.04
>27.9	12	21	75	17	8	
No. of units of RBC transfused in the operating room						
≤2	24	35	88	46	33	.18
>2	22	23	73	32	18	
No. of units of RBC transfused in the hospital						
≤4	25	51	96	60	40	.001
>4	21	21	62	14	10	

Abbreviations: AJCC, American Joint Committee on Cancer; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; NA, not applicable (median survivial not reached); PSC, primary sclerosing cholangitis; RBC, red blood cells.

SI conversion factors: To convert direct and total bilirubin levels to micromoles per liter, multiply by 17.1.

*Continuous variables were divided at the median value.

†Derived by log-rank or χ^2 test.

clinicopathological factors herein were associated with survival, our study supports the finding of others identifying tumor stage and grade and resection margins as significant associations with survival.[12-15,23-27] The frequency of recurrence was significant and clearly dictates investigation of adjuvant treatment strategies.

Table 4. Correlation of Clinical and Pathological Factors to Recurrence in Patients With Hilar Cholangiocarcinoma Undergoing Major Hepatic Resection*

Variable†	No. of Patients	Median Time to Recurrence, mo	Actuarial Recurrence, %			*P* Value‡
			1 y	3 y	5 y	
Sex						
Male	21	21	20	59	59	.02
Female	17	NA	6	25	40	
Age, y						
<60	19	43	10	38	52	.40
≥60	19	63	17	49	49	
ECOG status at surgery						
0	27	63	20	40	45	.61
1 or 2	11	43	0	49	66	
History of hypertension						
No	28	63	11	37	48	.47
Yes	10	17	20	60	60	
History of other malignancy						
No	35	43	12	45	54	.50
Yes	3	NA	33	33	33	
History of diabetes						
No	35	40	15	47	55	.15
Yes	3	NA	0	0	0	
History of PSC						
No	36	43	14	45	53	.31
Yes	2	NA	0	0	0	
History of hepatitis						
No	33	63	12	39	47	.11
Yes	5	13	25	NA	NA	
Resection margin						
Negative	34	63	12	41	49	.19
Positive	4	16	33	NA	NA	
Lymph node metastasis						
No	31	43	13	42	52	.16
Yes	6	16	20	60	60	
Caudate lobe resection						
No	21	32	21	55	62	.29
Yes	17	63	6	31	40	
Tumor grade						
1-2	18	NA	6	28	28	.005
3-4	20	32	22	58	75	
Maximum tumor size, cm						
≤3.0	28	63	11	34	44	.30
>3.0	10	32	20	71	71	
AJCC tumor stage						
T1-2/N0/M0	15	63	7	33	48	.34
T3/N0/M0	16	32	20	50	50	
T3/N1/M0	6	16	20	60	60	
Chemotherapy given						
Yes	17	40	19	44	60	.63
No	21	63	10	44	44	
AST level at diagnosis, U/L						
≤100	20	32	16	56	64	.16
>100	18	NA	12	29	37	
ALT level at diagnosis, U/L						
≤110	28	63	15	43	49	.60
>110	10	43	11	44	58	
Alkaline phosphatase level at diagnosis, U/L						
≤781	20	26	16	65	83	.004
>781	18	NA	12	18	18	
Direct bilirubin level at diagnosis, mg/dL						
≤6.4	20	63	0	35	46	.32
>6.4	18	32	31	55	55	
Total bilirubin level at diagnosis, mg/dL						
≤9.9	18	63	0	34	48	.54
>9.9	20	32	27	52	52	

(continued)

Table 4. Correlation of Clinical and Pathological Factors to Recurrence in Patients With Hilar Cholangiocarcinoma Undergoing Major Hepatic Resection* (cont)

Variable†	No. of Patients	Median Time to Recurrence, mo	Actuarial Recurrence, %			*P* Value‡
			1 y	3 y	5 y	
Albumin level at diagnosis, g/dL						
≤3.6	21	43	20	43	51	.66
>3.6	17	40	6	44	52	
Total protein level at diagnosis, mg/dL						
≤6.75	23	63	14	39	46	.33
>6.75	15	32	14	51	59	
Hemoglobin level at diagnosis, g/dL						
≤13.2	19	NA	6	36	36	.01
>13.2	19	32	22	51	68	
Platelet count at diagnosis, $\times 10^3/\mu L$						
≤298	21	63	19	34	48	.61
>298	17	32	6	55	55	
Prothrombin time at diagnosis, s						
≤11.7	21	43	14	47	54	.55
>11.7	17	NA	13	40	49	
Preoperative AST level, U/L						
≤91	21	40	15	47	56	.54
>91	17	63	12	39	46	
Preoperative ALT level, U/L						
≤80	30	63	14	40	50	.33
>80	8	21	14	57	57	
Preoperative alkaline phosphatase level, U/L						
≤693	21	26	26	67	67	.03
>693	17	NA	0	18	33	
Preoperative direct bilirubin level, mg/dL						
≤4.1	20	63	10	36	49	.72
>4.1	18	26	18	52	52	
Preoperative total bilirubin level, mg/dL						
≤5.7	20	63	5	36	47	.41
>5.7	18	21	24	50	50	
Preoperative albumin level, g/dL						
≤3.4f	22	63	23	45	45	.89
>3.4	16	43	0	41	58	
Preoperative total protein level, g/dL						
≤6.5	25	43	20	46	53	.73
>6.5	13	63	0	38	48	
Preoperative hemoglobin level, g/dL						
≤12.9	19	NA	6	36	36	.03
>12.9	19	32	22	51	68	
Preoperative platelet count, $\times 10^3/\mu L$						
≤286	20	63	15	30	39	.40
>286	18	32	12	58	65	
Preoperative prothrombin time, s						
≤11.7	20	32	16	63	70	.01
>11.7	18	NA	12	23	32	
Preoperative APTT, s						
≤27.9	27	63	12	36	47	.21
>27.9	11	21	19	62	62	
No. of units of RBC transfused in the operating room						
≤2	20	43	10	47	54	.55
>2	18	NA	18	38	47	
No. of units of RBC transfused in the hospital						
≤4	23	63	9	40	45	.42
>4	15	40	23	48	66	

Abbreviations: AJCC, American Joint Committee on Cancer; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; NA, not applicable (median time to recurrence not reached); PSC, primary sclerosing cholangitis; RBC, red blood cells.

SI conversion factors: To convert direct and total bilirubin levels to micromoles per liter, multiply by 17.1.

*Perioperative deaths and patients with R2 resections were excluded.

†Continuous variables were divided at the median value.

‡Derived by log-rank or χ^2 test.

The actual 5-year survival rate for patients undergoing resection of HC by partial major hepatectomy, bile duct resection, and regional lymphadenectomy was 26%. These findings are consistent with the predicted 5-year survival rate ranging from 29% to 40% reported by others performing similar operations during concurrent time

Table 5. Multivariable Analysis of Predictors for Patient Survival and Tumor Recurrence

Variable	Hazard Ratio	95% Confidence Interval for Hazard Ratio	*P* Value
	Survival		
History of hepatitis	4.26	1.57-11.51	.004
Direct bilirubin level at diagnosis >6.4 mg/dL	2.11	1.04-4.30	.04
>4 U of RBC transfused in the hospital*	3.38	1.70-6.82	.001
Male sex*	3.04	1.43-6.47	.004
	Recurrence		
Tumor grade 3 or 4*	3.62	1.29-10.14	.02

Abbreviation: RBC, red blood cells.
SI conversion factor: To convert direct bilirubin levels to micromoles per liter, multiply by 17.1.
*Validated using the bootstrap resampling technique.[22]

periods.[12-15,23-27] Similarly, our operative mortality and morbidity rates of 9% and 52%, respectively, are comparable with others who have reported perioperative mortality rates ranging from 0% to 14% and perioperative morbidity rates from 14% to 64%.[12-15,23-27] Although our perioperative risk decreased across the study period, our findings clearly show that the risk of resection is still significant. These findings, coupled with the reports of reduced risk from centers with special interest in HC and the low overall incidence of HC, support the referral of such patients to tertiary centers for operative management.

Two approaches have been proposed recently to reduce the perioperative risk of partial hepatectomy for HC: (1) preoperative biliary drainage of the anticipated hepatic remnant and (2) preoperative portal vein embolization (PVE) of the anticipated hepatic resection. Internal biliary drainage restores bilioenteric flow, which improves hepatic function, decreases the adverse systemic effects of cholestasis, and may decrease the risk of sepsis by restoration of the enterohepatic circulation of endotoxin-binding bile salts. With complete relief of jaundice by drainage, postoperative liver failure has been less than 10% and infectious complications were not increased.[27-29] Although most of our patients had preoperative biliary drainage, which was not applied in a standardized fashion, a lower total bilirubin level preoperatively was associated with improved survival. We have had no experience with PVE for HC. The rationale for PVE is to induce hypertrophy of the hepatic remnant thereby improving hepatic function and decreasing the risk of postoperative liver failure. Portal vein embolization is not indicated in the presence of an atrophy-hypertrophy complex associated with HC. Several recent reports suggest benefit with a decrease in postoperative liver failure to only 2% after resection of HC.[27,29] To date, PVE has usually been used with concurrent biliary drainage and whether drainage or PVE more significantly influences outcome is unknown. Further investigations of these modalities to reduce perioperative risk seem warranted.

We limited our study to patients undergoing major hepatic resection for HC. Although HC may be resected with curative intent without partial hepatectomy or with minor hepatectomy (<3 segments), intrahepatic biliary extension, direct hepatic parenchymal invasion at the hilar plate, unilobar vascular involvement, and the atrophy-hypertrophy complex more frequently dictate concurrent major hepatectomy for tumor clearance. The small number of patients accrued in our study period reflects our concern in weighing the perioperative risk against the limited survival rate expected for patients with incomplete resection, which occurs not infrequently. Indeed, despite improved resolution of most imaging modalities used to assess resectability of HC and staging laparoscopy, selection of patients for R0 resections remains imprecise.[30] Overall resectability rates currently range from 20% to 80%, and 10% to 50% of resections are R1.[12-15,23-27] Although median survival after R1 resection was 20 months herein, survival of patients after R1 resections of HC have ranged from 11 to 24 months elsewhere.[12-15,23-27] Until prospective quality of life data after R1 resection of HC support its efficacy, we believe that our current conservative position of careful selection of patients for operative management of HC is tenable.

Numerous studies have correlated various clinical and pathological factors with survival of patients with HC after resection. Cumulative evidence strongly supports hepatic resection as a significant predictor of survival. Additionally, low tumor stage, absence of lymph node metastases, R0 resection, caudate lobe resection, and the absence of lobar atrophy have been associated with an increase in survival.[24-31] Our findings are consistent with these reports and further showed that tumor grade was associated with survival. The association of sex with patient survival has previously been reported, but an association of prior hepatitis and volume of perioperative transfusion with poor survival has not been reported for HC. Although female sex was associated with prolonged survival, we are unaware of a cause of this association by hormonal responsiveness of this cancer. The perioperative transfusion is likely a surrogate marker for a complex hospital course and our 4 operative deaths had large transfusion requirements. Previous history of hepatitis (viral type unknown) may reflect both inadequate regenerative and functional capacity. The association of low serum alkaline phosphatase levels and greater tumor recurrence may be a statistically significant association without clinical importance. Although low serum alkaline phosphatase levels may be the result of a more dysplastic epithelium or even occult carcinoma in situ, we have not corroborated those histologic findings with the serum levels herein.

We do support the role of caudate lobectomy as an integral component of partial hepatectomy for HC despite our lack of correlation with survival because of the clinically occult but pathologically recognized extension into the caudate lobe ducts.[29,31] In contrast, we infrequently incorporate resection of all of segment 4 with right hepatectomy (segments 5-8) but extend the resection nonanatomically into segment 4B to provide an adequate parenchymal margin around the hilar plate because segment 4 ducts seldom arise directly anterior from the main left duct. Finally, we have been reluctant to incorporate portal venous resection and reconstruction into our practice because of the associated mortality and morbidity and limited long-term survival.[7,29]

Despite the relatively high complication and mortality rates for resection of HC compared with other hepatic tumors, the 26% 5-year survival rate is comparable to that of primary and metastatic cancer to the liver. However, the high local and regional failure rates and overall survival rate support the investigation of adjuvant therapies. Both systemic and local-regional modalities such as intraoperative radiation, brachytherapy, and photodynamic therapy warrant multi-institutional review.[32,33] For those patients with locally unresectable HC, recent results with aggressive neoadjuvant chemoirradiation and liver transplantation offer hope to highly select patients.[34,35]

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DISCUSSION

John J. Brems, MD, Burr Ridge, Ill: Hilar cholangiocarcinoma continues to be a very difficult carcinoma to treat. Cholangiocarcinoma has an incidence of 1 per 100 000 individuals per year in the United States. Today, surgical resection remains the only treatment to demonstrate improvement in long-term survival. Unfortunately, many of these patients present very late in the course of their disease and resection is often not possible.

The authors today presented a 20-year retrospective outcome study of 46 consecutive patients who had resection of a hilar cholangiocarcinoma by major hepatectomy, bile duct resection, and regional lymphadenectomy at the Mayo Clinic. These patients were all resected between 1979 and 1997; therefore, there is at least a 5-year interval follow-up of these patients. The study is weakened because this is a retrospective review and because it took place over a long time interval. During that time interval there have been major advances in imaging techniques and techniques for hepatic resection.

However, there is some very important information presented by the authors. They found in the resected specimens that 50% of the patients had extension of the hilar cholangiocarcinoma into the caudate lobe and all caudate lobe resections had negative margins. This is very important because in order to obtain a negative margin in many of these patients, it is now recognized that the caudate lobe needs to be resected when we resect the hilar cholangiocarcinoma.

They also found that a lower serum bilirubin level was associated with improved survival. This argues for early detection and for considering biliary decompression on these patients before resecting them.

The other important aspect of this study is that despite the study taking place over 20 years' time, they had an overall greater than 25% 5-year survival. This is very encouraging, especially when we consider the 5-year survival for pancreatic carcinoma and other types of hepatobiliary carcinomas. Therefore, we should aggressively try to resect these carcinomas and look for other treatment modalities to increase survival after resection.

I have questions I'd like to ask the authors. The authors have shown that these lesions can be resected with reasonable long-term survival. However, many times these patients are not resectable because the lesion is either diagnosed late or, at the time of resection, the patient is found to have extrahepatic disease. I would like to know what they consider an adequate workup before operating on these patients. Specifically, should we perform laparoscopy and endoscopic ultrasound or laparoscopic ultrasound on these patients to determine if they have unresectable lesions? If we could determine who is resectable and who isn't, this would decrease the number of laparotomies for unresectable disease.

My next 2 questions concern the portal vein. The first is what do they consider the role for portal vein embolization before resection of the hilar cholangiocarcinoma? Some authors have advocated that portal vein embolization should be performed to induce contralateral hypertrophy of the lobe of the liver that is not to be resected. However, it is questionable whether a jaundiced liver would hypertrophy.

Next, many times these patients are not resectable because of tangential portal vein involvement. What do they consider the role for portal vein resection in these patients?

The last question: The Mayo Clinic along with the University of Nebraska recently reported information about liver transplantation for cholangiocarcinoma. Up until recently it was felt that hilar cholangiocarcinoma was a contraindication to liver transplantation. The initial results were dismal and with the shortage of donors, it was not felt to be a good use of a scarce resource. However, recently the Mayo Clinic and the University of Nebraska developed protocols for these patients being treated with neoadjuvant radiochemotherapy followed by liver transplantation. The initial results are promising from both centers; however, the follow-up has not been long enough to really validate this option. I am curious to know how they determine which of their patients can be referred for liver transplantation and which of their patients are referred for resection. In addition, both groups have talked about the use of neoadjuvant chemoradiotherapy to downstage the tumor before liver transplantation. I was wondering what their thoughts are on utilizing this strategy in these tumors to downstage these patients before they undergo resection. This strategy has been utilized for esophageal and rectal carcinomas with promising results. I was wondering what the authors thought about this.

Dr Nagorney: Thank you, Dr Brems. Your questions are astute. We clearly admit the weaknesses of a retrospective analysis and the variations in technique that evolved over the study period as we learned how to approach this tumor, as others have. In regard to question 1 about reoperative evaluation of our patients, we emphasize the accuracy of cholangiography to get a very clear assessment of the hilar ducts. As the Sloan Kettering group has recommended, we have incorporated preoperative laparoscopy more frequently into our diagnostic evaluation. In general, we have utilized laparoscopy to exclude peritoneal disease or occult liver metastases. I have not been comfortable using laparoscopic ultrasound to assess the relationship of the tumor to the vessels. I still think it underestimates involvement.

You asked about portal vein embolization. We have not undertaken portal vein embolization in any of our patients with hilar cholangiocarcinoma. I think it is a useful tool, but I am not sure of the exact role of portal vein embolization at this time. I think preparing the patients for surgery requires decompression of the biliary tree, and decompression of the planned remnant lobe optimizes its function. The added advantage of portal vein embolization in enhancing the liver reserve is unknown.

Additionally, although some would undertake resection of hilar cholangiocarcinomas by trisegmentectomies, we often extend our resections nonanatomically into segment 4B to obtain margins around the involved liver. Seldom do the segment 4B ducts arise from the left main duct. By minimizing the volume of liver resected by nonanatomic extension on the basis of ductal anatomy, we seldom see the need for vein embolization.

Portal vein reconstruction is a difficult issue. Clearly portal vein reconstruction is much easier on the left than it is to the right because of the angulation of the left portal vein. You can simply take out the segmental resection of the left portal vein and do an end-to-end anastomosis. With the right portal vein, segmental resection often precludes such reconstruction and autogenous vein grafts are necessary. Consequently, we seldom reconstruct the right portal vein. Overall, I recommend segmental resection of the portal vein and end-to-end anastomosis rather than tangential excision because of the narrowing of venorrhaphy in my experience.

The last 2 questions relate to liver transplantation. We have had a protocol for liver transplantation for hilar cholangiocarcinoma since 1993. We have enrolled 51 patients in that protocol of which 28 have undergone transplantation. The results are promising to date. Even inclusive of all 51 patients enrolled with an intent-to-treat analysis, the 5-year survival exceeds 50%. Quite encouraging even compared to resection.

In general, we only employ liver transplantation for Bismuth type IV hilar cholangiocarcinomas. Moreover, we stage all patients by laparotomy prior to transplantation to exclude lymph node metastases. And finally, regarding neoadjuvant therapy, we have not employed neoadjuvant therapy except in our transplant patients. Knowing what the neoadjuvant therapy does to the ductal system with the external beam irradiation and iridium brachytherapy, the ducts are not hospitable to anastomosis. I think the real role for adjuvant therapy will be postoperative and the American College of Surgeons Oncology Group is addressing that issue, hopefully in a multi-institutional study.

Ernest E. Moore, MD, Denver, Colo: An intriguing finding of this review is the profound influence of blood transfusion on outcome. Do you have a speculation as to the mechanistic link? Is this simply a surrogate for more complicated operations, or is it, in fact, the immune consequences of stored red cells. In that light, have you modified your approach to blood

transfusion? Do you use a higher transfusion trigger? Have you looked at the age of your red cells and used fresher blood? And, of course, this invites the intriguing concept of using blood substitutes in oncologic surgery. Do you leukoreduce your stored red cells?

Dr Nagorney: I would have to say given the duration of this study that the primary relationship of transfusion to survival is related to the extent of the operation. In fact, several patients had quite extensive transfusion needs. I do not think the effect was related to the immunomodulatory effect of blood. I do think further investigation of the relationship is worth considering.

Stephen G. Remine, MD, Southfield, Mich: David, that was an absolutely outstanding report of some very difficult cases. Having been in the lion's den a few times with these kinds of cases, I just had 2 technical questions and also 2 questions related to management. I noticed that 20% of your patients came in without jaundice. In the unobstructed duct, particularly in the intrahepatic reconstructions, have you any hints on how to deal with the very thin walled duct and how to reconstruct it? I found this reconstruction to be extremely difficult and at times very treacherous.

Secondly, knowing that the resected margin and the positive lymph nodes are negative predictors of survival, has that changed how you intraoperatively approach these patients, or, like most of us, is that a finding after the fact once we get the tissue back?

Two other questions. One of the problems that I have been plagued with in our series is the multicentricity of some of these cases and how do you deal with that if you can identify it? And, finally, many of our colleagues in other specialties are not always as profoundly impressed with our results as we are. Particularly with these outstanding results that you have presented today, have you been successful in changing the philosophy of your colleagues in gastroenterology and radiology to support you?

Dr Nagorney: Thank you, Dr Remine. I will answer your last question first. I am not sure I have been able to change the philosophy of my colleagues—that is a difficult undertaking. I do think that we have convinced some that we do better with cholangiocarcinoma than with pancreatic carcinoma, but there is still a reluctance to push for resection by many of our colleagues.

How to address the thin duct on an unobstructed patient is difficult. I can only recommend careful technique and a small, thin, silastic biliary stent to bridge the anastomosis. I also tack the Roux limb to the liver to reduce tension on the anastomosis. I have not employed any other special technique like the mucosal graft technique for these anastomoses.

Regarding margins, we have been very conservative in our approach with resecting hilar cholangiocarcinoma because of our concern with margins. The data from the literature suggest that survival in patients with a positive margin is almost the same as no resection. Thus, we remain conservative in our approach.

The data regarding survival and lymph node metastases are sparse. We continue resection even if nodes are grossly involved provided that regional lymphadenectomy will clear all gross regional disease. Lymph node metastases will always remain a negative prognostic indicator.

We simply don't resect patients with multicentric tumors. If patients have multicentric tumors that are intrahepatic and don't extend beyond the cystic duct entry into the main bile duct, they are considered candidates for our liver transplant protocol.

Mark Talamonti, MD, Chicago, Ill: I have a question for you about the selection criteria for resection. There were 46 patients over 22 years, and I am sure that over that period of time you saw many more hilar cholangiocarcinomas that were probably resected but without concomitant hepatic resection. My first question has to do with how do you select who gets hepatic resection vs who does not and do you have data comparing those 2 groups in terms of survival if they did not have a hepatic resection but did have biliary resection without concomitant hepatic resection? Then in terms of the staging studies, I also have a question about the use of MRA [magnetic resonance angiography] and MRC [magnetic resonance cholangiography]. That has become increasingly more useful, at least in our practice, and has in many cases obviated manipulation of the biliary tract prior to surgery, and some studies would suggest a lower infection rate if you don't have to have stents placed preoperatively. I would welcome your comments about the role of MR [magnetic resonance] and MRC and MRA.

Dr Nagorney: Well, I think anybody with a type III hilar cholangiocarcinoma (either IIIa or IIIb) requires liver resection. The real issue gets to be with Bismuth type II hilar cholangiocarcinomas where there is not extension unilaterally into the intrahepatic ductal system. If there is direct hepatic invasion, we employ liver limited resection. It would be inappropriate to try to compare resections of the cholangiocarcinoma without liver resections for type III cancers because we would be leaving positive margins frequently. The so-called skeletonization procedures have gone out of vogue. We would tend to err on the side of doing a liver resection as opposed to not.

I agree that MRA and MRC are important, and we continue to evaluate those modalities. I don't think the resolution of MRC is equivalent to direct cholangiography. Although we use MRC, unless the hilar ductal anatomy is already defined, we perform direct cholangiography.

My own personal philosophy, although not proven at Mayo, is to espouse the views of Nimura, who favors preoperative drainage of the biliary tree. Our results herein show the incidence of postoperative infection was not affected by drainage. I would rather err on the side of making the liver functioning optimally before operation as opposed to not.

Katherine J-M Liu, MD, Chicago: Because we know that a clear resection or zero resection probably is one of the most important factors in terms of survival, actually the 25% of the 5-year survival is excellent considering it included R1 and R2 resections. Now, did you analyze your 5-year survival for simply the R0 resections?

The second question: you also have a few patients who had vascular involvement, not only the portal veins but also the hepatic arteries. In those patients, are they R0 resections and how does the vascular involvement affect their long-term survival?

Dr Nagorney: Yes, we did analyze for the R0 resections and even inclusive of perioperative deaths, R0 resection survival exceeds 30%. Regarding the vascular involvement, all patients who had vascular involvement had unilateral vascular involvement on the side of the resected liver. I can't tell you specifically if it was gross or microscopic involvement.