ORIGINAL ARTICLE

Improvement in Perioperative and Long-term Outcome After Surgical Treatment of Hilar Cholangiocarcinoma

Results of an Italian Multicenter Analysis of 440 Patients

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Objective: To evaluate improvements in operative and long-term results following surgery for hilar cholangiocarcinoma.

Design: Retrospective multicenter study including 17 Italian hepatobiliary surgery units.

Patients: A total of 440 patients who underwent resection for hilar cholangiocarcinoma from January 1, 1992, through December 31, 2007.

Main Outcome Measures: Postoperative mortality, morbidity, overall survival, and disease-free survival.

Results: Postoperative mortality and morbidity after liver resection were 10.1% and 47.6%, respectively. At multivariate logistic regression, extent of resection (right or right extended hepatectomy) and intraoperative blood transfusion were independent predictors of postoperative mortality ($P=.03$ and $P=.006$, respectively); in patients with jaundice, mortality was also higher without preoperative biliary drainage than with biliary drainage (14.3% vs 10.7%). During the study period, there was an increasingly aggressive approach, with more frequent caudate lobectomies, vascular resections, and resections for advanced tumors (T stage of 3 or greater and tumors with poor differentiation). Despite the aggressive approach, the blood transfusion rate decreased from 81.0% to 53.2%, and mortality slightly decreased from 13.6% to 10.8%. Median overall survival significantly increased from 16 to 30 months ($P=.05$). At multivariate analysis, R1 resection, lymph node metastases, and T stage of 3 or greater independently predicted overall and disease-free survival.

Conclusions: Surgery for hilar cholangiocarcinoma has improved with decreased operative risk despite a more aggressive surgical policy. Long-term survival after liver resection has also increased, despite the inclusion of cases with more advanced hilar cholangiocarcinoma. Preoperative biliary drainage was a safe strategy before right or right extended hepatectomy in patients with jaundice. Pathologic factors independently predicted overall and disease-free survival at multivariate analysis.

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HILAR CHOLANGIOCARCINOMA (HC), or Klatskin tumor,[1] represents more than 50% of all biliary tract cholangiocarcinomas.[2] Radical surgical resection is the only treatment offering a chance of long-term survival[3]; it combines resection of main biliary confluence with partial hepatectomy including the caudate lobe.[4-9] The central location of the tumor and its close relationship with vascular structures at the hepatic hilum have resulted in a low resectability rate and high morbidity and mortality.[3] During the past 2 decades, the rate of resectability has increased owing to wider application of aggressive surgery with concomitant vascular resection and reconstruction, and early and long-term outcomes have considerably improved.[10,11] Most articles about the changing trends in the surgical approach to HC report results from single institutions, with data on a few patients collected.[12,13] Moreover, the clinicopathologic characteristics of patients with HC differ from those of patients with intrahepatic cholangiocarcinoma involving the hepatic hilum and implicate a different prognosis after surgical resection,[14] whereas in many studies[7,15-17] the 2 conditions were considered to be the same entity.

The aim of this Italian multicenter study was to evaluate improvements in operative results and long-term outcome following surgical resection for HC during

Table 1. Characteristics of the 440 Patients

Characteristic	Value
Age, y	
Mean (SD)	64 (6.7)
Range	30-95
Sex, No. (%)	
Male	250 (56.8)
Female	190 (43.2)
Obstructive jaundice, No. (%)	304 (69.1)
Preoperative CEA, ng/mL	
Mean	252
Range	0-6354
Preoperative CA 19-9, U/mL	
Mean	2378
Range	0-141 000
Extent of biliary involvement, No. (%)[a]	
Type 1	36/440 (8.2)
Type 2	80/440 (18.2)
Type 3	304/440 (69.1)
Type 3a	115/304 (37.8)
Type 3b	126/304 (41.4)
Unknown	63/304 (20.7)
Type 4	20/440 (4.5)

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen.
SI conversion factors: To convert CEA to micrograms per liter and CA to kilounits per liter, multiply by 1.0.
[a] Bismuth-Corlette classification.

a 16-year period in a large cohort of patients with the same proven tumor entity.

METHODS

Data were collected from 17 hepatobiliary Italian centers, members of the Italian Chapter of the International Hepato-Pancreato-Biliary-Association (IHPBA). The study included patients who underwent resection from January 1, 1992, through December 31, 2007, for histologically proven HC.[1] Patients who underwent resection for intrahepatic cholangiocarcinoma involving the hepatic hilum were excluded. Centers that collected 40 or more cases during the established period were considered high-volume centers. Time trend analysis was performed to evaluate improvements along time in perioperative and long-term results after liver resection.

For each patient, the following data were collected: demographic information, clinical presentation, use and type of preoperative biliary drainage, use of preoperative portal vein embolization, and staging laparoscopy. Operative details included type of resection, use of pedicle clamping, and use of blood transfusions. Early and late results included postoperative mortality and morbidity, 5-year overall survival (OS) and disease-free survival (DFS), and recurrence rate. Pathologic data included histologic type (sclerosing or papillary), size of tumor, grading, presence of perineural invasion, radicality of resection (biliary margin status), invasion of biliary ducts of caudate lobe, and lymph node involvement. Pathologic tumor staging was based on the TNM classification of the International Union Against Cancer staging system (6th edition).[18] Extent of bile duct involvement was typed by the Bismuth-Corlette classification.[19] Liver resections were defined according to the terminology of the IHPBA.[20]

STATISTICAL ANALYSIS

Overall survival and DFS were calculated using the Kaplan-Meier method. Patients who postoperatively died were included in the OS analysis (intention-to-treat criteria) and excluded from the DFS analysis. Differences between survival rates were analyzed with the log-rank test.

The χ^2 test was used to compare proportions. Significance was defined as $P < .05$. The Cuzick nonparametric test for trend analysis across ordered groups[21] (an extension of the Wilcoxon rank-sum test) was performed to assess whether surgical outcomes and patient characteristics varied over time. Statistical analysis was performed using SPSS software, version 13.0 (SPSS, Inc).

Table 2. Type of Resection in 440 Patients

Type	No. (%)
Main biliary confluence excision alone	64/440 (14.5)
Associated liver resection	376/440 (85.5)
Right hepatectomy	25/376 (6.6)
With S 1	44/376 (11.7)
With S 4	10/376 (2.7)
With S 4-1	93/376 (24.7)
Left hepatectomy	28/376 (7.4)
With S 1	151/376 (40.2)
With S 5-8	1/376 (0.3)
With S 1-5-8	2/376 (0.5)
Mesohepatectomy (S 4-5-8)	19/376 (5.1)
With S 1	3/376 (0.8)

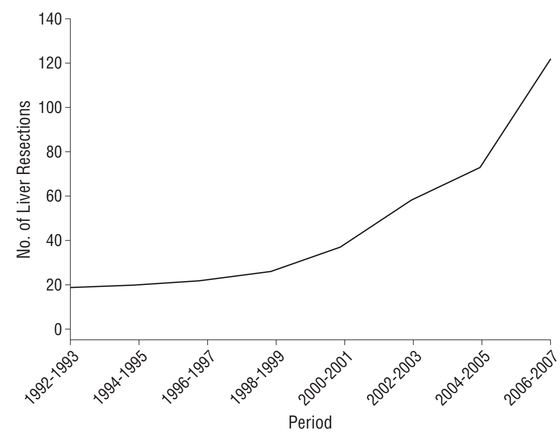

Figure 1. Number of liver resections for hilar cholangiocarcinoma during the period of study.

RESULTS

From January 1, 1992, through December 31, 2007, a total of 440 patients were treated with curative intent surgery for HC (**Table 1**). Five of the 17 centers (29.4%) reported 40 or more patients who underwent resection and accounted for 317 patients (72.0%).

Liver resection combined with main biliary confluence excision was performed in 376 patients (85.5%) (**Table 2**). **Figure 1** shows a steady yearly increase in the number of liver resections; during the most recent 2-year period listed (2006-2007), 121 hepatectomies were performed (32.2% of all hepatectomies).

Preoperative ultrasonography was performed in all patients. Preoperative evaluation was performed by abdominal computed tomography and magnetic reso-

Table 3. Operative Results After Surgical Treatment of Hilar Cholangiocarcinoma

Result	Value
Hepatic pedicle clamping, No. (%)	103/376 (27.4)
Duration, min	
Mean (SD)	30.7 (19.3)
Median (range)	25.5 (5-140)
Blood transfusions, No. (%)	208/440 (47.3)
No. of units	
Mean (SD)	3 (1.7)
Range	1-14
Postoperative mortality, No. (%)	38/440 (8.6)
After liver resection	38/376 (10.1)
After main biliary confluence resection	0/64
Cause of mortality, No. (%) of known causes	
Liver failure	13/27 (48.1)
Sepsis	8/27 (29.6)
Hemoperitoneum with multiorgan failure	3/27 (11.1)
Multiorgan failure	1/27 (3.7)
Pulmonary complications	1/27 (3.7)
Gastrointestinal hemorrhage	1/27 (3.7)
Not reported	11/38
Postoperative morbidity, No. (%) of survivors	191/402 (47.5)
After liver resection	161/338 (47.6)
After main biliary confluence resection	30/64 (46.8)
Postoperative morbidity, No. (%) of known causes	
Biliary fistula	37/146 (25.3)
Liver failure	25/146 (17.1)
Subphrenic abscess	20/146 (13.7)
Sepsis	18/146 (12.3)
Pulmonary complications	14/146 (9.6)
Cardiovascular complications	8/146 (5.5)
Hemoperitoneum	7/146 (4.8)
Ascites	4/146 (2.7)
Other causes	13/146 (8.9)
Not reported	45/191
Reintervention, No. (%)	28/440 (6.4)
After liver resection	24/376 (6.4)

nance cholangiopancreatography in 217 patients (49.3%), by computed tomography alone in 178 (40.5%), and by magnetic resonance cholangiopancreatography alone in 45 (10.2%). At imaging, a nodular lesion was documented in 218 patients (49.5%) and a focal stricture of main biliary confluence without evidence of neoplastic mass was documented in the remainder.

STAGING LAPAROSCOPY

Staging laparoscopy was routinely performed in 4 centers (23.5%), in a total of 88 patients. This procedure detected peritoneal carcinomatosis in 1 of the 88 patients (1.1%).

PREOPERATIVE BILIARY DRAINAGE

Preoperative biliary drainage was performed in 294 patients (66.8%). Of these 294 patients, it was performed percutaneously in 161 (54.8%), endoscopically in 95 (32.3%), by both procedures in 18 (6.1%), and by unspecified procedure in 20 (6.8%).

The mean (range) number of stents placed by endoscopic retrograde cholangiopancreatography was 1.4 (1.0-4.0). The mean (range) number of percutaneously placed biliary drainages was 1.3 (1.0-3.0). In 80.4% of percutaneously treated patients, a transpapillary drainage was placed.

Table 4. Multivariate Analysis of Predictive Factors for Postoperative Mortality After Liver Resection

Factor	Mortality, %	OR (95% CI)	*P* Value
Intraoperative blood transfusion: no vs yes	3.7 vs 14.9	3.96 (1.48-10.62)	.006
Extent of hepatectomy (right or right extended hepatectomy): no vs yes	6.0 vs 14.8	2.30 (1.07-4.99)	.03

Abbreviation: OR, odds ratio.

Preoperative cytology or histology of the neoplasm was sought in 33 of the 294 patients who underwent drainage (11.2%): by brushing for cytology in 19 and by biopsy for histology in 14. Malignancy was not confirmed in 18 patients: the overall sensitivity rate was 15 of 33 (45.5%), without significant differences for brushing (7 of 19 [36.8%]) vs biopsy (8 of 14 [57.1%]).

RIGHT PORTAL VEIN EMBOLIZATION

Right portal vein embolization was performed in 37 of 172 surgical procedures of right or right extended hepatectomies (21.5%). Liver resection followed after a mean (range) of 47 (30-90) days (median, 36 days).

OPERATIVE RESULTS

Operations and results are shown in Table 2 and **Table 3**. Caudate lobectomy was performed in 293 of 376 liver resections (77.9%).

Of all 440 patients, lymphadenectomy of hepatoduodenal ligament was performed in 423 (96.1%). This procedure was extended to para-aortic lymph nodes in 125 patients (28.4%).

Of 376 patients who underwent liver resections, the postoperative mortality was 10.1% (38 patients). Postoperative morbidity after liver resection (47.6%) or after main biliary confluence resection alone (46.8%) was not significantly different. The rate of reinterventions was 6.4% for both.

Risk of mortality was assessed in a multivariate logistic regression model including age, sex, extent of biliary involvement, extent of hepatectomy, caudate lobectomy, vascular resection, pedicle clamping, and intraoperative blood transfusion. Intraoperative transfusion ($P=.006$) and extent of hepatectomy (right or right extended hepatectomy) ($P=.03$) emerged as independent predictors of mortality (**Table 4**). **Table 5** shows differences in operative and pathologic factors between high- and low-volume centers.

The rate of liver resection was higher in high-volume than in low-volume centers: 90.9% (288 of 317) vs 71.5% (88 of 123) ($P<.001$). At multivariate logistic regression, blood transfusion and extent of hepatectomy were reconfirmed as predictors of postoperative mortality, whereas the factor high-volume center was not associated with significantly higher mortality (odds ratio, 1.66; $P=.32$), despite more aggressive surgical approaches.

Table 5. Operative and Pathologic Factors According to the Volume of Centers by Univariate Analysis[a]

Factor	No. (%) High Volume	No. (%) Low Volume	P Value
Biliary confluence excision alone	29/317 (9.2)	35/123 (28.5)	<.001
Caudate lobe resection	244/288 (84.7)	49/88 (55.7)	<.001
Vascular resection	33/288 (11.5)	9/88 (10.2)	.94
Blood transfusions	158/288 (54.8)	36/88 (40.9)	.02
Morbidity	129/288 (44.8)	32/88 (36.4)	.29
Mortality	33/288 (11.5)	5/88 (5.7)	.24
Bismuth type 3 or 4	250/288 (86.8)	67/88 (76.1)	.04
Stage III or IV	75/288 (26.0)	6/88 (6.8)	<.001
Perineural invasion	217/288 (75.3)	51/88 (57.9)	.02

[a] Centers that collected 40 or more cases during the established period were considered high-volume centers.

Table 6. Pathologic Factors in 440 Patients

Factor	Value
Histologic factor, No. (%)	
Sclerosing	415/440 (94.3)
Papillary	25/440 (5.7)
Tumor size, cm	
Mean (SD)	2.5 (1.2)
Range	0.5-5.5
Grading, No. (%)	
G1	76/403 (18.9)
G2	218/403 (54.1)
G3	107/403 (26.6)
G4	2/403 (0.5)
Unknown	37/440
Perineural invasion, No. (%)	305/440 (69.3)
Caudate lobe invasion, No. (%)[a]	37/154 (24.0)
Margin status, No. (%)	
R0 resections	340/440 (77.3)
After liver resection	298/376 (79.2)
After main biliary confluence resection	42/64 (65.6)
R1 resections	100/440 (22.7)
UICC stage, No. (%) of known	
IA	19/425 (4.5)
IB	78/425 (18.4)
IIA	135/425 (31.8)
IIB	104/425 (24.5)
III	83/425 (19.5)
IV	6/425 (1.4)
Unknown	15/440
Lymph node involvement, No. (%) of known	
N0	280/423 (66.2)
N1	143/423 (33.8)
Unknown	17/440

Abbreviation: UICC, International Union Against Cancer.[15]
[a] Data were available on 154 of the 293 caudate lobectomies.

LIVER RESECTION AND PREOPERATIVE BILIARY DRAINAGE

Among the 376 patients who underwent liver resection, 299 presented with obstructive jaundice. Of these 299 patients, 252 (84.3%) underwent preoperative biliary drainage and 47 (15.7%) did not. Risk of mortality (assessed by direct standardization to adjust for blood transfusion and extent of resection) tended to be higher following hepatectomy without biliary drainage than following hepatectomy with biliary drainage (14.3% vs 10.7%; $P = .41$).

PATHOLOGY

Final pathology showed nodular-sclerosing tumor in 94.3% of cases (**Table 6**). Data on neoplastic invasion of caudate lobe biliary ducts was available on 154 patients; invasion was found in 24.0% of them. R0 resections were performed in 340 patients (77.3%). There were 100 R1 resections; the cause was invasion of proximal bile duct margin in 89 patients (89.0%), of distal bile duct margin in 7 (7.0%), and of both margins in 4 (4.0%). The R0 resection rate was higher after associated liver resection than after biliary confluence resection alone (79.2% vs 65.6%; $P = .01$) (Table 6).

TIME TREND ANALYSIS OF OPERATIVE AND PATHOLOGIC RESULTS

Figure 2 shows the changing trends during the study period, assessed by locally weighted scatterplot smoothing. Postoperative mortality and morbidity peaked before 1996, then decreased until 2000, and thereafter moderately increased. During the last 4 years of study, compared with the initial 4 years, mortality and morbidity tended to decrease, the blood transfusion rate significantly decreased, and rates of associated vascular and caudate lobe resections and of hepatectomies for advanced stage and poorly differentiated tumors significantly increased.

SURVIVAL ANALYSIS

The 5-year OS after surgical resection was 25.5% and the 10-year OS was 19.9% (median survival, 25 months) (**Figure 3**). The impact of associated liver resection on improved long-term results was analyzed in a subgroup of patients operated on in the first period of study with follow-up of 8 years or longer: patients undergoing associated liver resection had a significantly higher 5-year OS afterward than did those after biliary confluence resection alone (26.6% vs 0.0%; $P = .02$), with a 10-year OS of 20.0% (**Figure 4**).

Five-year OS after R0-liver resection was not significantly different in high- vs low-volume centers (35.2% vs 35.8%; $P = .50$).

Time trend analysis showed a significant increase in median survival during the period of study (**Figure 5**). Median survival during the initial 4 years was lower than during the last 4 years (16 vs 30 months; $P = .05$).

Recurrence was noted in 54.5% of patients (219 of 402 patients, excluding postoperative deaths). Mean (range) time to recurrence was 17 (1-120) months (median, 12 months).

At univariate analysis (**Table 7**), 8 factors were associated with significantly lower OS: perineural invasion, R1 resection, lymph node metastases, stage III or greater, T stage of 3 or greater, grading of 2 or greater, age 60 years or older, and caudate lobe invasion. These same factors, excluding perineural invasion and age of 60 years or older, were predictive of DFS.

At multivariate analysis (**Table 8**), R1 resection, lymph node metastases, T stage of 3 or greater, and perineural

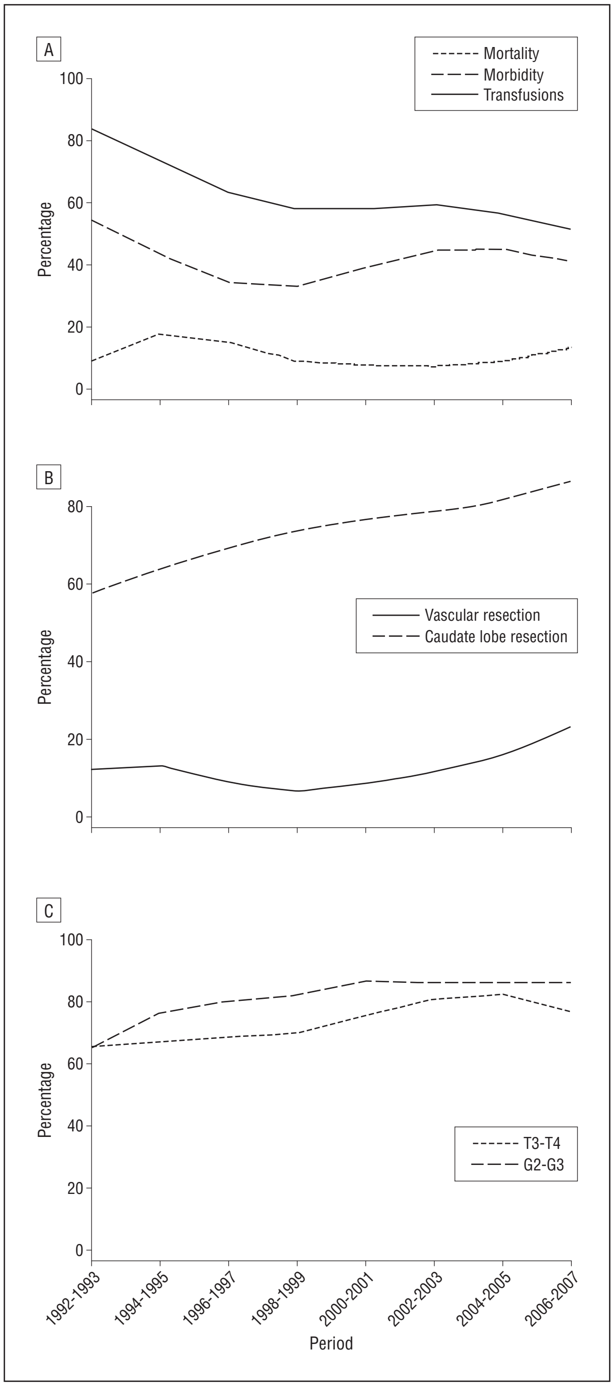

Figure 2. Time trend analysis of operative and pathologic results during the study period. A, Mortality and morbidity rates during the initial 4 years of the study were higher than during the final 4 years (13.6% and 52.3% vs 10.8% and 43.8%, respectively; $P = .27$). The use of blood transfusion significantly decreased from 81.0% during the initial 4 years to 53.2% during the final 4 years ($P = .002$). B, Rates of associated vascular resection and of caudate lobe resection significantly increased from 14.0% and 59.1% during the initial 4 years to 20.1% and 84.4% during the final 4 years ($P = .05$ and $P < .001$, respectively). C, Rates of resected T3-T4 tumors and of G2-G3 tumors significantly increased from 66.7% and 72.2% during the initial 4 years to 79.3% and 86.5% during the final 4 years ($P = .04$ and $P = .02$, respectively).

invasion were independent predictors of poor OS; except for perineural invasion, these same factors independently predicted poor DFS. Volume of the center was not an independent predictor of OS ($P = .11$) or DFS ($P = .72$).

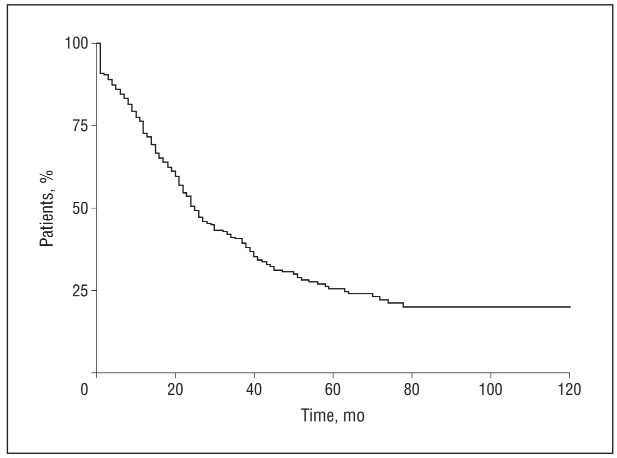

Figure 3. Overall survival after surgical resection for hilar cholangiocarcinoma. Five- and 10-year overall survival rates were 25.5% and 19.9%, respectively.

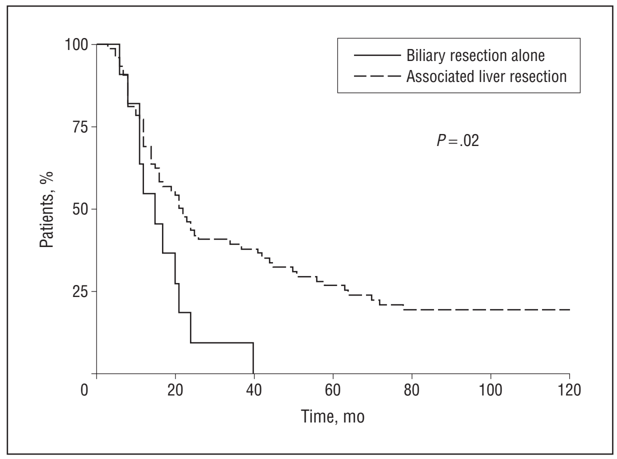

Figure 4. Overall survival of patients who underwent resection during the first period of study (1992-1999) according to the type of resection. Five-year overall survival following associated liver resection was significantly higher than that following main biliary confluence resection alone (26.6% vs 0.0%, respectively; $P = .02$). Ten-year survival after liver resection was 20.0%.

VASCULAR RESECTION

Vascular resection was performed in 42 of 376 hepatectomies (11.2%). Of these 42 patients, portal resection was performed in 35 (83.3%), hepatic artery resection in 5 (11.9%), and resection of both in 2 (4.8%).

Postoperative mortality after hepatectomy with combined vascular resection (19.0% [8 of 42 patients]) exceeded that of liver resection alone (9.0% [30 of 334 patients]) ($P = .04$). Final pathology confirmed vascular invasion in 22 of 42 patients (52.4%). Five-year OS after hepatectomy with vascular resection was 22.8%.

By stratifying patients according to the combination of vascular resection and T stage, excluding postoperative deaths, 5-year OS for T1 or T2 stage tumors was significantly higher than for T3 or T4 stage tumors, irrespective of the use of vascular resection (**Figure 6**).

COMMENT

To our knowledge, this is the first multicenter Italian study on surgical management of HC. Data on 440 patients were collected, and prognostic factors of 376 patients who underwent associated major hepatectomy were analyzed. To address a unique and specific tumor entity, only patients with histologically proven HC[1] were included. Patients with intrahepatic cholangiocarcinoma involving the hepatic hilum (perihilar cholangiocarcinoma) were excluded. Previously, both types of patients were often analyzed together because they required the same kind of hepatobiliary resection[7,15-17]; however, their prognosis is different, with better OS for patients with HC.[14,22] Our objective was to evaluate improvements in operative results and long-term outcome following surgical resection for HC during a 16-year period in a large cohort of patients having the same proven tumor entity.

Obstructive jaundice was the most common symptom (69.1%). With incomplete biliary obstruction it may be absent, and HC may be diagnosed from anorexia, pruritus, abnormal liver test results, or otherwise.[23]

All patients underwent preoperative computed tomography and/or magnetic resonance cholangiopancreatography; 49.3% of patients underwent both examinations. However, a nodular lesion at the hepatic hilum was evident in only 49.5% of cases. In the remainder, proximal biliary stenosis was shown. Diagnosis of HC is challenging, and no single imaging method exists for characterization of isolated hilar strictures.[24] Approximately 10% to 15% of patients who undergo operation for suspicion of HC are subsequently found to have benign disease.[25,26] Therefore, the need for preoperative histologic diagnosis of cholangiocarcinoma is often discussed.[27] The most common tissue sampling methods are brush cytology and forceps biopsy by endoscopic retrograde cholangiopancreatography. However, the sensitivity of brushing in detecting cancer ranges from 18% to 60%, and the sensitivity of biopsy ranges from 43% to 81%.[27] Consistent results were reported in this study in which the sensitivity of brushing and that of biopsy were 36.8% and 57.1%, respectively, suggesting that preoperative histologic diagnosis is not mandatory to evaluate the indication to surgery. Hence, differentiating benign strictures from cancer remains problematic, and the treatment approach for patients with suspicious hilar lesions should remain resection for presumed malignant tumor.[26]

Staging laparoscopy may identify unresectable extrahepatic biliary carcinoma, preventing unnecessary laparotomy in up to 20% of cases[28,29]; however, its role in patients with HC is yet undefined.[30] In our study, 23.5% of the centers routinely performed staging laparoscopy for HC, 88 patients underwent it before resection, and peritoneal carcinomatosis was detected in only 1 case (1.1%), suggesting that staging laparoscopy is not useful in patients with HC for preventing unnecessary laparotomies. Similar results come from a French multicenter study[31] of 56 patients operated on for HC in 2008: laparoscopy contraindicated laparotomy because of peritoneal carcinomatosis in only 1 case.[31] Indeed, the yield of staging laparoscopy is higher for gallbladder cancer, in which unresectability is mainly due to peritoneal and liver metastases, compared with HC, in which vascular and biliary infiltration are most frequently involved,[32] and the assessment of local resectability is often resolved after laparotomy and extensive dissection of portal and biliary structures.[32]

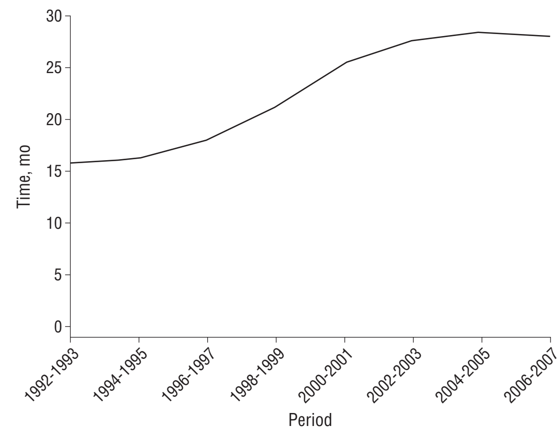

Figure 5. Time trend analysis of median survival after liver resection over the years. Median survival during the initial 4 years was significantly lower than during the final 4 years (16 vs 30 months; $P = .05$).

Bile duct resection combined with major hepatectomy is increasingly recognized as the standard treatment for HC, improving the obtainment of R0 resections and long-term survival.[3,4,12] In our study, the rate of R0 resections was higher with associated liver resection than with biliary confluence resection alone (79.2% vs 65.6%; $P = .01$). Of course, this type of resection is challenged by the close relationship between tumor and vascular structures at the hepatic hilum. In high-volume compared with low-volume centers in our study, this has resulted in significantly higher rates of associated liver resections (90.8% vs 71.5%; $P < .001$), of caudate lobe resections (84.7% vs 56.9%; $P < .001$), and of operations in patients with complex biliary strictures (Bismuth type 3 or 4) and with advanced tumor stages (stage III or IV and/or presence of perineural invasion). However, this did not significantly increase postoperative morbidity and mortality (Table 5), as confirmed by the lack of significance of the factor high-volume center with regard to mortality at multivariate logistic regressions.

The positive effect of R0 liver resection on OS and DFS was confirmed at multivariate analysis (Table 8). The effect on OS was reassessed in a subgroup of patients who underwent resection between 1992 and 1999, having follow-up of 8 years or longer. These truly actual (not actuarial) results demonstrated no 5-year OS following biliary confluence excision alone, whereas 5-year OS following liver resection was 26.6% and 10-year OS was 20.0%. Such patients can be considered cured, and these results resemble the excellent results reported following hepatectomy for colorectal liver metastases.[33,34]

Five-year OS after R0 liver resection was similar for high-volume vs low-volume centers (35.2% vs 35.8%; $P = .50$), although a significantly higher rate of advanced tumors (stage III or IV) with complex biliary strictures (Bismuth type 3 or 4) were resected in high-volume centers.

Survival after resection for HC improved in recent years together with improvements in surgical technique and perioperative care.[35,36] Ercolani et al[13] demonstrated how operative results and long-term outcome improved to-

Table 7. Univariate Predictors for Overall and Disease-Free Survival Following Associated Liver Resection

Predictor	No.	Median Survival, mo	5-Year Survival %	5-Year Survival *P* Value[a]	5-Year Disease Free %	5-Year Disease Free *P* Value[a]
Age, y						
<60	116	34	30.6	.04	22.7	.40
≥60	260	22	24.8		22.8	
Associated caudate lobe resection						
No	83	27	27.4	.90	27.0	.40
Yes	293	24	26.3		21.3	
Lymphadenectomy (hepatoduodenal ligament)						
Yes	291	26	27.3	.70	24.7	.70
No	85	24	25.5		22.0	
Histology						
Sclerosing	359	25	25.2	.19	22.2	.40
Papillary	17	30	47.7		31.3	
Grading						
G1	55	41	43.2		37.0	
G2-G3	290	24	23.1	.01	18.4	.002
Unknown	31					
Perineural invasion						
Yes	268	21	21.7	<.001	19.0	.16
No	108	40	40.4		29.7	
R0 resection						
Yes	298	27	32.0	<.001	27.2	<.001
No	78	14	5.8		3.3	
T stage						
T1-T2	86	45	47.2		45.5	
T3-T4	286	23	19.3	.003	14.4	<.001
Unknown	4					
N stage						
N0	236	39	34.7		33.7	
N1	124	15	10.7	<.001	5.8	<.001
Unknown	16					
Stage						
I-II	291	30	32.6		27.8	
III-IV	81	15	8.9	<.001	3.9	<.001
Unknown	4					
Caudate lobe invasion						
Yes	37	21	6.6		9.2	
No	117	30	34.8	.05	32.3	.005
Unknown	139					

[a] Log-rank test.

Table 8. Multivariate Analysis: Predictors for Overall and Disease-Free Survival Following Associated Liver Resection

Predictor	Hazard Ratio (95% CI)	*P* Value
For overall survival		
Perineural invasion	1.58 (1.03-2.42)	.03
R0 resection	0.65 (0.45-0.94)	.02
T3-T4 stage	1.86 (1.32-2.64)	<.001
N1 stage	2.32 (1.66-3.24)	<.001
For disease-free survival		
R0 resection	0.59 (0.40-0.85)	.005
T3-T4 stage	1.92 (1.25-2.96)	.003
N1 stage	2.48 (1.77-3.48)	<.001

gether with a more aggressive surgical policy. Our multicenter study (Figure 1) shows a progressive increase in the yearly rate of hepatectomies for HC, with 121 hepatectomies (32.2% of all hepatectomies in the 16-year period) performed in the final 2 years.

Time trend analysis (Figure 2) clearly shows changes over time in operative and pathologic results. Indeed, mortality and morbidity peaked before 1996 then trended downward until 2000. This was obviously correlated with advances in surgical technique and perioperative care, as confirmed by a steady, significant decrease in blood transfusion. After 2000, together with improved surgical expertise, there was a more aggressive surgical approach, with increasing rates of caudate lobectomies, vascular resections, and operations on poorly differentiated and advanced stage tumors. This aggressive policy resulted in a moderately increasing trend of operative risk. However, median OS after liver resection significantly increased over the years (Figure 5). Because adjuvant therapies have not significantly improved the long-term outcome after liver resection for HC, these advances are strictly correlated with increased expertise in hepatobiliary surgery.

Biliary drainage in patients with jaundice before liver resection for HC has been an object of debate.[37,38] Major

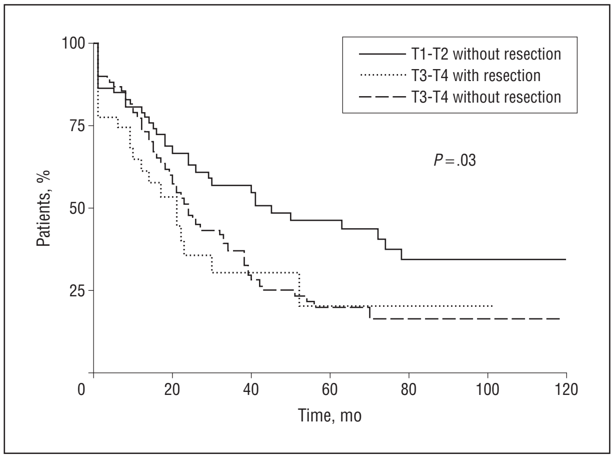

Figure 6. Overall survival (excluding postoperative deaths) according to the combination of vascular resection and T stage. Five-year overall survival of patients with T1-T2 stage tumor was significantly higher than that of patients with T3-T4 stage tumor irrespective of the use of vascular resection. T1-T2 without resection: 46.5%; T3-T4 without resection: 20.4%; T3-T4 with resection: 20.0%.

liver resection in patients with jaundice carries a high risk of postoperative liver failure.[37] Conversely, preoperative biliary drainage carries a 20% to 30% risk of cholangitis and sepsis, with increased postoperative infectious morbidity.[39] There are no prospective randomized studies analyzing the utility of biliary drainage before major hepatectomy for HC.[40] Although studies performed to demonstrate the benefits of preoperative biliary drainage were inconclusive, presently major hepatectomy combined with preoperative biliary drainage is established as a safer strategy for HC in Eastern and Western countries.[3,7,9,13,41] The Memorial Sloan Kettering Cancer Center experience[42] showed that adequate future liver remnant, even in patients with jaundice, can support an extended resection, whereas marginal future liver remnant requires biliary drainage to enhance postoperative function; future liver remnant volume of less than 30% appeared to be a strong indication for preoperative biliary drainage.[42] In our study, similar results were reported. Indeed, at multivariate logistic regressions, extent of hepatectomy and intraoperative blood transfusion were independent predictors of postoperative mortality. Most centers usually performed biliary drainage before major hepatectomy, and 84.3% of patients with jaundice underwent preoperative biliary drainage. Patients without biliary decompression before right or right extended hepatectomy had higher postoperative mortality than did those operated on following biliary drainage (14.3% vs 10.7%), although this did not reach statistical significance. These results suggest that preoperative biliary drainage should always be performed before right or right extended hepatectomy for HC in patients with jaundice.

Finally, the role of portal vein resection and reconstruction during operations for HC is still debated.[43-45] Neuhaus et al[43] proposed systematic portal vein resection as part of "no-touch" resection of the tumor, showing a 5-year OS of 65%; however, 60-day mortality was 17% and noncurative resections were excluded. Indeed, portal vein reconstruction increases the risk of major hepatectomy, with postoperative mortality of 10% to 20%.[3] In our study, postoperative mortality after combined vascular resection exceeded that of liver resection alone (19.0% vs 9.0%; $P = .04$), and OS for advanced HC (stage T3 or T4) was significantly lower compared with that for less advanced HC, irrespective of the use of vascular resection (Figure 6). These results were confirmed at multivariate analysis in which advanced T stage, and not vascular resection, was an independent predictor of OS and DFS, suggesting that systematic portal vein resection should not be recommended (Table 8).

In conclusion, our multicenter study showed that surgical management of HC has improved over the years with decreased operative risk despite more aggressive surgical policy. Long-term survival after curative liver resection significantly improved, despite the operation on patients with more advanced HC. Preoperative biliary drainage represented a safe strategy before major hepatectomy for HC in patients with jaundice. Finally, pathologic factors (such as advanced T stage, N1 stage, and R1 resection) were the only independent predictors of OS and DFS.

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