Major Hepatectomy for Hilar Cholangiocarcinoma Type 3 and 4: Prognostic Factors and Longterm Outcomes

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BACKGROUND: Radical operation for hilar cholangiocarcinoma, including major hepatectomy with vascular resection, seems to improve longterm survival. This study retrospectively evaluates several prognostic risk factors that can influence survival after resection of types 3 to 4 Klatskin tumors.

STUDY DESIGN: Between 1984 and 2003, 59 patients (36 men and 23 women) with types 3 to 4 hilar cholangiocarcinoma underwent liver resection with curative intent. Medical records and pathologic findings were reviewed to assess prognostic risk factors and survival. Disease-free and overall survival were analyzed using Kaplan-Meier and Cox proportional hazards models.

RESULTS: Survival rates at 1, 3, and 5 years were 82%, 45%, and 20% respectively. In-hospital mortality was 5% and morbidity was 42%. In multivariable analysis, male gender (relative risk [RR] = 5.4; 95% CI, 2.2 to 13.5), absence of preoperative chemotherapy (RR = 4; 95% CI, 1.5 to 10.7), R1 biliary tract margin (RR = 2.6; 95% CI, 1.1 to 4.4), and metastatic celiac lymph nodes (RR = 19.9; 95% CI, 4 to 71.4) were found to be independent factors for overall survival. Pedicular metastatic lymph nodes were not associated with poorer overall survival. If biliary positive-margin is the only risk factor, the 5-year estimated overall survival is 70%.

CONCLUSIONS: Major hepatectomy can improve outcomes of hilar cholangiocarcinoma. Compared with nonoperative treatment or R0 hepatectomy, R1 resection in patients with no other risk factor can offer longterm survival. (J Am Coll Surg 2007;204:250–260. © 2007 by the American College of Surgeons)

Hilar cholangiocarcinoma (Klatskin-type tumor[1]) is a rare neoplasm arising from a hilar bile duct and its secondary confluence. Tumor resection remains challenging because of its location close to major vascular structures and hepatic parenchyma. Because hilar cholangiocarcinoma has a slow progression along bile ducts, palliative procedures (biliary stenting, chemotherapy) have been widely used as a standard treatment[2,3] with poor outcomes. In the last decade, major hepatectomies have been performed with low mortality and morbidity.[4,5] For advanced Klatskin-type tumor[6,7] with extension to the secondary biliary confluence (Bismuth's classification[8] type 3 and 4; Fig. 1), an aggressive surgical strategy with extended hepatectomy and resection of involved vascular structures, if necessary, allowed for curative procedure. This study focuses on types 3 and 4 because of their complexity, ie, preoperative accurate assessment of the tumor, side of the hepatectomy, and technical limits particularly difficult to assess. Based on 20 years' experience, this study aims to identify the main prognostic factors for survival after resection of types 3 and 4 Klatskin tumors.

Competing Interests Declared: None.

Received August 31, 2005; Revised October 23, 2006; Accepted October 23, 2006.

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METHODS

Patients

From January 1984 to December 2003, 185 consecutive patients with a hilar cholangiocarcinoma were referred to our unit of hepatobiliary surgery. According to Bismuth's classification, 165 patients were diagnosed with types 3 and 4, 19 with types 1 and 2, and a single patient was an anastomotic recurrence after earlier hepatectomy. Evident extended disease at initial assessment (computed tomography and abdominal ultrasonography) led to a decision of palliative treatment for 83 patients (biliary stenting placed percutaneously or endoscopically,

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ISSN 1072-7515/07/$32.00
doi:10.1016/j.jamcollsurg.2006.10.028

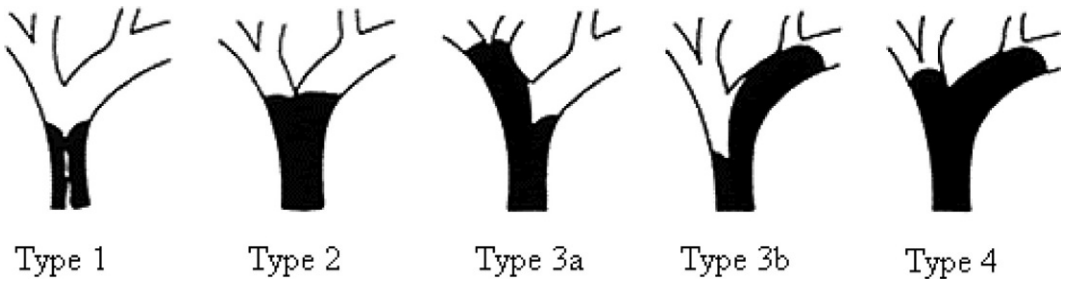

Figure 1. Bismuth's classification.

chemotherapy, and pain control when appropriate) and operation with curative intent for 82 patients. In 15 of 82 patients, peroperative findings contraindicated resection, 8 patients underwent liver transplantation and the remaining 59 patients (72% of 82 patients) underwent hepatic resection. The study was conducted on these 59 patients (52 with type 3, including 21 type 3a and 31 type 3b) and 7 with type 4. There were 23 women and 36 men. Mean age (±SD) was 59 ± 12 years (median 60 years). Before the procedure, 11 patients had already received chemotherapy (n = 9) or radiochemotherapy (n = 2) in another center.

Preoperative evaluation

Abdominal ultrasonography and abdominothoracic CT were systematically performed. Vascular invasion was evaluated by means of an arteriography. Since 1999, additional magnetic resonance cholangiopancreatography and vascular MRI have been performed on 20 patients (34% of 59 patients). MRI findings were similar to that of arteriography and percutaneous cholangiography. Preoperative vascular assessment showed 11 ipsilateral portal involvement, 1 bilateral portal involvement, 1 main portal vein extension and 3 hepatic artery involvement (1 hepatic artery division, 1 left hepatic artery with common hepatic artery presence, and 1 common hepatic artery with right hepatic artery presence). In 43 patients, angiography was considered as normal.

In all patients, biliary extension was assessed by percutaneous transhepatic cholangiography. Preoperative drainage was carried out at the end of the cholangiography when indicated by hepatic dysfunction (severe cytolysis), deterioration of the performance status, severe pruritis, or impaired renal function. The aim was to drain the future remnant liver after the planned hepatectomy. Biliary drainage was used for 48 patients (81% of 59 patients) during an average period of 60 ± 42 days.

To reduce postoperative risk of hepatic failure on a too small and cholestatic parenchyma, portal vein embolization has been performed since 1992 on 14 patients because of resection leaving < 40% of remnant parenchyma.[9,10] At the same time, the future remnant liver underwent systematic bile duct drainage. One month after embolization, the increase of the remnant liver was evaluated with a volumetric CT. The estimated gain was 43% ± 14% for the future remnant liver.

Our major incentive for resection was the possibility of complete removal of the tumoral disease (R0 resection). None of the planned resections were performed with a palliative intent. Contraindications to resection included medical comorbidities, distant metastatic disease, bilateral extensive intrahepatic extension, and extensive intrahepatic extension combined with contralateral vascular involvement or atrophy.

Surgical procedures

Complete exploration of the abdominal cavity was carried out to search for extrahepatic disease that would contraindicate resection. A systematic lymph node (LN) dissection of the hepatic pedicle was performed with a celiac LN dissection. Peripancreatic LNs were removed and analyzed if they were considered abnormal (eg, size, firm consistency). The common bile duct was resected en block from its pancreatic portion to its ipsilateral or

Table 1. Site of Recurrence (34 of 59 Patients)

Site of recurrence*	n
Peritoneum	13
Anastomotic	8
Hilar lymph nodes	6
Liver	7
Lung	4
Skin	2
Bone	1

*Multiple sites for seven patients.

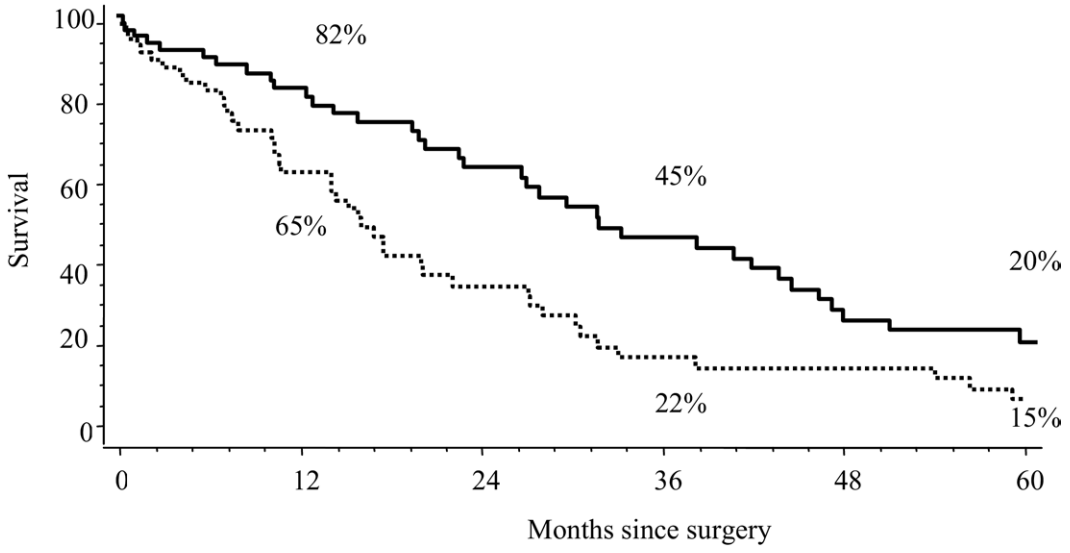

Figure 2. Overall and disease-free survival (n = 59). Solid line, overall survival; dotted line, disease-free survival.

bilateral secondary confluence, if necessary. Proximal and distal bile ducts underwent systematic frozen-section examination. In cases of positivity, additional resection was performed as far as it was technically feasible until clear margins were obtained.

Segment 1 was routinely resected. Biliary ducts draining segment 1 enter into the left and right hepatic ducts. Extension into the caudate lobe is common for a hilar cholangiocarcinoma. The side of the hepatectomy was decided according to either the liver atrophy or a favorable vascular anatomic variation. According to Couinaud's classification,[11] the different procedures included 6 right hepatectomy extended to segment 1; 13 right hepatectomy extended to segment 4 and 1; 32 left hepatectomy extended to segment 1; and 7 left hepatectomy extended to segment 5, 8, and 1. The hepatic artery and the portal vein were resected whenever an encasement was suspected. Simultaneous resection of the main portal vein occurred in five patients, making necessary a reconstruction that was performed by either direct anastomosis without graft or vein interposition. In one patient, a segmental resection of the middle hepatic artery was reconstructed by primary anastomosis.

Biliary continuity was restored by a Roux-en-Y of jejunum loop brought up in a transmesenteric fashion. Anastomosis was carried out in end-to-side manner. There were one to three bile ducts anastomoses. The remaining bile ducts were anastomosed separately when the stumps could not be linked together.

Histologic evaluation

Adenocarcinoma was diagnosed in all 59 patients with 36 well-differentiated, 15 poor or moderate differentiated, 2 mucus-secreting, and 1 papillary tumor. In five patients, the adenocarcinoma type was not specified. Hepatic resections were considered as curative (R0) when there was no evidence of residual microscopic disease (27 patients, 46%). Resection was R1 on the biliary tract for 19 patients (32%) and on the liver parenchyma for 13 patients (22%). Ten patients (17%) were R1 both on the liver parenchyma and the biliary tract. There was no case of resection leaving macroscopic disease (R2). For the microscopic disease, a microscopic vascular involvement was shown in 24 patients (41%), perineural infiltration in 46 patients (78%), isolated vascular emboli in 10 patients (17%), and lymphatic emboli in 5 patients (8%).

With regard to LN status, positive LNs were found in 30 patients (51%). Pedicular LNs were only positive in 26 patients (44%). Additional metastatic celiac LNs were observed in four patients (7%). There were no cases of isolated celiac LN involvement.

TNM classification was not used purposefully, as we chose to assess specific histologic findings for the prognostic analysis in this work.

Postoperative findings and followup

Twenty-five patients received adjuvant chemotherapy and one underwent radiochemotherapy. Normalization

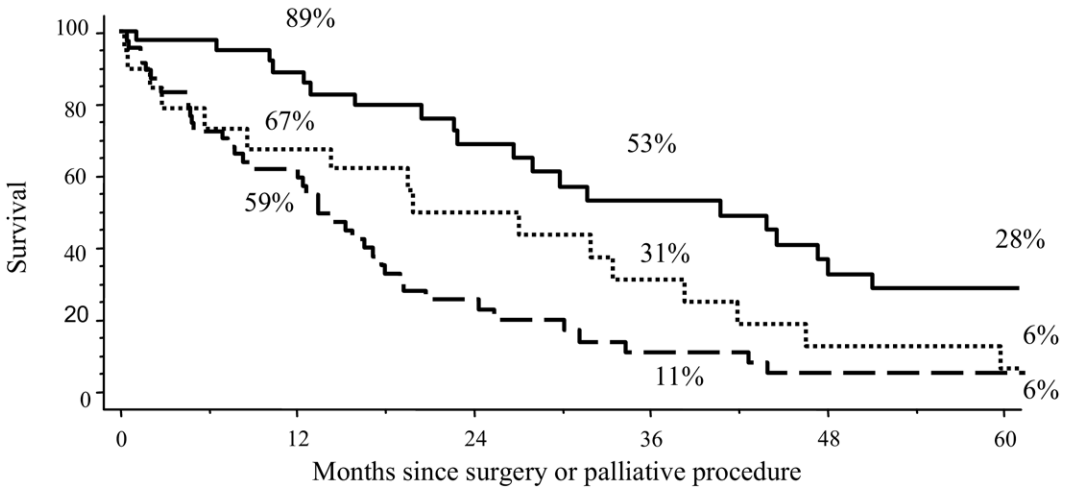

Figure 3. Overall survival according to type of resection. Solid line, R0 resection (n = 40); dotted line, R1 resection (n = 19); dashed line, no resection (n = 83).

of serum bilirubin level occurred within 1 month for 46 patients (78%). The remaining 13 patients normalized within 2 months. After discharge from hospital, systematic followup was continued every 3 months during the first 2 years and then every 6 months. This included clinical examination and abdominal echography. CT examination was performed yearly or in cases of suspected recurrence. Serum level of CEA and CA 19.9 were routinely measured to detect early recurrence.[12] Average followup was 31 months and no patient was lost during followup. Recurrence occurred for 34 patients (Table 1).

At the end of the study, 20 patients were still alive. Deaths (39 patients) were related to perioperative deaths (3 patients), with an average time to recurrence of 24 months (34 patients, see Table 1), heart failure (1 patient, 10 months after operation) and 1 patient from iatrogenic investigation (endovascular treatment for hepatic artery false aneurysm 3 months after operation).

Statistical analysis

Patients and tumor variables were evaluated to determine their prognostic influence on overall survival and disease-free survival. For disease-free survival, patients alive without recurrence were considered as censored at their last followup; all other patients with recurrence were not censored at the time of their recurrence, if any, or at the time of their death without recurrence. For quantitative items, evaluation of cutoff value was performed to determine the more discriminant value with regard to survival. Age value was tested at its median value ± 5 years to find the highest risk ratio with the most significant p value. The CA 19.9 cutoff value is in accordance with laboratory serum level normal value. The serum bilirubin level return to normal within 1 month was chosen as a clinically accepted cut point after this type of operation. Overall and disease-free survival probabilities were calculated using the Kaplan-Meier method and data were compared using log-rank test. A p value < 0.05 was considered significant. Multivariable analysis using a Cox model was done for all factors with a p value ≤ 0.15 at univariate analysis. Variables were tested until a final model with a p value < 0.05 for each factor was obtained. Estimation of survival was adjusted on risk factors.[13,14]

The statistical analyses were performed using SAS 9.1 (SAS Institute Inc).

RESULTS

Morbidity and mortality

Complications occurred in 25 (42%) of the 59 patients: 7 subphrenic abscess (6 treated by percutaneous drainage), 1 liver abscess, 2 liver failure, 3 prolonged ascitis, 3 external biliary fistula, 2 digestive fistula on the Roux-en-Y limb, 1 colonic fistula, 1 portal vein thrombosis (treated with heparin), 1 intraabdominal abscess, 1 angiocholitis, 1 intraabdominal bleeding, 1 hepatic artery aneurysm possibly because of a too-close dissection and 1 pneumopathy.

Thirty-day mortality was 5%: 1 intraabdominal bleeding, 1 septic shock, and 1 multiorgan failure.

Table 2. Univariate Analysis of Potential Predictors of Disease-Free Survival

Variable	n	Disease-free survival (%) 3 Y	5 Y	p Value*
Age (y)				
> 55	39	12	8	0.04†
≤ 55	20	39	26	
Gender				
Male	36	7	4	0.004†
Female	23	47	27	
Preoperative chemotherapy				
Present	11	47	23	0.15†
Absent	48	16	10	
CA 19.9 (IU/mL)				
> 37	37	14	14	0.62
< 37	8	34	17	
Portal vein embolization				
Present	14	18	0	0.6
Absent	45	22	17	
Vascular encasement at angiography				
Present	16	24	16	0.73
Absent	43	21	14	
Operative vascular resection				
Present	7	29	29	0.73
Absent	52	22	14	
Postoperative complication				
Present	25	11	5	0.05†
Absent	34	31	22	
Bilirubin return to normal (mo)				
> 1	13	0	0	0.01†
< 1	46	26	17	
Histologic differentiation				
Well	15	17	8	0.54
Poor/moderate	36	29	19	
Vascular invasion				
Present	24	20	10	0.65
Absent	35	23	14	
R1 on biliary tract				
Present	19	13	0	0.01†
Absent	40	26	22	
R1 on parenchyma				
Present	13	8	0	0.01†
Absent	46	27	20	
Perinervous invasion				
Present	46	19	13	0.31
Absent	12	31	21	
Vascular embolus				
Present	10	0	0	0.89
Absent	49	24	16	
Lymphatic embolus				
Present	5	27	27	0.51
Absent	54	22	13	
Pedicular lymph node metastasis				
Present	30	17	8	0.15†
Absent	29	29	23	
Celiac lymph node metastasis				
Present	4	0	0	0.14†
Absent	55	24	16	
Adjuvant chemo or radiochemo				
Present	43	24	17	0.4
Absent	16	18	9	

*Log-rank test.
†Variables included in multivariable analysis.

Survival

After tumor resection, overall survival at 1, 3, and 5 years was 82%, 45%, and 20%, respectively. The 1-, 3-, and 5-year disease-free survival rates were respectively 65%, 22%, and 15% (Fig. 2). Disease-free median survival time was 17 months and overall median survival time was 32 months. Overall survival, as a comparison, of unresected patients (n = 83) during the same period at 1, 3, and 5 years was 59%, 11%, and 6%, respectively (Fig. 3).

Prognostic factors studied are summarized in Tables 2 and 3.

For univariate analysis, age older than 55 years ($p = 0.04$); male gender ($p = 0.004$); postoperative complication ($p = 0.05$); serum bilirubin level return to normal (eg, 12 μmol/L) in more than 1 month ($p = 0.01$); R1 on parenchyma ($p = 0.01$); and R1 on biliary tract ($p = 0.01$), were prognostic factors for poorer disease-free survival. Except for microscopic parenchyma involvement, the same prognostic factors were identified for overall survival.

In multivariable analysis, male gender ($p = 0.001$), lack of preoperative chemotherapy ($p = 0.01$), R1 on parenchyma ($p = 0.004$), celiac LN involvement ($p < 0.001$), and serum bilirubin level return to normal in more than 1 month ($p = 0.01$), were factors found to be important for disease-free survival. For overall survival, male gender ($p = 0.0002$), lack of preoperative chemo-

Table 3. Univariate Analysis of Potential Predictors of Overall Survival

Variable	Category (n)	Overall survival (%) 3 Y	5 Y	p Value*
Age (y)				
> 55	39	30	13	0.03†
≤ 55	20	69	31	
Gender				
Male	36	31	8	0.003†
Female	23	69	40	
Preoperative chemotherapy				
Present	11	68	45	0.11†
Absent	48	39	13	
CA 19.9 (IU/mL)				
> 37	37	36	15	0.21
< 37	8	83	33	
Portal vein embolization				
Present	14	63	16	0.97
Absent	45	41	21	
Vascular encasement at angiography				
Present	16	59	22	0.99
Absent	43	38	18	
Operative vascular resection				
Present	7	43	21	0.57
Absent	52	46	20	
Postoperative complication				
Present	25	28	11	0.02†
Absent	34	58	26	
Bilirubin return to normal (mo)				
> 1	13	0	0	0.004†
< 1	46	51	22	
Histologic differentiation				
Well	15	43	22	0.35
Poor/moderate	36	50	22	
Vascular invasion				
Present	24	47	19	0.47
Absent	35	42	20	
R1 on biliary tract				
Present	19	31	6	0.01†
Absent	40	53	28	
R1 on parenchyma				
Present	13	38	8	0.11†
Absent	46	48	25	
Perinervous invasion				
Present	46	44	16	0.24
Absent	12	51	38	
Vascular embolus				
Present	10	9	0	0.64
Absent	49	40	21	
Lymphatic embolus				
Present	5	53	27	0.63
Absent	54	44	19	
Pedicular lymph node metastasis				
Present	30	38	13	0.06†
Absent	29	55	31	
Celiac lymph node metastasis				
Present	4	25	0	0.09†
Absent	55	47	22	
Adjuvant chemo or radiochemo				
Present	43	54	20	0.18
Absent	16	20	20	

*Log-rank test.
†Variables included in multivariable analysis.

therapy ($p = 0.005$), R1 on biliary tract ($p = 0.01$), and celiac LN involvement ($p < 0.0001$) were independent prognostic factors in patients with hilar cholangiocarcinoma who underwent macroscopically curative hepatectomy (Tables 4, 5). Tables 6 and 7 display the estimated rates of disease-free and overall survival adjusted for risk factors.

DISCUSSION

We report here a single-center experience of a rare tumor. This is one of the largest series dealing with types 3 and 4 hilar cholangiocarcinoma only. Data were recorded prospectively, but this is a retrospective study with its bias and heterogeneity. The size of the population and a 20-year experience can show interesting trends in surgical management of type 3 and 4 tumors.

Although hilar cholangiocarcinoma has a relatively slow progression, only radical procedure can provide longterm survival. In our series, median survival is 32 months for resected tumors. Although not directly comparable with or similar to these resected patients, patients who received palliative treatment of hilar cholangiocarcinoma in our institution had a 13-month median survival during the same period. Several points are still controversial about this procedure.

We did not perform any staging laparoscopy in this study. Laparoscopy combined with intraoperative ultrasonography spared 33% to 42.2% of patients an unnec-

Table 4. Prognostic Factors for Disease-Free Survival (n = 59) in Multivariable Cox Proportional Hazards Model

	Disease-free survival	
Prognostic factors	**RR (95% CI)**	**p Value**
Male gender	4 (1.8−9.2)	0.001
Lack of preoperative chemotherapy	3.1 (1.2−8)	0.01
R1 on parenchyma	2.9 (1.4−6)	0.004
Celiac lymph node involvement	12 (3−47)	< 0.001
Bilirubin return to normal > 1 mo	2.9 (1.2−6.8)	0.01

Other variables tested in the initial model: age, postoperative complication, R1 on biliary tract, pedicular lymph node metastasis.
RR, relative risk of recurrence.

Table 5. Prognostic Factors for Overall Survival (n = 59) in Multivariable Cox Proportional Hazards Model

	Overall survival	
Prognostic factors	**RR (95% CI)**	**p Value**
Male gender	5.4 (2.2−13.5)	0.0002
Lack of preoperative chemotherapy	4 (1.5−10.7)	0.005
R1 on biliary tract	2.6 (1.1−4.4)	0.01
Celiac lymph node involvement	19.9 (4−71.4)	< 0.0001

Other variables tested in the initial model: age, postoperative complication, R1 on parenchyma, pedicular lymph node metastasis, bilirubin return to normal > 1 mo.
RR, relative risk of death.

essary laparotomy, as advocated by several authors.[15,16] In our series, 15 patients (18% of 82 patients) underwent operation without resection. Accurate preoperative assessment could explain this difference.

The role of preoperative biliary drainage in the presence of obstructive jaundice has been reported in several articles. In a case-comparison study, Cherqui and colleagues[17] have shown a higher postoperative morbidity (50% versus 15%) in the jaundiced patients group. There were no substantial differences for mortality and liver failure between jaundiced and nonjaundiced patients. Two studies[18,19] have reported the outcomes of extended hepatectomy with preoperative biliary drainage and portal vein embolization (PVE), if necessary. Morbidity was 20% to 40% and mortality was 0% to 1.3%. The authors conclude that such a strategy leads to a reduction of the risks associated with major hepatectomy for hilar cholangiocarcinoma. In our series, preoperative biliary drainage had no influence on patient outcomes. We performed external biliary drainage to prevent bile colonization with intestinal flora and to protect the liver from prolonged cholestasis. Selective drainage of the future remnant liver seems to limit septic complications. Technically, it is possible to associate external biliary drainage with PVE when indicated. This was performed on 14 patients through an ileal vein with a Mac Burney incision or in a percutaneous approach according to portal vein encasement.[9,10] PVE did not lead to poorer survival outcomes (Tables 2, 3). PVE was specifically indicated for type 4. Six of the seven type 4 patients underwent this procedure. It limits postoperative liver failure for these very extended hepatectomies.[20]

An aggressive approach for hilar cholangiocarcinoma with portal vein resection, if necessary, is now recognized as a way to offer a better chance of longterm survival. This approach is now usually adopted by leading liver teams.[6,21,22] Mortality has been decreasing since the last decade. We report a 5% in-hospital mortality rate, a rate similar to the one reported in other publications (Table 8). Few series[18,24] deal with hepatectomies for hilar cholangiocarcinoma only. Morbidity remains quite high (about 50%) with this kind of procedure (Table 7). We experienced two transient liver failures and three prolonged ascitis resolved by symptomatic treatment, although Kawasaki and colleagues[19] or Seyama and colleagues[18] report no postoperative liver failure. These reports showed wide indications for PVE before major hepatectomies. PVE and preoperative external biliary drainage could improve the outcomes on these impaired cholestatic livers. Decrease of bilirubin serum-level resulting from drainage could also be considered as an indirect quality factor. For a matter of fact, slow decrease (longer than 1 month) for 13 patients is associated with substantially poorer outcomes. Such a pace of decrease has no straightforward explanation, but all the concerned patients underwent very extended resection with PVE for only three patients. Return to a normal serum level was obtained within 2 months for these 13 patients.

LN status is the most common risk factor found in multivariable analysis (Table 9). Kurosaki and colleagues,[27] while analyzing the lymphatic pathways of bile duct cancer, reported that pericholedocal LNs were key stations of spread toward the common hepatic artery and peripancreatic LNs. In our series, survival according to LN status was different when the involvement was pedicular or celiac. Presence of pedicular metastases had no statistically significant influence on survival ($p = 0.06$). Patients with isolated celiac involvement had a 5-year survival rate of 7%. Excluding these patients from resection is still a point of discussion in the surgical team. Although several authors reported similar findings concerning the LN status,[22,27-29] Kitagawa and colleagues[30]

Table 6. Estimation of Disease-Free Survival Adjusted for Risk Factors (n = 59)

Factor	Bilirubin return to normal > 1 mo	R1 on parenchyma	Lack of preoperative chemotherapy	Male gender	Positive celiac lymph nodes	Survival %		
						1 Y	3 Y	5 Y
0	−	−	−	−	−	97	84	75
1	+	−	−	−	−	92	60	43
	−	+	−	−	−	92	60	43
	−	−	+	−	−	91	58	41
	−	−	−	+	−	89	49	32
	−	−	−	−	+	70	12	3
2	+	+	−	−	−	77	22	9
	+	−	+	−	−	76	20	7
	+	−	−	+	−	70	13	4
	+	−	−	−	+	35	0	0
	−	+	+	−	−	76	20	7
	−	+	−	+	−	70	13	3
	−	+	−	−	+	35	0	0
	−	−	+	+	−	68	11	3
	−	−	+	−	+	32	0	0
	−	−	−	+	+	23	0	0
3	+	+	+	−	−	45	1	0
	+	+	−	+	−	36	0	0
	+	+	−	−	+	5	0	0
	+	−	+	+	−	33	0	0
	+	−	+	−	+	4	0	0
	+	−	−	+	+	1	0	0
	−	+	+	+	−	33	0	0
	−	+	+	−	+	4	0	0
	−	+	−	+	+	1	0	0
	−	−	+	+	+	1	0	0
4	+	+	+	+	−	4	0	0
	+	+	+	−	+	0	0	0
	+	+	−	+	+	0	0	0
	+	−	+	+	+	0	0	0
	−	+	+	+	+	0	0	0
5	+	+	+	+	+	0	0	0

Some combinations are not represented in the actual data analyzed.

did not show any difference in longterm outcomes among N0, N1, and N2 patients.

The ability to achieve a margin-negative resection remains challenging. Tumor submucosal spread extending from 1 to 2 cm beyond the radiographic abnormalities is a common feature. Peroperative frozen sections are essential to guide the site of bile duct resection, but they might not be accurate enough to discriminate tumor and sclerosing cholangitis.[22] This is illustrated by our rate of 32% microscopic biliary invasion. In our univariate and multivariable analyses, biliary positive-margin was found as a substantial factor for poor 5-year overall survival. If biliary positive-margin is the only factor, 5-year adjusted overall survival is 70% in our series. In our team, it seems that there is a place for palliative hepatectomy in this indication. Liver positive margins occurred in 13 patients with substantial poor outcomes for disease-free survival, even though only 2 of these 13 patients recurred in the parenchyma. We did not perform any systematic frozen sections on parenchyma, but this could be changed. In fact, it is usually easier to resect peritumoral liver than to extend resection to tertiary bile ducts.

The alternative to resection is liver transplantation. We do not report our experience here because only eight patients underwent transplantation. The last transplantation for this indication was performed in 1994 and the

Table 7. Estimation of Overall Survival Adjusted on Risk Factors (n = 59)

Factor	R1 on biliary tract	No preoperative chemotherapy	Male gender	Positive celiac lymph nodes	Survival %		
					1 Y	3 Y	5 Y
0	−	−	−	−	99	96	85
1	+	−	−	−	98	90	70
	−	+	−	−	96	83	53
	−	−	+	−	95	78	42
	−	−	−	+	85	47	7
2	+	+	−	−	92	67	24
	+	−	+	−	89	57	14
	+	−	−	+	69	18	0.3
	−	+	+	−	81	37	3
	−	+	−	+	52	5	0
	−	−	+	+	41	2	0
3	+	+	+	−	62	11	0
	+	+	−	+	23	0.1	0
	+	−	+	+	13	0	0
	−	+	+	+	3	0	0
4	+	+	+	+	0	0	0

Some of the combinations are not represented in the actual data analyzed.

patient is the only one still alive. For the moment, we stopped transplantation for hilar cholangiocarcinoma. Challenging preoperative assessment, shortage of liver grafts, and other transplantation priorities are the main reasons for this. Longterm survival rates of 20% to 30%[31] for hilar cholangiocarcinoma are common and similar to survival rates resulting from hepatic resections. In fact, selection criteria and use of neoadjuvant or adjuvant therapies are not thoroughly detailed in these publications. Recently, the Mayo Clinic reported[32] a protocol of neoadjuvant external beam plus bolus fluorouracil combined with transluminal boost of radiation and oral capecitabine. Then, a staging laparotomy was performed before patients remained eligible for liver transplantation. Twenty patients with locally unresectable hilar cholangiocarcinoma had transplantations with 80% survival at 5 years. This is about the same rate in our series for patients resected with no risk factor as shown in Table 7.

Neoadjuvant and adjuvant treatment reports are scarce in the literature related to curative treatments. In our series, 13 patients received chemotherapy and a combination of chemotherapy and radiotherapy for 2 of them before undergoing the procedure. These protocols were given as a palliative treatment before these patients were referred to our institution. Because 9 of the 11 patients came from other countries, the exact radiotherapeutic protocol was unknown. Drugs were fluorouracil and cisplatin without knowledge of the chemotherapeutic schedule. This kind of unexpected neoadjuvant treatment was found to have a substantial benefit on 5-year survival in multivariable analysis. Additional clinical trials are necessary before indicating a neoadjuvant treatment. Wiedmann and colleagues[33] report a phase II

Table 8. Mortality and Morbidity and 5-Year Survival Rates in Previous Reports (All Types of Klatskin's Tumor)

First author	Year	n	Mortality (%)	Morbidity (%)	5-y survival (%)
Launois[22]	1999	40	12.5	25	4.0
Capussotti[23]	2002	36	2.8	47.7	27.2
Ebata[24]	2003	52	9.6	84	9.9
Seyama[18]	2003	58	0.0	43	40
Kawasaki[19]	2003	79	1.3	20	40
Shimada[25]	2003	39	10.3	71.8	18
Lygidakis[26]	2004	58	3.4	5.1*	20
Current series	2004	59	5	42	20

*Reoperation only.

Table 9. Prognostic Factors of Overall Survival in Multivariable Analysis According to Different Series

First author	Year	n	Prognostic factors
Ebata[24]	2003	52	Histologic differentiation, lymph node metastasis, macroscopic portal vein invasion
Seyama[18]	2003	58	Lymph node metastasis
Kawasaki[19]	2003	79	Lymph node metastasis, resection margins
Current series	2004	59	Male gender, lack of preoperative chemotherapy, R1 on biliary tract, celiac lymph node metastasis

study on neoadjuvant photodynamic therapy. They found an efficient selective destruction of the superficial 4-mm layer of bile duct tumor with a 1-year recurrence-free survival rate of 83%. Efficacy of adjuvant treatment remains controversial. There is no evidence in the literature that chemotherapy is effective for hilar cholangiocarcinoma. Pitt and colleagues[34] did not improve survival with radiotherapy but most patients underwent R2 or palliative hepatectomy in their series. Adjuvant radiotherapy seemed to give a considerable survival advantage to patients with positive microscopic margins in the series of Schoenthaler and colleagues.[35] Todoroki and colleagues[36] also reported a 5-year 33.9% survival for patients with microscopic tumor residue treated by adjuvant radiotherapy. The benefit was even improved by both intraoperative and postoperative radiotherapy. Currently, with a low evidence-based medicine level, we give adjuvant chemotherapy in cases of microscopic disease (microscopic vascular involvement, perineural infiltration, positive LNs) and radiotherapy in case of R1 resection on biliary tract.

It appears that indication for palliative hepatectomy exists when biliary resection is R1. Major hepatectomy with the help of preoperative percutaneous drainage and PVE can improve outcomes of hilar cholangiocarcinoma. Neoadjuvant radiochemotherapy in the management of Klatskin tumor needs additional evaluation.

Author Contributions

Study conception and design: Castaing
Acquisition of data: Baton
Analysis and interpretation of data: Baton
Drafting of manuscript: Baton
Critical revision: Azoulay
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