

Contemporary Surgical Approach to Hilar Cholangiocarcinoma

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ABSTRACT: Background: The diagnostic and therapeutic approach to hilar cholangiocarcinoma and thus the prognosis have changed significantly over the last two decades. Nonetheless, hilar cholangiocarcinoma presents a complex surgical challenge.

Objectives: To assess the outcome of the radical approach for the management of types III and IV hilar cholangiocarcinoma.

Methods: We conducted a retrospective single-center study. Preoperative diagnosis was based on ultrasound, computed tomography and selective percutaneous cholangiography without tissue diagnosis. Surgery was radical and included en-bloc liver, extrahepatic biliary tree and hilar lymph nodes resection, followed by biliary reconstruction with hepaticojejunostomy.

Results: Fifteen patients (mean age 49 years, range 24–72) were managed accordingly. Anatomic classification of the biliary involvement was Bismuth-Corlette type IIIA (n=4), type IIIB (n=3) and type IV (n=8). The surgical procedures performed included four right hepatic lobectomies, five left hepatic lobectomies and six trisegmentectomies (all extended to the caudate lobe). Complete negative resection margins (R0) were accomplished in 12 cases (80%). Regional lymph node metastases were detected in five cases. There were two perioperative mortalities. Long-term follow-up (mean 30 months, range 6–72) revealed local recurrences in two cases, distant metastases in three, and both local and distant in two cases. Eleven patients are alive and 6 are without evidence of disease. The overall 2- and 5-year survival is 78% and 38% respectively.

Conclusions: In selected patients the aggressive surgical approach to hilar cholangiocarcinoma is justified and can result in long-term survival.

IMAJ 2011; 13: 99–103

KEY WORDS: hilar cholangiocarcinoma, diagnosis, surgical approach

A denocarcinoma of the hepatic duct at its bifurcation (hilar cholangiocarcinoma) was defined by Klatskin in 1965 [1]. Before 1990 most patients were considered inoperable; in a few cases local resection of the tumor was performed but the long-term outcome was poor. Thus, the perception of hilar cholangiocarcinoma among gastroenterologists, oncologists and even surgeons was of a non-curable disease. Since 1990, the selection criteria for resectability have changed radically, and a more aggressive approach with combined liver, bile duct and hilar lymph nodes resection improved overall survival [2]. For most patients with hilar cholangiocarcinoma the traditional local resection is no longer considered a curative treatment. Discussion of hilar cholangiocarcinoma requires practical anatomical definitions, such as the Bismuth-Corlette classification [3] [Figure 1].

Hilar cholangiocarcinoma has an extremely poor prognosis, with an average 5-year survival rate of 5–10% [4]. Following

Figure 1. The Bismuth-Corlette classification. **Type I:** tumors below the confluence of the left and right hepatic ducts. **Type II:** tumors reaching the confluence. **Types IIIa and IIIb:** tumors involving the common hepatic duct and either the right or left hepatic duct, respectively. **Type IV:** tumors that involve the confluence and both the right or left hepatic duct or multicentric tumors.

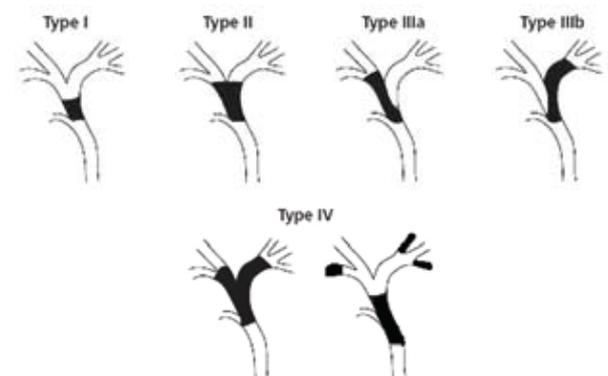


Table 1. Results of an aggressive surgical approach to hilar cholangiocarcinoma: comparison of data from published series

Study, year [ref]	N	Bismuth-Corlette classification			Resection type		Perioperative complications, major (%)	Perioperative mortality (%)	Overall survival (%)
		< III	III	IV	HL + EHBD	EHBD only			
Bismuth et al., 1992 [5]*	23	6 (26%)	17 (74%)	–	13 (57%)	10 (43%)	8.7%	0%	25% (3 yrs)
Klempnauer et al., 1997 [6]	151	27 (18%)	116 (77%)	8 (5%)	117 (77%)	34 (23%)	29.8%	9.9%	28.4% (5 yrs)
Jarnagin et al., 2001 [20]**	80	Blumgart's staging			62 (77%)	18 (23%)	64%	10%	30% (5 yrs)
Hemming et al., 2005 [15]	53	10 (19%)	NA	NA	52 (98%)	1 (2%)	40%	9%	35% (5 yrs)
Baton et al., 2007 [12]*	59	–	52 (88%)	7 (12%)	59 (100%)	–	42%	5%	20% (5 yrs)
Endo et al., 2008 [8]**	101	NA	NA	NA	83 (82%)	18 (18%)	55.4%	5%	31.4% (5 yrs)
Current study	15	–	7 (47%)	8 (53%)	15 (100%)	–	46%	13.3%	38% (5 yrs)

*, ** Series from the same institutions; the latter may include the same patients from the earlier series.

HL = hepatic lobectomy, EHBD = extrahepatic bile duct

curative resection, the two main prognostic factors are lymph node involvement [5-7] and histological margin status (R0 resection) [8]. Local tumor infiltration is characterized by perineural invasion and lymphangiosis carcinomatosa that usually extend beneath the intact epithelial lining, up to 2 cm from the tumor proximally into the liver and 1 cm distally into the hepatoduodenal ligament [9,10]. This is the rationale for applying an aggressive surgical approach to the treatment of hilar cholangiocarcinoma with intention to cure.

Bile duct resection alone leads to high local recurrence rates and almost zero 5-year survival due to early involvement of the hepatic ducts confluence and the caudate lobe branches [11]. In an innovative series of 59 patients with type III and IV hilar cholangiocarcinoma who underwent liver resection with curative intent, survival rates at 1, 3 and 5 years were 82%, 45% and 20% respectively [12]. Subsequently, in the last two decades most centers have adopted this approach and the outcomes are better compared to local resection only. Reported curative resection rates are 70% with 5-year survival ranging from 25 to 40% [Table 1].

The aim of this study was to present our experience and assess the outcome following implementation of the radical approach for the management of types III and IV hilar cholangiocarcinomas.

PATIENTS AND METHODS

DIAGNOSIS

Preoperative diagnosis was based on integration of the clinical presentation and correlating imaging findings. Three-phase high-resolution CT was the tool of choice to exclude metastases, to assess vascular involvement (arterial and portal), and for volumetric calculations. Although a few patients had undergone positron emission tomography-CT, magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography, we did not perform these

procedures routinely and did not demand tissue diagnosis before surgery.

CRITERIA OF RESECTABILITY

Principally, prediction of the ability to achieve R0 safe resection was the key for patient selection. Factors included absence of distant metastases, good performance status, sufficient remnant liver, ability to maintain arterial and portal flow to the remnant liver, and matched anatomic biliary involvement. Each case was studied and discussed accordingly.

PREOPERATIVE BILIARY DRAINAGE

For precise definition of the biliary involvement, we apply routine unilateral or bilateral percutaneous (antegrade) cholangiography and biliary drainage (percutaneous transhepatic biliary drainage). In patients with profound jaundice, we use this route for preoperative drainage. In others, we perform PTCs the day before surgery in order to minimize bacterial colonization of the bile ducts and interference with morphological interpretation.

LIVER VOLUME MANIPULATIONS

In the absence of the natural atrophy-hypertrophy complex, when the estimated remnant liver volume seems to be insufficient, we selectively embolize the portal branches of the planned sacrificed lobe. Selective unilateral PTBD also induces hypertrophy. Due to biliary drainage and/or portal embolization surgery was postponed for several weeks.

SURGERY

The procedure included open exploration and intraoperative ultrasound. This was followed by en-bloc liver resection of the affected lobe and the caudate lobe with the entire extrahepatic biliary tree and the hilar lymph nodes [Figure 2B].

PTC = percutaneous cholangiography

PTBD = percutaneous transhepatic biliary drainage

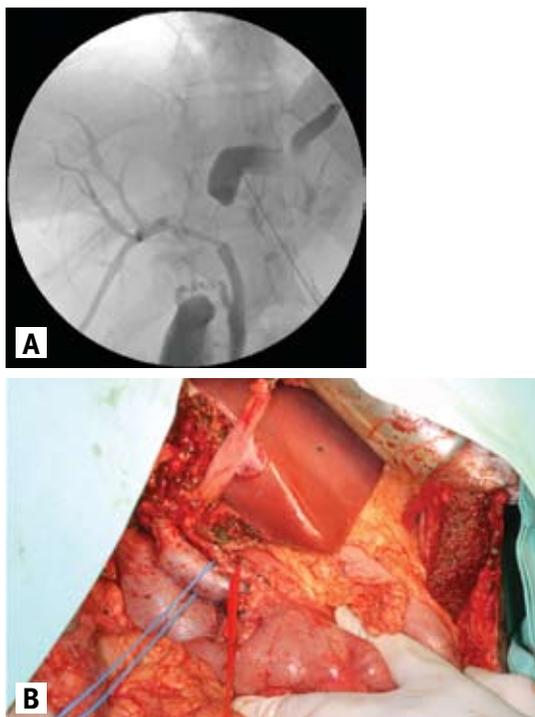
Figure 2. Left-sided approach. **[A]** Preoperative cholangiography of hilar cholangiocarcinoma (type IIIb). **[B]** Specimen of a left en-bloc liver-biliary tree resection. Ligatures mark the biliary margins (right hepatic duct and common bile duct). Forceps indicate the tumor at the bifurcation invading

the adjacent liver. **[C]** The remnant liver and hepatoduodenal ligament following a left-side resection. The portal vein (marked with forceps) and the hepatic artery (marked with white tape) are skeletonized. A PTBD catheter is seen in the right hepatic duct.



Figure 3. Right-sided approach. **[A]** Preoperative left duct cholangiography of hilar cholangiocarcinoma (type IV). The right duct is already drained with PTBD. **[B]** The remnant liver and hepatoduodenal ligament following an extended right-sided resection. The inferior vena cava, portal vein (blue tape) and hepatic artery (red tape) are skeletonized.

biliovascular involvement. Biliary reconstruction was based on (Roux en-Y) hepatico-jejunostomy to the bile duct(s) of the remnant liver. The anastomosis was performed over the pre-inserted PTBD catheter.



MARGIN ASSESSMENT

The bile duct edges in the resected specimen were marked and were submitted to frozen-section pathological evaluation. Resections were extended as needed (and if possible).

ADJUVANT TREATMENT

Given the limited data to prove efficacy of adjuvant chemo- and/or radiotherapy, this question was discussed individually for each patient. Most patients, however, were treated with Gemzar-based chemotherapy.

FOLLOW-UP

Follow-up included periodic outpatient clinic visits and monitoring of liver function tests and tumor markers. Imaging was applied in the event of clinical or laboratory suspicion of recurrence. PTBD was reapplied when local tumor recurrence interfered with biliary drainage. Patients with documented recurrence (local and/or metastatic) were treated by the medical oncologists.

This dissection left behind totally skeletonized common and proper hepatic arteries and the portal vein [Figure 2C, Figure 3B]. There were two main approaches to resection: left extended [Figure 2] and right extended [Figure 3], dictated by

RESULTS

Between 2004 and 2009 we treated 15 patients with hilar cholangiocarcinoma, Bismuth-Corlette type \geq III, applying these principles with curative intent. Excluded were local resections of type I and II hilar cholangiocarcinoma (4 cases), hepatic resections of intrahepatic cholangiocarcinoma (6 cases), radical resections of gall bladder cholangiocarcinoma (10 cases) and patients who underwent palliative resections (2 cases). Patients'

mean age was 49 years (range 24–72). Two young patients had a clear history of inflammatory bowel disease, but no history or hepatic morphology of primary sclerosing cholangitis. In another two, there was no documentation of earlier abnormal liver function tests, but the non-tumoral liver morphology was suggestive of primary sclerosing cholangitis.

PREOPERATIVE DIAGNOSIS

As described, the preoperative diagnosis was based on clinical features and imaging studies. However, brush cytology was available in five cases; in two of them the cytology confirmed the working diagnosis but in three (60%) the cytology was falsely negative. Tumor markers, including carcinoembryonic antigen and CA19-9, were analyzed in all patients and are available in 13 cases. CEA was within normal limits in all. CA19-9 was elevated in 11 of the 13 patients (85%) (mean value 195, range 50–510). However, these values might be influenced by concomitant cholestasis, instrumentation and episodes of cholangitis prior to the operation. In two cases that were excluded from the series (2/17, 11%), diagnosis and surgery were performed accordingly, but the final pathology revealed a benign stricture.

PREOPERATIVE CLASSIFICATION OF TUMORS

The Bismuth–Corlette classification (according to the preoperative antegrade PTC) was IIIA in four cases, IIIB in three and IV in eight. In three cases, preoperative CT scans and PET-CT revealed macroscopic hilar lymph node involvement. Three patients underwent right and segment IV portal vein embolization to induce atrophy-hypertrophy prior to trisegmentectomy.

PROCEDURES

All operations included en-bloc liver-biliary-lymphatic resections. The liver resections comprised right hepatic lobectomy in four cases, left hepatic lobectomy in five [Figure 2] and right hepatic trisegmentectomy in six [Figure 3], all extended to the caudate lobe. The extrahepatic resection included the gall bladder, common hepatic and common bile duct as far as its intra-pancreatic segment. Lymphadenectomy was to the level of the common hepatic artery and retropancreatic nodes.

PERIOPERATIVE OUTCOME

Two perioperative deaths occurred (13%) due to liver insufficiency, jaundice and ascites. These patients were elderly (72 and 66 years old). The deaths occurred 20 and 36 days following resections and the direct cause of death was sepsis with resistant bacteria (infected ascites in one case and hepatic microabscesses in the other). Major complications included transient liver insufficiency (3 cases, 20%), cholangitis (2 cases, 13%) and

bile leak (2 cases, 13%). Minor complications included symptomatic pleural effusion (3 cases, 20%) and wound infection (4 cases, 26%). All complications were managed conservatively and there was no need for reoperations.

PATHOLOGICAL RESULTS

Complete R0 biliary resection was achieved in 12 cases (80%). Regional lymph node metastases were detected in five cases.

LONG-TERM OUTCOME AND PATTERN OF RECURRENCE

Long-term follow-up (mean 30 months, range 6–72) revealed true local recurrence in the remnant liver bile duct in two cases, occurrence of distant metastases in three, and both in two cases. Metastases were found in the liver (n=3), retroperitoneal lymph nodes (n=3), peritoneal cavity (n=3) and lungs (n=1). For the entire group (an intention-to-treat perspective), using Kaplan Meier survival function-curve, the overall 2- and 5-year survival rates were 78% and 38% respectively.

DISCUSSION

DIAGNOSIS

Detection of hilar cholangiocarcinoma in extrahepatic bile duct strictures is a continuing challenge in clinical practice. Most cholangiocarcinomas become symptomatic when the tumor obstructs the biliary drainage system, causing painless jaundice. Because of its wide availability, computed tomography is one of the first studies obtained in patients with suspected biliary tract obstruction. Currently, a good quality MRCP is an optimal alternative investigation tool for suspected hilar cholangiocarcinoma. Although ERCP may provide some helpful information, antegrade PTC displays the intrahepatic bile ducts much more reliably and is the preferred direct cholangiographic study [10,14].

Most patients are referred after having had some studies done elsewhere, usually a CT scan and some form of direct cholangiography (PTC or ERCP). Although there is no evidence of benefit, most patients undergo biliary drainage prior to referral for resection. Ideally, biliary stents should not be inserted before resectability is assessed. The presence of any biliary stent interferes in the intraoperative determination of the tumors' proximal extent and causes inflammation in the porta hepatis [15]. In severely malnourished patients, patients with deep jaundice or those with episodes of acute suppurative cholangitis, PTBD should be applied [14].

Establishing a definitive tissue diagnosis of hilar cholangiocarcinoma preoperatively can be difficult or even impossible. In the absence of clear contraindication, exploration is indicated in all patients with suspicious hilar lesions even without tissue diagnosis.

CEA = carcinoembryonic antigen

PET-CT = positron emission tomography-computed tomography

MRCP = magnetic resonance cholangiopancreatography

ERCP = endoscopic retrograde cholangiopancreatography

SURGERY

Hilar cholangiocarcinoma continues to be a complex challenge for the surgeon. The only curative treatment for patients with this condition is surgery, which should be attempted only in specialized centers. Recent advances in surgical treatment have led to a more aggressive approach. An additional hepatic resection is defined as essential for a radical surgical approach.

For hilar cholangiocarcinoma, the Bismuth-Corlette classification [Figure 1] is a guide to the extent of surgery required (the objective being tumor-free margins > 5 mm) [14-16].

- In type I and II: en-bloc resection of the extrahepatic bile ducts and gallbladder with 5–10 mm bile duct margins and regional lymphadenectomy with Roux-en-Y hepaticojejunostomy.
- In type III: hilar resection plus right or left hepatectomy or trisegmentectomy.
- In type IV: right or left trisegmentectomy.

Bile ducts of the caudate lobe frequently appear as direct branches of the bile duct bifurcation. Thus, routine caudate lobectomy in hilar cholangiocarcinoma type III-IV is mandatory [17,18].

This current surgical approach may require application of new staging systems in the preoperative assessment of hilar cholangiocarcinoma. The Blumgart T-staging system, which incorporates the degree of biliary involvement as well as portal venous involvement and hepatic lobar atrophy, provides a strong correlation with eventual resectability, the need for hepatectomy and overall survival [19,20].

Strategies to optimize the functional liver remnant are essential. According to Hemming and colleagues [15], it would be reasonable to use preoperative portal vein embolization in all patients undergoing extended hepatectomy for hilar cholangiocarcinoma without preexisting lobar hypertrophy of the remnant liver [15]. Portal vein embolization may permit a margin-negative resection in patients who otherwise would be considered unresectable because of the residual liver remnant [13,15-16]. The reported operative mortality for extended hepatectomies for hilar cholangiocarcinoma is about 10% (in our series, 13%) [Table 1]. Strict patient selection and further optimization of the liver remnant may improve the surgical mortality rates.

CONCLUSIONS

The improved survival in the treatment of hilar cholangiocarcinoma is a result of the increased resectability rate and the margin-negative (R0) resection rate. Aggressive surgical techniques aimed at achieving negative margins became routine in specialized centers. Combined liver and

bile duct resection have acceptable mortality and morbidity rates and better long-term outcome than seen in historical controls.

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