Published in final edited form as:

Ann Surg Oncol. 2009 December ; 16(12): 3308–3315. doi:10.1245/s10434-009-0701-4.

Initial Presentation and Management of Hilar and Peripheral Cholangiocarcinoma: Is a Node-Positive Status or Potential Margin-Positive Result a Contraindication to Resection?

Kevin Tri Nguyen, MD, PhD, Jennifer Steel, PhD, Tsafrir Vanounou, MD, MBA, Allan Tsung, MD, J. Wallis Marsh, MD, MBA, David A. Geller, MD, and T. Clark Gamblin, MD, MS
Department of Surgery, UPMC Liver Cancer Center, University of Pittsburgh, Pittsburgh, Pennsylvania

Abstract

Background—Cholangiocarcinoma (CC) frequently presents at an advanced stage and the majority of patients are unresectable at diagnosis. We sought to examine our recent experience with surgical resection for hilar and peripheral CC.

Methods—A review of all CC patients who presented to our multidisciplinary liver cancer center for evaluation of their CC between January 2000 and August 2008 was performed. Demographics, therapeutic management, pathologic characteristics, and overall survival were analyzed.

Results—A total of 280 patients were evaluated over the 8-year period, and 222 patients (79%) were unresectable at presentation. Fifty-eight out of 280 patients were candidates for resection, of whom, 51 patients underwent resection. Hilar CC was identified in 27 patients (53%) and peripheral CC was present in 24 patients (47%). Morbidity and 90-day mortality were 61 and 9.8%, respectively. Overall, negative margin (R0) resection was achieved in 26 patients (51%). Using multivariate Cox regression analysis, only margin status was found to be a significant predictor of survival ($p = 0.009$). Compared with peripheral CC, hilar CC was associated with shorter overall survival ($p = 0.001$) and higher rates of positive margins ($p = 0.001$) and perineural invasion ($p = 0.02$), and no difference in angiolymphatic, portal vein, and lymph node involvement.

Conclusions—Survival benefits can be achieved with resection for cholangiocarcinoma. Given the lack of effective alternative therapy, when confronted with the potential risk of positive margins or isolated nodal disease, we continue to advocate aggressive surgical resection for both hilar and peripheral CC with the ultimate goal of negative margin resection.

Management of cholangiocarcinoma remains a significant challenge. Complete surgical resection provides the only potential for cure, but most patients present with unresectable disease.¹ Most clinical series on cholangiocarcinoma present patients referred for surgical resection alone, making it difficult to determine the resectability rate of this rare cancer. Three studies provided an estimate of the resectability rate in their series of cholangiocarcinoma patients presenting for initial evaluation for resection.^{2–4} They found that 32–42% of patients were resectable with curative intent, while 58.2–67.6% were unresectable, either at presentation or at exploration. The extent of resection has also been debated, but increasing evidence shows that concomitant liver resection in pursuit of complete resection of the bile duct cancer is associated with increased survival.^{2,3,5–21}

Complete resection with negative margins is the best option for patients. However, if there is concern that lymph nodes are involved or that obtaining negative margins may be difficult, should this preclude a patient from undergoing surgical resection? Kitagawa et al. found that long-term survival was still possible in patients with pN2 (periportal, common hepatic, posterior pancreaticoduodenal, celiac, and superior mesenteric lymph nodes) and pM1 disease, suggesting that aggressive surgical resection with extended lymph node dissection in selected patients with hilar cholangiocarcinoma was warranted.²² Hemming et al. found that patients with microscopically positive margin (R1 resection) still had some benefit in survival compared with patients with locally advanced, unresectable disease who were bypassed.¹⁹

In addition, few studies have compared hilar cholangiocarcinoma with peripheral cholangiocarcinoma. Nakagohri et al. compared their series of patients with hilar versus peripheral cholangiocarcinoma and found that patients with hilar cholangiocarcinoma had significantly worse 5-year survival and more frequent perineural invasion and nodal involvement.²³ Although many series on cholangiocarcinoma have been published, spanning multiple decades, the present study provides an analysis of patients' initial presentation with cholangiocarcinoma to the University of Pittsburgh Liver Cancer Center. Since January 2000, this modern series includes patients with unresectable cancer, to evaluate the proportion of patients with cholangiocarcinoma who were curative resection candidates. We also identified pathologic factors that are associated with survival. In addition, we compared hilar cholangiocarcinoma with peripheral cholangiocarcinoma and identified different pathologic features associated with each subtype.

METHODS

Patients

Between January 2000 and August 2008, a total of 280 patients with cholangiocarcinoma were evaluated at the University of Pittsburgh Liver Cancer Center. This study was performed under University of Pittsburgh Institutional Review Board approval. A history and physical examination, laboratory studies, and imaging studies, including a computed tomography (CT) scan or magnetic resonance imaging (MRI) study, were obtained. Diagnosis was based on imaging and biopsy. Tumors were classified as hilar cholangiocarcinoma if the tumor originated at the hilar bifurcation. Tumors that originated proximal to the hilar bifurcation were classified as peripheral cholangiocarcinoma. Resectability was based on imaging studies. Patients with elevated bilirubin due to bile obstruction from the cholangiocarcinoma underwent either endoscopic retro-grade cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) with stent placement. Predrainage and preoperative bilirubin levels were recorded. Patients with predicted functional liver reserve (FLR) <20%, underwent portal vein embolization.

Operative Details

For a planned open liver resection, patients were explored through bilateral subcostal incisions. Extrahepatic metastasis or extensive bilobar disease, not identified on CT scan or MRI, precluded further exploration and resection. Concomitant liver resection was performed with the extrahepatic bile duct in most cases in pursuit of a negative margin. If the caudate lobe was involved or close to the tumor margin, then a caudate lobectomy was also performed; however, a caudate lobectomy was not routinely performed. Hilar lymphadenectomy was performed for all hilar cholangiocarcinoma and selectively for peripheral cholangiocarcinoma. A standard hepaticojejunostomy with 50-cm isoperistaltic Roux-en-Y jejunal limb was constructed as needed.

Statistics

Demographic, perioperative, and postoperative data including sex, age, body mass index (BMI), transarterial chemoembolization (TACE), biliary drainage, tumor markers, operative time (OR) time, blood loss, tumor size, length of stay, mortality, and morbidity were obtained from a medical record review. The data were imported into SPSS v.16 for analysis. Descriptive statistics were employed to characterize the sample. Chi-square analyses were performed to test differences between pathological groups. Two-side p -value of <0.05 was considered statistically significant. Univariate Kaplan–Meier (Breslow) survival analysis was employed to test differences between groups in terms of median survival. For survival analysis, the five patients with perioperative deaths were excluded. Multivariate Cox regression analysis was used on variables that were suggested by univariate analysis to be significant.

RESULTS

Patient Characteristics

The majority of patients were male (59.3%) and median age was 60 years (range 22–91 years) (Table 1). Median body mass index (BMI) was 27 kg/m^2 (range $18\text{--}39.5 \text{ kg/m}^2$). At presentation, the majority of patients were unresectable 222/280 (79.3%) based on imaging. A total of 58 patients were taken to the operating room and explored for potential resection. Seven patients (2.5%) were found to be unresectable (four due to extrahepatic metastasis and three due to extensive bilobar disease at surgical exploration). The remaining 51 patients (18.2%) underwent surgical resection.

Perioperative treatment included transarterial chemoembolization (TACE), portal vein embolization (PVE), percutaneous transhepatic cholangiogram (PTC) with catheter placement, and endobiliary stent placement. A total of 106/280 patients (37.9%) underwent TACE. Of these patients, 99/229 (43.2%) were unresected patients and 7/51 (13.7%) were resected patients. Four of the resected patients underwent TACE before resection to downstage the tumor and three patients underwent TACE after resection for intrahepatic recurrence. At presentation, median bilirubin was 11.9 mg/dl (range $0.2\text{--}30.3 \text{ mg/dl}$). A total of 23/51 (45.1%) of the resected patients underwent biliary drainage: 13/51 (25.4%) received endoscopic endobiliary drainage, 4/51 (7.8%) received PTC placement prior to presentation, and 11/51 (21.6%) received PTC placement after presentation. Three patients underwent both endobiliary and PTC drainage. Median bilirubin for the resected patients prior to operation was 0.8 mg/dl (range $0.1\text{--}15.9 \text{ mg/dl}$). One patient (2%) underwent PVE.

In the resected patients, median carcinoembryonic antigen (CEA) level was 1.4 ng/ml (range $0.5\text{--}745.8 \text{ ng/ml}$; normal $<0.5 \text{ ng/ml}$), carbohydrate antigen 19-9 (CA 19-9) was 60.6 units/ml (range $4\text{--}19,000 \text{ units/ml}$; normal $<38.0 \text{ units/ml}$), and alpha-fetoprotein (AFP) was $4 \text{ } \mu\text{g/l}$ (range $2\text{--}15 \text{ } \mu\text{g/l}$; normal $<2 \text{ } \mu\text{g/l}$).

Perioperative Characteristics

Liver resection was performed in 48/51 (94.1%) of patients (Table 2). The most common liver resections were right lobectomy (18/51, 35.3%), left lobectomy (11/51, 21.6%), and extended right hepatectomy (8/51, 15.7%). En bloc caudate lobectomy was not routinely performed and was required in 15/51 (29.4%) of patients in pursuit of a R0 resection. Hilar lymphadenectomy was performed in 42/51 (82.3%) of patients. Roux-en-Y biliary reconstruction was required in 29/51 (56.9%) of patients for postoperative biliary drainage. Portal vein and arterial reconstruction were required in 4/51 (7.8%) and 1/51 (2%) of patients, respectively.

Bile duct resection without liver resection was performed in three patients. One patient had in situ cholangiocarcinoma with negative proximal and distal bile duct margins; therefore, liver resection was not performed. In two patients, the distal margin just superior to the duodenum was positive on frozen section, suggesting that a Whipple resection in addition to the liver resection would be necessary to clear the tumor; however, this was deemed high risk and therefore palliative bypass was performed for these patients.

For the 51 patients who underwent resection, median operative time was 458 min (range 96–777 min) with median blood loss of 150 ml (range 50–1,800 ml). Median tumor size was 6 cm (range 0.8–19 cm). Median length of hospital stay was 9 days (range 1–62 days).

Five deaths (9.8%) occurred in our series during the 90-day perioperative period, all in patients with hilar cholangiocarcinoma who underwent right lobectomy. When mortality rates were analyzed separately between patients with hilar and peripheral cholangiocarcinoma, the mortality rates were 18.5% (5/27) and 0% (0/24), respectively. None of the patients who died underwent portal vein embolization. Of the five patients who died, four patients developed liver failure, three patients had renal failure, one patient progressed to sepsis, and one patient developed portal vein thrombosis. One patient died of sepsis from a bowel perforation that required re-exploration. The median CA 19-9 level of the five patients was 257 units/ml (range 69–1,231.1 units/ml). All five patients had biliary drainage (two ERCP and stent placed, three PTC placed). Pathological characteristics of the five patients were as follows: 4/5 R1 status; 1 well-differentiated, 2 moderately differentiated, 2 poorly differentiated grade tumors; 5/5 positive perineural invasion; 3/5 positive angiolymphatic invasion; 3/5 positive portal vein invasion; 2/5 lymph node invasion.

Complications occurred in 31/51 (61%) patients. Median Clavien grade classification for complications was grade III (range I–V). Of the 51 patients who were resected, liver-related complications included liver failure ($n = 4$), portal vein thrombosis ($n = 2$), bile leak requiring ERCP and stent placement ($n = 3$), bile leak controlled with operative drain ($n = 2$), bile leak requiring re-exploration and revision of hepaticojejunostomy ($n = 1$), biliary obstruction requiring PTC catheter placement ($n = 1$), and ascites ($n = 2$). Surgery-related complications included wound infections ($n = 5$), bleeding from inferior vena cava (IVC) requiring re-exploration ($n = 1$), bowel perforation requiring re-exploration ($n = 1$), fascial dehiscence ($n = 1$), and intra-abdominal abscess requiring drain placement ($n = 2$). Other general complications included renal failure requiring dialysis ($n = 3$), transient renal insufficiency ($n = 2$), urinary tract infection ($n = 2$), pleural effusion requiring catheter placement ($n = 4$), deep vein thrombosis/pulmonary embolism (DVT/PE) ($n = 2$), stroke ($n = 1$), hemolytic reaction from blood transfusion ($n = 1$), and alcohol withdrawal ($n = 1$).

Factors Associated with Survival

Median survival for all 280 patients evaluated with cholangiocarcinoma at UPMC liver cancer center was 13 months (Table 3). Median survival for unresected patients was significantly worse than survival of all patients who underwent surgical resection (11 months versus 17 months, $p = 0.03$). Hilar cholangiocarcinoma was present in 27/51 (53.9%) patients and peripheral cholangiocarcinoma was present in 24/51 (47.1%) patients. Five perioperative deaths occurred in patients with hilar cholangiocarcinoma; therefore, these patients were not included in the long-term survival analysis (Tables 3 and 4). When comparing patients who underwent resection for hilar cholangiocarcinoma with those who underwent resection for peripheral cholangiocarcinoma, patients with hilar cholangiocarcinoma had a worse outcome with median survival of 12 months, compared with patients with peripheral cholangiocarcinoma who had median survivals of 20 months ($p = 0.007$).

Margin status was the major factor affecting survival. R0 resection was achieved in 51% of patients. Patients who underwent resection, regardless of tumor position or margin status, had median survival of 17 months, compared with unresected patients who had median survival of 11 months ($p = 0.03$). Patients with R0 resection had a significantly improved outcome with median survival of 30 months, compared with patients with R1 resection who had median survival of 11 months ($p = 0.001$). Margin status was further assessed at the distal bile duct margin (21.5% positive) and the proximal bile duct/parenchymal margin (37.2% positive). Patients with negative proximal duct/parenchymal margin had median survival of 30 months, compared with 11 months for patients with positive proximal duct/parenchymal margin ($p = 0.001$). Patients with negative distal duct margin also had better survival with median survival of 20 months, compared with patients with positive distal duct margin who had median survival of 8 months ($p = 0.001$).

Of the parameters that were assessed using Kaplan–Meier (Breslow) univariate analyses (Table 3), tumor location (hilar/peripheral) ($p = 0.001$), margin status ($p = 0.001$), and perineural invasion ($p = 0.02$) were significantly associated with overall survival. Tumor stage ($p = 0.44$), angiolymphatic invasion ($p = 0.32$), portal vein invasion ($p = 0.78$), and lymph node metastasis ($p = 0.38$) did not affect overall survival.

The three factors that were found to be significant using univariate analyses (Kaplan–Meier) were included in a Cox regression multivariate analysis, evaluating predictors of survival (see below). The model, which included tumor location of tumor, margin status, and perineural invasion, was significant (chi-square = 18.1, $p = 0.001$). Margin status was the only significant predictor ($p = 0.006$), with positive margins being associated with decreased survival. A trend toward significance was observed, with peripheral tumors being associated with longer survival ($p = 0.17$) and perineural invasion being associated with decreased survival ($p = 0.13$).

Hilar Versus Peripheral Cholangiocarcinoma

When comparing hilar versus peripheral cholangiocarcinoma (Table 4), resection for hilar cholangiocarcinoma was associated with a significantly higher rate of R1 margin status (70% versus 22%, $p = 0.001$). The R1 status was based on a higher rate of positive proximal bile duct/parenchymal margin (57% versus 22%, $p = 0.02$) or positive distal bile duct margin (45% versus 0%, $p = 0.003$). In addition, hilar cholangiocarcinoma was associated with a significantly higher rate of perineural invasion (91% versus 40%, $p = 0.001$). There was no significant difference in the rate of positive angiolymphatic invasion (54% versus 62%, $p = 0.63$), portal vein invasion on pathologic specimen (16% versus 13%, $p = 0.80$) or lymph node metastasis (47% versus 64%, $p = 0.39$) between hilar and peripheral cholangiocarcinoma, respectively.

DISCUSSION

We present one of few studies to evaluate the percentage of patients with resectable cholangiocarcinoma with emphasis on prognostic factors that affect survival and comparisons between hilar and peripheral cholangiocarcinoma. Previous studies have found that 35.6–41.8% of patients who presented at a tertiary medical care center with various stages of cholangiocarcinoma are resectable with curative intent.^{2,3} We found that only 18.2% of our patients were resectable, while 81.8% were unresectable at initial presentation or at exploration. Our low resectability rate further emphasizes the need for earlier referral to a hepatobiliary surgeon; however, this is difficult given that patients often initially present to their primary care physician with advanced disease.

The overall mortality and morbidity rates were 9.8 and 61%, respectively, which are comparable to reported mortality and morbidity rates of 0–10 and 26–64%, respectively.^{2–4,19,20,22,24–26} Among the hilar cholangiocarcinoma patients, the mortality rate was 18.5%, which underscores the complex nature of this subtype of cholangiocarcinoma and the operation required for complete resection. Liver failure occurred in four of the five patients who died during the perioperative period. None underwent portal vein embolization. Bile leaks occurred in six patients (11.8%), with only one patient requiring re-exploration and the remainder treated conservatively with percutaneous drainage and/or ERCP and stent placement.

We found that, even with the possibility of positive margins or lymph node involvement, patients who underwent resection had significantly improved survival compared with patients who were unresected. Achieving R0 resection is the ultimate goal, as this was the primary factor associated with improved survival using multivariate analysis. Median survival for R1 resections did not appear to be improved over unresected patients; however, R0 resection cannot be achieved without aggressive attempts at complete surgical resection. Contrary to other reports, we did not find lymph node involvement to be associated with survival.^{4,20,22,23,25} We also found that patients with hilar cholangiocarcinoma had poorer survival compared with patients with peripheral cholangiocarcinoma. This may be due to the higher rate of positive margins and perineural invasion observed after resection for hilar cholangiocarcinoma.

Most studies on cholangiocarcinoma focus on hilar cholangiocarcinoma. Nakagohri et al. recently provided their institutional experience comparing hilar with peripheral cholangiocarcinoma over a 16-year period from 1981 to 1997.²³ Resectability rates were not assessed; however, similar to our results, they found a significantly worse outcome after surgical resection for hilar versus peripheral cholangiocarcinoma (5-year overall survival 4% versus 43%, respectively; $p = 0.005$) and a significantly worse outcome after resection with positive versus negative margins (5-year overall survival 8% versus 38%, respectively; $p = 0.008$). Compared with peripheral cholangiocarcinoma, hilar cholangiocarcinoma had more positive margins (88% versus 29%), more perineural invasion (100% versus 29%), and more lymph node metastasis (85% versus 7%). In addition, they found that perineural invasion (positive versus negative; 5-year survival of 7% versus 50%, respectively; $p = 0.008$) and lymph node metastasis (positive versus negative; 5-year survival of 0% versus 41%, respectively; $p = 0.0004$) were significant prognostic indicators of outcome. Our results found that perineural invasion was more prevalent in patients with hilar cholangiocarcinoma and associated with shorter survival in patients without perineural invasion; however, we did not find lymph node invasion as a predictor of worse outcome. Of note, in our series, lymph node metastasis was present in only 33.3% of all resected patients, 37% of resected hilar cholangiocarcinoma and 29.2% of resected peripheral cholangiocarcinoma. In Nakagohri et al.'s study, patients with hilar cholangiocarcinoma had 100% perineural invasion and 85% lymph node metastasis; however, in addition, they had 88% positive margin, which could be the main driving factor associated with poor survival, rather than perineural invasion and lymph node metastasis.

Endo et al. (2008) presented their experience on peripheral, intrahepatic cholangiocarcinoma.⁴ They noted an increase incidence of peripheral cholangiocarcinoma over their 16-year study period. They also found that lymph node metastasis was a poor prognostic indicator of survival. Lymph node metastasis occurred in 8.5% of patients with median disease-free survival of 7 months and median disease-specific survival of 14 months compared with patients without lymph node metastasis who had median disease-free survival of 16 months ($p = 0.009$) and median disease-specific survival of 36 months ($p < 0.001$). Interestingly, surgical margins did not significantly affect disease-free ($p = 0.56$) or

disease-specific survival ($p = 0.095$). They argued that “patients with large, node-positive or multifocal intrahepatic cholangiocarcinoma seem to derive little benefit” from resection. This is in contrast to our finding that lymph node status was not a prognostic factor associated with survival and that margin status was the significant factor associated with survival. Jarnigan et al. also found that lymph node involvement had no impact on survival in patients with hilar cholangiocarcinoma and that complete resection with negative margin remains the only therapy that offers the possibility of long-term survival.² The literature remains controversial, as the two previously mentioned articles with differing findings are from the same institution.^{2,4}

Similar to our findings, Hemming et al. found that patients who underwent an R0 resection had longer actuarial survival than patients with positive margins (median survival 53 months versus 24 months, $p < 0.01$), which still had improved survival over patients who received palliative bypass (median survival 24 months versus 12 months, $p < 0.05$), suggesting that resection, even with positive margin, was more beneficial, compared with no resection.¹⁹ There was a difference in 5-year survival in patients with and without lymph node metastasis, but this did not reach statistical significance. The authors argued that negative margin status was the single most important factor in achieving prolonged survival.

Baton et al. also argued that R1 resection, in patients with no other risk factor, offered long-term survival.²⁴ Based on a 20-year series of 59 resections, R0 resection was achieved in 46% of patients and positive lymph nodes were found in 51% of patients. Morbidity and mortality were 42 and 5%, respectively. For resected patients, median survival was 32 months with overall survival at 1-, 3-, and 5-year of 82, 45, and 20%, respectively, compared with the 1-, 3-, and 5-year survival of 59, 11, and 6%, respectively, in unresected patients. After multivariate analysis, male gender ($p = 0.0002$), lack of preoperative chemotherapy ($p = 0.005$), R1 on biliary tract ($p = 0.01$), and celiac LN involvement ($p < 0.0001$) were independent prognostic factors for poor overall survival. Of note, while celiac lymph node metastasis was predictive of poor overall survival, lymph node metastasis was not, although a trend was observed ($p = 0.06$). Ito et al. found that patients who underwent an R0 resection had median disease-specific survival of 65 months, compared with 4 months in unresected patients; but, in addition, patients who underwent an R1/R2 resection still had better disease-specific survival of 16 months compared with unresected patients ($p < 0.001$).³

CONCLUSIONS

We report a large series of patients presenting with cholangiocarcinoma in the modern era. Our work shows that the majority of patients present with unresectable disease. Obtaining a negative margin is the most vital aspect of surgical resection for cholangiocarcinoma. In addition, resection for hilar cholangiocarcinoma was significantly associated with a higher rate of R1 resection and significantly worse survival compared with resection for peripheral cholangiocarcinoma. The presence of positive hilar lymph nodes was not associated with decrease survival and therefore does not preclude surgical resection.

REFERENCES

1. Launois B, Campion JP, Brissot P, Gosselin M. Carcinoma of the hepatic hilus Surgical management and the case for resection. *Ann Surg.* 1979; 190(2):151–7. [PubMed: 223508]
2. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg.* 2001; 234(4):507–17. discussion 517–9. [PubMed: 11573044]
3. Ito F, Agni R, Rettammel RJ, et al. Resection of hilar cholangiocarcinoma: concomitant liver resection decreases hepatic recurrence. *Ann Surg.* 2008; 248(2):273–9. [PubMed: 18650638]

4. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg.* 2008; 248(1):84–96. [PubMed: 18580211]
5. Beazley RM, Hadjis N, Benjamin IS, Blumgart LH. Clinico-pathological aspects of high bile duct cancer. Experience with resection and bypass surgical treatments. *Ann Surg.* 1984; 199(6):623–36. [PubMed: 6329110]
6. Nimura Y, Hayakawa N, Kamiya J, et al. Hepatic segmentectomy with caudate lobe resection for bile duct carcinoma of the hepatic hilus. *World J Surg.* 1990; 14(4):535–43. [PubMed: 2166381]
7. Tashiro S, Tsuji T, Kanemitsu K, et al. Prolongation of survival for carcinoma at the hepatic duct confluence. *Surgery.* 1993; 113(3):270–8. [PubMed: 7680142]
8. Sugiura Y, Nakamura S, Iida S, et al. Extensive resection of the bile ducts combined with liver resection for cancer of the main hepatic duct junction: a cooperative study of the Keio Bile Duct Cancer Study Group. *Surgery.* 1994; 115(4):445–51. [PubMed: 8165536]
9. Miyagawa S, Makuuchi M, Kawasaki S. Outcome of extended right hepatectomy after biliary drainage in hilar bile duct cancer. *Arch Surg.* 1995; 130(7):759–63. [PubMed: 7611866]
10. Pichlmayr R, Weimann A, Klempnauer J, et al. Surgical treatment in proximal bile duct cancer. A single-center experience. *Ann Surg.* 1996; 224(5):628–38. [PubMed: 8916878]
11. Su CH, Tsay SH, Wu CC, et al. Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. *Ann Surg.* 1996; 223(4):384–94. [PubMed: 8633917]
12. Iwatsuki S, Todo S, Marsh JW, et al. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. *J Am Coll Surg.* 1998; 187(4):358–64. [PubMed: 9783781]
13. Ogura Y, Kawarada Y. Surgical strategies for carcinoma of the hepatic duct confluence. *Br J Surg.* 1998; 85(1):20–4. [PubMed: 9462376]
14. Ishiyama S, Fuse A, Kuzu H, et al. Results of surgical treatments and prognostic factors for hepatic hilar bile duct cancer. *J Hepatobiliary Pancreat Surg.* 1998; 5(4):429–36. [PubMed: 9931393]
15. Miyazaki M, Ito H, Nakagawa K, et al. Parenchyma-preserving hepatectomy in the surgical treatment of hilar cholangiocarcinoma. *J Am Coll Surg.* 1999; 189(6):575–83. [PubMed: 10589594]
16. Kosuge T, Yamamoto J, Shimada K, et al. Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. *Ann Surg.* 1999; 230(5):663–71. [PubMed: 10561090]
17. Neuhaus P, Jonas S, Bechstein WO, et al. Extended resections for hilar cholangiocarcinoma. *Ann Surg.* 1999; 230(6):808–18. discussion 819. [PubMed: 10615936]
18. Todoroki T, Kawamoto T, Koike N, et al. Radical resection of hilar bile duct carcinoma and predictors of survival. *Br J Surg.* 2000; 87(3):306–13. [PubMed: 10718799]
19. Hemming AW, Reed AI, Fujita S, et al. Surgical management of hilar cholangiocarcinoma. *Ann Surg.* 2005; 241(5):693–9. discussion 699–702. [PubMed: 15849505]
20. Seyama Y, Kubota K, Sano K, et al. Long-term outcome of extended hemihepatectomy for hilar bile duct cancer with no mortality and high survival rate. *Ann Surg.* 2003; 238(1):73–83. [PubMed: 12832968]
21. Washburn WK, Lewis WD, Jenkins RL. Aggressive surgical resection for cholangiocarcinoma. *Arch Surg.* 1995; 130(3):270–6. [PubMed: 7534059]
22. Kitagawa Y, Nagino M, Kamiya J, et al. Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and paraaortic node dissection. *Ann Surg.* 2001; 233(3):385–92. [PubMed: 11224627]
23. Nakagohri T, Asano T, Kinoshita H, et al. Aggressive surgical resection for hilar-invasive and peripheral intrahepatic cholangiocarcinoma. *World J Surg.* 2003; 27(3):289–93. [PubMed: 12607053]
24. Baton O, Azoulay D, Adam DV, Castaing D. Major hepatectomy for hilar cholangiocarcinoma type 3 and 4: prognostic factors and longterm outcomes. *J Am Coll Surg.* 2007; 204(2):250–60. [PubMed: 17254929]

25. Klempnauer J, Ridder GJ, von Wasielewski R, et al. Resectional surgery of hilar cholangiocarcinoma: a multivariate analysis of prognostic factors. *J Clin Oncol.* 1997; 15(3):947–54. [PubMed: 9060532]
26. Rea DJ, Munoz-Juarez M, Farnell MB, et al. Major hepatic resection for hilar cholangiocarcinoma: analysis of 46 patients. *Arch Surg.* 2004; 139(5):514–23. discussion 523–5. [PubMed: 15136352]

TABLE 1
Demographics, and peri- and postoperative characteristics of patients with cholangiocarcinoma (2000–2008)

Total no. of patients	280
Sex	
Male	166 (59.3%)
Female	114 (40.7%)
Age (median)	60 years (22–91)
BMI (median)	27 kg/m ² (18–39.5 kg/m ²)
Resectability (%)	
Unresectable at presentation	222 (79.3%)
Explored and resected	51 (18.2%)
Explored and found unresectable ^a	7 (2.5%)
TACE treatment	
Total patients who received TACE (%)	106/280 (37.9%)
Resected patients who received TACE (%)	7/51 (13.7%)
Unresected patients who received TACE (%)	99/228 (43.4%)
TACE treatments (median)	4 (1–32)
Total resected patients with biliary drainage (%)	23/51 (45.1%)
Resected patients with endobiliary stent	13/51 (25.4%)
Resected patients with PTC placed prior to presentation	4/51 (7.8%)
Resected patients with PTC placement after presentation	11/51 (21.6%)
Perioperative bilirubin	
Predrainage bilirubin (median)	11.9 mg/dl (0.2–30.3 mg/dl)
Preoperative bilirubin (median)	0.8 mg/dl (0.1–15.9 mg/dl)
Tumor markers of resected patients	
CEA (median)	1.4 ng/ml (0.5–745.8 ng/ml)
CA19-9 (median)	60.6 units/ml (4–19,000 units/ml)
AFP (median)	4 µg/l (2–15 µg/l)
Surgical patients requiring (%)	
PVE	1/51 (2.0%)
Liver resection	48/51 (94.1%)

En bloc caudate lobectomy	15/51 (29.4%)
Hilar lymphadenectomy	42/51 (82.3%)
Roux-en-Y biliary reconstruction	29/51 (56.9%)
Portal vein reconstruction	4/51 (7.8%)
Arterial reconstruction	1/51 (2.0%)
OR time (median, range)	458 min (96–777 min)
Blood loss (median, range)	150 ml (50–1800 ml)
Resected tumor size (median)	6 cm (0.8–19 cm)
Length of stay (median, range)	9 days (1–62 days)
Perioperative mortality (90-days) (%)	5/51 (9.8%)
Perioperative morbidity (90-days) (%)	31/51 (61%)

TACE transarterial chemoembolization, PVE portal vein embolization, CEA carcinoembryonic antigen, CA 19-9 carbohydrate antigen 19-9, AFP alpha-fetoprotein

^aExtra-hepatic metastasis (*n* = 4), extensive bilobar disease (*n* = 3)

TABLE 2

Type of resection performed for cholangiocarcinoma

Right lobectomy (<i>n</i> , %)	18 (35.3%)
Left lobectomy (<i>n</i> , %)	11 (21.6%)
Extended right hepatectomy (<i>n</i> , %)	8 (15.7%)
Bile duct resection (<i>n</i> , %)	3 (5.9%)
Partial right lobectomy (<i>n</i> , %)	2 (3.9%)
Extended left hepatectomy (<i>n</i> , %)	2 (3.9%)
Central liver resection (<i>n</i> , %)	2 (3.9%)
Laparoscopic wedge resection (<i>n</i> , %)	2 (3.9%)
Left lateral sectionectomy (<i>n</i> , %)	1 (2.0%)
Segmentectomy (<i>n</i> , %)	1 (2.0%)
Total hepatectomy and ex vivo extended left hepatectomy with autotransplantation (<i>n</i> , %)	1 (2.0%)

TABLE 3

Kaplan–Meier (Breslow) survival analyses by pathological characteristics of patients with cholangiocarcinoma

	n	Median survival (months)	p-value
Total no. of patients	275	13	
Unresected patients	229	11	0.03
Resected patients	46	17	
Hilar cholangiocarcinoma	22	12	0.007
Peripheral cholangiocarcinoma	24	20	
Margin status			
R0 resection	24	30	0.001
R1 resection	19	11	
Proximal bile duct/parenchymal margin			
Negative	27	30	0.001
Positive	17	11	
Distal bile duct margin			
Negative	25	20	0.001
Positive	9	8	
T stage			
T1	3	31	0.44
T2	15	30	
T3	15	14	
T4	4	13	
Tumor grade			
Moderately differentiated	30	17	0.62
Moderately to poorly differentiated	10	13	
Poorly differentiated	6	30	
Perineural invasion			
Negative	14	31	0.02
Positive	28	14	
Angiolymphatic invasion			
Negative	18	31	0.32
Positive	25	14	
Portal vein invasion			
Negative	36	17	0.78
Positive	6	14	
Lymph node involvement			
Negative	13	14	0.38
Positive	15	13	

TABLE 4

Chi-square analyses of tumor location and pathological characteristics

	Hilar cholangiocarcinoma (n = 22)		Peripheral cholangiocarcinoma (n = 24)		Chi-square <i>p</i> -value (two-sided)
	Negative <i>n</i> (%)	Positive <i>n</i> (%)	Negative <i>n</i> (%)	Positive <i>n</i> (%)	
Overall margin (R0-R1)	6 (30)	14 (70)	18 (78)	5 (22)	10.1 0.001
Proximal bile duct/parenchymal margin	9 (43)	12 (57)	18 (78)	5 (22)	5.8 0.02
Distal bile duct margin	11 (55)	9 (45)	14 (100)	0 (0)	8.6 0.003
Perineural invasion	2 (9)	20 (91)	12 (60)	8 (40)	12.2 0.001
Angiolymphatic invasion	10 (46)	12 (54)	8 (38)	12 (62)	0.24 0.63
Portal vein invasion	16 (84)	3 (16)	20 (87)	3 (13)	0.06 0.80
Lymph node metastasis	9 (53)	8 (47)	4 (36)	7 (64)	0.74 0.39