Recurrence of hilar cholangiocarcinoma after surgical resection: is there a role of surgery?

Ahmed Shehta[a], Mohamed A. Wahab[a], Helmy Ezzat[a], Youssif Elmahdy[a], Rihame Abdel-Wahab[b], Khaled A. Wahab[c]

[a]Department of Surgery, Liver Transplantation Unit, Gastrointestinal Surgery Center, [b]Department of Radiology, College of Medicine, [c]Department of Surgical Oncology, Oncology Center, Mansoura University, Mansoura, Egypt

Correspondence to Mohamed A. Wahab, MD, Department of Surgery, Liver Transplantation Unit, Gastrointestinal Surgery Center, College of Medicine, Mansoura University, Mansoura 35516, Egypt.
e-mail: wahab_m_eg@yahoo.com

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Aim
To evaluate our experience in management of recurrent perihilar cholangiocarcinoma (pCCA) and to detect whether surgical re-resection is of value in these cases or not.
Patients and methods
We revised our data for patients who underwent surgical resection for pCCA during the period between May 1995 and December 2010.
Results
During this period, 263 cases underwent surgical exploration for pCCA. After a median follow-up duration of 18 months (4–89), recurrence occurred in 136 (51.7%) patients and mortality occurred in 157 (59.7%) patients. The 1-, 3-, and 5-year disease-free and overall survival rates were 82.7, 41.5, and 35% and 86.7, 52, and 47.6%, respectively.
Nine redo-resections were performed for eight (3%) patients with recurrence at biliary anastomosis.
The redo-surgery group achieved a better overall survival rates when compared with biliary drainage group (Log-rank=0.046) and when compared with the nonoperated group (Log-rank=0.032).
Conclusion
Surgical re-resection of recurrent pCCA is a feasible and technically challenging procedure in selected patients. It is associated with acceptable perioperative morbidities and provides a better survival benefit compared with other palliative procedures.

Keywords:
perihilar cholangiocarcinoma, recurrence, surgical resection

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Introduction

Cholangiocarcinoma (CCA) is considered the most common biliary tract malignancy accounting for ~10–20% of primary liver cancers [1]. Perihilar cholangiocarcinoma (pCCA) is the commonest variant of CCA representing almost 50–67% of all cases [2].

Surgical resection remains the mainstay of the radical treatment of pCCA [3]. Recently, the outcomes of radical resection of pCCA has improved owing to the advances in the surgical techniques and perioperative patient care [4,5]. However, the long-term outcomes after surgical resection remain poor owing to high incidence of tumor recurrence [6,7].

Recurrent pCCA usually comes with as local anastomotic recurrence, liver secondaries, lymph nodes secondaries, peritoneal secondaries, and distant metastasis. Local anastomotic recurrence is the commonest type of pCCA recurrence [8]. Patients with recurrent pCCA are managed with palliative chemotherapy or radiotherapy combined with palliative biliary tract drainage [9–11]. On the contrary, some case series had shown good value for surgical intervention in selected cases with recurrent biliary tree malignancies [12–14]; however, it remains unclear whether surgery for these cases can provide a better overall survival compared with other palliative modalities.

The aim of our work is to review our experience with surgical management for selected patients with recurrent pCCA and to evaluate whether surgical re-resection is beneficial or not.

Patients and methods

Study design

We revised data of cases who underwent surgical resection for pathologically proven pCCA with

curative intent by a single surgeon (M.A.W.) during the period between May 1995 and December 2010 at Gastrointestinal Surgery Center, Mansoura University, Egypt. This study was approved by institutional review board and local ethical committee at Faculty of Medicine, Mansoura University. A written consent was obtained from each patient prior to surgical intervention after explanation of possible risks of the surgery.

Preoperative assessment

Preoperative evaluation protocol had been described elsewhere [15]. Generally, assessment of the extent of the pCCA was accomplished by triphasic abdominal computed tomography (CT), together with magnetic resonance cholangiopancreatography. Preoperative biliary drainage was done in patients with cholangitis by percutaneous transhepatic drainage, which was more preferred, or by endoscopic retrograde cholangiopancreatography [16].

Operative technique

The surgical technique had been described elsewhere [15,17,18]. The choice of the extent of liver resection was dependent upon the preoperative evaluation of tumor extent and liver functions, presence or absence of liver cirrhosis or lobar atrophy, and intraoperative findings such as the tumor extent and vascular invasion. Hepatic resection was accomplished with an energy device (Harmonic Wave Open Shears; Ethicon, Cincinnati, OH, USA) with or without intermittent clamping of the hepatic inflow (Pringle's maneuver). All cases underwent extrahepatic biliary resection and excision of locoregional lymph nodes.

Postoperative care

After surgery, all patients were admitted to the ICU and then to the surgical ward for follow-up. Follow-up laboratory tests and radiological evaluation were done daily. Radiologically guided tube drainage was performed in case of confirmed surgical collections.

Postoperative morbidity is defined as adverse events occurring during the period of the first 60 days after operation. It is clinically classified depending on the standardized Clavien–Dindo grading system. Major complications are demarcated as grade III or higher [19]. Postoperative biliary fistula and posthepatectomy liver decompensation are defined according to the International Study Group of Liver Surgery [20,21].

Follow up

After discharge, cases were frequently followed up in the outpatient clinic. Follow-up appointments were performed at 1, 3, and 6 months postoperatively and afterward every 6 months. Follow-up appointment comprised detailed clinical checkup, routine laboratory examination including serum tumor markers' levels such as carcinoembryonic antigen and carbohydrate antigen 19–9, and abdominal ultrasound and CT to delineate the possibility of tumor recurrence.

Confirmation of recurrence

Upon clinical or laboratory suspicion of tumor recurrence, a metastatic workup was performed including triphasic abdominal CT and/or abdominal MRI, CT of the chest, and bone scan to confirm the presence of tumor recurrence.

With the presence of any suspicious lesion on radiological studies, a closer monitoring with serial studies was done. The progression of any suspicious lesion by serial studies or the appearance of new lesions was considered as an evidence of tumor recurrence.

Indication of surgery for recurrence

In our center, surgical exploration for tumor recurrence was decided for patients with good general status with solitary local anastomotic recurrence that was potentially resectable on follow-up radiological studies. Patients with local anastomotic recurrence that deemed unresectable on follow-up radiology were managed by palliative percutaneous transhepatic drainage. Patients with poor general status or multisite recurrences received palliative supportive care.

In our experience, only eight patients with local anastomotic site recurrences were potentially resectable and received surgical excision. Patients with hepatic and extrahepatic recurrences experienced multifocal recurrences and were unresectable.

We compared patients with anastomotic biliary recurrence who received either redo-surgical resection versus palliative biliary drainage. We did not include any patients with recurrences at other sites because one of them received surgical treatment for recurrence.

Study outcomes

The primary outcome of this study is the survival outcome after surgical resection for recurrence after curative intent resection of pCCA.

Statistical analysis

Categorical variables were written as numbers (percentage), and continuous variables were

expressed as median (range). Comparison between groups was done using χ^2 or Mann–Whitney test when applicable. Survival rates were better evaluated by Kaplan–Meier method, and comparison between groups was done by Log-rank test. Statistical analysis was performed using the SPSS 20 software (IBM, Chicago, Illinois, USA). We considered *P* value less than 0.05 as a statistically significant outcome.

Results

A total of 263 patients underwent surgical resection for pathologically proven pCCA and were included in the study.

Preoperative characteristics

The preoperative criteria of the study patients are shown in Table 1. A total of 107 (40.7%) patients had associated hepatitis C virus.

Operative and postoperative outcomes

Operative and postoperative data of the study patients are shown in Table 2. Liver cirrhosis was found in 120 (45.6%) patients. The median hospital stay was 12 days (3–50). Biliary leakage occurred in 80 (30.4%) patients.

Pathological data

Pathological data of the study patients are shown in Table 2.

Survival outcomes

The long-term follow-up data are shown in Table 3. The median follow-up duration was 18 months (4–89). Mortality occurred in 157 (59.7%) patients. The 1-, 3-, and 5-year survival rates were 86.7, 52, and 47.6%, respectively (Fig. 1a).

Table 1 Preoperative characteristics of the study patients

Variables	Data [*n* (%)]
Age (years)	54 (23–75)
Sex	
Male	164 (62.4)
Female	99 (37.6)
Presentation	
Abdominal pain	90 (34.2)
Jaundice	262 (99.6)
Weight loss	120 (45.6)
Serum albumin (g/dl)	3.7 (2.2–5.6)
Serum bilirubin (mg/dl)	15 (0.5–46.5)
SGOT (IU/l)	24 (15–557)
SGPT (IU/l)	80 (23–691)
Carbohydrate antigen (IU/l)	300 (10–1080)
Hepatitis C virus	107 (40.7)
Hepatitis B virus	4 (1.5)
Preoperative biliary drainage	
ERCP	35 (13.3)
PTD	82 (31.2)
Serum total bilirubin before surgery (mg/dl)	12 (0.5–36)

ERCP, endoscopic retrograde cholangiopancreatography; PTD, percutaneous transhepatic biliary drainage.

Tumor recurrence

Tumor recurrence occurred in 136 (51.7%) patients. Recurrence data are shown in Table 3. Recurrence occurred most commonly in the remnant liver [58 (22.1%) patients]. The 1-, 3-, and 5-year disease-free rates were 82.7, 41.5, and 35%, respectively (Fig. 1b).

Surgery for recurrence

Nine redo-resections were performed for eight (3%) patients with recurrence at the biliary anastomotic site. Other patients with biliary anastomotic recurrences underwent only palliative percutaneous biliary drainage (Fig. 2). No re-resections were performed for patients with hepatic or extrahepatic recurrences. Those patients received only palliative supportive care.

Resection of local anastomotic recurrence was performed in all patients with adequate bile duct resection margin, and restoration of biliary-enteric anastomoses were performed (Fig. 3). Associated

Table 2 Operative, postoperative, and pathological data of the study patients

Variables	Data [*n* (%)]
Operative data	
Liver state	
Normal	143 (54.4)
Cirrhosis	120 (45.6)
Liver resection extent	
Localized	91 (34.6)
Hepatectomy	172 (65.4)
(Left/right hemihepatectomy)	100 (38)/72 (27.4)
Caudate lobectomy	85 (32.3)
Operation time (h)	4 (1.5–8)
Blood transfusion	69 (26.2)
Postoperative data	
Hospital stay (days)	12 (3–50)
Bile leakage	80 (30.4)
Wound infection	57 (21.7)
Liver dysfunction	45 (17.1)
Abdominal collection	43 (16.3)
Internal hemorrhage	14 (5.3)
Pathological data	
Tumor differentiation	
Well	115 (43.7)
Moderate	89 (33.8)
Poor	59 (22.4)
Lymph nodes	
Positive	93 (35.4)
Negative	170 (64.6)
Cut margin	
R0	151 (57.4)
R1	112 (42.6)

Table 3 Long-term follow up data of the study patients.

Variables	Data
Follow up duration (month)	18 (4–89)
Mortality on follow up	157 (59.7%)
Recurrence time (month)	15 (4–89)
Recurrence	136 (51.7%)
Recurrence site	
Anastomotic	42 (15.9%)
Hepatic	58 (22.1%)
Lymph nodes	18 (6.8%)
Peritoneal	8 (3%)
Pulmonary	6 (2.2%)
Bone	4 (1.5%)
Recurrence treatment	
Supportive	94 (35.7%)
Biliary drainage	34 (12.9%)
Redo-surgery	8 (3%)

segmental portal vein resection was done in two (25%) patients.

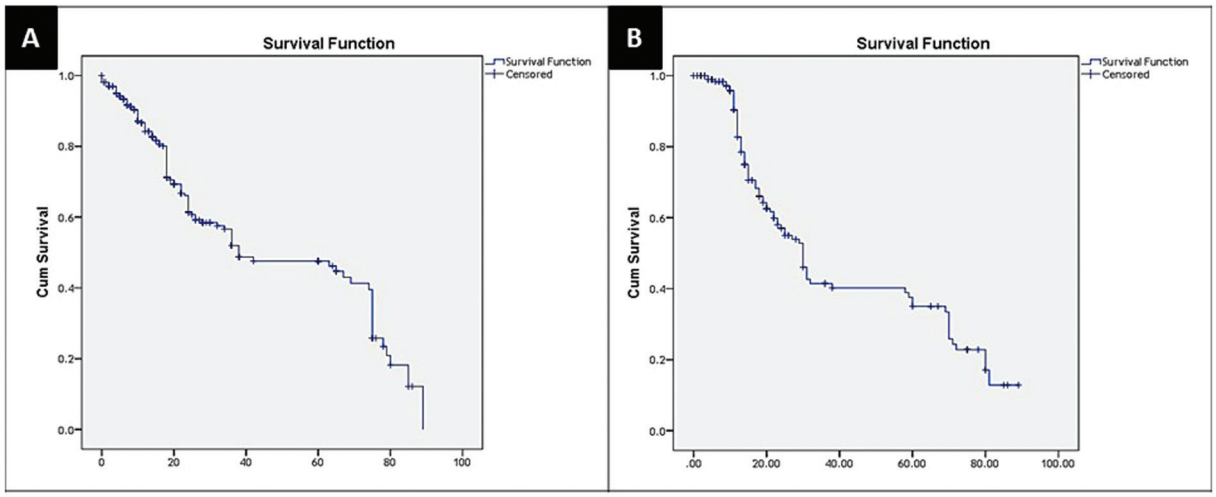
Anastomotic recurrence (surgery vs. biliary drainage)

Comparative data between patients with anastomotic recurrence who received redo-resection versus palliative biliary drainage are shown in Table 4.

Survival outcomes of redo-surgery patients:

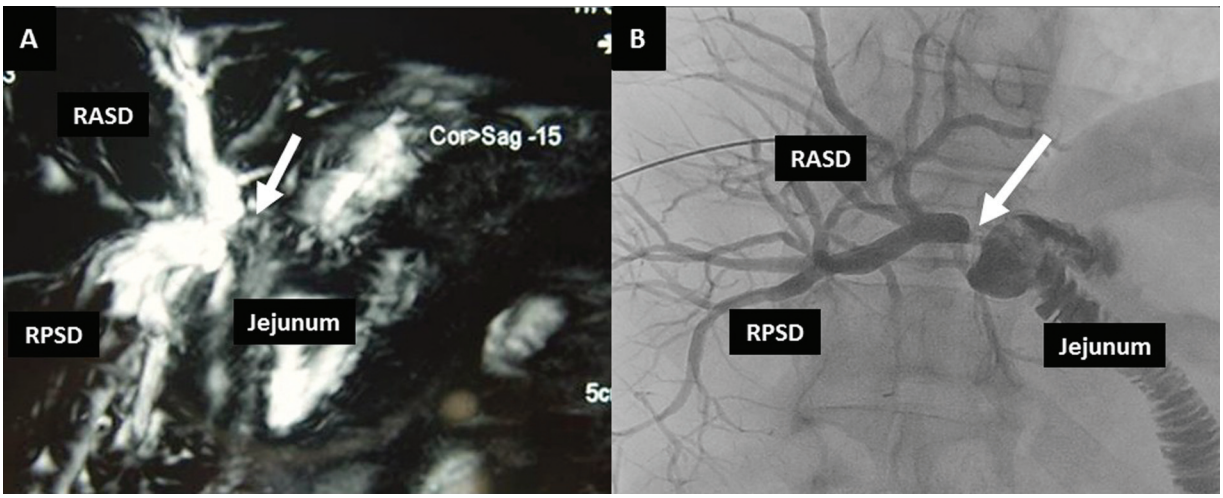
(1) Redo-surgery versus biliary drainage patients. The 1-, 3-, and 5-year overall survival rates for redo-surgery group were 87.5, 62.5, and 46.9%, and 1-, 3-, and 5-year overall survival rates for

Figure 1



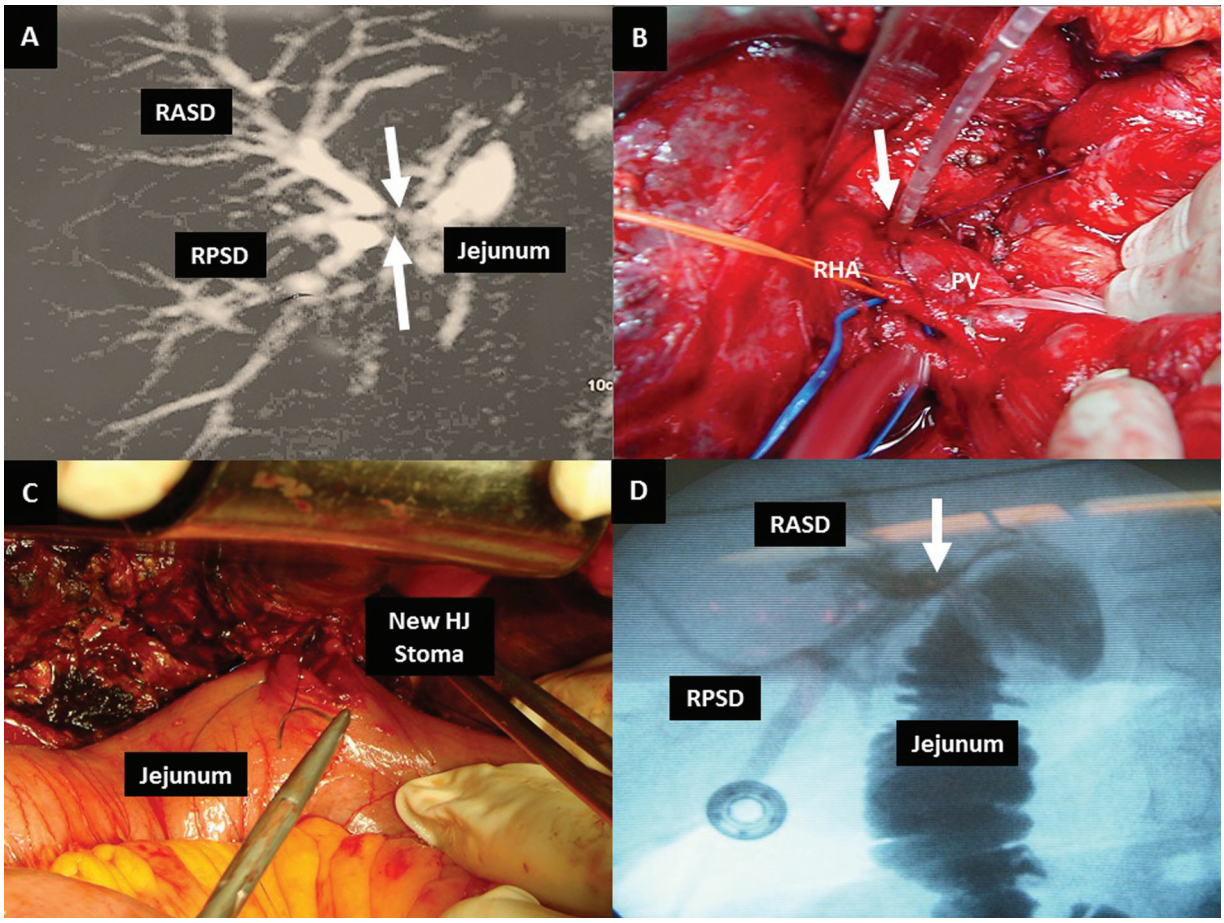
(a) Overall survival curve of all study cases. (b) Disease-free survival of all study cases.

Figure 2



(a) Magnetic resonance cholangiopancreatography showing local anastomotic recurrence after left hemihepatectomy (arrow indicates the site of local anastomotic stricture). (b) Percutaneous transhepatic biliary drainage for palliation of obstructive jaundice (arrow indicates the site of local anastomotic stricture). RASD, right anterior sectorial duct; RPSD, right posterior sectorial duct.

Figure 3



(a) Magnetic resonance cholangiopancreatography showing local anastomotic recurrence after left hemihepatectomy (arrow indicates the site of local anastomotic stricture). (b) Operative photograph after dissection of local recurrent tumor at the site of biliary-enteric anastomosis (arrow indicate the site of biliary anastomotic site). (c) Operative photograph during performing new hepaticojejunostomy over transjejunal stent. (d) Intraoperative cholangiogram through transjejunal stent showing adequate biliary-enteric anastomosis (arrow). HJ, hepaticojejunostomy; PV, portal vein; RHA, right hepatic artery; RASD, right anterior sectorial duct; RPSD, right posterior sectorial duct.

biliary drainage group were, 87, 46.4, and 23.2%, respectively (Log-rank=0.046) (Fig. 4a).

(2) Operated versus nonoperated patients.
Moreover, we compared the redo-surgery patients with all other recurrent patients. The 1-, 3-, and 5-year overall survival rates for the operated group were 87.5, 62.5, and 46.9%; and 1-, 3-, and 5-year overall survival rate for the nonoperated group were 88.6, 45.6, and 26.7%, respectively (Log-rank=0.032) (Fig. 4b).

Discussion

Surgery is considered the curative treatment for pCCA cases. Radical resection of pCCA is one of the technically demanding surgeries owing to the close relationship of pCCA to major hepatic vascular structures with subsequent vascular invasion [3]. Standardized radical surgery includes resection of the extrahepatic biliary tree with related hemi-liver and caudate lobe together with regional lymphadenectomy [22]. However, the long-term outcomes of surgical resection remain poor owing to high incidence of tumor recurrence. Reported 5-year overall survival rates after resection of pCCA are around 22–40% [14,23,24].

Recurrent pCCA usually presents as local anastomotic recurrence, liver metastasis, lymph nodes metastasis, peritoneal metastasis, and distant metastasis [8]. Komaya *et al.* [22] addressed the effect of achieving R0 resection on the pattern of pCCA recurrence. They found that R0 patients experienced more distant metastasis rather than local anastomotic recurrence. Peritoneum followed by the liver were the commonest sites of pCCA recurrences. On the contrary, R1 resection patients experienced more local anastomotic recurrence rather than distant metastasis owing to remnant microscopic disease. They advocated performing more aggressive resections to avoid R1 resections. In our study, tumor recurrence occurred in 136 (51.7%) patients

Table 4 Comparison between patients with local anastomotic recurrence

	Redo-Surgery Group (*N*=8)	Biliary Drainage Group (*N*=34)	*P* value
Preoperative characteristics			
Age	52 (35–65)	49 (23–67)	0.29
Sex			
Male	4 (50%)	21 (61.8%)	0.681
Female	4 (50%)	13 (38.2%)	
Presentation			
Abdominal pain	5 (62.5%)	14 (41.2%)	0.418
Jaundice	8 (100%)	34 (100%)	–-
Weight loss	1 (12.5%)	14 (41.2%)	0.218
Hepatitis C virus	4 (50%)	15 (44.1%)	0.541
Hepatitis B virus	0	0	–-
Preoperative biliary drainage			
ERCP	3 (37.5%)	10 (29.4%)	0.673
PTD	2 (25%)	8 (23.5%)	0.645
Serum bilirubin before surgery (mg/dl)	6.2 (1–23)	11 (1–36)	
Perioperative data			
Liver state			
Normal	5 (62.5%)	16 (47.1%)	0.688
Cirrhosis	3 (37.5%)	18 (52.9%)	
Liver resection extent			
Localized resection	2 (25%)	4 (11.8%)	0.574
Hepatectomy	6 (75%)	30 (88.2%)	
Caudate lobectomy	3 (37.5%)	14 (41.2%)	0.627
Operation time (hours)	4 (2.5–6.5)	4 (2–6)	0.508
Blood transfusion	1 (12.5%)	4 (11.8%)	0.691
Hospital stay (days)	13.5 (7–31)	14 (4–22)	0.832
Pathological Data			
Differentiation			
Well	5 (62.5%)	17 (50%)	0.724
Moderate	2 (25%)	8 (23.6%)	
Poor	1 (12.5%)	9 (26.4%)	
Lymph nodes			
Positive	5 (62.5%)	12 (35.3%)	0.238
Negative	3 (37.5%)	22 (64.7%)	
Resection margin			
R0	7 (87.5%)	16 (47.1%)	0.098
R1	1 (12.5%)	18 (52.9%)	

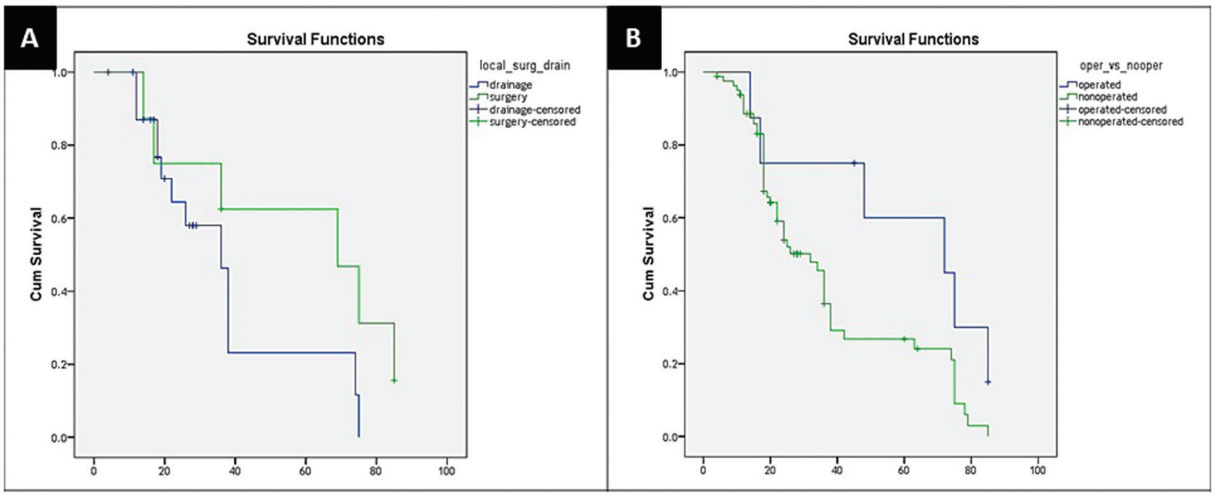
ERCP, endoscopic retrograde cholangiopancreatography; PTD, percutaneous transhepatic biliary drainage.

with 5-year disease-free survival rate of 35%, and 5-year overall survival rate of 47.6%. The commonest sites of tumor recurrence were hepatic metastasis [58 (22.1%) patients] followed by local anastomotic recurrence [42 (15.9%) patients].

In our study, R0 resection was accomplished among 151 (57.4%) patients, whereas R1 resection was performed in 112 (42.6%) patients. This is attributed to the controversial issue regarding the management of pCCA on a background of liver cirrhosis. The presence of liver cirrhosis affects the surgeon's decision to perform a major liver resection to avoid liver decompensation. Moreover, we had addressed more aggressive pathological features of pCCA on top of liver cirrhosis in terms of tumor differentiation and nodal metastasis [15]. In the current study, liver cirrhosis was identified in 120 (45.6%) patients.

Patients with recurrent pCCA are usually managed by different chemotherapeutic regimens with or without radiotherapy. However, the outcomes of those regimens remain poor [9–11,25]. On the contrary, some reports from highly specialized centers had shown beneficial outcomes of surgical re-resection for selected cases with recurrent biliary tract tumors [12–14]. They reported variable types of resections for biliary tract recurrences including locoregional recurrences, liver metastasis, chest wall and abdominal wall metastasis, solitary pulmonary metastasis, and lymph nodes metastasis.

Figure 4



(a) Overall survival curves of cases with anastomotic recurrence (redo-surgery vs. palliative biliary drainage). (b) Overall survival curves of all recurrent cases (operated vs. nonoperated).

In our center, we considered surgical re-resection for selected cases of recurrent pCCA. Surgical re-resection was applied for cases with locoregional recurrences that seemed resectable on preoperative detailed radiological studies, absence of other distant metastasis, and in patients with good general status. Those selection criteria are similar to those adopted by Takahashi *et al.* [12] and Noji *et al.* [14].

Noji *et al.* [14] addressed an important question regarding the optimal timing for surgical intervention after recurrence of biliary tract cancers. They addressed the importance of an observation period before surgical intervention to exclude patients with rapidly progressive or disseminating recurrences. They also addressed that a 3-month observation period is recommended. On the contrary, other studies did not address that issue [8,12]. In our center, we did not apply any observation period and preferred immediate intervention when the recurrence seemed potentially resectable on preoperative radiological studies for fear of tumor progression during the observation period. Currently, there is no specific guide regarding the optimal observation period and future studies are required to clarify this issue.

In our study, patients who underwent surgical re-resection for recurrent pCCA had better survival outcomes compared with patients who underwent only palliative biliary drainage for locoregional recurrence (P=0.046) and with patients who received palliative supportive care (P=0.032). This is similar to the findings reported by Miyazaki *et al.* [13] who addressed that survival was more improved among cases who underwent resection for recurrence when compared to cases who received only chemotherapy or best supportive care (62 vs. 17% vs. 13% at 3 years and 54 vs. 7.4% vs. 5% at 5 years; P=0.0006). Similarly, Takahashi *et al.* [12] reported that survival for patients who underwent resection for recurrence was better when compared with patients who did not undergo resection for recurrence (66 vs. 23% at 3 years and 35 vs. 11% at 5 years; P<0.001).

Surgical re-resection for locally recurrent pCCA is a technically demanding procedure that requires a great experience in hepatobiliary surgery. Resection of locoregional recurrences may require complex vascular resections and multiple biliary-enteric anastomoses. In our study, two (25%) patients required portal vein resections owing to local tumor invasion and all patients required multiple biliary-enteric anastomoses. All the patients recovered well without any postoperative mortalities. One of the interesting findings in our study was that we noticed that local anastomotic recurrence occurred in four (50%) patients who underwent previous left hemihepatectomy. This is related to the relatively short right hepatic duct with different branching patterns, which is associated with a relatively narrow bile duct resection margin.

Limitations of this study include that it is a retrospective single-surgeon experience. Moreover, it included a limited number of patients, but this was owing to the unique nature of the study patients who would be qualified for re-resection of recurrent pCCA.

Conclusion

In conclusion, we retrospectively reviewed a single-surgeon experience of surgical re-resection for recurrent pCCA in selected patients. Our study showed that surgical re-resection of recurrent pCCA is a feasible and technically challenging procedure. Surgical re-resection of recurrent pCCA is associated with acceptable perioperative morbidities and provides a better survival benefit compared with other palliative procedures. Future multicenter studies including large number of cases are required to prove these findings.

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Nil.

Conflicts of interest

There are no conflict of interest.

References

1 Lim JH. Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. Am J Roentgenol 2003; 181:819–827.

2 Ghouri YA, Mian I, Blechacz B. Cancer review: cholangiocarcinoma. J Carcinog 2015; 14:1.

3 Kambakamba P, DeOliveira ML. Perihilar cholangiocarcinoma: paradigms of surgical management. Am J Surg 2014; 208:563–570.

4 Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, *et al.* Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 2008; 248:84–96.

5 Sano T, Shimada K, Sakamoto Y, Yamamoto J, Yamasaki S, Kosuge T. One hundred two consecutive hepatobiliary resections for perihilar cholangiocarcinoma with zero mortality. Ann Surg 2006; 244:240–247.

6 Kobayashi A, Miwa S, Nakata T, Miyagawa S. Disease recurrence patterns after R0 resection of hilar cholangiocarcinoma. Br J Surg 2010; 97:56–64.

7 Jung SJ, Woo SM, Park HK, Lee WJ, Han MA, han SS, *et al.* Patterns of initial disease recurrence after resection of biliary tract cancer. Oncology 2012; 83:83–90.

8 Miyazaki M, Shimizu H, Yoshitomi H, Kato A, Furukawa K, Takayashiki T, *et al.* Clinical implications of surgical resection for recurrent biliary tract cancer, Does it work or not?. Ann Gastroenterol Surg 2017; 1:164–170.

9 Ramirez-Merino N, Aix SP, Cortes-Funes H. Chemotherapy for cholangiocarcinoma: an update. World J Gastrointest Oncol 2013; 5:171–176.

10 Sasaki T, Isayama H, Nakai Y, Koike K. Current status of chemotherapy for the treatment of advanced biliary tract cancer. Korean J Intern Med 2013; 28:515–524.

11 Zeng ZC, Tang ZY, Fan J, Zhou J, Qin LX, Ye SL, *et al.* Consideration of the role of radiotherapy for unresectable intrahepatic cholangiocarcinoma: a retrospective analysis of 75 patients. Cancer J 2006; 12:113–122.

12 Takahashi Y, Ebata T, Yokoyama Y, Igami T, Sugawara G, Mizuno T, *et al.* Surgery for recurrent biliary tract cancer: a single-center experience with 74 consecutive resections. Ann Surg 2015; 262:121–129.

13 Miyazaki Y, Kokudo T, Amikura K, Kageyama Y, Takahashi A, Ohkohchi N, *et al.* Survival of surgery for recurrent biliary tract cancer: a single-center experience and systematic review of literature. Jap J Clin Oncol 2017; 47:206–212.

14 Noji T, Tsuchikawa T, Mizota T, Okamura K, Nakamura T, Tamoto E, *et al.* Surgery for recurrent biliary carcinoma: results for 27 recurrent cases. World J Surg Oncol 2015; 13:82–87.

15 Abdelwahab M, El Nakeeb A, Salah T, Hamed H, El Sorogy M, Shehta A, *et al.* Hilar cholangiocarcinoma in cirrhotic liver: a case–control study. Int J Surg 2014; 12:762–767.

16 Wahab MA, El Hanafy E, El Nakeeb A, Hamdy E, Atif E, Sultan AM. Postoperative outcome after major liver resection in jaundiced patients with proximal bile duct cancer without preoperative biliary drainage. Dig Surg 2015; 32:426–432.

17 Wahab MA, Fathy O, Sultan AM, Salah T, Elshoubary M, Elyazid AY, *et al.* Hilar cholangiocarcinoma fifteen-year experience with 243 patients at a single Egyptian center. J Solid Tumors 2011; 1:112.

18 Wahab MA, Shehta A, Ali M. Surgical strategies for the management of perihilar cholangiocarcinoma. Surg Gastroenterol 2018; 23:230–240.

19 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240:205–213.

20 Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, *et al.* Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011; 149:680–688.

21 Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, *et al.* Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011; 149:713–724.

22 Komaya K, Ebata T, Yokoyama Y, Igami T, Sugawara G, Mizuno T, *et al.* Recurrence after curative-intent resection of perihilar cholangiocarcinoma: analysis of a large cohort with a close postoperative follow-up approach. Surgery 2018; 163:732–738.

23 Hirano S, Kondo S, Tanaka E, Shichinohe T, Tsuchikawa T, Kato K, *et al.* Outcome of surgical treatment of hilar cholangiocarcinoma: a special reference to postoperative morbidity and mortality. J Hepatobiliary Pancreat Sci 2010; 17:455–462.

24 Ruys AT, van Haelst S, Busch OR, Rauws EA, Gouma DJ, van Gulik TM. Long-term survival in hilar cholangiocarcinoma also possible in unresectable patients. World J Surg 2012; 36:2179–2186.

25 Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, *et al.* Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010; 362:1273–1281.