Surgical Strategies for the Management of Perihilar Cholangiocarcinoma

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ABSTRACT

Cholangiocarcinoma is a fatal cancer arising from the biliary endothelium. Perihilar cholangiocarcinoma (pCCA) is the most common variant of cholangiocarcinoma, with increasing incidence worldwide. Most pCCA patients present with unresectable disease at the time of diagnosis, and many patients are found to be unresectable after surgical exploration. pCCA carries a poor prognosis as more than 65% of the patients are presented with non-resectable disease at the time of diagnosis, and about 10% to 45% of patients are found to be unresectable after surgical exploration. Surgical resection is the main stay of treatment of pCCA. The close anatomic relationship of pCCA to major hepatic vascular structures with subsequent frequent vascular invasion makes surgical resection one of the most challenging surgical procedures. To achieve a radical resection for pCCA, resection should involve resection of involved intra- and extrahepatic biliary tree with safety margin, resection of related hemi-liver according to the tumor extension, caudate lobectomy, lymphadenectomy including loco-regional lymph nodes and biliary tract reconstruction through biliary-enteric anastomoses. Despite the modern major advancements in surgical techniques and multidisciplinary management over the past years, surgical resection remains associated with high perioperative morbidities and poor survival outcomes. This aim of this review is to address the recent advances in surgical treatment for pCCA and its impact on patients' survival.

Key words: perihilar cholangiocarcinoma, surgical resection, liver transplantation

INTRODUCTION

Cholangiocarcinoma (CCA) is the most common biliary tract malignancy and the second most common primary hepatic malignancy accounting for about 10–20% of primary liver cancers (1). According to its site of origin and the tumor biology, CCA is divided into three subtypes, intrahepatic, perihilar and, distal CCA. Perihilar cholangiocarcinoma (pCCA) is the most common form worldwide accounting for about 50-67% of all cases (2). pCCA was firstly described by Gerald Klatskin in 1965 (3).

Nowadays, surgical resection is the main stay of treatment of pCCA. Radical resection of pCCA is one of the most challenging surgical procedures due to

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the close anatomic relationship of pCCA to major hepatic vascular structures with subsequent vascular invasion (4). However, pCCA carries a poor prognosis as more than 65% of the patients are presented with non-resectable disease at the time of diagnosis, and about 10% to 45% of patients are found to be unresectable after surgical exploration (5-7). Also, surgical resection is associated with substantial perioperative morbidity (4).

The aim of this review is to provide an overview of pCCA and address recent surgical challenges and strategies in the management of pCCA.

ETIOLOGY

The etiology of pCCA is not clearly understood. Several risk factors have been associated to the development of pCCA including primary sclerosing cholangitis (8), liver fluke infestation in South-East Asia (9), Choledochal cysts and Caroli's disease (10), hepatolithiasis, and exposure to toxic agents such as thorotrast and dioxin (11).

STAGING

Several staging systems had been proposed for pCCA. Bismuth and Corlette firstly proposed a classification system for pCCA depending on the anatomical extension of the disease (*table 1*)(12). The Memorial Sloan-Kettering Cancer System (MSKCC) proposed another classification system for pCCA depending the tumor extent to the second order biliary radicals, portal venous invasion, and hepatic lobar atrophy (*table 2*)(13). This system provides a good frame to define resectability of pCCA, but it lacks evaluation of nodal or distant metastases.

The American Joint Committee on Cancer Staging system (AJCC/UICC) 7th edition includes all tumor, lymph nodes, and distant metastasis (TNM) for evaluation of pCCA (*table 3*)(14). The AJCC/UICC staging system focuses on both local vascular invasion, lymph nodes

Table 1 - Bismuth-Corlette classification system

Type	Anatomical Location
I	Involving common hepatic duct distal to the biliary confluence
II	Involving the biliary confluence
III a	Involving the biliary confluence and right hepatic duct
b	Involving the biliary confluence and left hepatic duct
IV	Extending to the bifurcation of left and right hepatic ducts

invasion and distant metastases, but its use in the preoperative evaluation of resectability is minimal. Recently, the International Group of pCCA proposed a new staging system. The new system includes the Bismuth-Corlette classification, the MSKCC staging system, and the AJCC/UICC staging system. The new system includes extent of bile duct involvement, tumor size and morphology, portal vein and hepatic artery involvement, liver remnant volume and underlying liver disease, and lymph node or distant metastases (15).

DIAGNOSIS

Most patients with pCCA present with painless obstructive jaundice, which may be associated with vague abdominal pain, and weight loss. In about 10%, cholangitis is the initial presentation (6, 16, 17). On laboratory evaluation, pCCA patients show elevation of serum cholestatic parameters. Carbohydrate antigen 19-9 (CA 19-9) is the most commonly used tumor marker, however it has a poor sensitivity and specificity for early detection of pCCA (18).

Radiologically, abdominal ultrasonography has a limited role in preoperative setting. Multidetector dynamic computer tomography (CT) plays an essential role in preoperative planning. It allows evaluation of tumor extent, the extent of vascular and lymph nodes involvement (2, 5).

Magnetic resonance imaging (MRI) with magnetic resonance cholangio-pancreatography (MRCP) are

Table 2 - Memorial Sloan-Kettering Cancer System

Stage	Criteria			
	Biliary confluence invasion	2 nd order biliary radical invasion	Portal vein invasion	Hepatic lobar atrophy
T1	Yes	+/- unilateral	No	No
T2	Yes	+/- unilateral	Ipsilateral	+/- ipsilateral
T3	Yes	bilateral	Yes/No	Yes/No
	Yes	unilateral	contralateral	Yes/No
	Yes	unilateral	Yes/No	contralateral
	Yes	+/- unilateral	bilateral	Yes/No

Table 3 - TNM and American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Staging Systems for Perihilar Cholangiocarcinoma

Stage	Criteria		
Tumor (T) stage			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ (intraductal tumor)		
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue		
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue		
T2b	Tumor invades adjacent hepatic parenchyma		
T3	Tumor invades unilateral branches of the PV or HA		
T4	Tumor invades main PV or its branches b/l, CHA, second-order bile ducts b/l, unilateral second-order bile ducts with contralateral PV or HA involvement		
Lymph Node(N) stage			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	Regional lymph node metastasis: hilar (along CBD, cystic duct, HA or PV)		
N2	Metastasis to periaortic, pericaval, SMA or coeliac lymph nodes.		
Metastasis (M) stage			
M0	No distant metastases		
M1	Distant metastases		
AJCC/UICC stage	Tumor	Node	Metastasis
0	Tis	N0	M0
I	T1	N0	M0
II	T2a or 2b	N0	M0
III A	T3	N0	M0
III B	T4	N0	M0
III C	Any T	N1	M0
IVA	Any T	N2	M0
IV B	Any T	Any N	M1

essential in preoperative surgical planning and evaluation of the disease extent inside the biliary tree (*fig. 1*)(19). A common diagnostic challenge is the distinction between benign and malignant biliary strictures. IgG4 associated cholangiopathy is a main differential diagnosis, so checking serum concentration of IgG4 is essential (20).

Positron emission tomography (PET-CT) is rarely used in the setting of pCCA (21, 22). Endoscopic ultrasound (EUS) can be used in the preoperative workup to detect tumor and lymph nodes extension (23). Attempts of biopsy from the pCCA or lymph nodes must be avoided as it may result in potential tumor dissemination excluding the patient from potentially curative liver transplantation (5, 22).

PREOPERATIVE BILIARY DRAINAGE

The role of preoperative biliary drainage (PBD) in

pCCA patients remains a controversial issue. There is no proof that routine preoperative biliary drainage facilitates resection or reduces postoperative complication (6).

PBD can be achieved percutaneously by percutaneous transhepatic biliary drainage (PTBD)(*fig. 2-a*), or endoscopically by endoscopic retrograde cholangiopancreatography (ERCP)(*fig. 2-b,c*). PTBD is more appropriate for PBD as it minimizes the risk of biliary tract seeding and inflammatory reactions (24).

The main advantages of PBD are acquisition of a diagnostic cholangiogram to evaluate the disease extent and collection of brush samples from the biliary epithelium for cytologic analysis. In contrary, the use of biliary stents had been associated with higher incidence of postoperative infectious complications (6, 24).

PBD can be performed selectively or totally. Selective PBD is recommended for Bismuth type III-A requiring right hemi-hepatectomy, Bismuth type IV, and

Figure 1 - Magnetic resonance cholangiopancreatography of perihilar cholangiocarcinoma.
(a) Type 1. (b) Type IIIa. (c) Type IIIb.
(d) Type IV (CBD = common bile duct, RHD = right hepatic duct, LHD = left hepatic duct)

Figure 2 - (a) Percutaneous transhepatic cholangiogram for type IV lesion (arrows indicating bilateral cholangiogram needles). (b, c) Endoscopic retrograde cholangio-pancreatography for type IV lesion (arrows indicating bilateral biliary stents) (CBD = common bile duct, RHD = right hepatic duct, LHD = left hepatic duct)

with preoperative portal vein embolization with neo-adjuvant chemo-radiotherapy. This is usually sufficient in most cases. Total PBD is recommended in the development of cholangitis or slow decrease of serum bilirubin after selective PBD (24, 25).

TREATMENT

Radical surgical resection with adequate safety margin is the standard of care for pCCA patients. In selected cases, orthotopic liver transplantation can be done.

SURGICAL RESECTION

Surgical management is the only potentially curative treatment for pCCA patients. Surgical resection combined with adjuvant or neoadjuvant therapies is the most preferred management approach.

Rational of surgical treatment

To achieve a radical resection for pCCA patients, the following criteria should be fulfilled:

- * Resection of involved intra- and extrahepatic biliary tree with clear margins.
- * Resection of related hemi-liver according to the tumor extension.
- * Routine caudate lobectomy (segmentectomy I).
- * Standard lymphadenectomy including loco-regional lymph nodes.
- * Biliary tract reconstruction through biliary-enteric anastomoses.

Surgery from localized resection to radical resection

Initially, isolated resection of the extrahepatic biliary system was proposed. It was associated with acceptable mortality rates, but the recurrence rate was high with rates between 50% to 70% (26).

In 1992, Bismuth et al. introduced different surgical approaches for different pCCA types depending on their anatomical classification. Isolated bile duct resection with safety margin for type I and II tumors. Hemihepatectomy with hepaticojejunostomy for types IIIa and IIIb tumors (figs. 3, 4). They

Figure 3 - Right hemi-hepatectomy for type IIIa lesion. (a) Preoperative magnetic resonance cholangiopancreatography. (b) Preoperative computed tomography (portal phase). (c) Operative photo of mobilized right hemiliver with hanging maneuver (arrows indicate hanging tape). (d) Operative photo of the operative bed after right hemi-hepatectomy and caudate lobectomy and extrahepatic biliary system resection. E: Operative photo of left hepatico-jejunostomy (arrow). (f) Postoperative specimen after right hemi-hepatectomy and caudate lobectomy and extrahepatic biliary system resection (CBD = common bile duct, RHD = right hepatic duct, LHD = left hepatic duct, MHV = middle hepatic vein, IVC = inferior vena cava, PV = portal vein, GB = gall bladder)

Figure 4 - Left hemi-hepatectomy for type IIIb lesion. (a) Preoperative magnetic resonance cholangiopancreatography. **(b)** Operative photo showing atrophic left hemi-liver. **(c, d)** Operative photo of the operative bed after left hemi-hepatectomy and caudate lobectomy and extrahepatic biliary system resection. **(e)** Operative photo of right hepatico-jejunostomy (arrow). **(f)** Postoperative specimen after left hemi-hepatectomy and caudate lobectomy and extrahepatic biliary system resection (CBD = common bile duct, RHD = right hepatic duct, LHD = left hepatic duct, RHA = right hepatic artery, MHV = middle hepatic vein, IVC = inferior vena cava, PV = portal vein, CHA = common hepatic artery, GB = gall bladder)

defined type IV tumors as unresectable (27).

In 1990, Nimura et al. introduced the principle of routine caudate segmentectomy for pCCA patients (28). Their assumption was based on the infiltrative nature of the disease which tend to spread along biliary branches of the caudate lobe that may cause tumor recurrence. Several studies have subsequently confirmed the value of this oncological principle regarding the achievement of R0 resection and improved 5-year survival rates (29-31).

Nowadays, resection of the involved intra- and extrahepatic bile ducts, with related hemi-liver and caudate lobe, is the standard of care for resectable cases. With advancements of surgical techniques and perioperative care, dramatic improvement of the outcomes of those resections is noticed.

Contra-indications of surgical resection

Patients are excluded from surgical resection if they had a bilateral tumor extension involving both left and right secondary biliary radicles, unilobar involvement

with encasement of contralateral portal vein or hepatic artery, bilateral vascular involvement, presence of distant metastases, underlying liver disease (advanced fibrosis, cirrhosis), if future liver remnant is less than 20-30% and no or poor response to portal vein embolization, and presence of severe co-morbidities prohibiting major surgical procedures (22).

Extent of lymphadenectomy

One of the most important prognostic factors after resection of pCCA is lymph node involvement. It had been shown that lymph node metastasis occurs in more than 30% of pCCA patients (22).

The AJCC/UICC 7th edition recommended a minimum retrieval of 15 lymph nodes for appropriate staging (14). However, this was not accepted by most groups because of the need for extended dissection, with subsequent prolonged operation time and intraoperative blood loss. Most groups report average lymph nodes retrieval of 3-10 lymph nodes (32-34). We recommend lymphadenectomy of locoregional lymph nodes starting from

the celiac trunk up to the hilum enbloc with the mass. The locoregional lymph nodes include the cystic duct, pericholedochal, hilar, periportal, hepatic artery, and retroduodenal nodes (35). The need for extended lymphadenectomy is no longer recommended and did not prove a survival advantage.

Liver cirrhosis

Patients with underlying liver cirrhosis are specifically complex. Cirrhotic patients are at an increased risk of bleeding, sepsis, and hepatic decompensation (36). No guideline has been issued for the management of resectable pCCA in cirrhotic patients. In the presence of cirrhosis, the management of pCCA requires careful patient selection, good perioperative care, adequate counseling on operative risk and good decision on extent of resection.

Surgical resection should be limited to patients with well compensated chronic liver diseases. The extent of surgical resection is dependent on the balance between radicality and adequate hepatic reserve in cirrhotic patients to avoid posthepatectomy liver dysfunction.

Such surgical resections should be limited to experienced surgeons in high volume centers where there is expertise in the management of liver cirrhosis and postoperative complications(35).

Improvement of residual liver volume

In pCCA cases in which resectability is prohibited by low residual liver volume (especially when extended resections are planned as right or left trisectionectomy), *preoperative portal vein embolization* (PVE) of the affected lobe can be done.

Makuuchi et al. firstly introduced the concept of preoperative PVE of the affected hemi-liver to induce compensatory hypertrophy of the non occluded future liver remnant and prevent posthepatectomy liver failure (37). Afterwards, Kubota et al. described the criteria to define ideal patients who will benefit from preoperative PVE, depending on indocyanine green test and hepatic volumetry (38). This concept had proved great effectiveness with acceptable morbidity and mortality rates. Abulkhir et al. in a meta-analysis regarding PVE before major hepatic resection found that the future liver volume increased by about 8–27% with morbidity rates less than 3% and no mortality. They advocated that if the liver remnant less than 20% or the degree of hypertrophy is less than 5% after pre-operative PVE, hepatic resection is considered high-risk and should be contraindicated (39).

Improvement of the patients' general condition and liver functions before PVE is essential to have satisfactory outcomes. Biliary drainage is advisable before preoperative PVE to rest the liver and relief biliary radicals' dilatations in the remnant liver (4).

A newly introduced alternative for preoperative PVE in cases with low residual liver volume the *ALPPS procedure*. ALPPS procedure refers to Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy.

This novel approach is based on the principle that hepatic regeneration is at most stimulated by hepatic parenchymal transection together with increased portal venous blood flow. Also, it overcomes limited hepatic volume improvement due to the presence of collaterals between the residual and resected hepatic segments (40).

The procedure consists of two stages. Initially, ligation of the ipsilateral portal vein and in situ liver splitting is performed. The patient is observed for 1 to 3 weeks the assess growth of the future liver remnant. The definitive surgical resection is then performed after confirmation of adequate volume increase on CT. This procedure proved high effectiveness in cases with low residual future liver remnant in which preoperative PVE was insufficient or failed (41, 42).

Vascular resections

pCCA is known of its close anatomic relationship to major hepatic vasculature (portal vein and hepatic artery). So local vascular invasion is frequently faced during surgery for pCCA (4). In initial reports on pCCA, most authors did not advocate extensive vascular resections and such approaches were only limited to few case reports. Also, vascular resections were associated with increased complexity of the surgery, increased blood loss, and high perioperative mortality (43, 44).

With refinements of surgical techniques, several centers had reported portal vein resections for pCCA patients with acceptable perioperative morbidity and mortality (45-47). Neuhaus et al. introduced the concept of hilar-en-bloc resection or no-touch technique. This concept includes extended right hemi-hepatectomy with pre-emptive portal vein resection and reconstruction. It was associated with high post-operative mortality but with better overall survival rate (48).

With acceptance of portal venous resections, some surgeons started to address combined portal vein and hepatic artery resections and reconstructions (49, 50). However, this was not greatly supported by others surgeons because it is increasing the complexity of the

operation without proven benefit on the short- or long-term outcomes (51).

Finally, we can conclude that portal vein resection is widely accepted by most centers, but the real long-term benefits from this complex surgery remain controversial. Combined hepatic artery and portal vein resection is one of the most complicated and technically demanding procedures in hepatobiliary surgery and its benefit remains debated.

Minimally invasive approach

Laparoscopic liver resection had gained acceptance among hepatobiliary surgeons. In the field of pCCA, the application of laparoscopic approach is still not accepted as an alternative to standard open approach. Laparoscopic resection of pCCA is a technically challenging procedure including laparoscopic hepatoduodenal lymphadenectomy, hemi-hepatectomy with caudate lobectomy, and hepaticojejunostomy.

Only a limited number of case series have been reported in selected cases from highly specialized centers (52-54). Although the initial appear encouraging, the long term oncological outcomes have not been proven till now.

POSTOPERATIVE ADJUVANT THERAPY

Adjuvant chemotherapy and targeted radiation in addition to surgery is the most preferred management approach. Recent studies showed improved overall survival in pCCA patients treated with adjuvant chemoradiation (55-57). Chemotherapy decreases the risk of distant tumor recurrence while radiotherapy reduces the risk of local recurrence especially in node-positive or margin-positive (R1) patients (58).

ORTHOTOPIC LIVER TRANSPLANTATION

Orthotopic liver transplantation (OLT) with neoadjuvant chemo-radiotherapy provides a promising option in patients with unresectable tumors. OLT is preferred in patients with primary sclerosing cholangitis and/or liver cirrhosis due to the limited hepatic reserves. OLT with neoadjuvant chemoradiotherapy can achieve 5-year disease free survival rates ranging between 65-70% (59,60).

Exclusion criteria from OLT

The Mayo clinic adopted specific exclusion criteria for patients with unresectable pCCA from OLT. Those

criteria include tumor size exceeding 3 cm in radial diameter, presence of uncontrolled infection, prior radiation or chemotherapy, prior biliary resection or attempted resection, attempted trans-peritoneal biopsy (percutaneous or EUS guided), presence of intrahepatic metastases, evidence of extrahepatic disease or lymph node spread, and history of other malignancy within the last 5 years (61).

POSTOPERATIVE OUTCOMES AND SURVIVAL

Postoperative morbidity and mortality rates have decreased in recent years. Postoperative morbidities after radical resection had been reported to range between 9 – 80% in previous studies as shown in *table 4*. Major postoperative morbidities include biliary leaks and fistulae, intraabdominal abscesses, post-hepatectomy liver dysfunction, and sepsis (29). Postoperative mortality rates after radical resection range between 5 – 10% in previous studies and mostly related to infectious complications as shown in *table 4*. Post-hepatectomy liver failure is an unusual cause for postoperative mortality especially in cirrhotic patients (35).

After radical resection for pCCA, the overall 5-year survival rates had been reported to be range from 11% to 45% in previous studies as shown in *table 4*. Several prognostic factors had been identified to affect the survival after radical resection of pCCA. Among them, surgical margin status and lymph node metastases had been identified to be the most important prognostic factors affecting the survival (29, 46). Other prognostic factors include liver status, extent of liver resection, caudate lobe resection, tumor differentiation, tumoral vascular invasion, perineural tumor infiltration, and adjuvant chemotherapy and radiation (6, 35).

NON-RESECTABLE PERIHILAR CHOLANGIOCARCINOMA

For patients with locally unresectable tumors who are not candidates for OLT, biliary drainage together with definitive chemoradiation is the preferred approach. Definitive chemo-radiotherapy includes external beam radiotherapy plus chemotherapy (5-fluorouracil-based regimens, or gemcitabine-based regimens, or combining cisplatin with gemcitabine) with or without intraluminal brachytherapy (16, 22).

Biliary drainage is essential to improve patient survival and avoid complications related to recurrent cholangitis. Biliary drainage can be done endoscopically or percutaneously by self-expandable biliary stents.

Table 4 - Studies of liver resection for perihilar cholangiocarcinoma (NA = not addressed)

Author	Publication Year	Cases number	Morbidity (%)	Early Mortality (%)	5 years Overall Survival (%)
DeOliveira et al. (65)	2007	173	62	5	NA
Hirano et al. (66)	2010	94	45	4	36
Lee et al. (67)	2010	302	43	3	36
Unno et al. (68)	2010	125	49	8	35
Shimizu et al. (69)	2010	172	44	6	28
Young et al. (70)	2011	83	64	7	20
Wahab et al. (71)	2011	243	35	6.6	16
Neuhaus et al. (48)	2012	50	NA	11	58
Ribero et al. (72)	2012	75	NA	10	28
Cannon et al. (73)	2012	59	39	5.1	NA
De Jong et al. (46)	2012	305	NA	7	20
Matsuo et al. (74)	2012	157	59	9	38
Cheng et al. (75)	2012	171	NA	3	14
Kow et al. (76)	2012	127	6	0	35
Nagino et al. (77)	2013	574	57	47	33
Song et al. (78)	2013	230	9	4	39
Lim et al. (79)	2013	52	31	0	23
Hosokawa et al. (80)	2014	61	51	3	25
Matsumoto et al. (81)	2014	174	45	4	36
Xiong et al. (82)	2015	52	34	4	13

Bilateral biliary stents increase the risk of stent-related complications (62).

Novel modalities that are being used and are still under evaluation include photodynamic therapy and targeted therapies such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (erlotinib and lapatinib), anti-EGFR antibodies (cetuximab and panitumumab), angiogenesis inhibitors (sorafenib and bevacizumab), and MEK1 and MEK2 inhibitors (selumetinib) (16, 63, 64).

In summary, pCCA is an aggressive malignancy that is increasing in the past years. Management of pCCA requires collaboration of multidisciplinary teams for tailoring of the most appropriate approach for each individual case. Currently radical resection of pCCA followed by adjuvant therapy is the standard of care. In selected patients who are not suitable for resection, neoadjuvant therapy followed by liver transplantation may offer a further approach with curative intent.

Conflicts of Interest

No conflicts of interest were declared.

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