

Resection for Klatskin tumors: technical complexities and results

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Abstract: Klatskin's tumors, actually-redefined as perihilar cholangiocarcinoma (phCCA) do represent 50–70 % of all CCAs and develop in a context of chronic inflammation and cholestasis of bile ducts. Surgical resection provides the only chance of cure for this disease but is technically challenging because of the complex, intimate and variable relationship between biliary and vascular structures at this location. Five years survival rates range between 25–45% (median 27–58 months) in case of R0 resection and 0–23% (median 12–21 months) in case of R1 resection respectively. It should be noted that the major costs of high radicality are represented by relative high morbidity and mortality rates (i.e., 20–66% and 0–9% respectively). Considering the fact that radical resection may represent the only curative treatment of phCCA, we focused our review on surgical planning and techniques that may improve resectability rates and outcomes for locally advanced phCCA. The surgical treatment of phCCA can be successful when following aspects have been fulfilled: (I) accurate preoperative diagnostic aimed to identify the tumor in all its details (localization and extension) and to study all the risk factors influencing a posthepatectomy liver failure (PHLF): i.e., liver volume, liver function, liver quality, haemodynamics and patient characteristics; (II) High end surgical skills taking in consideration the local extension of the tumor and the vascular invasion which usually require an extended hepatic resection and often a vascular resection; (III) adequate postoperative management aimed to avoid major complications (i.e., PHLF and biliary complications). These are technically challenging operations and must be performed in a high volume centres by hepato-biliary-pancreas (HBP)-surgeons with experience in microsurgical vascular techniques.

Keywords: Perihilar cholangiocarcinoma; Klatskin; surgery

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Introduction

Definition

William Altemeier in 1957 (1) and Gerald Klatskin in 1965 (2) were the first who described cholangiocarcinoma (CCA) as tumor entity arising between the bile ducts (BDs)' confluence and the insertion of the cystic duct into the common BD. Klatskin tumors have been redefined as perihilar CCA (phCCA) and constitute 50–70% of all CCAs (3–6).

Epidemiology

phCCA develops in a context of chronic inflammation and cholestasis usually secondary to:

- ❖ PSC (primary sclerosing cholangitis);
- ❖ Liver flukes (mainly spread in Asiatic countries);
- ❖ Hepatolithiasis;
- ❖ Caroli's disease;
- ❖ Congenital hepatic fibrosis;
- ❖ Choledochal cysts;

- ❖ Viral hepatitis B and C infection;
- ❖ Liver cirrhosis;
- ❖ Chemical compounds—dioxin, thorotrast;
- ❖ Obesity and diabetes.

However, epidemiological reports are heterogeneous because, on the one hand, the definition and classification of the tumor entity has undergone several changes in recent decades (7). On the other hand, there are significant regional differences, particularly between the United States and Europe compared to Asian countries (8). The latter seems to reflect the geographical distribution of environmental and genetic predisposing influences for the development of CCA (9). The incidence of phCCA increases with age; usually, the tumor occurs between 60 and 70 years of age (10).

Growth pattern

phCCA are usually adenocarcinomas arising from periductal glands located in the intra- or extrahepatic BD epithelium (11).

According to their growth pattern the Liver Cancer Study Group of Japan proposed three different types of phCCA (4): (I) intraductal; (II) periductal or (III) mass forming.

Additionally, phCCA may grow longitudinally (into the liver) or radially (into adjacent structures) (12).

Classification and staging systems

An optimal staging system should provide information about prognosis, guide the therapy and allow their comparison. Different classifications were proposed for phCCA. We identified two types of classifications: surgical and oncological. The first type is based on preoperative imaging and it is useful in planning the operation but does not correlate well with prognosis, whereas the second one provides better information about prognosis, but is limited by the need of histology. Therefore, it could be applied only postoperative.

Surgical classification

The most famous surgical Bismuth-Corlette (1975) classification differentiates four types of tumor focusing just on BD invasion (see *Table 1*) (14). Although old, it is still nowadays the most used classification that easily depicts the phCCA at its presentation.

Despite the close correlation between tumor localization within the biliary confluence and portal vein (PV) or hepatic artery (HA) infiltration, this classification does not provide

any information about circumferential extension as well as local or distal metastases.

Oncological classification

From an oncological point of view the following four factors have been reported as main prognostic ones:

- (I) Extension of tumour within the biliary tree;
- (II) Vascular invasion;
- (III) Lobar atrophy;
- (IV) Metastatic disease.

However, other aspects as lymph node metastases, tumor differentiation, perineural invasion, surgical margins are well known independent prognostic factors in phCCA (13,15). For this reason, oncological classifications consider also local and distal invasion.

In this context, two major staging systems are commonly used: (I) the American Joint Cancer Committee/Union Internationale Contre le Cancer (AJCC/UICC) and (II) the Memorial Sloan-Kettering Cancer System (MSKCC) (see *Table 1*).

The AJCC/UICC is constantly reviewed to improve its prognostic predictive power and it arises the best once histology is obtained (16). Starting from the 7th edition of the AJCC/UICC staging system the phCCA is an independent entity (see *Table 1*). The major limit is that it can be used only in resected patients (17,18).

On the other hand, the MSKCC system mixes histology and imaging aspects like tumor extension, portal venous invasion, and hepatic lobar atrophy (13,19). For this reason, the MSKCC can be useful also preoperatively to plan the global therapeutic strategy. However, it does not provide information about metastasis.

Recently, two additional classifications, still in need of validation, have been proposed: (I) the Mayo Clinic Classification and (II) the De Oliveira Classification.

The Mayo Clinic classification includes additional factors such as the size and multifocality of the primary tumour, the nodal and extraregional metastatic burden, and clinical features such as jaundice and performance status (20).

The DeOliveira classification considers following aspects (21): (I) BD invasion; (II) tumor size; (III) tumor form (F); (IV) more than 180° of involvement of the HA; (V) more than 180° of involvement of the PV; (VI) liver remnant volume; (VII) underlying liver disease (D); (VIII) lymph nodes; (IX) metastasis.

The DeOliveira classification does represent the sum of the most important surgical aspects, which should be considered when planning an operation for phCCA.

Table 1 Comparison of the main used classification of phCCA

Classification	Bismuth-Corlette	AJCC/UICC (TNM)	Blumberg-Jarnagin (MSKCC) (13)
X and 0	–	TX: primary tumor cannot be assessed T0: no evidence of tumor Tis: tumor <i>in situ</i>	–
Type 1	CHD below the confluence	T1: confined to the bile duct, with extension up to the muscle layer of fibrous tissue	The tumor involves the biliary confluence with unilateral involvement up to secondary biliary radicles. There is no portal vein involvement or liver atrophy
Type 2	Type I to the confluence	T2a: tumor invades beyond the wall of the bile duct to surrounding adipose tissue T2b: invades adjacent hepatic parenchyma	The tumor involves the biliary confluence with unilateral involvement up to secondary biliary radicles. There is ipsilateral portal vein involvement or ipsilateral hepatic lobar atrophy
Type 3	IIla: type 2 + RHD; IIlb: type 2 + LHD	T3: tumor invades unilateral branches of the portal vein or hepatic artery	The tumor involves the biliary confluence with bilateral involvement up to secondary biliary radicles, unilateral extension to secondary biliary radicles with contralateral portal vein involvement, unilateral involvement up to secondary biliary radicles with contralateral hepatic lobar atrophy, or main/bilateral portal vein involvement.
Type 4	Type IIIa + IIIb or more	T4: tumor invades main portal vein or its branches bilaterally, or the common hepatic artery or the second-order biliary radicals bilaterally, or unilateral second order biliary radicles with contralateral portal vein or hepatic artery involvement Nx: Cannot be assessed; N0: no regional lymph node metastases; N1: regional lymph node metastases to nodes along the cystic duct, common bile duct, hepatic artery, and portal vein; N2: metastases to periaortic, pericaaval, superior mesenteric artery, and/or celiac artery nodes Mx: cannot be assessed; M0: no metastases; M1: distant metastases present	–

phCCA, perihilar cholangiocarcinoma; CHD, common hepatic duct; RHD, main right hepatic duct; LHD, main left hepatic duct.

Role and limits of surgery

Surgical resection provides the only chance of cure for this disease but is technically challenging because of the complex, intimate and variable relationship between biliary and vascular structures at this location (19,22,23).

Resectability ranges from 32% to 80%, but surgical margins are microscopically involved in 20–30% of patients who undergo resection (13,15,23–30). R0 resection is linked

to improved survival, and major hepatic resection including caudate lobectomy is necessary to obtain clear longitudinal and radial margins (13,15,23–30).

Five-year survival rates range between 25–45% (median 27–58 months) in case of R0 resection and 0–23% (median 12–21 months) in case of R1 resection respectively (31,32).

The major costs of high radicality are represented by relatively high morbidity and mortality rates (i.e., 20–66% and 0–9% respectively) (13,15,23–30).

Aim

Considering that radical resection may represent the only curative treatment of phCCA, we focused our review on surgical planning and techniques that may improve resectability rates and outcomes for locally advanced phCCA (i.e., stage III and IV tumors according the Bismuth classification, with biliary extension into both hepatic ducts, bilateral extension to second order BDs or vascular involvement).

Surgical strategy

The surgical treatment of phCCA can be successful when following aspects have been fulfilled:

- (I) Accurate preoperative diagnostic aimed to identify the tumor in all its details (localization and extension) and to study all the risk factors influencing a posthepatectomy liver failure (PHLF): i.e., liver volume, liver function, liver quality, haemodynamics and patient characteristics;
- (II) Precise surgical technique taking in consideration the local extension of the tumor and the vascular invasion;
- (III) Adequate postoperative management aimed to avoid major complications (i.e., PHLF and biliary complications).

Preoperative diagnostic

The primary role of preoperative diagnostic is to determine (or exclude) the diagnosis of phCCA and its staging in terms of spread into the BDs, the liver parenchyma, PV and HA invasion, as well as metastatic disease. Secondly the liver anatomy, volumetry and functionality should be also preoperatively investigated.

Although a lot different radiological and endoscopically methods are available, the diagnosis of phCCA remains challenging, due to lack of sensibility or specificity of the different methods. For this reason, a combination of the various procedures should be considered.

Imaging

Triple phase computed tomography (CT)

While conventional CT has a low accuracy, high-resolution CT can precisely predict resectability in most phCCA. Despite it plays a main role in determine the vascular

involvement and metastatic disease, in some cases it could lack in delineate the BD invasion and detect low volume peritoneal metastases or nodal disease (33-36). Therefore, it should be always accompanied by an MRI.

Magnetic resonance cholangiopancreatography (MRCP)

MRCP and particular contrast-enhanced magnetic resonance cholangiography is the tool of choice to determine the biliary extend of phCCA, associated lobar atrophy and loss of liver volume with a sensitivity of 94% and specificity of 100% (37). It is also able to determine vascular inflow. The use of contrast-enhanced MRI (CE-MRI) with gadolinium-based contrast agents (Gd-EOB-DTPA) allows also more accurate depiction of benign or malignant liver lesions than CT (38-41).

CT and MRCP should be always combined (39).

Positron emission tomography (PET)

The use of PET in phCCA is still debated. It shows a low sensitivity for the diagnosis of primary lesion, as phCCA, like the non-malignant tumors, are not fludeoxyglucose (FDG)-avid (19,39,42,43).

Endobiliary procedures

Cholangiography

A percutaneous or endoscopic cholangiography has the capacity of a better visualization of the BDs. It is reported a sensibility of 84% and specificity of 97% (37). Considering that a lot of patients will undergo a biliary stent placement, it is an easy additional information also about anatomy of intrahepatic biliary tree (44). However, these techniques are associated with a risk of cholangitis as well as tumor dissemination (33,45).

Endosonography (EUS)

EUS can determine the involvement of extraregional lymph nodes and, in case of intraductal ultrasound (IDUS) also the BDs and periductal tissue can be examined, raising the accuracy of the examination up to 90% (46,47).

Brush cytology

Brush cytology has an excellent specificity but poor sensitivity. Moreover, a definitively positive result is achievable in just 40% of patients. Therefore, a negative result does not exclude a phCCA (48).

Cholangioscopy

Cholangioscopy allows a direct visualization of BD and therefore enables guided biopsies, increasing sensitivity and specificity to detect the phCCA (49-51).

Biopsy

Percutaneous or laparoscopic biopsy is not recommended as it has low sensitivity and increases risk of tumour dissemination (39,52).

Explorative laparoscopy

As mentioned above, CT and MRI imaging lack in detecting low volume peritoneal metastases. Despite the improvement of imaging sensibility increased in the last years (23,53-55), 20% to 50% of patients still present liver or peritoneal metastatic disease at the time of surgical exploration (13,19,56,57). Explorative laparoscopy, with opening of the lesser sac and examination of the common HA and its lymph node, has been proposed to detect occult metastasis and prevent the patient an unneeded laparotomy. This method can reveal up to 45% of the metastasis with an accuracy of 32–72% (33,43,58-61).

Preoperative prophylaxis of PHLF

According to the International Study Group of Liver Surgery (ISGLS), PHLF is defined as “*a post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5*” (62). It is the most feared complication occurring after liver resection with volumetric or functional insufficient future remnant liver (FRL). Its clinical presentation ranges from slight hepatic insufficiency to liver and multiorgan failure with requirement of intensive care.

For this reason, every patient with a suspected phCCA should be presented to a high-volume center to undergo a precise diagnostic, selection and therapeutical decision to maximize the oncological outcome and minimize the operative risks.

Following factors do usually influence the occurrence of a PHLF: (I) patient's characteristics/comorbidities; (II) FRL volume; (III) liver quality; (IV) liver function; (V) inflow and outflow

Patient assessment

Patients with suspected phCCA usually present with painless jaundice, pale stools and dark urine. Lab values shows the haematological hallmarks of obstructive cholestasis (33,63).

Mortality seen after PHLF is likely multi-factorial and many patient-related factors play a main role. Diabetes, obesity, malnutrition and frailty, hepatitis, renal insufficiency, comorbidities and age older than 65 years are associated with PHLF (64-71). Miscellaneous scores, like Karnofski and ECOG performance status or the Charlson Comorbidity Index, are used to assess the global patient status, but there is no agreement in the literature. Few studies also suggested performance status, comorbidities, and albumin serum concentrations as prognostic factors (72,73). Some mortality risk scores were proposed (69,74), however a validation is still needed.

Still, improving the patient's condition at the time of surgery is mandatory to optimize the outcome.

Liver assessment

Volumetry

Different studies showed that the volumetric assessment of FRL correlates with remnant liver function and the risk of PHLF (75). It could be defined as future liver remnant volume to total liver volume percentage (TLV/FRL) or to body weight, known also as rest volume to body weight ratio (RVBWR) (76,77).

Following ranges have been suggested: TLV/FRL >25% or RVBWR >0.5% in patients with a normal liver, or up to >30–40% and 0.8% in patients with cholestasis or suspected poor liver quality (75,78-86).

Volumetry can be assessed either manually, semi-automatic or automatic with software-assisted image postprocessing liver volumetry (SAIP) (87-89) and can be both CT- or MRI-based (90-93).

However, an interdisciplinary work between hepatobiliary-pancreas (HBP)-surgeon and radiologist is mandatory in order to determine the cut line in case of complex resection (e.g., extended left).

Liver quality

The performance of FRL is not only a matter of liver volume but it is directly related to the quality of the liver parenchyma, which in turn is mainly dictated by underlying diseases such as fibrosis, steatosis or cirrhosis (94-97).

Liver quality can be assessed preoperatively by means of following procedures:

Biopsy

Liver biopsy represents the gold standard, as can provide exact information about liver quality (95). However, it could be associated with false negative results due to sampling errors and it is an invasive technique that can be associated to complications as bleeding or infections (52,98-100).

For this reason, the development of non-invasive techniques, particularly elastography and MRI is to be preferred preoperatively.

Ultrasonography

High frequency ultrasound is a feasible and inexpensive tool that can suggest a poor liver quality due attenuation parameters (101). However, it shows a moderate sensitivity and need of clinician expertise (102).

Elastography

Several ultrasound elastography techniques have been developed to detect liver fibrosis [transient elastography, real time elastography (RTE), acoustic radiation force impulse imaging (ARFI) and shear wave elastography (SWE)]. The European Federation of Societies for Ultrasound in Medicine and Biology guidelines suggests that values above 6.8–7.6 kPa indicate the presence of significant fibrosis and that those ranging between 11.0–13.6 kPa may indicate cirrhosis (103). Promising results using elastography to predict PHLF were already published (104-106).

MRI

As conventional MRI can assess just indirect information in case of cirrhosis or portal hypertension, a lot of different MRI-based techniques [MR elastography, Diffusion-weighted MR imaging (DWI), gadoxetic acid disodium (Gd-EOB-DTPA)] are now available to assess hepatic steatosis and fibrosis and the results are comparable to US-based elastography techniques.

Moreover, these MRI-based techniques are the most accurate for measuring liver fat content and, contrary to US-based imaging, are feasible also in obese patient or with ascites, and allow an evaluation of the whole liver (107-110).

On the other side, these methods are expensive, associated to long examination time, patient compliance and could be limited by hepatic iron overload, vascular and biliary congestion (110-113).

MRI allows the segmental assessment of steatosis and can

be used to assess fibrosis, making it a potential one-stop-shop modality for both liver anatomy as well as function.

CT

Liver attenuation obtained with CT-scan, compared with that observed in the spleen can indicate hepatic steatosis (75,114). However, CT has a low sensitivity in detecting fibrosis.

Liver function

The volumetric assessment of the liver should be complemented by liver function-specific assays. Various methods were proposed. Most of them can assess the global function of the liver based on blood assays and new imaging procedures (i.e., functional scintigraphy or MRI) are able to assess the segmental liver function.

Biochemistry

Various laboratory parameters show the synthetic or extraction capacity of the liver. They include coagulation parameters [prothrombin time (PT)/Quick/INR as well as coagulation factors], protein (albumin, total protein), cholinesterase (CHE) (115,116) and cholestasis parameters (bilirubin, gGT, ALP). Different series showed inconsistent findings as predictors of PHLF when taken singularly or in association as in the ISGLS score (117-121).

In fact, these parameters can be influenced from several other factors (i.e., loss, deficiency state, substitution) as well as by other diseases such as systemic inflammation, the nephrotic syndrome, malnutrition, or protein-losing enteropathy.

Indocyanine green clearance test (ICG)

The ICG test is the worldwide most use test in liver surgery (122). It is based on the capacity of ICG to be excreted, after intravenous administration, exclusively by the liver without biotransformation (123,124).

After intravenous administration the ICG plasma disappearance rate after 15 minutes can be measured by pulse spectrophotometry (ICG-15) (125). The safety limit in predicting safe liver resection of ICG-15 varies in the different studies from 15% to 20% (126-130).

However, in up to 20% of patients the severity of liver disease is underestimated due to hyperbilirubinemia, as the uptake is facilitated by common hepatic transporters, and impaired blood flow, as in case of intrahepatic shunting (129).

¹³C-methacetin breath test (LiMAx)

The LiMAx breath test is based on the metabolism of ¹³C-methacetin by the liver cytochrome CYP1A2. It assesses the global liver function but the authors suggest using the percentage of FLR to TLV as the percentage of functionality of the FRL. The normal cutoff value is set at 311–575 µg/kg/h (131). Notwithstanding, this ignores the lacking uniformity of the liver function throughout the liver (122). Moreover, besides the slightly availability of the device, different factors as smoking, nutrition and visceral hemodynamics can affect the results (132).

Hepatobiliary scintigraphy (HBS)

Hepatobiliary scintigraphy (HBS) can finally show the regionality of the liver function. The most discussed are ^{99m}Tc-galactosyl serum albumin scintigraphy (^{99m}Tc-GSA) and ^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HIDA), that shows respectively the uptake and excretion capacity of the liver.

^{99m}Tc-GSA

^{99m}Tc-GSA is uptake only in the liver and is unaffected by hyperbilirubinemia (133). Combined with dynamic single photon emission CT (SPECT-CT) allows an accurate three-dimensional measurement of FRL preoperatively also in cholestatic patients (134,135).

Various studies already shown that the uptake ratio of FRL correlate well with postoperative liver function parameters and this method can be used to predict postoperative outcome (135-141).

The applicability of ^{99m}Tc-GSA SPECT-CT in monitoring FRL after PV embolization (PVE) has been evaluated several times. The increase in FRL function after PVE was more pronounced compared to the volumetric increase measured with CT volumetry (142,143).

Three-dimensional SPECT-CT provides additional adequate anatomical information (144).

^{99m}Tc-HIDA

Mebrofenin is a lidocaine analogue that similar to ICG, is uptaken and excreted from the liver without undergoing any biotransformation (145-147). Moreover, ^{99m}Tc-mebrofenin shows the lowest displacement by bilirubin in case of hyperbilirubinemia. For this reason it is particularly indicated in cholestatic diseases (148).

As the results are similar to ICG clearance test (149), HIDA correlates with postoperative FRL function and allows a segmental view of it (147,150-153). A ^{99m}Tc-mebrofenin uptake in the FRL <2.69%/min/m² is associated to a high postoperative liver failure (152,154).

^{99m}Tc-mebrofenin HBS with SPECT-CT is gaining applicability in monitoring regeneration after PVE or liver resection. Recent reports have indicated that the increase in FRL function is more pronounced than the increase in FRL volume (144,150). This finding suggests that the time interval between PVE and liver resection should not be determined by volumetric parameters alone.

MRI with gadolinium ethoxybenzyl

diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)

Gd-EOB-DTPA is a liver-specific contrast agent. Approximately 50% is excreted by hepatocytes and the rest by the kidneys.

First proposed in 1993, data on the assessment of liver function using MRI with Gd-EOB-DTPA confirmed the possibility of segmental liver function assessment using MRI (155-163).

In- and out-flow assessment

In- and out-flow assessment implies not only the liver anatomy but also the regional territorial liver mapping, functional volumes, and outflow congestion volumes (164,165).

A three-dimensional computer-assisted surgical planning (3D-CASP) software could be helpful to determine the resection plane (164,166). 3D-CASP is based on information derived from CT and MRI and can provide inflow and outflow virtual analyses as well as determine safely perfused and drained retained liver volumes. In case of extended liver resection, knowing that outflow obstruction could lead to PHLF (167,168), this technique could contribute to provide information about the middle hepatic vein territory (169).

Augmentation techniques

If the risk of PHLF is set, while planning an extended hepatectomy, augmentation techniques to increase the volume and the function of the FRL of can be considered. These includes PVE and associating liver partition and PV ligation for staged hepatectomy (ALPPS).

PVE

Embolisation of main PV branches induces, due to deviation of the total PV flow to the still perfused liver, hypertrophy of the remnant liver (170,171). It is reported

an average increase of the FRL in 3 weeks between 8–46% (80,172).

A new assessment of volumetry and functionality, as above described, should be assessed 3–4 weeks after PVE to determine the degree of hypertrophy (171). Besides the already mentioned volumetric and scintigraphic parameters, a degree of hypertrophy >5% is associated with improved patient outcomes (173).

This procedure is associated with low morbidity and very low mortality, even though cholangiosepsis is reported (53,80,172,174,175). In planning of an extended right resection the PVE of segment 4 should be also considered, if technically feasible (176). In selected cases with insufficient hypertrophy of the FRL, an additional embolization of the ipsilateral hepatic vein could be considered to force the FRL growth (177,178). Transhepatic ipsilateral approach should be preferred to contralateral approach to avoid an injury of the FRL.

The resectability of the FRL is achieved in more than 70%, while a dropout due tumor progress is reported in 23% (179,180).

In case of planned extended left trisectionectomy, a left PVE could be also considered (181).

ALPPS

ALPPS is a two-staged surgical procedure that consider ligation or transection of right PV (RPV) branch combined with parenchymal transection along the falciform ligament (182,183). The parenchymal transection avoids formation of new contralateral vessel as well as increases inflammation response. This technique has shown a 74% increase in the volume of the FRL in less than two weeks and could be also proposed as salvage after failed PVE (184).

However, it is also associated with high postoperative morbidity and mortality of quite 48% in patients with phCCA (185,186). For this reason, actually ALPPS is not recommended in patients with phCCA and should be indicated just in highly selected patients.

Preoperative biliary drainage (PBD)

Aim of the biliary drainage of the FRL is ameliorating the bile flow, primarily to relief the jaundice and improve liver function and secondarily to enhance the regeneration capacity of the liver, which may decrease PHLF risk and mortality. On the other hand, it increases infection rates and could seed tumor along the percutaneous catheter

tract. This can result in sepsis and delay in therapy. For this reason, the use of PBD is still widely debated and studies demonstrating unconditional efficacy are lacking (54,187,188). A large European multicentric study showed reduced mortality in patients undergoing extended right hepatectomy, but curiously not in extended left (189), while an Asian meta-analysis did not show any benefit in patient with potentially resectable Klatskin tumor receiving a PBD (190).

Nowadays the use of a biliary stent is indicated in patients with congestive cholangitis, severe hyperbilirubinaemia-induced malnutrition or hepatic or renal insufficiency, as well as in patients undergoing preoperative PVE or neoadjuvant therapy (39,191). In patients with adequate nutritional status, slightly elevated bilirubin and no cholangitis the PBD could be avoided to prioritize surgery (190).

Some centers suggest a preoperative total bilirubin level of <2–3 mg/dL, and therefore PBD can still be recommended (39,188).

In case of bilateral cholestasis, the PBD should be placed on the FRL site to improve liver recovery and regeneration (69).

A PBD could be placed endoscopically by mean of a retrograde cholangiopancreatography [endoscopic biliary drainage (EBD) or nasobiliary] or percutaneous by mean of a transhepatic cholangiography (PTCD) (39,192). The main advantage of EBD is the reduce risk of seeding metastasis compared with PTCD. However, in patients undergoing PVE or chemotherapy it should be regularly changed. It can trigger ascending cholangitis in the FRL but it is not possible to sample the bile to obtain information about microbiology. An alternative could be the endoscopic nasobiliary drainage, which correlates with decreased cholangitis compared with EBD and permits sampling. Some groups recommend it as the ideal method. However, it is associated with patient discomfort imposed by nasal drainage (193,194). Furthermore, the time from EBD insertion to a satisfactory biliary level is faster with the endoscopic approach than with PTCD (33).

PTCD does not have to be regularly changed and permits sampling, too. However, due the transhepatic insertion it takes with it the risk of implantation metastasis as well as injury of the FRL.

In addition, PTCD has also a diagnostic role as they provide much better delineation of the intrahepatic extent of endobiliary tumour (195–197).

In addition, more than 50% of patients with an EBD require later a PTCD to achieve the required therapeutic

effect (198).

In conclusion a PBD should be used just in case of strictly indication and possibly after the imaging is over to avoid artefacts.

Surgical pitfalls

Kind of resection

The decision of which kind of resection may allow the best radicality usually depends from the combination of the following factors:

- (I) Tumor stage according to Bismuth-Corlette classification:
 - ❖ IIIa: right trisectionectomy (ERH);
 - ❖ IIIb: left hepatectomy (LH)—left trisectionectomy;
 - ❖ IV: right/left trisectionectomy.
- (II) FRL: in case of inadequate FRL and inability of augmentation of FRL, or in case of irreversible hypotrophy of one liver lobe, the strategy can be changed;
- (III) Vascular infiltration: although nowadays complex vascular resection and reconstruction are feasible (but usually in tertiary centre with high experience in this context) the vascular infiltration of right or left vascular pedicle may influence the decision-making process of which kind of resection.

We suggest to perform whenever possible an ERH based on following aspects (12):

- (I) Separate left hepatic vein providing independent venous drainage of segment 2 and 3;
- (II) Umbilical plate (“own hilum”) containing separate BD and PV confluence (Rex sinus);
- (III) Left hepatic duct (LHD) of long extrahepatic segment well accessible for surgical assessment.

Approach to the BD

For a correct approach to BD, following relevant anatomical aspects should be kept in mind (22):

The right hepatic duct (RHD) is more often involved by tumour up to its second-order branches because it is short and bifurcates early. The anatomy of the RHD bifurcation plays an important role in determining whether the right anterior sector is best preserved or resected. The RHD bifurcation has two major anatomical variations. The “normal” supraportal course of the right posterior sectoral duct (RPSD) is seen in approximately 85% of patients while

the remaining have an infraportal RPSD (44,199,200). This anatomy is clearly discernable on cholangiography where the supraportal RPSD forms the so-called Hjortso’s Crook (44). A supraportal RPSD limits the extent of resection beyond the bifurcation of the RHD, is technically more difficult to anastomose and more likely to be associated with anastomotic leakage (15% *vs.* 0%) when the right anterior sector is preserved (199). Since the supraportal RPSD encircles the right anterior PV, resection of this vein and segments V and VIII permits resection of an additional 6–9 mm of BD and improves the likelihood of a negative surgical margin (89.6% *vs.* 97.7%) (44,200). On the other hand, patients with an infraportal RPSD are able to achieve a microscopically clear proximal surgical margin with parenchymal division just to the right of the principal plane (0% *vs.* 37% R1 resection) (199).

On the other side, the LHD is long and branches into its second-order ducts are far away from the hilum in the umbilical fissure.

The limit of BD resection towards the left is the left border of the umbilical portion of the LPV. This limit lies proximal to the confluence of B2 and B3 by about 5–10 mm and is reached after division of the portal branches to segment 4 (201).

The caudate lobe BDs drain close to the hilum and are invariably involved by tumour, which is why caudate lobe resection is an inherent part of the operation for phCCA. They travel superior to the PV bifurcation and this relationship with the PV explains why the superior aspect of the PV bifurcation is first to be involved by tumour (202,203).

According to the anatomical pillars mentioned above, the surgical approach to different stages of phCCA can vary as follows:

Bismuth-Corlette IIIa:

Two main options are available: (I) central resection (unusual) or (II) right trisectionectomy (ERH) (usual).

In case of infraportal anatomy of RHD (seldom) the tumour may be adequately resected with parenchymal resection of segments I and IVb. In case of supraportal anatomy of RHD (often) a central resection of segments I, IVb, V and VIII is needed.

Usually, when the left lateral section is of adequate volume (primary or after PVE) an ERH is an easier alternative to central resection. However, atrophy of the right lobe and/or involvement of right hepatic artery would take away the option of preserving the right posterior sector

and make ERH necessary.

Bismuth-Corlette IIIb:

In case of absence of right lobar atrophy or vascular involvement a LH usually extended to the second order branches is the standard procedure.

Bismuth-Corlette IV:

In this case an ERH or partially extended LH are the main options. The choice between these operations is once again dictated by the nature of associated vascular involvement and parenchymal atrophy. If neither are present, a left-sided resection would be preferable in order to preserve parenchyma.

When the right lobe is atrophic or there is significant RPV involvement, the resection of choice is ERH. The left BD needs to be divided at the left border of the umbilical portion of the PV in order to extend the resection beyond the confluence of segments 2 and 3 BDs (201).

Approach to PV

phCCA often but not always do adhere or infiltrate the PV bifurcation. In the past such a situation was considered a sign of unresectability (25).

Nowadays, PV resection is now performed in 10–40% of phCCA resections with consequent increase of long-term survival rates but at costs of significant high rates of morbidity and mortality (23,25,204).

Therefore, it is actual consensus that PV bifurcation should be resected only when tumour adherence or tumor infiltration has been detected. In this context, the strategy of PV resection a priori according to the Neuhaus' School has not been yet validated (22,24,205–208).

In case of right sided resection, the reconstruction of PV between the main stump and the left branch of PV in an end to end fashion is usually not a problem being due to its long extrahepatic length and easy access to the vein within the umbilical fissure beyond the limit of the tumour. In case of resection of more than 5-cm vein an interposition graft may be indicated.

The reconstruction of RPV is more demanding since the RPV is usually short and bifurcates early. In difficult cases a Y-interposition-graft may be necessary (22)

To avoid a twist of the PV anastomosis we suggest to put orientation stitches at the left side of both PV stumps before cutting the PV.

Approach to HA

Also, in this case following anatomical aspects should be taken in mind:

- (I) The left HA (LHA) lies at the left border of the porta hepatis, away from the biliary confluence, travels straight to the Rex recess and is rarely involved by tumour. Notwithstanding, it is important to exclude involvement of the LHA within the umbilical fissure before embarking on ERH;
- (II) The RHA runs between the BD anteriorly and the PV posteriorly, slightly inferior to the biliary confluence and because of its position is often involved in phCCA. It must be noted that contralateral involvement of the RHA is common even in left-sided phCCAs (type IIIb) and in such a case an arterial resection may become necessary. In this context a replaced RHA from the superior mesenteric artery may be advantageous since it lies to the right side of the biliary confluence so it may escape involvement in left sided tumours.

Arterial resection

The infiltration or abutment/encasement of the HA does not represent nowadays a contraindication to resection but it requires its resection and reconstruction. This is mainly true in case of left-sided resections (usually for phCCA Bismuth type IIIb) in which the RHA is wedged between tumour and PV and its maintenance is relevant for the arterial perfusion of the future remnant right liver lobe.

Resection with reconstruction with/without different interpositions grafts is technically demanding and requires high expertise (209). If arterial reconstruction can be correctly and safely performed the oncological results are excellent (i.e., 1-, 3- and 5-year survivals in this group of patients was 78.9%, 36.3% and 30.3%, respectively (210). Therefore, the reported results in the literature are quite different in terms of patency, morbidity and mortality rates (211–215).

In this context HBP tertiary centres with experience in segmental transplantation and microsurgical vascular reconstruction [i.e., living donor liver transplantation (LDLT) and pediatric liver transplantation) do offer the best results (22,210).

It should be noted that in same cases of left sided resections with involvement of RHA, the RHA itself can be

excised a priori with no need of reconstruction at the only condition that mobilization of the right lobe of the liver has been kept to a minimum so as to preserve arterial collaterals from the diaphragm, intercostal vessels and retroperitoneal vessels (216-218). An alternative to that (i.e., impossibility of preservation of RHA and complete mobilisation of right liver lobe) the arterialization of PV can be considered as a salvage procedure (219).

Resection of caudate lobe (segment 1)

In all cases of phCCA Bismuth-Corlette III-IV the resection of segment 1 associated to right or left trisectionectomy is mandatory since the caudate lobe BDs drain close to the hilum and are invariably involved by tumour (22-24,192,220).

In this context, improved R0 resection rates and survival associated with caudate lobectomy for patients with Bismuth-Corlette type III and IV lesions have been demonstrated in several retrospective series (221-223).

Lymphadenectomy

Lymphnode involvement plays a significant negative prognostic value. Unfortunately, there is a poor correlation between lymph node size and positivity on imaging (224,225) being PET-scan eventually more specific (226).

Although the benefit of lymphadenectomy and its extent on patient survival remains controversial, the procedure is essential to obtain an accurate and reliable tumor staging (25,227).

Therefore, a systematic mandatory N1 lymphadenectomy (216-218) has been suggested by most of the authors (23,192) with possible but discussable extension to N2 level.

Hepatopancreatoduodenectomy

Hepatopancreatoduodenectomy is indicated for advanced phCCA with either distal biliary tract involvement or extensive lymph node metastases along the hepatoduodenal ligament and behind the pancreatic head to achieve surgical R0 resection (228,229).

Recently published studies (*Table 2*) showed that this extended surgical approach in the context of local advanced CCA is feasible in highly specialized centers. Notwithstanding, due to the overall limited number of patients accompanied by high morbidity and also high mortality in some case series hepatopancreatoduodenectomy

still remains controversial and a general recommendation cannot be given (238).

Perineural infiltration

Several retrospective studies including a recent meta-analysis (239) have identified perineural sheath invasion as an independent prognostic factor in terms of overall survival (23,31,204,206,227,240-254) as well as disease-free survival (255-257). Furthermore, its occurrence seems to be associated with a more advanced tumor stage particularly T-stage and UICC-stage (258,259). Despite these findings, perineural sheath infiltration, as well as other tumor-specific, non-surgical factors (e.g., grading, microvascular invasion), is yet not included in common classifications for phCCA aimed at prognosis (5,13,21,239,260,261). In this regard, a revised classification system might provide improved information for the prediction of patient survival (253) and potential risk of recurrence. This data could help to identify patients who possibly benefit most from adjuvant chemotherapy. Several partly ongoing trials investigate the value of adjuvant chemotherapy in the context of biliary tract cancers, but complete results of these trial are yet to be published (262-264).

In general, perineural sheath invasion has no influence on the extent of surgery, because its status only can be determined by histopathological assessment after completion of tumor resection.

Minimal invasive surgery

Due to its complexity phCCA still represents a purely open surgery procedure. The minimal invasive laparoscopic surgery does play role only as staging procedure (49,56).

Neoadjuvant treatment

Neoadjuvant treatment (radiotherapy, chemotherapy or combination of both procedures) for locally advanced phCCA seems not to influence the oncological outcome in terms of disease-free survival (DFS) and overall survival (OS). However, it may allow tumor downstaging and improve tumor resectability (49,265). Prospective randomized studies at this regard are still missing.

Conclusions

Surgery remains the only curative treatment of phCCA if a

Table 2 Comparison of recent series with hepatopancreatoduodenectomy (only cholangiocarcinoma, i.e., gall bladder carcinoma is excluded)

Author	Year	n cases	Maj. Hepat. [%]	R0 [%]	Morbidity [%]	Mortality [%]	5-year survival
Hirono (230)	2006	6	100	–	100	16.7	–
Miwa (231)	2007	14	85.7	78.6	30.8*	0	51.9
Wakai (232)	2008	17	100	58.8	82*	29.4	11.8
Kaneoka (233)	2010	14	92.9	64.3	57.1	0	50
Hemming (234)	2010	13	–	–	35*	0	24
Ebata (235)	2012	85	92.9	72.9	77.6	2.4	37.4
Lim (236)	2012	13	100	54.5	91*	0	32.3
Sakamoto (237)	2013	14	100	57.1	95*	0	53

*, including different tumor entities.

R0 situation can be reached.

For this reason, advanced phCCA usually requires an extended hepatic resection and often a vascular resection.

In order to reach a R0 situation and to avoid a PHLF an accurate preoperative interdisciplinary study of the tumor extension, liver status (i.e., volume, quality and function of FRL) is mandatory.

A predominantly right-sided tumour is best treated by extended right hepatectomy and is likely to need PV resection.

An advanced left-sided tumour requires left trisectionectomy preferably using a left-sided approach to resection, and is likely to require PV as well as right hepatic arterial resection.

These are technically challenging operations and must be performed in a high volume centres by surgeons with experience in microsurgical techniques.

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Footnote

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