DISSERTATION

Establishment of a prognosis score after major hepatectomy in patients with perihilar cholangiocarcinoma

Erstellung eines Prognosescores nach erweiterter Leberresektion bei Patienten mit perihilären Cholangiokarzinomen

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

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Datum der Promotion: 23.03.2024

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ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ALT	Alanine-Aminotransferase
ASA	American Society of Anaesthesiology
AST	Aspartate-Aminotransferase
BilIN	Biliary intraepithelial neoplasms
CBD	Common bile duct
CCA	Cholangiocarcinomas
CEA	Carcinoembryonic Antigen
CIBD	Chronic inflammatory bowel disease
CT	Computer Tomography
CTx	Chemotherapy
dCCA	Distal cholangiocarcinoma
dept.	Department
ERC	Endoscopic retrograde cholangiography
EUS	Endosonography
FLRV	Future Liver Remnant Volume
HCC	Hepatocellular carcinoma
iCCA	Intrahepatic cholangiocarcinoma
IG	Intraductal-growing
IPNB	Intraductal papillary neoplasms of the bile duct
MF	mass-forming
MRCP	Magnetic Resonance-Cholangiopancreaticography
MRI	Magnetic resonance imaging
MTS	Metastases
PBG	Peribiliary glands
pCCA	Perihilar cholangiocarcinoma
PI	Periductal-infiltrating
PSC	Primary sclerosing cholangitis
PTC	Percutaneous transhepatic cholangiography
PVE	Portal Vein Embolisation
PVR	Portal vein resection

RCTx	Radiochemotherapy
REMAHEP	Recurrence risk after Major Hepatectomy
RTx	Radiotherapy
TNF	Tumour necrosis factor
TNM	Tumour-node-matestasis
UICC	Union for International Cancer Control

1. Abstract

1.1 Introduction

Aggressive tumour growth and high recurrence rates even following radical resection gives great need for the development of a novel prognostic score in perihilar cholangiocarcinoma (pCCA) patients. This study aims at the development of a new prognosis score for highly malignant perihilar cholangiocarcinomas building on the already established Fong Score for risk stratification regarding tumour recurrence in patients with hepatically metastasised colorectal carcinoma.

1.2 Patients and methods

The cohort included 270 patients with histopathologically confirmed pCCA, having undergone major hepatectomy with curative intent were analysed. Factors found in an univariate regression model ($p<0.1$), potentially impacting disease-free survival were then tested using multivariate cox regression analysis.

1.3 Results

Inversely and independently associated with 5-year DFS variables were found to be R1, V1 and N+ status (all $p<0.05$). Assigning a point value of one for each variable, a prognostic score of 0-3 was calculated. A highly significant correlation ($p<0.001$) with lower scores (0) being associated with good prognosis and higher scores (3) associating with bad prognosis was found. The established score strongly correlated to DFS and OS (both $p<0.001$). The receiver operating characteristic (ROC) curve analysis showed a better accuracy when compared to conventional scoring systems (Union for international cancer control, UICC score, Area under the curve, AUC = 0.728 vs. 0.698). Patients with a score > 0 tended to have better overall survival if they received adjuvant chemotherapy ($p =0.051$).

1.4 Conclusion

The score can contribute to an individualised therapeutic approach in pCCA patients. Testing should commence on larger, multicentre cohorts for validation. Inclusion of CA 19-9 in score modification should be considered.

2. Abstrakt

2.1 Einleitung

Das Ziel dieser Arbeit ist die Entwicklung eines neuen Prognosescores für hochmaligne perihilare Cholangiokarzinome nach kurativer Resektion, aufbauend auf dem bereits etablierten Fong-Score zur Risikostratifizierung hinsichtlich des Tumorrezidivs bei Patienten mit hepatisch metastasiertem kolorektalen Karzinom.

2.2 Patienten und Methoden

Die Kohorte umfasste 270 Patienten mit histopathologisch bestätigtem pCCA nach kurativ intendierter Major-Leberresektion. Variablen, die im univariaten Regressionsmodell eine Assoziation mit dem krankheitsfreiesn Überleben (engl. disease-free survival, DFS) zeigten ($p<0,1$), wurden anschließend mittels multivariater Cox-Regressionsanalyse getestet.

1.3 Ergebnisse

Die Variablen R1, V1 und N+-Status sind unabhängige Risikofaktoren für ein schlechteres 5-Jahres-DFS (alle $p<0,05$). Unter Zuweisung eines Punktwertes von 1 für jede Variable wurde ein prognostischer Score von 0-3 berechnet. Der ermittelte Score korrelierte stark mit DFS und Gesamtüberleben (egl. Overall survival, OS, beide $p<0,001$), wobei niedrige Werte mit einer guten, hohe Werte mit einer schlechten Gesamtprognose assoziiert waren. Die Analyse der Receiver-Operating-Characteristic (ROC)-Kurve zeigte eine bessere Genauigkeit im Vergleich zu herkömmlichen Scoring-Systemen (Area under the curve, AUC = 0,728 vs. 0,698). Patienten mit einem Score > 0 hatten tendenziell ein besseres Gesamtüberleben, wenn sie eine adjuvante Chemotherapie erhielten ($p =0,051$).

1.4 Schlussfolgerung

Der Score kann zu einem individualisierten Therapieansatz bei pCCA-Patienten beitragen. Zur Validierung sollten Tests an größeren, multizentrischen Kohorten durchgeführt werden. Die Einbeziehung von CA 19-9 in die Modifizierung des Scores sollte erwogen werden.

3. Introduction

Despite being a rare malignancy of the biliary tract, perihilar cholangiocarcinoma (pCCA, also known as Klatskin tumour) are characterised by their poor prognosis [1]. Due to their usually 'silent' growth, patients often present at an advanced stage of the disease. Surgical resection is the only curative treatment option, however only a fraction of affected individuals (approximately 35%) are diagnosed at an early enough stage for consideration of resection with curative intent [2]. However, the tumours are characterised by an aggressive tumour biology. Even in patients, in which radical resection can be performed, recurrence rates are high leading to low 5-year survival rates [3].

The Fong score was created for patients with hepatically metastasised colorectal carcinoma [4]. It helps evaluate survival and plan future treatment, monitoring intervals, as well as being used to compare patient data across different studies and institutions [4]. In addition it aids in patient information and assessment of recurrence risk (further details in part 7) [4]. So far, works on the establishment of a postoperative prognostic score for perihilar cholangiocarcinoma do not exist. Based upon the successful use of the Fong score, the possibility of instituting a new prognostic score for pCCA surgery was examined and tested. This is regarded as essential given the high recurrence rates and tumour related mortality in the long-term course characteristic for pCCA [5–7]. Better identification of high risk patients and assessment of individual recurrence probability could also help optimise adjuvant therapy [6]. Furthermore patients and practitioners alike can benefit from improved risk assessment.

3.1 Definition

Cholangiocarcinomas (CCA) are neoplasms of the bile duct system which are categorised by their location into intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA) [8]. Perihilar cholangiocarcinomas arise from extrahepatic epithelial tissue and are proximal in location to the cystic duct, arising within the hilar region of the liver [9].

Another name for this type of tumour is Klatskin tumour, so called after Gerald Klatskin who first described them in 1965 [10].

3.2 Anatomy and histology

Varying in size and morphology, the biliary system is highly heterogeneous. It can be divided into intrahepatic and extrahepatic parts [11,12]. The intrahepatic part begins at the canals of Hering connecting bile canaliculi between hepatocytes then goes on to form bile ductules and finally interlobular bile ducts[13,11]. These then continue into septal, interlobular, area and segmental ducts. Septal and interlobular ducts smaller than 300 μm are considered as small intrahepatic bile ducts [14,15,11]. Area and segmental ducts bigger than 300 μm as large intrahepatic ducts. They differ in embryological and histological features. The small bile ducts are lined with surface epithelium comprised of small cuboidal cholangiocytes [14,15]. Larger ducts' epithelium is composed of tall, cylindric cholangiocytes containing mucin producing cells and also feature glands within their walls known as peribiliary glands (PBGs) [13,11,14]. Extrahepatically the left and right hepatic ducts lead into the common hepatic duct, the choledochus (bile duct) to the cystic duct and the gallbladder. Extrahepatic bile ducts are summarised as 'perihilar bile ducts' [12,14].

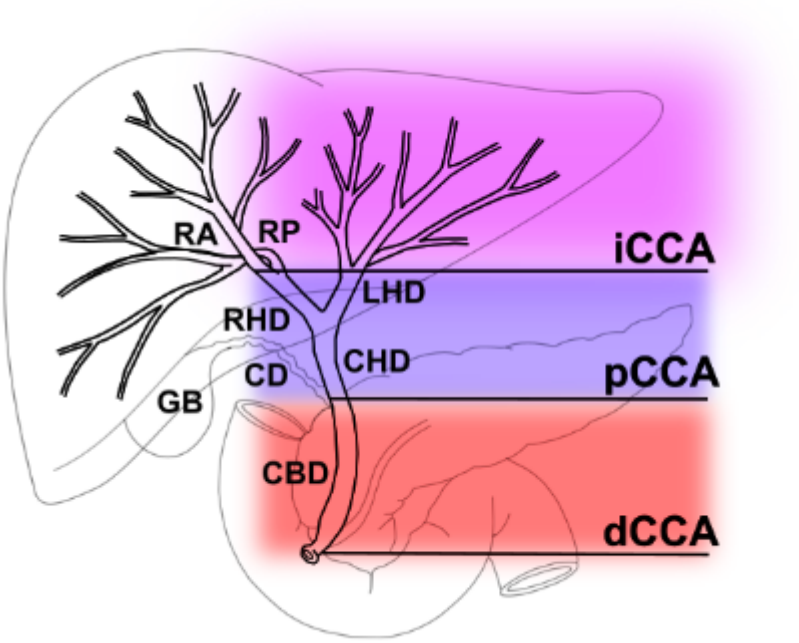
Cholangiocarcinomas can arise anywhere along the biliary system.

Intrahepatic cholangiocarcinomas are located above the second degree branches of the hepatic duct potentially arising from the segmental to the smaller branches of hepatic biliary tree [16,11,14].

The distinctive point for perihilar cholangiocarcinomas is the proximal location to the cystic duct [17]. Proximal referring to the direction of bile flow within the biliary system. It can be located in the area between the second degree bile duct and where the cystic duct inserts into the common bile duct [17,18]. They can arise anywhere on the left and right hepatic bile ducts as well as their junction, [16,17,11].

Distal cholangiocarcinomas arise on the common bile duct (CBD) and can stretch to, but not including the ampulla of Vateri. They can be difficult to distinguish from pancreatic head carcinomas if found within the intrapancreatic portion of the CBD [11,14].

Figure 1 - Cholangiocarcinomas



Own graphic based on visual art by the University of Texas MD Anderson Cancer Center © 2014 [19]

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RA, right anterior segmental duct; RP, right posterior segmental duct; RHD, right hepatic duct; LHD, left hepatic duct; CHD, common hepatic duct; CD, cystic duct; GB, gallbladder

3.3 Epidemiology, etiology and risk factors

Cholangiocarcinomas make up 3% of gastrointestinal neoplasms making them a rare group of tumours overall [18]. However, being the second most common hepatobiliary malignancy following hepatocellular carcinoma [8,20]. Of all CCA, 50% are pCCA [21,22]. Incidences vary strongly worldwide with the highest incidence being found in the Asian countries (>80/100,000 Inhabitants) whereas in Europe and the US incidence is much lower (1-3/100,000 Inhabitants) [23,24]. Men are more frequently affected than women (0.47 vs. 0.25 per 1,000,000 per year) [22]. Typical age-groups for first diagnosis are between the 5th and 6th decades. A diagnosis before the age of 40 is very rare [18]. Patients with primary sclerosing cholangitis (PSC) are an exception since often being diagnosed at a younger age. PSC could also be identified as one of the primary risk factors for developing pCCA [25]. The greatly varying Incidence and much higher incidence rate in Asia seems to be attributed to a higher incidence of risk factors [24]. One risk factor are parasitic infections such as the Clonorchis sinensis or the Opisthorchis viverrini that mostly occur in the asian regions [26]. Other risk factors including liver cirrhosis, diabetes mellitus, CIBD (chronic inflammatory bowel disease) and chronic infection with hepatitis-B or C viruses, as well as milder inflictions such as choledocholithiasis were suggested, but could so far not be unanimously agreed upon [25,27]. The nature of the malignancy remains sporadic and in a majority of cases no risk factor can be identified [22]. The knowledge about the molecular background of this tumour is still limited. However, chronic inflammation leading to genetic mutations in tumour-suppressor-genes, DNA-mismatch-genes and protooncogenes, as well as causing reactive cell proliferation has been suggested to be the root of malignant changes in the bile duct epithelium [28]. Inflammatory mediators like Interleukin-6 and TNF-alpha (tumour necrosis factor), as well as the growth factor EGFR seem to be playing a crucial role in the activation and deactivation of regulatory genes such as myc, p53, KRAS and TP53 [18,28–30].

3.4 Pathology

The macroscopic pattern of growth in iCCA are classified into mass-forming (MF), periductal-infiltrating (PI) and intraductal-growing (IG) types [31]. Perihilar cholangiocarcinomas are predominantly of the periductal-infiltrating type. These poorly defined nodular sclerosing tumours often present with diffuse infiltration of adjacent structures (≈80%) [32][31],[32]. Less frequently, they can present as intraductal-papillary tumours corresponding to the IG-type of iCCA [11]. This type represents the malignant progression of intraductal papillary neoplasms of the bile duct (IPNB) [11]. Nodular sclerosing type pCCA correspond to the PI-type in iCCA and are often preceded by a group of preinvasive lesions termed biliary intraepithelial neoplasms (BillN) [11,32].

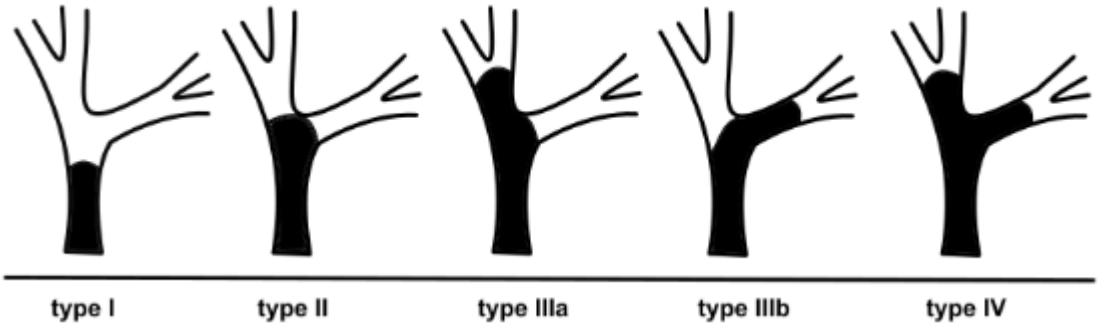
90% to 95% of all CCA are moderate to poorly differentiated adenocarcinomas [31]. Other histological subtypes are encountered rarely [18]. They show a characteristically highly desmoplastic stroma and mucin expression [14]. Expression of CK7 and CK19 proteins is often found, but this is also commonly expressed in HCC [14].

3.5 Classification and staging

3.5.1 Bismuth-Corlette Classification

This is the current standard classification system used for assessment of preoperative patients with hilar cholangiocarcinomas. It describes the extent of tumour growth in the bile duct system by division into distinct anatomic locations. It does not give any information regarding the therapeutic objective most suitable for a patient. The categorisation (Figure 1) in regard to the hepatic bifurcation does not take into account involvement of blood vessels or resectability [33,34].

Figure 2 - Bismuth-Corlette Classification



Own graphic based on Bismuth et al. [34]

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Blackened areas represent tumour mass

3.5.2 UICC-TNM staging system

The American Joint Committee on Cancer (AJCC) provides key pathological information based on histological data provided by the World health organisation and utilisation of the standard TNM (tumour-node-metastasis) classification system recognised by the UICC (Union for International Cancer Control), as shown in Table 1 [9]. It is the standard pathological staging system used for pCCA.

In addition to the TNM factors other descriptors for residual tumour mass, labelled “R” (Rx - cannot be assessed, R0 - no residual tumour, R1 - microscopic residual tumour and R2 - macroscopic residual tumour), as well as for the histological grade labelled “G” (Gx - no assessment, G1 - well differentiated, G2 - moderately differentiated, G3 - poorly differentiated, G4 - undifferentiated) are being used [9,35].

The latest, 2017 8th edition of the system included changes to staging tumours invading the portal vein . Since R0 resections became more achievable through hepatectomy including vascular resection and reconstruction T4 tumours have been downstaged from stage IVa to IIIb [35].

Table 1 - UICC-TNM Classification for perihilar cholangiocarcinoma [36]

Stage 0		Tis, N0, M0
Stage I		T1, N0, M0
Stage II		T2a–b, N0, M0
Stage III	IIIA	T3, N0, M0
	IIIB	T4, N0, M0
	IIIC	Any T, N1, M0
Stage IV	IVA	Any T, N2, M0
	IVB	Any T, Any N, M1
Tis		Carcinoma *in situ*/high-grade dysplasia.
TX		Primary tumour cannot be assessed.
T1		Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue.
T2a		Tumour invades beyond the wall of the bile duct to surround adipose tissue.
T2b		Tumour invades adjacent hepatic parenchyma.
T3		Tumour invades unilateral branches of the portal vein or hepatic artery.
T4		Tumour invades the main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement.
NX		Regional lymph nodes cannot be assessed.
N0		No regional lymph node metastasis.
N1		One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes.
N2		Four or more positive lymph nodes from the sites described for N1.
M0		No distant metastasis.
M1		Distant metastasis.

M = distant metastasis; N = regional lymph nodes; T = primary tumour

3.6 Clinical symptoms

In 90% of patients, the presenting symptom is painless jaundice, in 10% it is cholangitis [8]. First symptoms often pertain to the occurrence of cholestasis and include pruritus, darkened urine and acholic stools. Patients can also present with nonspecific epigastric pain and can show a positive Courvoisier's-sign (palpable, enlarged, painless gallbladder) [31].
Sixty-five percent of all pCAA patients present with accompanying symptoms, such as anorexia and fatigue [31]. The latter being mainly due to the often late diagnosis of pCAA in its advanced stages [37].

Often it is the distinctions between benign and malignant biliary duct strictures that proves difficult, with around 15% of suspicious strictures later proven to be benign [38]. Diagnostic methods firstly need to exclude benign differential diagnoses like choledocholitheasis, iatrogenic biliary tract injuries and very rare cases of eosinophilic cholangitis [5,38,30, 31]. Malignant differential diagnoses include the exclusion of gallbladder carcinomas and metastases of other tumours [5].

Presentation of symptoms often correlates with late tumour stage which leads to some difficulty in finding the diagnosis [3,37]. Furthermore, targeted diagnostics often prove difficult due to small tumour size and complicated anatomical position [24,37]. Patients with icterus of unclear cause will firstly get laboratory tests done followed by sonography and cross sectional imaging techniques or additional interventional diagnostic [37,39,32].

3.7 Diagnosis

Laboratory blood tests are the first diagnostic tool and often show nonspecific elevation of liver parameters (AST,ALT) and parameters for cholestasis (bilirubin, glutamyl-transferase, alkaline phosphatase) [5]. Significant elevation of bilirubin above 75 µmol/L points towards a malignant rather than a benign process within the biliary tract [40]. Cholangitis will classically present with inflammatory parameter elevation (leukocytes, C-reactive protein, procalcitonin) [41,42].
In order to rule out IgG4-cholangiopathy the IgG4 serum concentration levels have to be evaluated [31]. Elevation can point towards eosinophilic cholangitis but does not exclude cholangiocarcinoma [37].
The tumour marker Carbohydrate Antigen 19-9 (CA 19-9) for gastrointestinal, hepatobiliary, as well as gynaecological and pancreatic tumours is relatively nonspecific as it can also be elevated in cholangitis, cholestasis and with nicotine consumption [39,41]. However, very high levels of CA 19-9 correlate with advanced stage tumours and unfavourable disease progression and outcomes [43]. Evaluation should always be combined with other diagnostic methods [39]. Especially since levels within the reference range do not exclude the existence of pCCA[36]. It is important to note that false negative values can occur in 10% of Lewis-Antigen-non-producers since these patients are unable to produce CA 19-9 [37]. In general, CA 19-9 levels lower than 100 U/L have a negative predictive value of 92% [31].

Since no imaging technique has shown clear superiority over the others, a combination of multiphase, contrast medium enhanced computer tomography (CT) and magnetic resonance imaging (MRI) is being used [44]. CT imaging has proven effective for the assessment of lymph node involvement (sensitivity 61%, specificity 88%) and identification of remote metastases (sensitivity 67%, specificity 94%), as well as evaluation of longitudinal tumour extent [44,45]. Another non-invasive diagnostic method includes magnetic resonance cholangiopancreaticography (MRCP) which has proven very efficient in combination with simple MRI for determining the localisation and spread of ductal tumours [44]. The use of Positron Emission Tomography (PET-scan) as a diagnostic method is mostly reserved for diagnosis of remote metastases (MTS) or lymph node MTS [37].

Invasive diagnostic procedures allow for extraction of biopsies for further cytological analysis. They entail endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC) and endosonography (EUS) [44]. Besides diagnostic purposes, they enable biliary decompression in case of obstruction using drainage or stent implementation [18,25]. Since Cholangiography uses a camera it allows for very targeted sampling through visualisation of the biliary tract epithelium [44]. This in turn heightens the cytological sensitivity [46]. Mostly being used for assessment of lymph node status, EUS also allows for biopsies by fine needle aspiration [47].

3.8 Surgical approaches/concepts

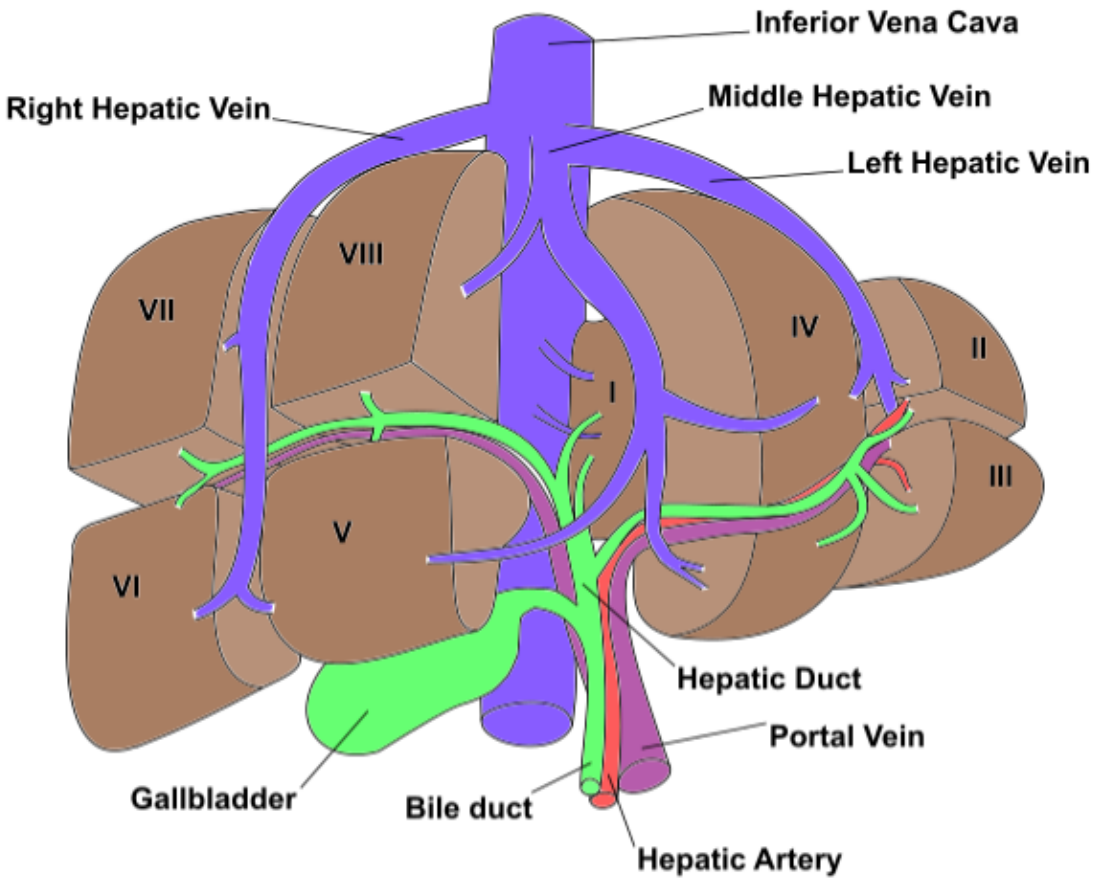
Due to the aforementioned late stage diagnosis and locally advanced tumour growth resection is only an option in about 20-35% of patients [47].
If a pCCA is rated as resectable it is most important to create optimal conditions in order to ensure a low rate of perioperative mortality and safe R0 resection [37,48]. For planning of the surgery it is also important to assess the future liver remnant volume (FLRV) as well as liver function [28, 38]. FLR can be calculated by using CT- or MRI-Volumetry [49]. Liver function is estimated through laboratory parameters and transaminase levels or with the LiMAx-Test® (maximum liver function capacity), which measures the levels of 13C-Methacetin during expiration [49]. If results indicate bad liver function or low FLRV this can be indicative for the need for portal vein embolisation (PVE) [50–52]

After careful review of imaging, endoscopic and laboratory findings an individual decision concerning the type of resection method is being made [53]. However, in some cases the final decision concerning resectability of the tumour can only be made intraoperatively [3,53]. In order to achieve negative resection margins despite infiltrative growth and location within the liver hilum, a resection of the hepatic bifurcation, the extrahepatic biliary duct, as well as major liver resection is needed [47,54–57]. Generally regarded as a non-curative type of resection, the limited extrahepatic biliary tract resection involves no resection of liver parenchyma [53]. This strictly ductal resection method is associated with high recurrence and lowered

overall survival rates due to its less radical approach when tackling this highly infiltrative growth, which often entails invasion of the perineural shaft [56].

In most cases, a regional lymphadenectomy is performed along with removal of the tumour mass [47]. Here, lymph nodes along the biliary ducts within the hepatoduodenal ligament, surrounding the portal vein and liver artery are being removed [56]. Subsequent to the resection, a biliary reconstruction has to take place [53,55]. This is done by creating a biliodigestive anastomosis through Roux-en-Y-hepaticojejunostomy [55]. Transanastomotic drains to aid healing can be put in and removed after 3-5 weeks following cholangiography [55].

Figure 3 - Liver segments



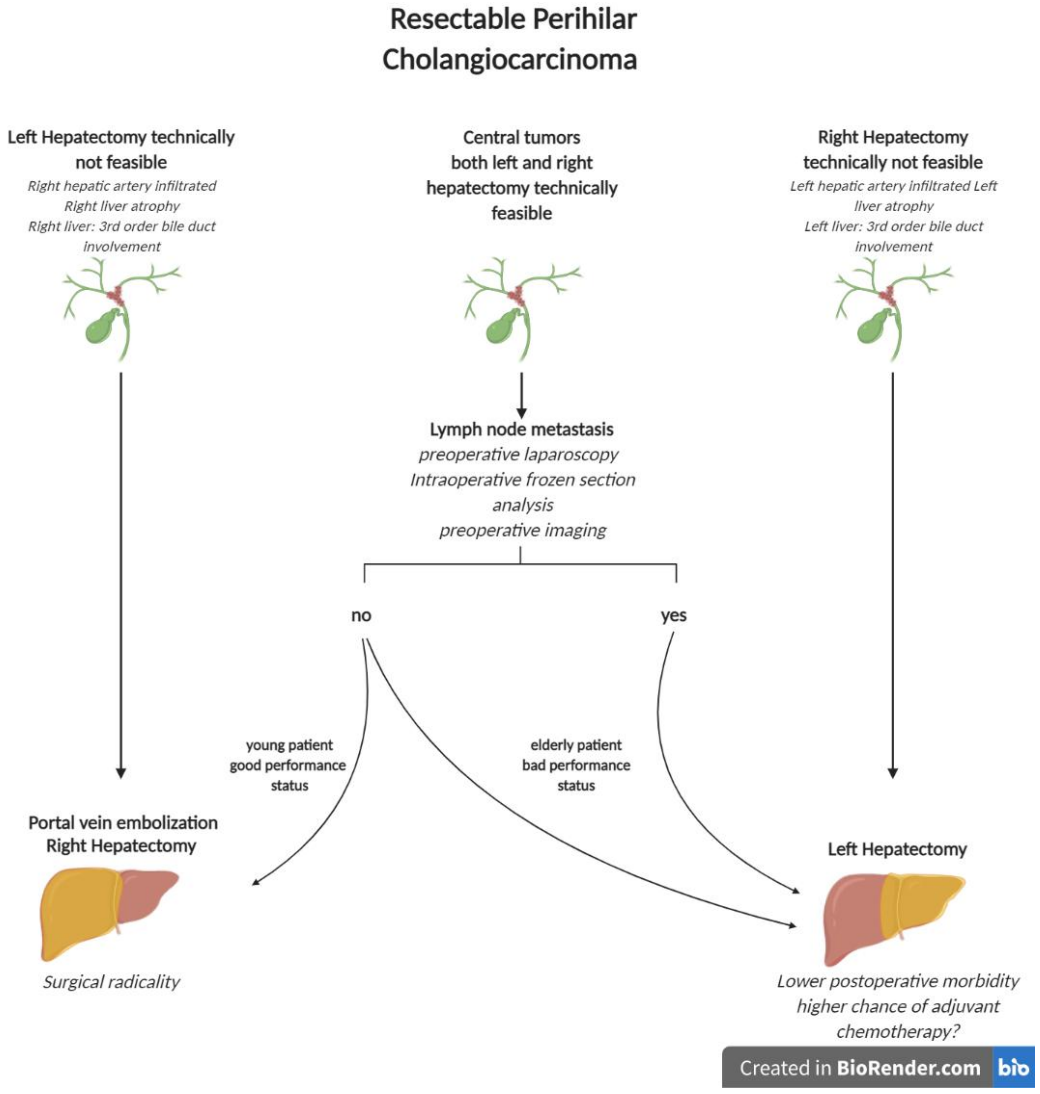
Own graphic created with inkscape.org based on liver anatomy [58]

3.9 Curative resections = major Hemihepatectomy

Aside from liver transplant which is limited to patients with unresectable pCCA within defined criteria in the setting of clinical trials, there are four main resection methods regarded as curative surgical approaches [3]. Extended left and right hepatectomy and left and right trisectionectomy or [3,55,57]. Since left or right hepatectomy in pCCA surgery always includes additional segment I resection, these procedures have to be considered extended (hemi-)hepatectomies.
In rare cases, like with severe liver dysfunction, differing atypical resections can be performed in order to preserve more liver parenchyma [48]. More extended liver resections such as right trisectionectomy has led to higher rates of R0 resections, but is associated with high operative morbidity and mortality owed largely to postresectional liver failure [3,55,57].

Generally, the chosen method is based on the pattern of growth into the intrahepatic biliary tree, infiltration of the portal vein and liver artery, as well as the volume of future liver remnant [47]. As stated above, resection must generally include segment I (caudate lobe) due to its immediate proximity to the hepatic bile ducts [57]. In the pioneering days of pCCA surgery, the dogma was that Bismuth type I, II and IIIa are eligible for right sided hepatectomy, whereas Bismuth type IIIb tumours were usually resected by left sided hepatectomy [33]. Nowadays, however, the decision on which side to resect is made on the basis of other anatomical criteria such as local infiltration of second- or third-order ipsilateral vascular or biliary structures, as well as general clinical factors such as patient age or presumed lymph node status of the patient (Figure 4) [59].

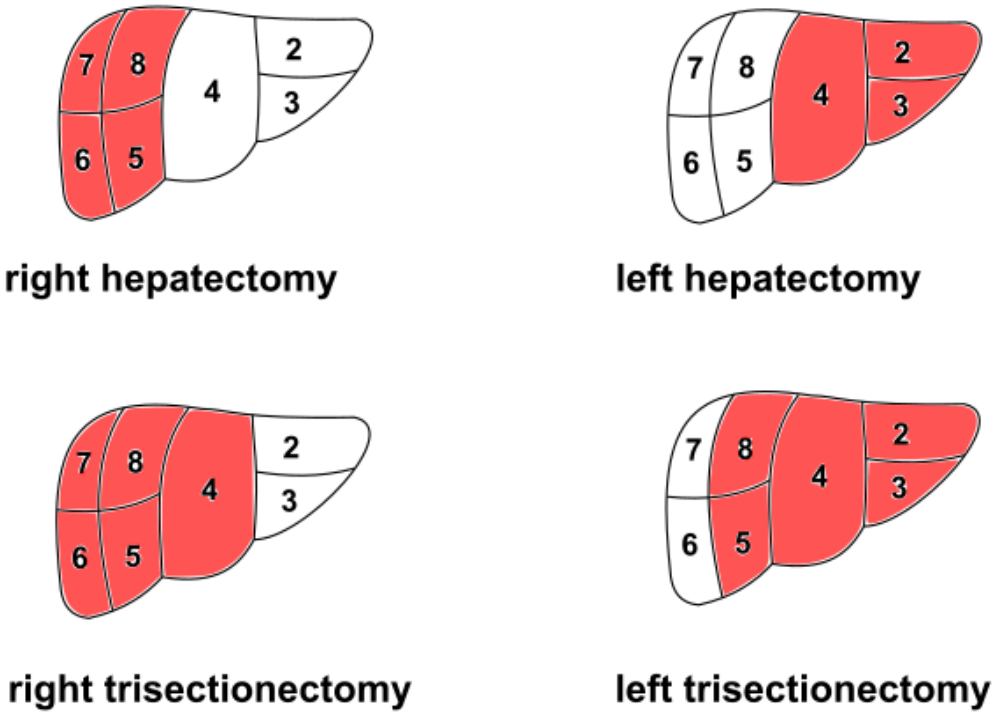
Figure 4 - Decision tree with regards to the preferred surgical approach



Own drawing based on Benzing et al. [59]

Bismuth type IV tumours extending into segmental ducts on both sides used to be resectable only in selected cases [55]. Nonetheless, at the Department of Surgery, Charité – Universitätsmedizin Berlin a retrospective study of patients having undergone major hepatectomy for treatment of pCAA showed 43% of patients to be classified as Bismuth IV [59]. Resectability has become more achievable thanks to improved surgical procedures and advanced preoperative preparation [20,55].

Figure 5 - Schematic illustration of resection margins



Couinaud Liver segments indicated by numbers 2-7 (Segment 1 located dorsally)
Shaded areas indicate resected segments
White areas indicate remnant segments after resection
Own graphic created using inkscape.org

3.9.1 Extended left hepatectomy

In patients with strictly left sided tumours, or very low liver reserve a left sided trisectionectomy can be indicated. It includes the segments I-V and VIII [48,60]. A particular challenge in this procedure is the preservation of the right liver artery, which typically runs dorsally to the hepatic fork and common hepatic duct and therefore often lies very close to the tumour [61]. Left sided resection therefore often

necessitates the preservation or reconstruction of the right portal vein and liver artery leading to higher chance of tumour cell dissemination [56].
Furthermore, biliary reconstruction can be complicated by numerous biliary apertures created due to very large resection margins, which can lead to a higher risk of failure of anastomosis [62].

3.9.2 Extended right hepatectomy and preoperative portal vein embolisation

Since the biliary fork is most often located on the right side within the hepatoduodenal ligament a right sided approach is often preferred, ensuring a radical resection of pCAA [47,56]. Additionally the left liver artery tends to run at a distance from tumour tissue and therefore does not need to be resected or reconstructed within tumour vicinity, further decreasing the risk for tumour dissemination [53,56]. If needed, the right liver artery can be removed en bloc [33]. The comparatively longer extent of the left hepatic duct allows for its resection before dividing into smaller branches simplifying the task of biliary reconstruction [53]. An unfavorable consequence of this procedure is the much lower postoperative FLRV (remaining segments II and III have much lower volume than remaining segments VI and VII in left sided resection), often requiring liver augmentation with portal vein embolisation [50,56]. By embolisation of the portal vein two to six weeks prior to surgical intervention, a hypertrophy within the remaining, tumour free liver segments is achieved [50,51,63]. Indicative for PVE is the estimation of future liver remnant volume, with most centres utilising it when FLRV is <25% (modified <35% with concomitant bad liver function) [48,49,63]. At the Department of Surgery, Charité - Universitätsmedizin Berlin standardised PVE before extended right hepatectomy is done [53].

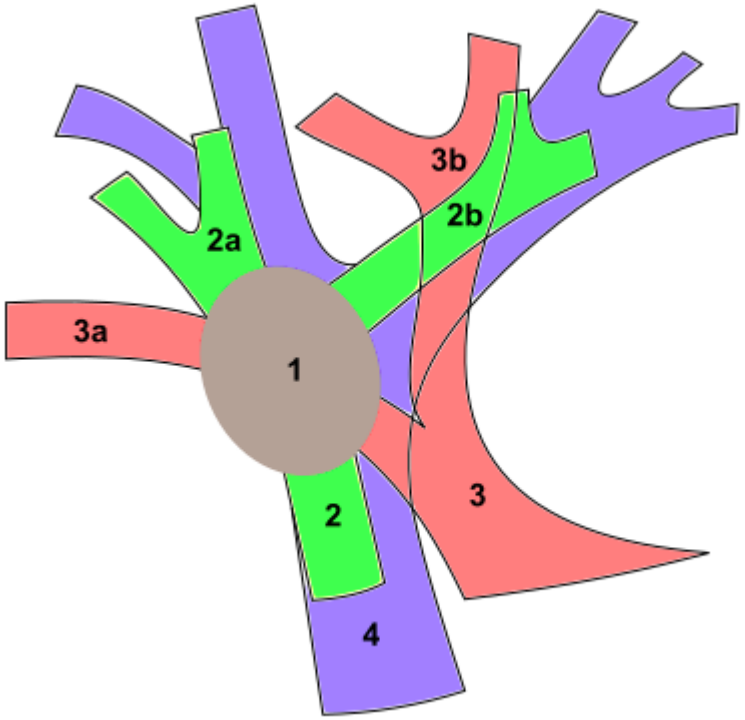
3.9.3 Hilar en-bloc resection

First established in 1990 by Neuhaus et al. this method combines right-sided trisectomy with en-bloc resection of the portal artery fork and removal of lymph nodes from the hepatoduodenal ligament, coeliac trunk, as well as peripancreatic region [56]. By avoiding any manipulation of the vessels in the immediate tumour vicinity risk of spreading tumour cells is reduced significantly [56]. 5-year-survival rates shown

following the introduction of this “no-touch-technique” improved to 58% compared with 29% following extended liver resection [56,64].

Limitations of the method include it only being applicable for right-sided resection since the liver artery is running too close to the biliary bifurcation and would have to be cut if a left sided resection was attempted [43,64]. Further disadvantages are those of standard right-sided trisectionectomy (see above).

Figure 6 - Schematic visualisation of liver hilum anatomy



1 tumour 2 common bile duct 2a right hepatic duct 2b left hepatic duct

3 common hepatic duct 3a right hepatic artery 3b left hepatic artery 4 portal vein

Own graphic based on Neuhaus et al. [64] created using inkscape.org

3.10 Adjuvant chemotherapy

The low 5-year-survival rates after surgical resection are largely attributed to high rates of recurrence [6,65,66]. Postoperative chemotherapy (CTx), radiotherapy (RTx), or combination of both (RCTx) is often recommended to reduce the risk of recurrence, despite studies still failing to better define clear benefits of adjuvant therapy [65,67]. Especially RTx alone has not shown convincing enough results [68–70]. Nevertheless, when comparing long-term survival over the last 20 years an improvement from around 19% to now up to 35% can be found [21,65,69,71].

New results of the BILCAP phase 3 study indicate an improved survival in case of administered gemcitabine/cisplatin adjuvant CTx [72]. Further studies are currently examining the effect of newer adjuvant agents and immunotherapy [73].

3.11 Recurrence patterns and long-term survival

PCCA are characterised by an aggressive tumour biology with early recurrence rates [3,31]. Recurrence can either occur as local recurrence, lymph-nodal recurrence, distant metastases or peritoneal carcinosis [6,7,74].

Long term survival is closely linked to recurrence rates and can only be achieved in case radical surgical resection is performed [6].

Despite recent improvements in surgical and adjuvant management, prognosis is still poor [75]. 5-year-survival varies greatly in literature, due to highly selective cohorts, eastern/western centres often being difficult to compare, preferred surgical method and application of pre- and postoperative therapies [2,3,21,64,76]. Most of all the lack of a unified tool, determining factors contributing to reduced long-term survival rates has to be acknowledged, as well as addressed.

3.12 Prognostic factors

In order to assess the long-term prognosis following surgical resection, prognostic factors have been analysed in numerous studies most commonly finding: N status, R status, Ca 19-9, negative resection margins, tumour differentiation, and negative lymph node status to be relevant factors [21,76–80]. A meta-analysis by Bird et al. highlighted the significance of prognostic variables in determining the overall survival

[80]. After analysing different studies with a total of 4599 patients they found T status, lymph node involvement, invasion of microvasculature, perineural invasion, differentiation of tumour and age to have the most significant effect on overall survival [80]. A negligible effect on overall survival was found when assessing the significance of tumour size and sex and due to high degrees of con-comitant heterogeneity the significance of resection margins and PVR also had to be dismissed [80]. Likewise the value of preoperative CA 19-9 could not yet be defined, but showed significant effect on pooled evaluation [80].

3.13 Value/importance of prognostic scores after surgical resection of malignant tumours

Prognostic scores are an important instrument both for clinicians and patients in times where paradigms shift from a “one fits all” concept to highly individualised treatment and follow-up plans.

Born out of the need for a more specific scoring system the fong score is a prognostic tool for the evaluation of recurrence and mortality risks in patients with hepatically metastasised colorectal carcinoma after curative intention hepatectomy [4]. It can provide guidance when planning for interventional procedures and adjuvant therapy and aids in assessment of the overall survival rate after surgical intervention [4]. Thereby it helps in patient consultations and the planning of postoperative monitoring by providing a better evaluation of the individual life expectancy [4]. Another advantage is the better comparability of patient data across different institutions and study programs [4].

Parameters of the score are created by giving yes/no answers to lymph node positivity, disease free interval <12 months (from diagnosis of the primary tumour to diagnosis of liver metastases), >1 primary tumour, CEA value (carcinoembryonic antigen) >200 ng/ml and size of the largest tumour >5cm [4].

The need for better comparability is also evident when looking at vastly differing mortality rates of cohorts in eastern and western centres [81]. Olthof et al. found median overall survival at 56 months in the East versus 43 months in the West, musing that this could be due to differing types of disease and tumour biology, as well

as deliberating the differences in therapy (with western resection often being more radical) as being accountable for the notable difference [81].

A 2015 study by Saito et al. succeeded in identifying preoperative factors for the prediction of overall survival rates in their cohort of 121 patients with pCAA [82]. Their analysis showed, that preoperative levels of serum C-reactive protein (CRP) > 0.5 mg/dL, carcinoembryonic antigen (CEA) > 7.0 ng/mL, albumin < 3.5 g/dL and platelet–lymphocyte ratio >150 were independent factors for prediction of postoperative survival [82]. T status, N status, perineural and portal vein invasion, as well as surgical margins were also found to be significant prognostic factors [82]. However, multivariate analyses was focused on finding independent preoperative factors, thus creating the preoperative prognostic score (PPS) [82].
Peng et al. examined 244 patients with bismuth-corlette type IV pCCAs only, in their 2019 study on creating a scoring system to predict early recurrence [75]. Using uni- and multivariate analysis they showed that, by scoring N status, CA19-9 level, lymphovascular invasion status and resection margin, early recurrence rates could successfully be predicted [75]. Although including only patients with type IV tumours significantly limits the scope of this study, it also aims to optimise postoperative surveillance and adjuvant therapy.

4. Aims and hypothesis

The objective of this dissertation is to identify suitable parameters which can then be used in the definition of a new prognostic score of patients with pCCA. This should allow for easier identification of specific prognostic factors linked to recurrence-free survival, as well as 1-, 3-, and 5-year survival rates. Analogously to the analysis of the aforementioned Fong score, patient data from the given cohort study is to be analysed to determine which post operative information will yield fitting prognostic criteria.

Hypotheses

The following hypotheses can be postulated:

- parameters for the definition and use of prognostic factors in patients with pCCA and after major hepatectomy can be identified
- there are factors specific to the patients, the tumour itself and the therapy chosen, which can be adduced as a prognostic tool to determine disease-free survival
- based on these factors a prognostic score expressing the correlation between recurrency patterns and tumour related mortality (AUC > 0.7) can be created

Aims

Based on these hypotheses, the following study aims can be formulated:

- Description and survival analysis of a cohort of patients who underwent major hepatectomy for pCCA in curative intent
- Detection of independent risk factors for decreased disease-free and overall survival after major hepatectomy for pCCA
- Implementation of a prognostic scoring system identifying patients who are at risk for tumour recurrence after curative resection of pCCA

5. Methods

In a first step, currently used classification systems were analysed for their weaknesses in the assessment of postoperative mortality and risk of pCAA. For this purpose a systematic literature search utilising the databases PubMed and Google Scholar was carried out with MeSH (Medical Subject Headings); “perihilar cholangiocarcinoma” AND “prognosis” OR “postoperative prognosis”, as well as “Fong score” OR “colorectal carcinoma” AND “score”. Next the criteria used in the Fong score were assessed on their applicability, non-applicability and modifiability in the case of the perihilar cholangiocarcinoma (pCCA). Lastly, patient data from the subsequently defined cohort study was used to propose and test a new postoperative prognostic score designated for patients with pCAA.

5.1. Study design

In this retrospective study, data of patients having undergone major hepatectomy for perihilar cholangiocarcinoma between January of 2005 and July of 2018, at the Department of Surgery, Charité - Universitätsmedizin Berlin, Campus Charité-Mitte and Campus Virchow Klinikum was analysed. This study was approved by the local ethics committee (EA2/006/16 and EA1/358/16).

With regards to the outcome parameters, the primary endpoint was median disease-free survival (DFS) according to the calculated prognostic score. Secondary endpoints were median overall survival (OS) according to the prognostic score as well as the accuracy of the newly established scoring system (AUC).

5.2. Inclusion and exclusion criteria

Inclusion criteria were as follows:

- Histologically confirmed diagnosis of pCCA
- Curatively intendend resection of pCCA (major hepatectomy)
- Age > 18 years
- Full medical documentation available.

Patients were excluded from the analysis in case one of the following criteria was met:

- Presence of distant metastatic disease (peritoneal, intrahepatic or distant organs)
- Palliative reactions, including extrahepatic bile duct resections without major hepatectomy
- Multivisceral resections including hepatopancreaticoduodenectomy (HPD) procedures
- Incomplete medical documentation

5.3 Data collection

Patients with pCCA were identified by searching the clinical information system using specified International Statistical Classification of Diseases and Related Health Problems (ICD 10) and “Operationen- und Prozedurenschlüssel” (OPS) codes. To filter for patients with extrahepatic cholangiocarcinoma, the code C24.0 was used. To filter for the respective hepatectomy procedures, the following codes were used: 5-502.1 (left hemihepatectomy, segments 2, 3, 4a, 4b), 5-502.2 (right hemihepatectomy, segments 5 - 8), 5-502.3 (extended right hemihepatectomy, segments 4 - 8), 5-502.6 (right trisectionectomy segments 1 and 4 to 8). Data selected for further analysis was gathered from the digital files. These files include primarily reports from the laboratory, radiology, pathology and surgical documentation reports, such as discharge papers and documents of tumour conferences held. Additionally, monitoring documents from the surgical, or oncological outpatient clinics were reviewed for postoperative evaluation and survival rates. For this purpose,

information on overall and disease-free survival was surveyed from follow-up reports generated by the university outpatient departments.

5.4. Patient baseline data

Patient data on age, gender, weight, BMI, preoperative laboratory parameters, tumour related data (disease stage, histopathological reports) and therapy related data (method of resection, side, duration, postoperative complications, 90-day mortality, readmission and information on recurrence) were obtained from the electronic database SAP (SAP ERB 6.0 and SAP Netweaver 7.5, Oracle 12.2, SAP Walldorf, germany).

5.5. Preoperative evaluation

Baseline characteristics and overall condition were gathered from anaesthesiological protocols. From preoperative laboratory testing maximum transaminase levels, bilirubin levels and CA 19-9 values were obtained. In addition, data on implementation of preoperative biliary drainage, PVE and occurence of cholangitis was selected. Lastly, all patients were categorised into the classification of Bismuth and Corlette, following CT or MRI.

5.6. Surgery and histopathological data

Data on resection margins, lymph node status, perineural invasion and microvascular invasion was taken out of pathological reports included in discharge papers. Information on resection method and side operated on, as well as extent of lymphadenectomy, vascular resection and possible reconstruction was extracted from surgery protocols. Utilising the gathered data in combination with the latest TNM classification at the time of resection, patients were then assigned a tumour stage according to the UICC (7th edition).

5.7. Postoperative morbidity and mortality

Complications were recorded by analysing discharge letters, reviewing the diagnosis list (ICD-10 codes), and by obtaining information from surgical, radiological or

gastroenterology department intervention reports. The Dindo-Clavien classification was chosen for grading, and complications with grade ≥IIIa were considered severe complications [83]. Since 2017, every file of patients who are discharged from the Department of Surgery at Charité postoperative complications contains a quality management form where complications are recorded seperately including the grading according to the Dindo-Clavien classification. Postoperative liver failure was defined using the International Study Group of Liver Surgery (ISGLS) classification [84].

Length of hospital and intensive care unit (ICU) stay were obtained from ICU transfer reports and discharge letters. The length of hospital stay was defined as the period between resection and discharge date in days. The 90-day mortality refers to all deaths occurring within 90 days postoperatively.

5.7. Follow-up and survival analysis

Surveillance and follow-up was carried out in associated outpatient clinics, as well as by patients' general practitioners. For calculation of survival with the Kaplan-Meier curve, the date of postoperative discharge was used. Last documented patient/practitioner contact served as an end point for the analysis. Similarly calculation of disease free survival was calculated using the date of recurrence diagnosis as an end point.

5.8. Statistical evaluation

For the statistical analysis IBM SPSS Statistics for MacOS, version 25.0 (IBM Corp., Armonk, NY, US) was used. Descriptive statistics included the presentation of categorial and continuous variables. Categorial variables were depicted as count and percentage, continuous variables are displayed as median and range. These data were compared using nonparametric tests. A uni- and multivariate analysis for identification of independent risk factors for tumour recurrence was carried out. Based on the identification of markers, a point value was then assigned to the presence of one of these parameters. The so calculated models' predictive character was then tested by calculating OS and DS rates in accordance with the scoring system. The accuracy of the scoring system was calculated using Receiver operating

characteristic (ROC) curve analysis by measuring the area under the curve (AUC). The level of significance for all evaluations was found at 5%, with a p-value ≤ 0.05 being regarded as significant.

5.9. Calculation of the Recurrence risk after Major Hepatectomy for Perihilar cholangiocarcinoma (REMAHEP) score

The factors that were identified as independent prognosticators in the multivariate analysis were taken as the basis to calculate the prognosis score. Patients with missing variables were left out and not included in the calculation of the score.
A score of 1 point was assigned to each of these variables. The prognostic score was calculated by summing up all points. The score ranges from 0 to 3 to points.

6 Results

6.1 Baseline characteristics

In total 270 patients have been identified by application of inclusion and exclusion criteria. The 90-day mortality was found to be 14% (n=38), these patients were excluded from further analysis. Patients were predominantly male with 60% (n=138). The mean age was found at 64 years (range 33-86). Presence of comorbidities and general preoperative systemic state was classified according to the American Society of Anaesthesiology Score (ASA score). Preoperatively assessed patients were predominantly (57%, n = 133) found to have only mild systemic disease (ASA 2), 36% (n = 84) showed severe systemic disease (ASA 3) and only 1% (n = 2) were found to be in a potentially life threatening state (ASA 4). 6% (n = 13) were classified as suffering from no systemic disease preoperatively. Biliary drainage before surgery was done in the majority of patients (85%, n = 196), with only 39% showing signs of preoperative cholangitis (n = 90). As for laboratory parameters, the median transaminase levels showed only slight elevation (ASAT = 59 U/l, ALAT = 71 U/l), as did the only marginally elevated mean bilirubin level (1.2 mg/dl). Preoperative CA 19-9 levels were available in 143 patients (62%). The median CA 19-9 was found to be elevated at 64 kU/l, with the range showing 32,670 kU/l at the highest. Adjuvant chemotherapy (aCTx) was not administered in 76% of cases (n = 171).

Table 2 shows all patient data as collected prior to the resection, as well as application of aCTx.

Table 2 - Baseline characteristics

	Resected perihilar cholangiocarcinoma n = 232
Age [1]	64 (33 - 86)
BMI [1]	24.8 (16 - 40.8)
Gender [2]	
male	138 (60)
female	94 (40)
ASA score [2]	
1	13 (6)
2	133 (57)
3	84 (36)
4	2 (1)
Preoperative biliary drainage[2]	
Yes	196 (85)
No	36 (16)
Preoperative cholangitis[2]	
Yes	90 (39)
No	141 (61)
Preoperative ALAT (U/l)[1]	71 (9 - 924)
Preoperative ASAT(U/l)[1]	59 (13 - 1396)
Preoperative bilirubin levels (mg/dl) [1]	1.2 (0.2 - 19.8)
Carbohydrate Antigen 19-9 (kU/l) [1]	64 (1 - 32670)
Adjuvant Chemotherapy [2]	
Yes	53 (24)
No	171 (76)

[1] Data is presented as median and range, [2] Data is presented as count and proportions (%)

6.2. Histopathological findings

The majority of patients showed complex, advanced stage, histopathologically G2 (68%, n = 154, Table 3) perihilar cholangiocarcinoma with Bismuth-Corlette stage IV in 42% (n = 97). Correspondingly, 39% (n = 89) and 41% (n = 93) were classified as being UICC stage II and IIIb respectively. R0 resection could be achieved in 70% of cases (n = 160). A slight majority of patients showed lymph node negativity (57%, n = 131) and microvascular invasion was present in the vast majority, 82% of cases (n = 169). However perineural sheath invasion was only present in a minority of 12% (n = 23). Accompanying lymphangitis could be seen in only 40% of patients (n = 81). Table 3 provides an overview of all histopathological findings.

Table 3 - Histopathological findings

	Resected perihilar cholangiocarcinoma n = 232
Bismuth-Corlette [2]	
I	11 (5)
II	17 (8)
IIIa	53 (23)
IIIb	48 (21)
IV	97 (42)
UICC Stage [2]	
I	11 (5)
II	89 (39)
IIIa	29 (13)
IIIb	93 (41)
IV	7 (3)
Resection margin [2]	
R0	160 (70)
R1	68 (30)
Lymph node status [2]	
N0	131 (57)
N+	98 (43)
Microvascular invasion [2]	
V0	37 (18)
V1	169 (82)
Histopathological grading [2]	
Grade 1	14 (6)
Grade 2	154 (68)
Grade 3	59 (26)
Perineural sheath infiltration [2]	
V0	164 (88)
V1	23 (12)
Lymphangitis carcinomatosa [2]	
Yes	81 (40)
No	121 (60)
UICC Stage [2]	
Tis	1 (0)
1	15 (7)
2a	71 (31)
2b	70 (30)
3	68 (29)
4	7 (3)

[1] Data is presented as median and range,
[2] Data is presented as count and proportions (%)

6.3. Surgical procedures and postoperative morbidity

As inclusion/exclusion criteria specified, all 232 patients had undergone hepatectomy. In 58% (n = 135, Table 4) this was carried out on the right side, of which a clear majority (54% of overall resections, n = 125) entailed right trisectionectomy. Left sided resections were most often (27% of all resections, n = 62) carried out as extended left hepatectomies and only 15% of all resections (n = 35) were left trisectionectomy. Prevalence of Hilar en bloc resections was split equally with 50% of patients (n = 117) not having undergone this type of procedure. Similarly portal vein resection was performed in a slight majority of 55% of patients (n = 127). Preoperative portal vein embolisation was not done 59% (n = 137). Surgical complications were assessed using the Clavien-Dindo classification. Accordingly, severe complication defined as grade IIIa (intervention without need for general anaesthesia) up to grade IVb (multiorgan dysfunction) was found in 59% of this cohort (n = 137). Note, grade V complications (death of the patients) were excluded since these patients were not part of the study cohort. Table 4 depicts all surgery related variables including postoperative morbidity.

Table 4 - Surgical procedures and postoperative morbidity

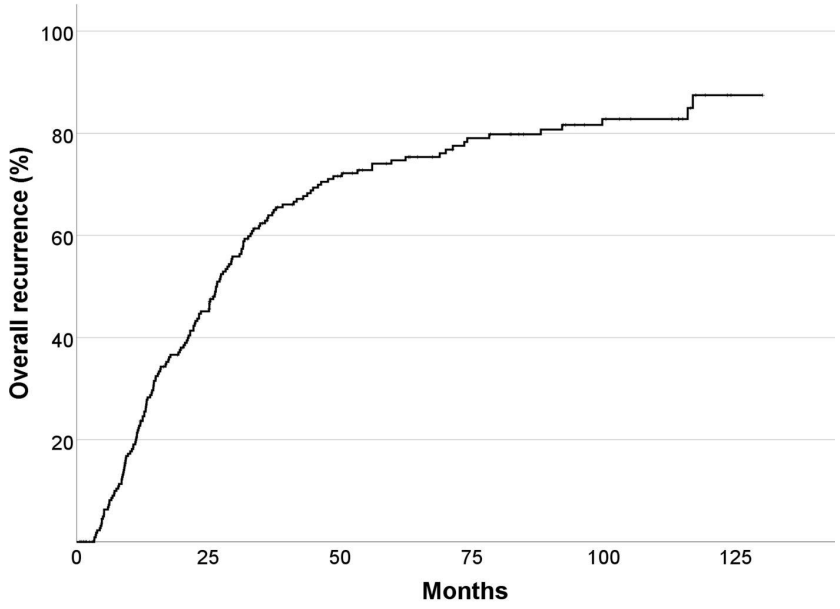
	Resected perihilar cholangiocarcinoma n = 232
Resection side [2]	
Left hepatectomy	97 (42)
Extended left hepatectomy	62 (27)
Left trisectionectomy	35 (15)
Right hepatectomy	135 (58)
Extended right hepatectomy	10 (4)
Right trisectionectomy	125 (54)
Portal vein resection [2]	
Yes	127 (55)
No	105 (45)
Hilar en bloc resection [2]	
Yes	115 (50)
No	117 (50)
Portal vein embolisation [2]	
Yes	95 (41)
No	137 (59)
Postoperative bile leak	64 (28)
Severe complications (grade IIIa - IVb) [2]	137 (59)

[1] Data is presented as median and range, [2] Data is presented as count and proportions (%)

6.4. Follow-up and overall survival

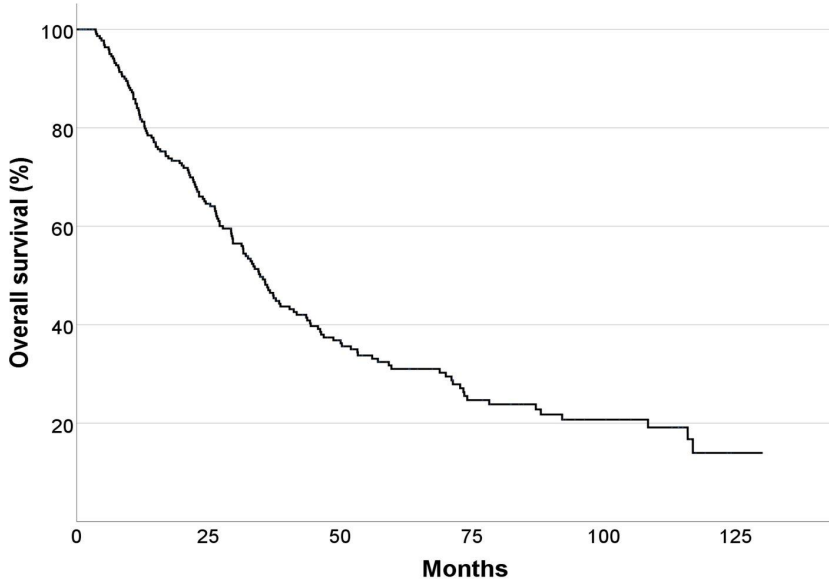
Median follow-up was 30 (1 - 136) months. Median disease-free (mDFS) reached 26.6 (22.8 - 30.4) months (Figure 7). The 1- 3- and 5 year DFS rates were 77%, 35% and 21%, respectively.

Figure 7 - Kaplan Meier curve showing disease-free survival of patients after major hepatectomy for perihilar cholangiocarcinoma



Median overall survival (mOS) was found to be 35.3 (31.1 - 39.6) months (**Figure 8**). The 1- 3- and 5 year survival rates were 83%, 55% and 25%, respectively.

Figure 8 - Kaplan Meier curve showing overall survival of patients after major hepatectomy for perihilar cholangiocarcinoma



6.5. Correlation of survival and Bismuth / UICC classification systems.

Neither DFS nor OS were found to be associated with the Bismuth stage (both $p > 0.05$, Figure 9).

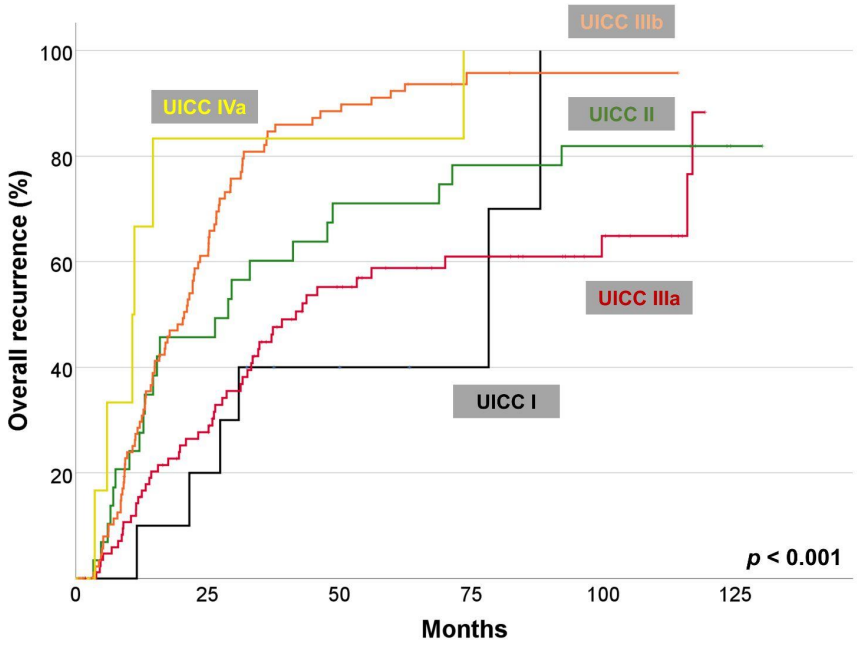
When analysing all patients who underwent major hepatectomy for pCCA in curative intent according to the UICC stage, median DFS was highest in stage I and lowest in stage IVa (Figure 10). However, the lowest 5-year DFS rate was found in stage IIIb (7%). The exact DFS data including the corresponding DFS rates can be found in Table 5.

Table 5 - Disease-free survival after major hepatectomy for perihilar cholangiocarcinoma according to the Union for International Cancer Control (UICC) stage

UICC Stage	Disease-free survival (months, 95 % CI)	P value	1-year DFS	P value	3-year DFS	P value	5-year DFS	P value
I	78.3 (0.0 – 165.1)		91%		60%		50%	
II	40.6 (30.1 – 51.0)		85%		53%		32%	
IIIa	28.9 (10.9 – 47.0)	**<0.001**	76%	**0.018**	39%	**<0.001**	29%	**0.001**
IIIb	20.6 (15.9 – 25.2)		71%		17%		7%	
IVa	10.7 (4.5 – 17.0)		33%		17%		17%	

UICC = Union for International Cancer Control, DFS = disease-free survival

Figure 9 - Kaplan Meier curve showing overall recurrence of patients after major hepatectomy for perihilar cholangiocarcinoma according to Union Internationale Contre le Cancer (UICC) stage



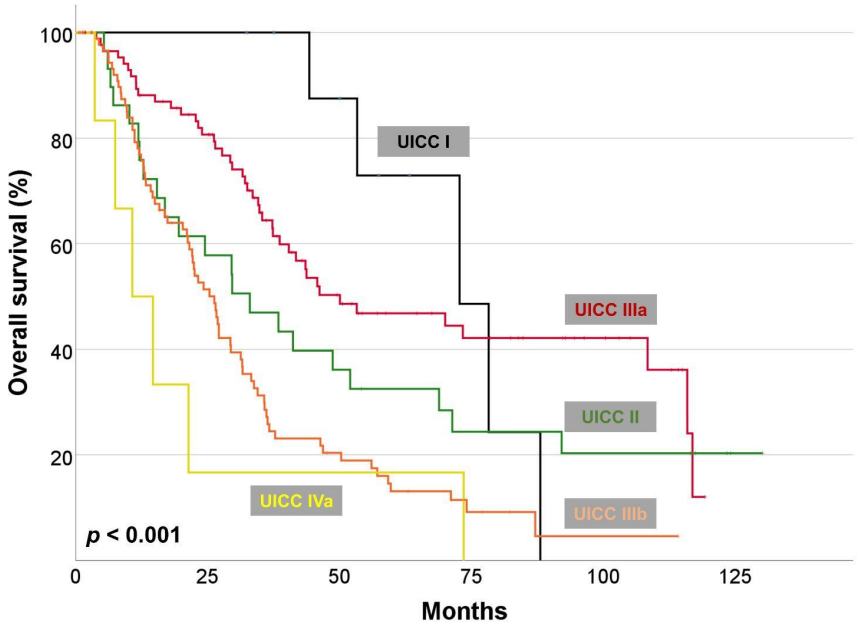
When analysing median OS according to the UICC stage, the longest OS was found in stage I and the shortest in stage IVa (**Table 6**). Of note, the 5-year OS rate was higher in stage IVa compared to stage IIIb (**Figure 11**).

Table 6 - Overall survival after major hepatectomy for perihilar cholangiocarcinoma according to the Union for International Cancer Control (UICC) stage

Prognostic score	Disease-free survival (months, 95% CI)	P value	1-year OS	P value	3-year OS	P value	5-year OS	P value
I	78.3 (66.7 - 89.9)		100%		100%		71%	
II	50.1 (21.3 - 78.9)		88%		61%		36%	
IIIa	33.0 (15.2 - 50.8)	**0,001**	79%	**0,041**	46%	**<0,001**	30%	**0,001**
IIIb	26.3 (21.6 - 31.0)		78%		27%		12%	
IVa	10.7 (2.1 - 19.3)		50%		17%		17%	

UICC = Union for International Cancer Control, OS = overall survival

Figure 10 - Kaplan Meier curve showing survival of patients after major hepatectomy for perihilar cholangiocarcinoma according to Union Internationale Contre le Cancer (UICC) stage



6.6. Univariate cox regression analysis of factors potentially impacting overall and disease-free survival

In order to detect factors that were associated with disease-free survival, a univariate cox regression analysis was performed examining various demographic and histopathologic varbiables. Lower T stage, negative lymph node status (N0), no lymphovascular (L0) and microvascular invasion (V0), as well as tumour-free resection margins (R0 status) were found to be associated with 5-year DFS (all $p<0.05$, Table 7). Furthermore, higher preoperative CA 19-9 levels (cut-off of 100 kU/l) was found to be associated with 5-year DFS (HR: 2.012 [1.332 - 3.039], $p = 0.001$). However, due to the fact that only 62% of all patients had available CA 19-9 levels, this variable was not included in the further multivariate analysis.

Table 7 - Univariate analysis of factors influencing 5-year disease-free survival in patients with perihilar cholangiocarcinoma who underwent surgical resection

Variable	HR (95% CI)	*P* value
Age (>65 years)	1.153 (0.841 - 1.579	0.377
Bismuth-Corlette > II	1.244 (0.740 - 2.091)	0.410
T Stage >2b	1.398 (1.009 - 1.937)	**0.044**
N Status (N0)	2.051 (1.483 - 2.837)	**<0.001**
Resection margin (R1)	1.595 (1.142 - 2.226)	**0.006**
Histopathological Grading		
G1	Reference	
G2	1.291 (0.652 - 2.555)	0.464
G3	1.576 (0.768 - 3.236)	0.215
Perineural sheath infiltration (Pn1)	0.839 (0.452 - 1.558)	0.578
Lymphovascular invasion (L1)	1.317 (0.935 - 1.854)	**0.116**
Microvascular invasion (V1)	1.781 (1.183 - 2.681)	**0.006**
No adjuvant chemotherapy	1.155 (0.790 - 1.687)	0.457
Resection side (left)	1.109 (0.807 - 1.524)	0.525
Postoperative bile leak	1.422 (1.000 - 2.024)	**0.050**
ASA Score > 2	1.066 (0.773 - 1.469)	0.696

6.7. Multivariate cox regression analysis of factors potentially impacting overall and disease-free survival

All factors that were associated with DFS in the univariate regression model ($p<0.1$) were subsequently tested in a multivariate regression model. Of the five variables tested, R1, V1 and N+ status were inversely and independently associated with 5-year DFS (all $p<0.05$, Table 8).

Table 8 - Multivariate cox regression analysis of factors influencing 5-year disease-free survival in patients with perihilar cholangiocarcinoma who underwent surgical resection

Variable	HR (95% CI)	*P* value
Resection margin (R1)	1.547 (1.032 - 2.319)	**0.035**
Microvascular invasion (V1)	2.005 (1.248 - 3.220)	**0.004**
N Status (N+)	1.709 (1.156 - 2.525)	**0.007**
T Stage >2b	1.412 (0.926 - 2.155)	0.109
Postoperative bile leak	1.125 (0.732 - 1.730)	0.592
Lymphovascular invasion (L1)	1,176 (0.761 - 1.819)	0.466

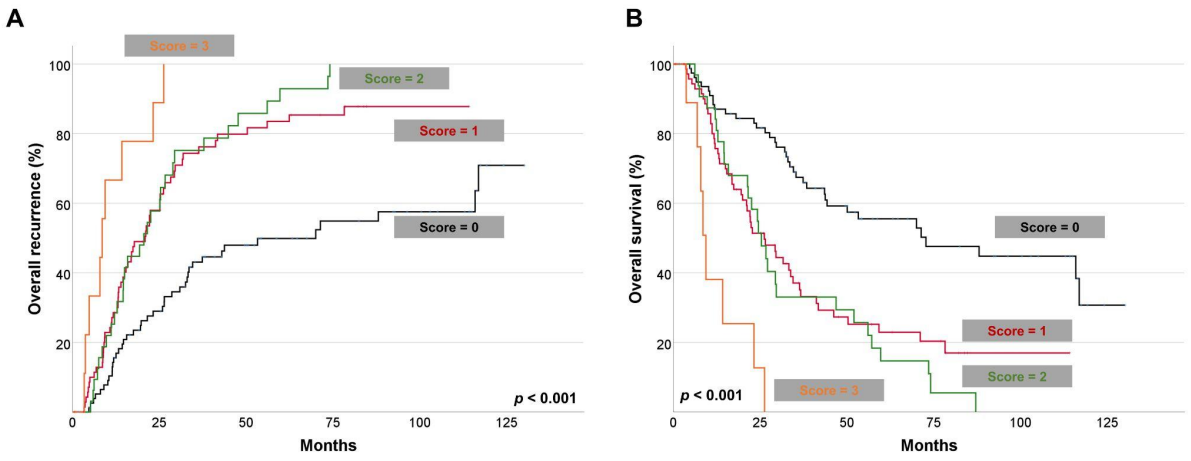
6.8. Calculation of the REMAHEP prognostic score

In order to calculate the prognostic score, each independent risk factor found in the multivariate cox analysis depicted in Table 8 was assigned one point. All points were then summed up and the prognostic score ranging from 0 - 3 was calculated.

Due to missing values in some cases, not all patients could be included. A score was only calculated when all three variables were complete. This was the case in 199 patients (86%). Of these 199 patients, 82 (41%) had a score of 0, 72 (31%) had a score of 1, 32 (14%) of 2, and 13 (6%) patients had a score of 3.

When analysing the scoring system according to the disease-free and overall survival of patients after MH for PHC, a highly significant correlation ($p<0.001$) was found with the scoring system with lower scores (0) being associated with an overall good prognosis and higher scores (3) with a bad prognosis. Scores of 1 and 2 points showed very similar DFS and OS survival curves (Figure 11).

Figure 11 - Kaplan Meier curve showing A) disease-free survival and B) overall survival of patients after major hepatectomy for perihilar cholangiocarcinoma according to the calculated prognostic score



Due to the almost exact parallel course of the Kaplan Meier curves of patients with scores of 1 or 2 points, these scores were summed up to one category. Figure 12 depicts the updated DFS curves with scores of 1 and 2 summarised as one single category. The respective median DFS and 1-, 3-, and 5-year DFS rates are shown in Table 8.

Figure 12 - Overall recurrence rates according to REMAHEP prognostic score

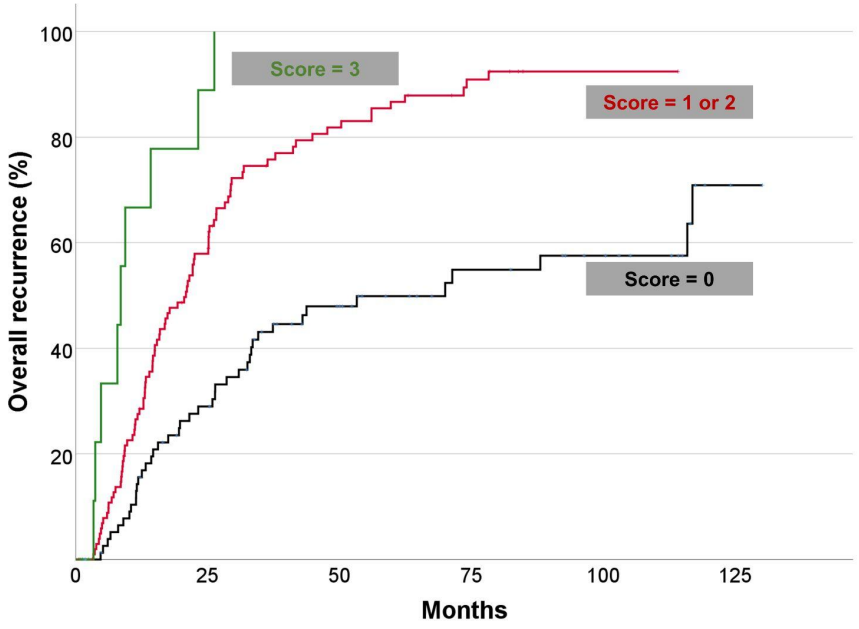


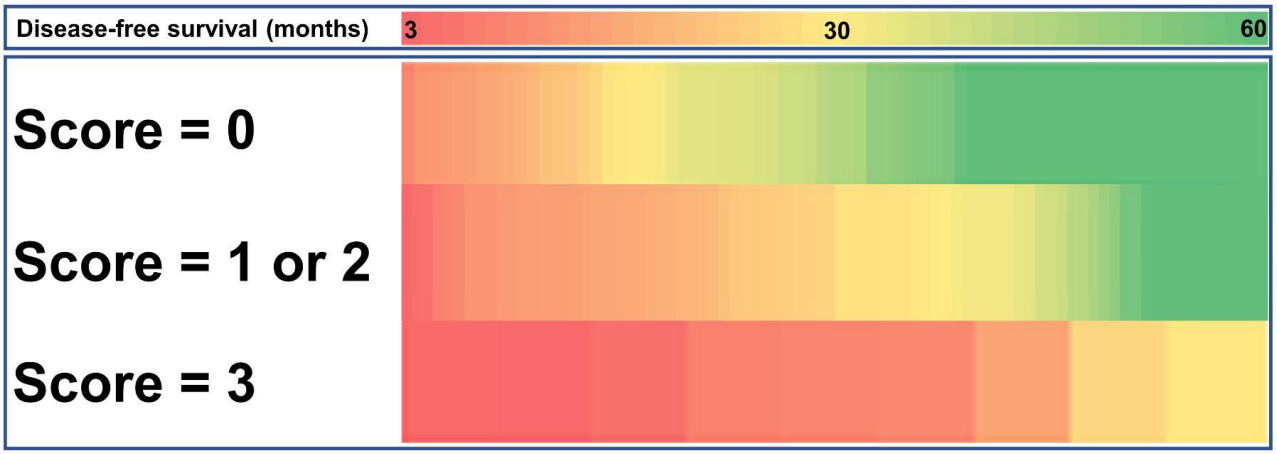
Table 9 - Disease-free survival after major hepatectomy for perihilar cholangiocarcinoma according to the calculated prognostic score

Prognostic score	Disease-free survival (months, 95% CI)	1-year DSF	P value	3-year DSF	P value	5-year DSF	P value
0	70.0 (21.4 - 118.7)	85%		55%		40%	
1 or 2	36.5 (16.3 - 25.5)	72%	**0,002**	23%	**<0,001**	12%	**<0,001**
3	16.7 (6.7 - 10.4)	33%		0%		0%	

DFS = disease-free survival

Figure 14 shows the distribution of 5-year DFS in months according to the prognostic score in a heatmap. Long-term DFS was only achieved in categories 0 and 1 / 2. Patients who had a score of 3 were characterised by early disease-recurrence.

Figure 13 - Heatmap showing the 5-year disease-free survival according to calculated prognostic score (minimum follow-up 12 months). Each coloured block represents one patient



Similar to DFS, there was also a strong association of OS and the prognostic scoring system (p<0.001) which is shown in **Figure 13.** The respective median DFS and 1-, 3-, and 5-year DFS rates are shown in **Table 9**.

Figure 14 - Overall survival rates according to the prognostic score

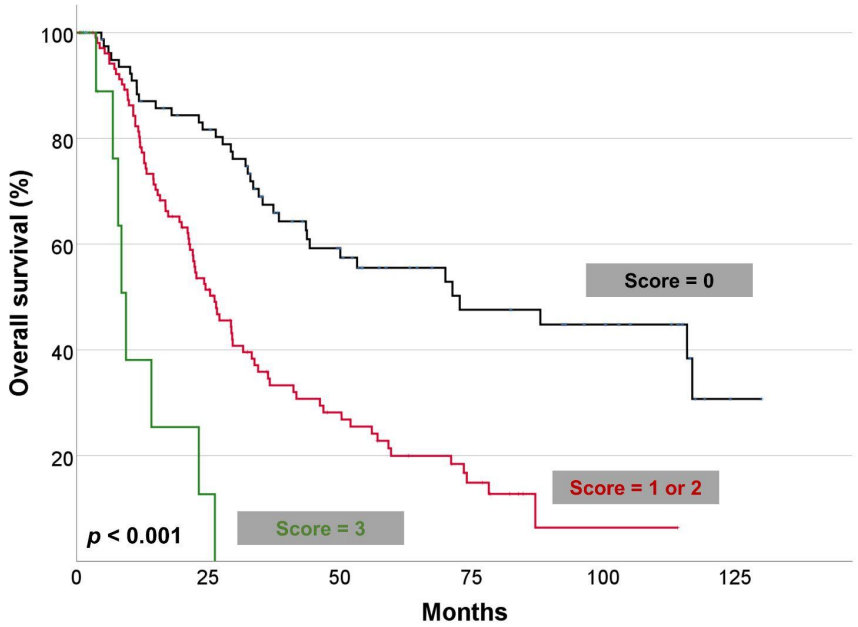


Table 10 - Overall survival after major hepatectomy for perihilar cholangiocarcinoma according to the new prognostic score

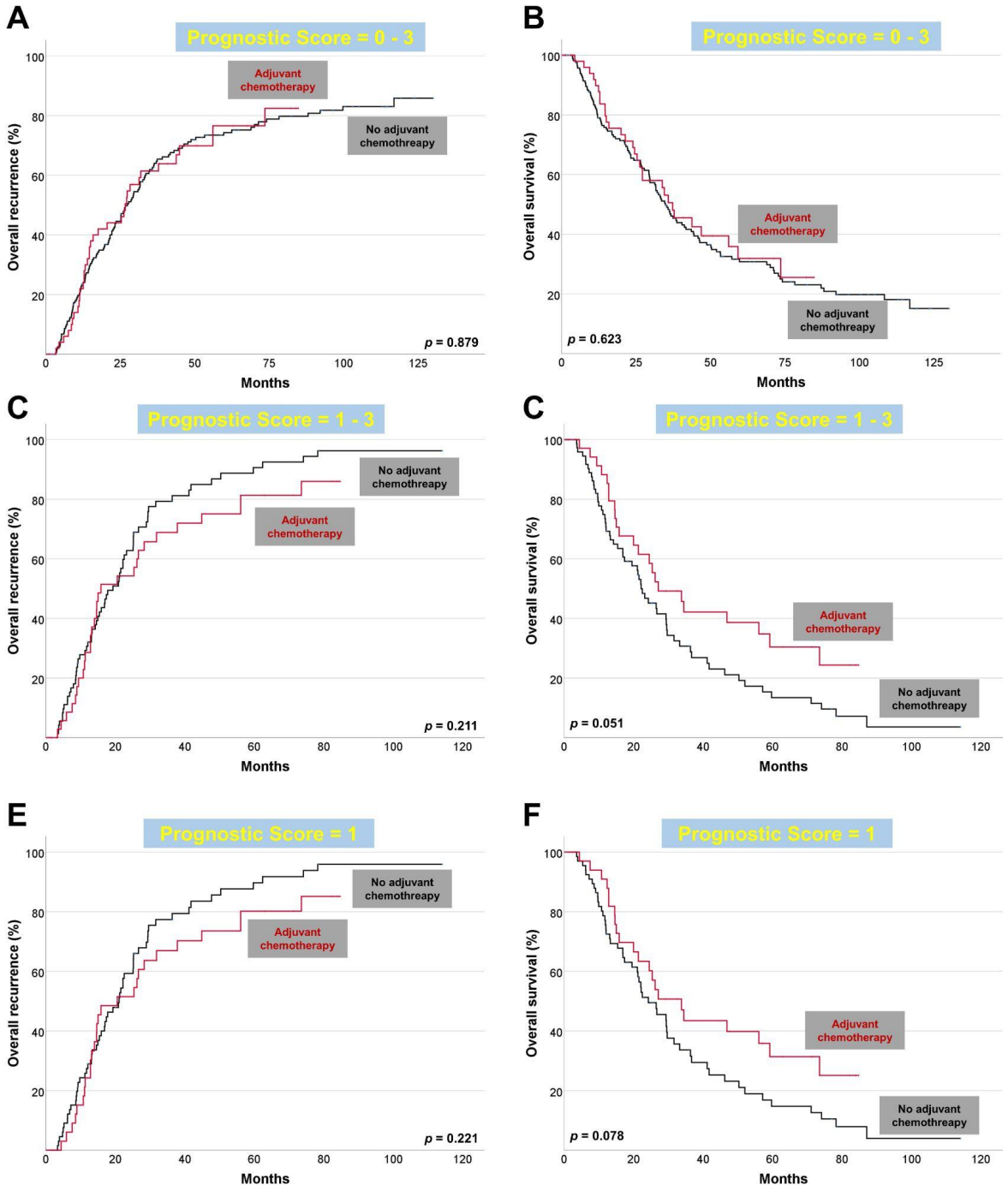
Prog-nostic score	Overall survival (months, 95 % CI)	*P* value	1-year OS	*P* value	3-year OS	*P* value	5-year OS	*P* value
0	72.8 (22.0 - 123.5)		87%		65%		45%	
1 or 2	26.2 (20.1 - 32.3)	**<0.001**	80%	**0.003**	32%	**<0.001**	16%	**0.001**
3	9.4 (7.4 - 11.4)		38%		0%		0%	

OS = overall survival

6.9. Benefit of adjuvant chemotherapy according to prognostic score

In a next step, it should be assessed whether there is a difference in long-term survival of patients with different prognostic scores depending on the fact whether they have received aCTx or not. Adjuvant chemotherapy (aCTx+) compared to no adjuvant chemotherapy (aCTx-) per se was not associated with improved survival when all patients irrespective of their prognostic score were included in the analysis. Median DFS and OS for aCTx- were 25.2 months (19.6 - 30.8) and 33.5 months (27.1 - 40.0), respectively vs. 26.2 months (12.8 - 39.7) and 43.8 months (18.8 - 68.7) for aCTx+, respectively (p = 0.623 and 0.988, Figure 15 A and B). Although short of statistical significance, there was a trend towards improved overall survival in patients with scores ranging between 1 and 3 if they had received adjuvant chemotherapy (22.2 months [17.2 - 27.2] for aCTx- vs. 27.1 months [15.4 - 38.9] for aCTx+, p = 0.051, Figure 15 D). DFS showed a similar trend (Figure 15C). Figure 15E and F depicts DFS and OS in patients with a score of 1. Further subgroup analyses were not performed due to a low case number in the respective groups.

Figure 15 - Kaplan Meier curve showing disease-free survival (DFS) and overall survival (OS) for patients with different prognostic scores depending on their adjuvant chemotherapy status A) DFS and B) OS in all patients. C) DFS and D) OS in patients with prognostic scores between 1 and 3. E) DFS and F) OS in patients with prognostic scores of 1

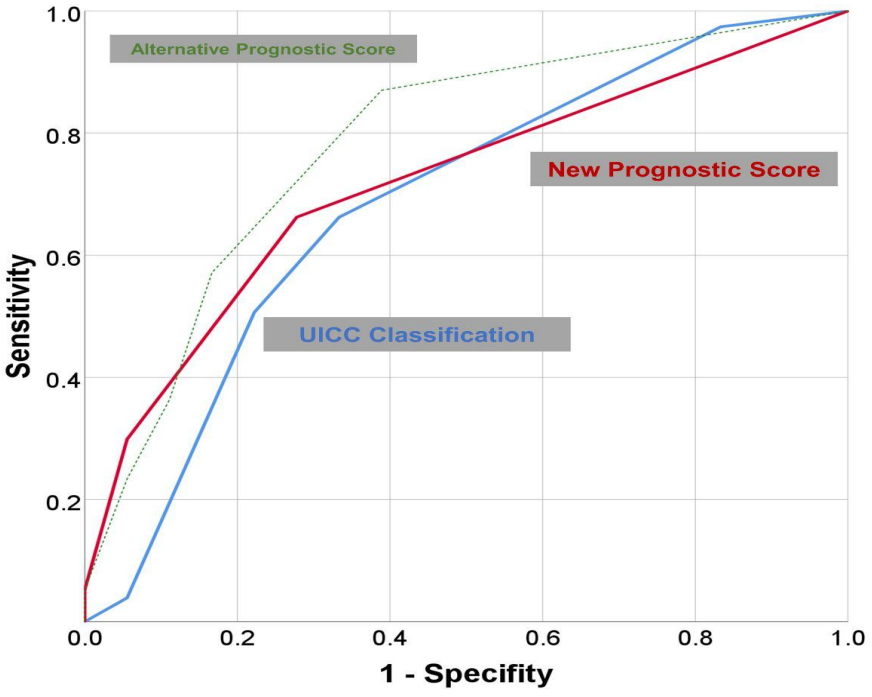


6.10. Test validation and accuracy of the REMAHEP prognostic score

The receiver operating characteristic (ROC) curve analysis showed an area under the curve (AUC) for the prognostic score of 0.729 which relates to a fair test accuracy. In comparison, the UICC scoring system had an AUC of 0.698 (poor to fair accuracy, Figure 16).

For aforementioned reasons, CA19-9 was not included in the calculation of the scoring system (too many missing numbers). When including all variables that were associated with 5-year DFS in the univariate cox regression analysis in the calculation of the score (R, V, N, T > 2b, CA 19-9 > 100 kU/l), a prognostic score could be calculated for 123 patients (53%). However, the so created score ranging from 0 to 6 had an even greater AUC (0.782, fair to good accuracy, Figure 16). Nonetheless, this score was not used in the present study due to the high proportion of missing values.

Figure 16 - Receiver operating characteristic (ROC) curve analysis of the Union for International Cancer Control (UICC, blue line) stage and the new REMAHEP prognostic score (red line) showing a greater area under the curve (AUC). The green line depicts an alternative prognostic model that was not used in the present study due to a high number of missing variables



7. Discussion

Current staging and classification systems such as the Bismuth and UICC classification are helpful tools when it comes to classifying the stage of the disease and determining therapeutic strategies. However, they have limited accuracy when it comes to predicting overall and disease-free survival of patients with pCCA after surgical resection. The present retrospective study sought to characterise and describe a single-centre cohort of patients who underwent major hepatectomy with resection of the extrahepatic bile ducts for pCCA in curative intent. Based on that, a uni- and multivariate regression analysis was performed evaluating factors of prognostic significance. We identified the three histopathological variables R, N and V status, respectively, as independently associated with disease-free survival. In a second step, the REMAHEP prognostic score was created assigning each of the three factors one point, if the variable was positive. The total score was created by summing up the three points, thus, a total score ranging from 0 to 3 was calculated.

The Bismuth classification was not found to be associated with survival. We further found that the newly created REMAHEP prognostic score showed a very strong association with both DFS and OS. The comparison with the UICC classification showed an improved correlation of the respective score and both DFS and OS.

The present study further revealed that aCTx did not significantly impact overall and disease-free survival. However, there appeared to be a trend towards improved survival when excluding patients who had a score of 0. The differences were, however, short of statistical significance.

7.1 Comparison of overall and disease-free survival with other studies

The findings of the present study with regards to long-term survival are in line with previous reports underlining the aggressive tumour biology of pCCA. Median DFS was 26.6 months (5-year DFS 21%) and mOS was 35.3 months (5-year OS 25%). Earlier studies found median OS and DFS between 26-35 [6,79,81,85–90] 17-18 months [79,85,88,91,92]. It is noteworthy that the results presented in the present study are survival data excluding 90-day mortality, which is likely to explain the slightly better results regarding OS and DFS when compared to other studies.

When comparing mere survival data, it has to be taken into account that there appear to be patient-specific differences between eastern and western centres such as BMI, age and ASA score which lead to differences in postoperative morbidity and mortality and long-term survival. In general, these differences in postoperative mortality may be attributed to a higher proportion of multimorbid patients in western centres [81,92]. Another problem when reporting and comparing DFS and OS data emerges when considering that there are differences with regards to follow-up ranging from around 20 months to 70 months [90,92,93]. This may in part be attributed to the fact that the data is available in large accessible cancer registries in some countries [94].

Another factor that limits the comparability of these findings is the fact that patient characteristics and operative strategies differ between different centres. For example, there are key differences in Bismuth stages. The predominant Bismuth stage in the present cohort was Bismuth IV accounting for 42% of all tumours whereas there are only 9% of Bismuth IV tumours in the largest dutch HBP centre. Similarly, UICC stage tends to be higher in Berlin than compared with other centres [95]. This has led to the implementation of adjusted surgical approaches such as routine portal vein resection and hilar en bloc resection [64]. Despite the fact that the benefits of these techniques remain debatable [64,96], it can be assumed that both differences in patient characteristics and operative strategies lead to different oncological outcomes that are hard to compare given the overall low numbers of patients with pCCA. Nonetheless, the proportion of patients who had R0 resection of pCCA in the present study (70%) is comparable with the outcomes of previous reports which ranges from 63 to 76 percent and appears to be independent of the resection side [93,97,98].

Another factor that impacts on overall survival is the application of aCTx. Capecitabine has been routinely applied at Charité since 2017 as adjuvant treatment based on biliary tract cancer findings of the BILCAP trial [72]. However, in most reports, no exact information on adjuvant therapy are available [59,74,93]. Most studies reporting on oncological outcomes of resected pCCA patients include patient cases spanning over more than a decade, due to the rarity of the disease [90,93]. Nagino et al. for example found a time-dependent effect of the decade in which patients were operated on overall survival with a statistically significant trend towards

better overall survival if the patient has been operated on in more recent years [93]. This time-dependent effect may have several reasons including a change of adjuvant therapy which is suggested to modify the oncological outcome at least for some subsets of patients [59]. In addition, improvements of perioperative management leading to decreased blood loss and shorter operative times may play a role in this regard [93].

7.2 Comparison of independent prognostic factors after resection of pCCA

Multiple reports have been published on the outcome after surgical resection of pCCA including multivariate analyses that have been performed to find factors of prognostic significance. Most reports agree that a higher grading (G2 and G3), N+, V1, R1, Pn1 as well as higher T stages (T3/4) are independent factors that are associated with a poor prognosis as well as higher CA19-9 levels [6,56,74,75,88,93,99].

Furthermore, a recently published meta-analysis from 2021 found that, in addition to the aforementioned factors, preoperative bilirubin levels, major vascular involvement, and L1 status were independently associated with worse overall survival [89]. Additionally, aCTx was found to improve overall survival.

In order to calculate the prognostic scoring system, a multivariate analysis was performed to find variables independently linked to DFS rather than OS. This analysis revealed that only R-, N- and V-status were of independent prognostic significance in terms of DFS.

Nonetheless, these established prognostic factors do not appear to be valid for all subsets of patients, including aCTx. In a previous study from the Department of Surgery, Charité University Medicine, it was found that R0 status and V0 status were independently associated with better long-term survival when analysing all patients who underwent MH in curative intent [59]. In lymph node negative patients (N0), only R0 status was independently associated with longer overall survival. Interestingly, the most important factor with prognostic significance in patients who had lymph node metastases (N+) was aCTx [59]. This supports the findings from the present study

where we could show that patients who have risk factors for tumour-recurrence (scores 1 - 3) may actually benefit from aCTx.

7.3 Comparison of different prognostic scoring systems after curatively intendend resection of pCCA

When establishing a staging or prognostic scoring system, several assumptions must be made on the requirements of the staging system: a) it should be able to describe the prognosis and natural history of the malignancy, b) it should be of use for clinicians to guide therapy, c) it should enable researchers to compare oncological outcomes between different facilities [100].

DeOliveira and colleagues proposed a new staging system for patients with pCCA that includes - besides established factors from the TNM classification - additional information on tumour infiltrated bile ducts, portal vein, hepatic artery as well as the histological tumour form (e.g. sclerosing or mass-forming), as well as data on the future liver remnant. However, this proposed staging system does not provide the prediction of tumour-recurrence or long-term survival [100].

The Bismuth-Corlette classification for pCCA was established as a tool to assess aspects of local tumour growth and surgical anatomy [101]. It does, however, not include histopathological and other factors of oncological importance (e.g. lymph node involvement, tumour size or distant metastases) and does therefore not correlate with DFS and OS as demonstrated in the present study. Similarly, the Blumgart T-stage system has been established to assess resectability but does not provide information on long-term survival [2].

Most commonly, the AJCC or UICC staging system is used to determine the risk of recurrence and to calculate long-term prognosis of patients after MH for pCCA. In the present study, the 7th edition was used. The AJCC/UICC staging system is being updated every couple of years in order to further improve its accuracy [9]. Substantial changes from the 6th to the 7th edition for example included the differentiation between pCCA and dCCA [102,103]. The 8th edition was published in 2017. In this

version, some modifications were made with regards to T-, N- and stage category [104,105].

Some authors have examined the accuracy of several editions of the AJCC staging system. Hau et al. compared the 7th and the 8th edition and found no significant differences in terms of long-term prognosis with an AUC of 0.61 (7th edition) and 0.69 (8th edition) [106]. The evidence from this study is limited due to the small sample size (n=91). This trend was confirmed by another study, which found a slightly improved discriminatory ability of the 8th edition when compared to the 7th edition. Nonetheless, the authors found no stage-specific reduction in 5-year survival rates independent of the AJCC version that was used (7th edition - 5-year survival rates of 71%, 34% and 34% in stages I, II and IVa with no actual 5-year survivors in the stages IIIa, IIIb and IVb; 8th edition - 5-year survival rates of 71%, 35%, 23%, 19%, 22% in stages I, II, IIIa, IIIb and IIIc with no 5-year survivors in stages IVa and IVb) [107]. These observations were also made in the present study, where we found a bad discrimination of 5-year DFS and OS rates especially in advanced stages. This is in line with the ROC curve analyses and comparisons between the UICC staging system and the scoring system that is presented here.

In 1999, Fong and colleagues proposed a new way of establishing a prognostic scoring system for patients with colorectal liver metastases [4]. The PERCHORE score established in the present study has been calculated accordingly. There are two other pCCA-specific prognosis scores that can be calculated. Saiko et al. presented a preoperative prognosis score that includes preoperative CRP and CEA levels as well as platelet-lymphocyte ratio levels allowing the authors to calculate a score between 0 and 4 [82]. They found significant differences with regards to OS and DFS between scores 0 and 1 as well as between 3 and 4. Patients with scores of 1 and 2 had similar OS and DFS. Although the authors used different prognostic factors to calculate their scoring system, there are some parallels between their report and the present study. We also found similar OS and DFS curves for patients who have 1 and 2 risk factors, the scores were therefore combined to 1 score. More than 2 risk factors, however, appear to significantly worsen the long-term prognosis. Of note, Saiko et al. also found no mentionable correlation of OS and UICC stage.

There are some limitations in the study presented by Saiko et al. Firstly, the score is calculated based on only 121 patients. Secondly, they also included patients after extrahepatic bile duct resection as well which is nowadays considered a palliative treatment option [108]. Thirdly, their analysis does not provide a ROC curve analysis which may mainly be attributed to the low number of patients. The scoring system of Saiko et al. could not be tested with the database of the present study since most of the preoperative laboratory values were not available. Furthermore, preoperative routine tumour marker determination in Berlin includes CA19-9 rather than CEA.

A second scoring system was proposed by Peng and colleagues who analysed data of 244 patients with Bismuth IV pCCA [75]. In their analysis, the authors defined 21 months as a cutoff for early recurrence. Subsequently, they performed a uni- and multivariate analysis to determine factors that were independently associated with early recurrence. They found CA19-9 (U/mL) <200, R0 resection, N0 stage (vs. N1 or N2) as well as L0 stage to be associated with a lower change of early recurrence. There is no data on the accuracy of their scoring system, a ROC curve analysis was not performed. Interestingly, the authors could also demonstrate that patients with higher scores benefit more from aCTx in terms of early recurrence as opposed to patients who have lower risk scores. Furthermore, they found CA19-9 levels to be of prognostic significance and therefore included it in the calculation of the prognostic score. Although this is in line with the findings of the present study CA19-9 was not used to calculate the prognostic score due to the high proportion of missing values.

7.4 Implications on adjuvant chemotherapy

For many years, there was no evidence on the impact of aCTx after major hepatectomy for pCCA. Chemotherapy was administered based on individual decision-making [109]. This is underlined by the findings of the present study, where only 24% of patients received chemotherapy which usually consisted of either gemcitabine or fluorouracil (5-FU), alone or in combination. Another factor that may have led to the low rate of aCTx is the high proportion of patients suffering from major complications after pCCA surgery. This is a common phenomenon in patients who

underwent hepatobiliary and pancreatic surgery due to high morbidity rates [110,111]. The aCTx should be initiated within 12 weeks after surgery [72].

As stated above, the results of the BILCAP study changed the paradigm in adjuvant therapy of pCCA [72]. From 2017 on, all patients were recommended to receive aCTx. Nonetheless, the basis of curative treatment of pCCA remains radical surgical resection [64,93]. However, the treatment paradigm is currently changing towards a more tailored approach of patients with resectable pCCA. For instance, patients who have lymph node metastases may benefit from less aggressive surgical therapies since in these patients, aCTx appears to be one of the most important factors prolonging OS and DFS. In these patients it may be advisable to perform parenchyma-sparing liver resections that are associated with lower postoperative morbidity, rather than performing extended hepatectomy procedures that may cause a delay of aCTx [59,75].

These findings are supported by the results of the present study. We found that patients with a prognostic score of 0 (i.e. no risk factors for early recurrence) do not have a statistically significant survival benefit from aCTx, whereas this effect is observed in patients with scores > 0.

These insights may raise concerns if major hepatectomy is justified at all in patients with evidence of advanced (e.g. N+) disease preoperatively since the most important factor is aCTx. However, based on this data, radical surgical resection should be recommended to each patient with resectable pCCA who is fit for surgery. Even in the higher risk groups with scores of 1 or 2, long-term survival is possible with a mOS of 26 months. In contrast, patients receiving palliative chemotherapy alone for locally advanced or metastatic cholangiocarcinoma have a mOS of 11 months [112]. This means that the majority of patients with resectable pCCA has a significant survival benefit when compared to palliative chemotherapy, even if risk factors for recurrence are present. Only patients who have a score of 3 appear to have a mOS (9.4 months) that is comparable to patients receiving palliative chemotherapy.

7.5 Limitations and Strengths

The present study has several limitations. Firstly, despite being calculated based on a rather large sample of 232 patients with pCCA, the generalisability is limited since we were not able to test the score on another cohort of pCCA patients. Thus, the accuracy may not be as superior as is suggested in the present study. This is why there is a strong need for confirmatory studies in the future.

Secondly, some patients had to be excluded due to missing variables (such as V or R status) which further decreases the accuracy of the suggested prognostic scoring system. In particular, the variable Ca19-9 is of major importance when analysing prognostic factors of curatively resected pCCA patients [59]. Since it was missing in 38% of patients, we decided not to include it in the multivariate analysis. The alternative scoring system including Ca19-9, however, showed even improved accuracy in the ROC curve analysis. Therefore, it will be mandatory to take this important variable into account when analysing the data of larger cohorts. Peng and colleagues for example have integrated this variable in their scoring system underlining its importance in this matter [75].

Thirdly, follow-up data are inconsistent with some patients lost to follow-up directly after being discharged from the hospital. This is due to the lack of large centralised databases where follow-up data are collected. Most patients leave the city of the primary care centre immediately postoperatively, follow-up is carried out near their home towns.
This leads to a fourth shortcoming which is the lack of sufficient data on the type, duration and dosing of adjuvant chemotherapy. Furthermore, information on early termination of chemotherapy due to toxicity is missing. All these factors may significantly impact recurrence and overall survival.

Nonetheless, this study has some strengths, including the fact that the scoring system is based on a multivariate analysis with highly significant prognostic factors. Although the overall number of patients is limited, a good AUC was found in the ROC curve analysis implying there already is a good accuracy of the suggested scoring system in the current setting. Also, one has to consider that pCCA is a rare disease

and this cohort study represents a rather large cohort of curatively resected pCCA patients.

Moreover, the analysed database includes a large number of clinically relevant variables indicating that the present multivariate analysis is very likely to display clinically meaningful parameters, relevant for long-term disease-free survival.
As stated above, pCCA is a malignancy with an aggressive tumour biology. Its rarity, however, is why it is still poorly understood, making it necessary to intensify research on this topic. Thus, understanding factors of prognostic significance of this rare disease is important to both clinicians and patients in order to know the risk of recurrence and to plan adjuvant treatments and follow-up.

7.6 Outlook and clinical applicability

The prognosis score presented here has already shown promising results in a sufficiently large cohort with regard to risk stratification of pCCA patients after surgical resection. The testing and validation in a large patient cohort is still pending and should be done as suggested above, possibly with modification of the score (e.g. with inclusion of CA 19-9). This could be achieved by evaluating it in retrospective multicentre studies in the future. Ideally, a prospective survey shoud be performed, although this being difficult to implement due to low incidence of the disease.
Clinical applicability envisions a score which can be given to each patient upon discharge from the hospital, illustrating how to assess the patient's risk of recurrence.
The present study also provides evidence that patients with unfavourable prognostic factors might benefit from aCTx in particular (scores 1-3). The data could be the basis for further studies, e.g., to apply more aggressive chemotherapy regimens to patients with higher prognostic scores. This development representing a further step towards more individualised medicine. Based on the given results, adjuvant therapy can be adapted, e.g. by extending the treatment interval or intensifying the chemotherapy regimen.
In principle, the establishment of modes of analyses and scores for pCCA is important, since pPCCA has been sparsely studied and is often discussed together

with iCC and gallbladder carcinoma in various guidelines [113,114]). This greatly contradicts the idea of individualised medicine.

7.8 Summary

The present study sought to identify factors of prognostic significance after major hepatectomy at the Department of Surgery, Charité University, for pCCA. Using these factors, a new prognostic scoring system should be established.

Median follow-up of the whole cohort was 30 (1 - 136) months. Median DFS was 26.6 (22.8 - 30.4) months. The 1- 3- and 5 year DFS rates were 77%, 35% and 21%, respectively. Median OS was found to be 35.3 (31.1 - 39.6) months. The 1- 3- and 5 year disease-free survival rates were 83%, 55% and 25%, respectively.

The following factors had a negative impact on disease-free survival in the multivariate analysis: no tumour-free resection margins (R1 status), lymph node metastases (N+ status), and microvascular invasion (V1 status). In case the variable was positive, one value point was given. All value points were summed up to calculate the prognostic score which resulted in a minimum score of 0 and a maximum score of 3.

The score was strongly correlated to both DFS and OS (both $p<0.001$). The ROC curve analysis showed a better accuracy when compared to conventional scoring systems (UICC score, AUC 0.728 vs. 0.698). As opposed to the new prognostic scoring system, the UICC classification system failed (especially in the long-term, i.e. at three and five years after surgical resection) to accurately display differences in DFS and OS according to the UICC stage. In addition, there is evidence that patients who have 1 or more risk factors (Prognostic Score > 0) may benefit significantly more from receiving adjuvant chemotherapy than patients who have no risk factors (Prognostic Score = 0). In the background of the current literature, these findings are of importance since they may contribute to a more individualised therapeutic approach in pCCA patients. This becomes evident when considering the fact that pCCA is often underrepresented in guidelines and summarised with other entities such as gallbladder carcinoma and iCCA.

The data and the scoring system presented in this study needs to be tested on larger, multicentre cohorts in order to validate its accuracy. When doing this, CA19-9 should be tested as part of the scoring system since the present study showed evidence that it may further improve the accuracy of the proposed scoring system.

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Eidesstattliche Versicherung

„Ich, Thea-Charlotte Fritsch, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: [Erstellung eines Prognosescores nach erweiterter Leberresektion bei Patienten mit perihilären Cholangiokarzinomen, Establishment of a prognosis score after major hepatectomy in patients with perihilar cholangiocarcinoma] selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Ort, Datum	Unterschrift

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Danksagung

An dieser Stelle möchte ich all den Menschen meinen Dank aussprechen, die an der Umsetzung dieser Dissertation beteiligt waren.

Zunächst muss ich mich herzlich bei dem Leiter der Chirurgischen Klinik (Campus Charité-Mitte und Campus Virchow Klinikum) Charité Universitätsmedizin Berlin Herrn Prof. Dr. med. Johann Pratschke und bei dem Fachbereichsleiter Pankreas Herrn Prof. Dr. med. Moritz Schmelzle bedanken, für die Bewilligung dieser Arbeit, sowie der Bereitstellung aller erforderlichen Datensätze.

Ganz besonderer Dank gilt meinem Doktorvater Herrn Priv.-Doz. Dr. med. Felix Krenzien für die Ermöglichung dieser Dissertation und Seiner Geduld in der Einreichungsphase.

Die Umsetzung wäre zweifelsohne nicht möglich gewesen ohne die außerordentliche Unterstützung meines Zweitbetreuers Herrn Priv.-Doz. Dr. med. Christian Benzing, dem ich zu großem Dank verpflichtet bin.

Ich möchte mich außerdem bei meiner Freundin und Mitdoktorandin Frau Dr. med. Filiz Atik bedanken, für viele gemeinsame Stunden am Schreibtisch, Unterstützung und Rat.

Bescheinigung des akkreditierten Statistikers

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Bescheinigung

Hiermit bescheinige ich, dass *Thea-Charlotte Fritsch* innerhalb der Service Unit Biometrie des Instituts für Biometrie und klinische Epidemiologie (iBikE) bei mir eine statistische Beratung zu einem Promotionsvorhaben wahrgenommen hat. Folgende Beratungstermine wurden wahrgenommen:

- Termin 1: 15.09.2022

Folgende wesentliche Ratschläge hinsichtlich einer sinnvollen Auswertung und Interpretation der Daten wurden während der Beratung erteilt:

- Die Problematik Variablenselektion auf Basis von signifikanten Effekten in einer Reihe univariater Regressionen erläutert
- Overfitting und die damit verbundene Problematik erklärt
- Hinweise bezüglich der Darstellung der Ergebnisse

Diese Bescheinigung garantiert nicht die richtige Umsetzung der in der Beratung gemachten Vorschläge, die korrekte Durchführung der empfohlenen statistischen Verfahren und die richtige Darstellung und Interpretation der Ergebnisse. Die Verantwortung hierfür obliegt allein dem Promovierenden. Das Institut für Biometrie und klinische Epidemiologie übernimmt hierfür keine Haftung.

Datum: 31.10.2022

[redacted]

Unterschrift BeraterIn, Institutsstempel

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