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DISSERTATION

A tailored approach in lymph node positive perihilar cholangiocarcinoma

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Vorwort

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Abbreviations

AJCC *American Joint Committee on Cancer*

ALT *Alanine transferase*

AST *Aspartate transferase*

CA19-9 *Carbohydrate antigen 19-9*

CCA *Cholangiocarcinoma*

CD *Clavien-Dindo classification of surgical complications*

CEA *Carcinoembryonic antigen*

CT *Computed tomography*

DFS *Disease free survival*

ERCP *Endoscopic retrograde cholangiopancreatography*

FDG *Glucose analog fluorodeoxyglucose*

FFP *Fresh frozen plasma*

GGT *Gamma-glutamyl transferase*

HCC *Hepatocellular carcinoma*

ICU stay *Retention time at the intensive care unit*

MH *Major hepatectomy*

mOS *Mean overall survival*

MRC *Contrast-enhanced MR cholangiography*

MRI *Magnetic resonance imaging*

OS *Overall survival*

PET *Positron emission tomography*

PHC Perihilar cholangiocarcinoma

PSC *Primary sclerosing cholangitis*

PTC *Percutaneous cholangiography*

RBC concentrate *Red blood cell concentrate*

0 Abstrakt

0.1 Einleitung

Die chirurgische Resektion oder Lebertransplantation stellen immer noch die einzige kurative Behandlungsmöglichkeit des Perihilären Cholangiokarzinoms (PHC) dar, die Langzeitüberleben ermöglichen. Das PHC befindet sich an der Bifurkation des Ductus choledochus in unmittelbarer Nähe der Portalvene und Aa. hepaticae, sodass in der Regel eine erweiterte Leberresektion erforderlich ist, um einen freien Resektionsrand zu erhalten. Wann immer es technisch möglich ist, gilt die erweiterte Rechtsresektion der erweiterten Linksresektion gegenüber aus anatomischen Gründen als überlegen, um einen Tumor-freien Resektionsrand zu erhalten. Patienten mit Lymphknotenmetastasen (N+) haben ein hohes Risiko für ein Tumor-Rezidiv, auch nach einer radikalen Resektion. Daher bleibt unklar, ob die gegenwärtige radikale Operationsstrategie der erweiterten Rechtsresektion die hohe Morbidität und Mortalität dieses Ansatzes bei N+ Patienten überwiegt.

0.2 Patienten und Methodik

Zwischen 2005 und 2015 erhielten 231 Patienten mit neu diagnostiziertem PHC eine kurativ intendierte Major Hepatektomie (MH) in der Abteilung für Viszeralchirurgie am Universitätsklinikum Charité Campus Virchow und Campus Mitte. In dieser retrospektiven Kohortenstudie wurden alle Daten aus Krankenakten erhoben und das Langzeitüberleben mit Hilfe der Kaplan Meier Methode ausgewertet.

0.3 Ergebnisse

Die 231 Patienten, die in dieser Studie eingeschlossen wurden, unterzogen sich einer MH für PHC mit 1,-3-, und 5-Jahres Gesamtüberlebensrate (OS) und Rezidiv-freien Überlebensraten (DFS) von jeweils 72%, 48%, 36% und 60%, 22%, 12%. Dabei waren innerhalb der gesamten Kohorte das OS und das DFS bei Patienten mit Tumor-freiem Resektionsrand (R0) signifikant besser, verglichen mit dem der Patienten mit befallenem Resektionsrand (R1). Von Bedeutung war, dass sich in der N+ Patientenuntergruppe (n = 109, 47%) das Gesamtüberleben und das Rezidiv-freie Überleben hinsichtlich eines R0 oder R1 Resektionsrandes nicht unterschied (beide $p > 0,05$). Die erweiterte Linksresektion war mit einem besseren OS und DFS

assoziiert, verglichen mit der erweiterten Rechtsresektion (p = 0,008 und p = 0,003) innerhalb dieser N+ Untergruppe. Darüber hinaus war es bei Patienten, die einer erweiterten Linksresektion unterzogen wurden wahrscheinlicher, dass sie eine adjuvante Chemotherapie erhielten (p = 0,022). Dies ist von großer Bedeutung, da die adjuvante Chemotherapie, neben der histologischen Graduierung (p = 0,041), der einzige unabhängige prognostische Faktor für N+ Patienten (p = 0,002) war.

0.4 Schlussfolgerung

Patienten mit PHC und positivem Lymphknotenstatus profitieren möglicherweise mehr von weniger aggressiven Operationsmethoden, da diese mit einer geringeren Morbidität einhergehen und damit die Chance eines besseren Überlebens durch adjuvante Chemotherapie ermöglicht. Präoperative Lymphknoten-Diagnostik könnte dazu beitragen, diejenigen Patienten zu identifizieren, die tatsächlich von einer radikalen Herangehensweise profitieren.

1 Abstract

1.1 Introduction

Surgical resection or liver transplantation remain the only curative treatments that can offer long-term survival for perihilar cholangiocarcinoma (PHC). PHC involves the confluence of the bilateral hepatic ducts where the main portal and hepatic arterial branches are near one another, thereby requiring an extended hepatectomy for achieving a negative resection margin (R0). Whenever feasible, extended right hepatectomy is believed to be superior to extended left hepatectomy to obtain R0 status, for anatomical reasons. However, right hepatectomy is associated with significantly higher postoperative morbidity and mortality. Patients with lymph node metastases (N+) are at high risk for tumor recurrence, even after radical surgical resection. Therefore, it remains unclear whether the current surgical principles of extended right hepatectomy outweigh the high morbidity and mortality of this approach in N+ patients.

1.2 Patients and methods

Between 2005 and 2015, 231 patients with a newly PHC received a curative intended major hepatectomy (MH) at the department of visceral surgery at Charité – Universitätsmedizin Berlin, Campus Virchow or Campus Mitte. In this retrospective cohort study, all data were collected from medical records, and long-term survival was analyzed using the Kaplan-Meier method.

1.3 Results

The 231 patients included in this study underwent MH for PHC with 1-, 3-, and 5-year overall survival (OS) rates and disease-free survival (DFS) rates of 72%, 48%, 36% and 60%, 22%, 12%, respectively. Within the whole cohort, patients with R0 status had significantly better OS and DFS compared to patients with a positive resection margin (R1; both $p < 0.05$). Of note, within the N+ subgroup (n = 109, 47%), the OS and DFS did not differ between R0 and R1 resections (both $p > 0.05$). Extended left hepatectomy was associated with improved OS and DFS when compared to extended right hepatectomy ($p = 0.008$ and $p = 0.003$) within this N+ subgroup. Furthermore, patients undergoing extended left hepatectomy were more likely to

receive adjuvant chemotherapy (p = 0.022). This is of great importance as adjuvant chemotherapy, in addition to histopathological grading (p = 0.041), was the only independent prognostic factor for N+ patients (p = 0.002).

1.4 Conclusions

Patients with PHC and N+ status might benefit more from locally less aggressive operation concepts, as this involves a lower morbidity and therefore offers the chance to improve the survival rate through adjuvant chemotherapy. Preoperative lymph node sampling might help to identify patients who actually benefit from radical surgery approaches.

2 Introduction

2.1 Synopsis and motivation

Perihilar cholangiocarcinoma (PHC) are rare malignant tumors of the bile duct system, located at the liver hilum. The life expectancy of patients with PHC is poor, ranging between 26 and 32 months (median overall survival)[1-5] after curative-intent surgery. Most patients, however, are ineligible fur curative-intent resection due to metastatic or locally advanced disease and therefore die within a few months. Only about one third of the patients with PHC are eligible for resection at the time of diagnosis [6,7]. The only option for curative treatment consists of the surgical resection of the tumor, or the rarely conducted liver transplantation [8,9]. Through improved operation techniques and optimized perioperative management, the life expectancy has increased within the last few years – however the survival rates of patients, even after curative-intent resection, are still not satisfactory [10,11]. In order to increase survival rates, many high-volume centers have established more radical operation methods, encompassing extended liver resection including segment 1, regional lymphadenectomy and conditional portal venous resection, translating into favorable long-term survival [10,12]. At Charité – Universitätsmedizin Berlin, major hepatectomy is considered the “gold standard” for treatment of PHC. Surgical strategies for extensive approaches include the so-called *hilar en-bloc resection*[13] and the extended right hepatectomy [14], resulting in improved overall survival. However, the morbidity and mortality of these extensive approaches exceed that of other hepatobiliary and pancreatic operations [13,15,16]. When comparing the factor *hilar en bloc resection* to standard major hepatectomy, the postoperative mortality is slightly elevated in experienced centers (30- and 90-day mortalities were 8.8% and 12.4% after hilar en bloc resection, and 7.7% and 11.2% after standard major hepatectomy) [13]. The postoperative mortality of extended hepatectomy ranged been 7% and 16% over the last years [15,17-19]. Also, the postoperative morbidity and mortality of the more extensive right-sided hepatectomies exceed left-sided hepatectomies [20]. Consequently, patients who do not benefit from extensive surgery in terms of long-term survival must be identified,.

A strong parameter associated with a significantly poorer prognosis after an operation, and often present in patients with perihilar cholangiocarcinoma, is the

presence of lymphatic metastases, wherein additionally the number of examined lymph nodes seems to have a significant prognostic value [21-24]. Therefore, identification of lymph node metastases is obligatory before liver transplantation, and lymph node metastases are regarded as a contraindication for operation (e.g., pro-duct002 trial, DRKS00013276). In contrast, the lymph node status does not change the surgical strategy in liver resection [25,26].

So far, there has been lack of information in the literature about whether PHC N+ patients also benefit from more extensive resections such as extended right hepatectomy and hilar en bloc resections or from less radical surgical approaches, in particular left-sided hepatectomies.

2.2 Definition and epidemiology

Cholangiocarcinoma are very rare tumors that account for approximately 2% of all malign tumors. They are, however, the second most common hepatobiliary malignancy after hepatocellular carcinoma (HCC) [27]. In Germany, around 5,000 people a year are diagnosed with bile duct or gallbladder tumors [28]. The incidence of cholangiocarcinoma (CCA) varies widely in different geographic regions, however, with the highest incidence in Southeast Asia and the lowest in Australia [29]. CCA can be distinguished into intra- and extrahepatic variants. They emerge through a malign transformation of the epithelium and can occur anywhere along the biliary tract from the ampulla of Vater to the intrahepatic biliary radicals, but the hepatic duct bifurcation is the most frequently involved site [30,31]. It is mostly diagnosed in late tumor stages after the age of 40 years, as the cholangiocarcinoma – except in patients with primary sclerosing cholangitis – is usually clinically silent until the tumor obstructs the bile duct [29]. Furthermore, the aggressive growth pattern of PHC, leading to early local spreading, is responsible for diagnosis in late tumor stages [32].

Carcinoma of the hepatic duct bifurcation were first described by *Altemeir* in 1957 as a separate entity and the first cases were reported by *Klatskin* in 1965. Subsequently, cholangiocarcinoma at this location now carry the eponym of *Klatskin* tumors [31].

They represent 60-70% of all CCA, whereas intrahepatic tumors account for 5-10% and distal extrahepatic tumors account for 20-30% [33]. Intrahepatic CCA are defined as those primarily situated in the liver that only marginally involve the extrahepatic

biliary tree. Perihilar tumors, on the other hand, are specified as those involving the hepatic duct bifurcation, even if there is a significant intrahepatic component. Distal CCA evolve from the distal extrahepatic, or intrapancreatic, portion of the bile duct, typically requiring pancreatoduodenectomy.

2.3 Extrahepatic bile duct anatomy

The extrahepatic bile ducts include parts of the right and left hepatic ducts outside the liver, the common hepatic duct, and the common bile duct. They can be further divided into the perihilar (hilum) and the distal region.

- Perihilar (hilum) region: Site where the right and left hepatic ducts exit the liver and confluence together building the common hepatic duct, which is located proximal to the origin of the cystic duct. The perihilar cholangiocarcinoma of this region are also known as Klatskin tumors.
- Distal extrahepatic region: This site includes the common bile duct and leads into the small intestine. The region also provides the origin of the term distal cholangiocarcinoma.

2.4 Etiology and risk factors

Most cases of cholangiocarcinoma occur occasionally and the exact etiology remains unclear. Several pathologic conditions, however, resulting in either acute or chronic biliary tract epithelial injury, may predispose someone to malignant change. Primary sclerosing cholangitis (PSC), an idiopathic inflammatory condition of the biliary tree, has been clearly associated with the development of cholangiocarcinoma. The lifetime risk of cholangiocellular carcinoma in patients with PSC varies from 7% to 20%, and the annual incidence rate lies between 0.6-1.5% depending upon the methods used to establish the diagnosis and the length of the follow-up period [34]. The reported prevalence of cholangiocellular carcinoma in PSC reaches up to 36% [35]. According to a European multicenter study [36], 50% of cholangiocarcinoma cases are diagnosed within one year after the diagnosis of PSC. Patients with the diagnosis of PSC should therefore be screened and monitored in the first few years after the diagnosis.

Congenital biliary cystic disease, such as choledochal cysts or Caroli's disease, has also been associated with malignant transformation. The incidence of cholangiocarcinoma in adults with biliary cysts ranges from 10% to 30% [37,38]. These conditions appear to be related to an anomalous pancreaticobiliary duct junction leading to reflux of pancreatic secretions into the bile duct and thus favoring chronic inflammation and bacterial contamination [39,40]. The endemic areas of Southeast Asia infected with liver flukes (e.g. Opishorchis viverrini, Clonorchis sinesnsis) have a key role in the pathogenesis of CCA. The infection caused by eating poorly cooked fish leads to the settling of worms in the biliary system, resulting in chronic biliary obstruction and inflammation [41,42]. In addition, several chemical agents and radionuclides [43-45], obesity [46], alcohol [47], and tobacco smoking [48] appear to be risk factors for tumor occurrence. Also, cirrhosis from any cause was found to be associated with an increased risk of cholangiocellular carcinoma [49]. In contrast, hepatitis C virus infection only appears to be associated with hepatocellular carcinoma and intrahepatic cholangiocarcinoma but not with PHC [50,51].
Additionally, patients with a history of biliary-enteric drainage procedures for a benign disease have an increased risk of developing the tumor [52].

2.5 Pathology

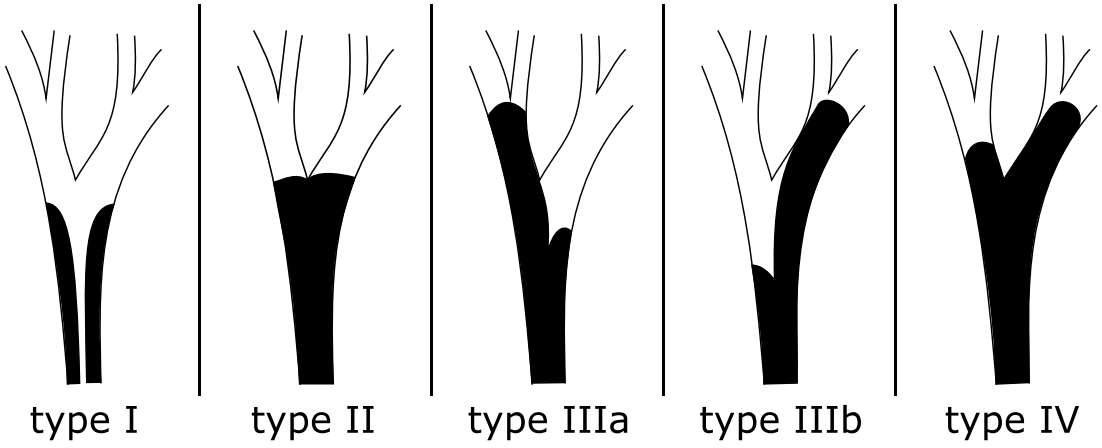
The growth patterns of hilar cholangiocarcinoma include either transmural invasion of the biliary ducts and extension into periductal tissues and adjacent structures or longitudinal extension along the bile ducts in the submucosa [45].
Based on the macroscopic appearance, three different subtypes have been categorized: sclerosing, nodular, and papillary. Among these subtypes, the sclerosing variety is the most common at the hilum, appearing as annular thickening of the duct wall with a locally invasive growth pattern, invading periductal neural tissues as well as major vascular structures of the hilum and resulting in fibrosis. The nodular form, located in the upper and mid bile duct, is characterized by irregular intraluminal nodules along the bile ducts. Tumors presenting both types are called nodular sclerosing. In the mid to distal bile duct, the papillary form is common, i.e., a friable tumor with an intraluminal growth pattern, with late transmural extension that is unlikely to invade adjacent structures leading to a favorable prognosis [53].

2.6 Classification

2.6.1 Bismuth-Corlette classification

The Bismuth-Corlette classification is the current preoperative standard to assess the local extension of hilar cholangiocarcinoma (**Figure 1**). Type I tumors are located below the confluence of the left and right hepatic ducts, whereas type II tumors reach the confluence but do not involve the right or left hepatic ducts. Type III tumors infiltrate the common hepatic duct and either the right (IIIa) or the left (IIIb) hepatic duct. Type IV tumors involve the confluence and both the right and left hepatic ducts [54]. This classification describes the anatomic location of the tumor and its extension into the bile duct system. However, it does not play any role regarding the therapeutic objective (either resection, or palliative) or the side of resection (right-or left-sided hepatectomy). Therefore, it cannot be used to evaluate the prognosis of a surgical candidate.

Figure 1: Bismuth-Corlette classification



Source: Author‘s drawing; figure created with Inkscape.org

2.6.2 AJCC staging system for perihilar bile duct cancer

The PHC is currently staged using the American Joint Committee on Cancer (AJCC) staging system, which incorporates a standardized TNM classification of the disease. In general, staging provides prognostic information and allows for comparison of survival rates between patients. In comparison with the previous AJCC 7th edition [55], in the 8th edition [56], published in 2017, the T4 tumors are downstaged from stage IVa

to IIIb because R0 resections are more achievable by undertaking caudate hepatectomy and concomitant vascular resection and reconstruction.

Apart from factors included in the AJCC 8th edition [56], several other histopathological, demographic and surgical characteristics with predictive value have been reported, but as the findings have been partially contradictory, the exact impact on the outcome after surgery is not clear. **Table 1** shows the TNM stage of perihilar bile duct carcinoma [56].

Table 1: TNM Stage of perihilar bile duct carcinoma

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 tumor cannot be assessed.
T1		Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue.
T2a		Tumor invades beyond the wall of the bile duct to surround adipose tissue.
T2b		Tumor invades adjacent hepatic parenchyma.
T3		Tumor invades unilateral branches of the portal vein or hepatic artery.
T4		Tumor 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 tumor.

2.7 Clinical symptoms and diagnosis

Diagnosing a PHC is difficult and therefore it is often detected in an advanced stage. As the tumor is located in the area of the hepatic duct bifurcation, even small tumors

can stenose or occlude the common bile duct, which leads to cholestasis in the liver and gall bladder. In most cases, painless jaundice is the most common first symptom of cholestasis, followed by pruritus, acholic stools, and darkened urine. In advanced stages, some patients present with abdominal pain mistakenly attributed to gallstone disease. Concomitant general tumor signs such as fever, night sweat, and weight loss can occur. In advanced stages, nonspecific epigastric pain is present, and consequently, after a detailed anamnesis and physical examination in which the Courvoisier-sign including painless jaundice and an extended, painless gall bladder might be detected, the diagnostic is completed by measuring laboratory parameters and non-invasive or invasive imaging methods.

The laboratory parameters are not specific but can indicate a cholestasis. Because of the occlusion of the biliary tract, the bilirubin, alkaline phosphatase, gamma-glutamyl transferase (GGT), alanine transferase (ALT) and aspartate transferase (AST) can be elevated. Serum tumor markers, more precisely carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), are used for diagnosis and follow up of hilar cholangiocarcinoma, but they can also be elevated in patients with gastric, pancreatic, or colonic carcinoma, and in non-malignant cholestatic liver disease.

Among the imaging modalities, abdominal sonography is often the first method used as it is non-invasive, cheap, and easily available. In addition to detection of cholangiocarcinoma, it helps to exclude more common etiologies for obstructive jaundice such as choledocholithiasis. In experienced hands, it can help to evaluate the extent of biliary involvement and invasion of the periductal tissues. Duplex ultrasonography can provide the first step in predicting vascular involvement. If the sonographic findings support the suspicion of malignancy within the hepatic bifurcation, the next step would be sectional imaging – specifically computed tomography (CT) and/or magnetic resonance imaging (MRI) – to evaluate the local resectability. Regarding the preoperative imaging, it is essential not only to be able to evaluate the local extent of the disease, but also to detect vascular invasion, hepatic lobar atrophy and intrahepatic or distant metastases.
CT scan accuracy for evaluating the bile duct involvement is 86%, with sensitivity and specificity for portal vein involvement of 89% and 92%, for hepatic artery of 83% and

93%, and for lymph node involvement of 61% and 88%, respectively [57]. However, contrast-enhanced MR cholangiography (MRC) shows better results in demarcating the extent of bile duct lesion.

An optimal procedure to diagnose and evaluate hilar cholangiocarcinoma should include T1- and T2-weighted abdominal MRI pulse sequences, diffusion-weighted imaging (DWI), and multiphase contrast-enhanced sequences obtained in the arterial, portal venous, and delayed phases.

As those methods are limited by the detection of small lymph node involvement and differentiation of tumor from scarring after therapy, functional imaging is being developed. In highly selected cases, Positron emission tomography (PET) using glucose analog fluorodeoxyglucose (FDG) can help to distinguish the metabolic differences between benign and malignant cells, leading to the detection of unsuspected metastases in about 30% of patients and major changes in therapy. However, in a PET imaging study from 2004, FDG-PET imaging showed a high false-negative rate for cholangiocarcinoma of the infiltrating type (mass <1cm). Furthermore, foci of inflammation due to biliary stents or acute cholangitis accumulated FDG and thus interfered with the interpretation of the FDG imaging [58].

In addition to radiological imaging tools, there are also invasive methods such as endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous cholangiography (PTC). Both of these methods allow histological material to be collected and stents to be inserted to ensure the flow of bile. Unfortunately, there is a high risk of needle tract seeding of bacteria by this method, leading to cholangitis or pancreatitis. As the transhepatic access of PTC can lead to bleeding complications, it is only implemented if ERCP has failed or is infeasible because of stenosis not amenable to endoscopic retrograde cholangiography [59].

2.8 Prognosis and prognostic factors

In recent studies, the median overall survival (OS) ranged from 26-32 months and the median disease-free survival (DFS) from 17-18 months. OS rates at 1,3, 5 and 10 years were 60-84%, 37-46%, 20-32%, and 22-24%, respectively [1-5].

The prognosis depends partially on the tumor’s anatomic location as this affects its resectability. Because it grows near to major blood vessels and the diffuse extension

within the liver, a bile duct tumor can be difficult to resect. Complete resection with negative surgical margins offers the only chance of cure for bile duct cancer, as effective conservative therapies are lacking. This is why a negative resection margin represents the most important prognostic factor for long-term overall survival [2].

According to a recent meta-analysis of 24 studies by Bird et al. [60], there are several essential tumor variables predicting overall survival not included in the AJCC classification. The prognostic factors summarized by this meta-analysis with a significant effect on OS were: T category (T3 and T4 *versus* T1 and T2, HR 1.49, 1.30-1.70), lymph node involvement (HR 1.78, 1.65-1.93), microvascular invasion (HR 1.49, 1.34-1.68), perineural invasion (HR 1.54, 1.40-1.68), tumor differentiation (HR 1.54, 1.38-1,72) and age (cut-off inconsistent between the ages of 58 and 70 years, HR 1.16). In this meta-analysis, portal vein resection (HR 1.54, 1.15-1.70) and resection margin status (HR 1.77, 1.57-1.99) showed very heterogenic but also significant effects on postoperative prognosis. However, sex, tumor size and preoperative CA 19-9 levels were not significant parameters in this comparison study. [60]

Further significant preoperative parameters from other studies were caudate lobe invasion (HR 11.75, 1.65-83.33) [2] and initial bilirubin levels >10mg/dL [61]. Regarding the treatment related factors, studies found that preoperative biliary drainage (HR 2.21, 1.14-4.27) [4], perioperative blood transfusion (HR 1.58, 1.05-2.37) [4] and adjuvant gemcitabine-based chemotherapy (HR 0.19, 0.06-0.56) [2,62] were independent prognostic factors.

2.9 Palliative therapy

As hilar cholangiocarcinoma has an aggressive tumor-biology, most perihilar cholangiocarcinoma patients present with a locally advanced unresectable status or metastasis. Moreover, the local or distant recurrence rate in patients with microscopically involved margins after R0 resection can be as high as 53% [63]. Therefore palliative treatment is necessary to increase the survival time and improve the quality of life for those patients.

2.9.1 Biliary drainage

When the biliary system is obstructed by tumor tissue, the cholestasis can lead to jaundice and facilitates bacterial infections of the biliary tracts. The bile flow must therefore be re-established by placing plastic or metal stents into the obstruction sites via endoscopic retrograde cholangiography (ERC). If access through the stomach and the duodenum is not feasible, an alternative approach through the abdominal wall can be taken. In this percutaneous transhepatic cholangiography, the bile tract is punctured by a fine needle under sonographic or radiologic control. The inserted drainage can be internalized later ("Yamakawa/Münchner drainage"), so that the bile flows into the small intestine [64].

2.9.2 Chemotherapy

Chemotherapy is the first-line therapy for patients with unresectable PHC.
Gemcitabine (GEM), cisplatin, and fluorouracil (as single agents or in combination) are recommended by the National Comprehensive Cancer Network (NCCN) for the treatment of unresectable cholangiocarcinoma. Regarding preoperative or adjuvant treatment, studies have shown no clear benefit of chemotherapy [65,66].

2.9.3 Radio frequency ablation therapy

Another palliative strategy is intraductal radio frequency ablation therapy. A probe is placed next to the tumor via ERC and then destroyed by electric heat. This therapy is normally used in combination with other multimodal treatment methods such as chemotherapy and/or drainage [64,67].

2.10 Curative therapy by liver transplantation

Liver transplantation can only be conducted in selected cases and therefore remains an exception in terms of curative therapy options [8,9]. Among highly selected patients that meet the criteria for transplantation, including those with unresectable, solitary tumors of less than 3cm in radial diameter, without evidence of lymph node metastases, and those with resectable disease in presence of primary sclerosing cholangitis (PSC), investigators from the Mayo Clinic reported a 5-year survival of 82% after transplantation [68]. The Mayo protocol has since been taken over by many transplant programs, and similarly favorable results have been demonstrated [69].

2.11 Curative therapy by surgical resection

The prognosis of hilar cholangiocarcinoma is poor. Less than half of newly diagnosed Klatskin tumors are resectable [70]. Most of the cases are treated in a palliative manner with chemotherapy, radiotherapy, photodynamic therapy and/or stents. As the response to systemic chemotherapy and/or radiation therapy regimes for the hilar cholangiocarcinoma is very limited, resection provides the only curative therapy [71].

2.11.1 Extent of surgery

As PHC often grow diffusely infiltrating along the bile ducts and often affect periductal connective tissue and liver parenchyma in an early stage, a radical surgical approach is needed to achieve negative resection margins [13,72]. By default, the operation includes a resection of the extrahepatic bile duct system in combination with a liver resection, regional lymph node sampling and hepatobiliary reconstruction.

The extent and technique of surgery depend on the tumor stage, the predominance of tumor on one side of the liver, the calculated future liver remnant, and the department in which the therapy is performed. At the Department of Surgery, Campus Charité-Mitte and Campus Virchow Klinikum, all PHC are resected by open surgery. In general liver surgery, but not within the PHC, small, superficial tumors can be removed by non-anatomical liver resection – a cave-shaped or wedge-shaped resection of the tumor which is advantageous in patients with liver cirrhosis. Segment- and bisegmentectomy are primarily conducted for tumors in the left liver area, removing one or two of the total eight liver segments; again, this procedure cannot be applied for PHC due to the earlier mentioned aggressive tumor biology. For PHC, major hepatectomy is considered the “gold standard”, alongside experimental surgical therapies such as liver transplantation (e.g., pro-duct002 trial, DRKS00013276) [8,73].

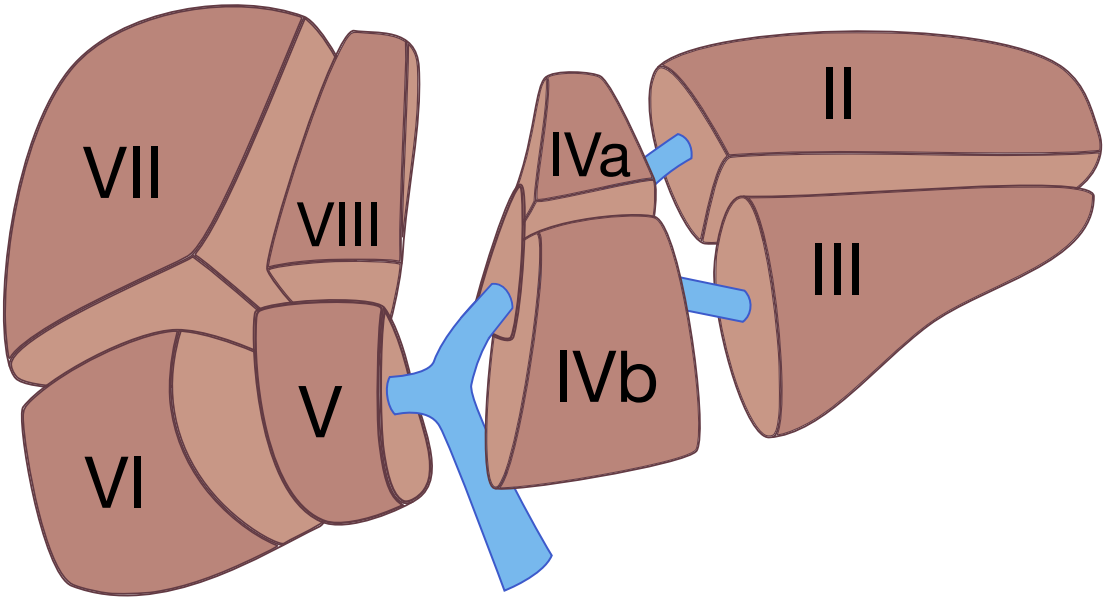
2.11.2 Techniques of hepatectomy

The hemihepatectomy technique involves removing half of the liver tissue, either the right or the left side, and usually includes the first lobe because of its anatomical proximity to the hepatic bile ducts. The surgical strategy is often determined by the specific tumor pattern with intraductal and periductal-infiltrating growth in terms of preferring either right or left-sided resections. Nevertheless, extended hepatectomy

on the right side should be favored whenever the future liver remnant allows it. The reason lies in the anatomical distance of the left hepatic area to the tumor-carrying bile ducts and the later branching into the left liver segments, leading to a great resection margin [14]. The fact that the left portal vein can be easily reconstructed allowing a resection using the no-touch technique is an additional argument for the extended right hepatectomy from an oncological point of view, as it seems to improve long-term survival [13,15]. The so-called *hilar en-bloc resection* or *no touch technique* was developed to resect tumors in advanced stages and was primarily postulated by Peter Neuhaus [13,74]. The en-bloc resection involves an extended hepatectomy, for example, resection of the six liver segments 1 and 4 to 8 (trisectionectomy on the right side) with excision of the extrahepatic bile ducts en bloc with the portal vein bifurcation and the right hepatic artery. After this operation the liver remnant contains only about 25% of the original liver volume, so that a preoperative portal vein embolization (PVE) is used to increase the future liver remnant.

The newly developed ALPPS (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy) treatment is an alternative to PVE. In the first step, the liver tissue is separated and one side of the portal vein is closed. After 5-10 days, the liver resection is completed if the CT imaging shows sufficient growth of the future liver remnant [75]. **Figure 2** shows the distribution of the 8 liver segments, each supplied by the inflow of one portal triad, consisting of one bile duct, one artery, and one vein. The right liver part consists of segments I-IV, the left part of segments V-VIII. This functional structure is not equal to the anatomical structure in which the liver is divided into 4 lobes.

Figure 2: Liver segments according to functional structure



Source: Author‘s drawing; figure created with Inkscape.org

2.11.3 Postoperative morbidity and mortality

Although extended right hepatectomy provides a great long-term survival outcome, a considerable number of patients do not inevitably benefit from radical surgery, for example patients with positive lymph node status, patients with a small future liver remnant or patients with positive radial margin status [76,77]. With regard to a small future liver remnant, it is obvious that the morbidity and mortality of this radical technique of surgery exceed less extended hepatobiliary or pancreatic operations, e.g. bile duct resections alone, and should be evaluated in this regard [13,15]. Therefore, the circumstances under which patients do not benefit from radical surgery in relation to long-term survival need to be assessed properly. In studies from the last few years, in-hospital mortality and morbidity after radical curative-intent resections was rather high and lay between 3-8% and 29-53% [1-5]. The hilar en-bloc resection is also a factor increasing postoperative mortality, even in experienced centers (30- and 90-day mortalities were 8.8% and 12.4% after hilar en bloc resection, and 7.7% and 11.2% after standard major hepatectomy, respectively), and is therefore very controversial in literature [13].

Regarding extended left hepatectomies, oncological compromises are often unavoidable, for instance the dissection of the right hepatic artery from the tumor.

Despite the oncologic disadvantage, this procedure goes hand in hand with lower morbidity and mortality and might be a good option for patients who do not benefit from the excessive approach.

As patients with positive Lymph node metastases (N+) already have significantly poorer long-term survival rates and higher risk for tumor recurrence, compared to patients with negative lymph node status [21-24], it needs to be assessed whether they profit from radical operation methods such as hilar en-bloc resection and extended trisectionectomy on the right side.

Regarding postoperative outcome, there have been many studies published lately using a short-term quality criterion called *textbook outcome (TO)* in hepatobiliary and pancreatic surgery for matters of comparability [78-81]. The concept of TO is to summarize the different outcome parameters, such as the absence of major complications (meaning > grade III according to Dindo-Clavien), no 30-day mortality, and no prolonged hospital stay. The chances of achieving a textbook outcome after pancreatic and hepatic surgery were greater at major versus minor teaching hospitals, indicating that pancreatic and liver resections should be regionalized to high-volume centers [80].

2.11.4 Postoperative chemotherapy

Adjuvant treatment after curative intended surgery is discussed controversially. For example, the BILCAP study suggested that patients with lymph node infiltration should receive adjuvant chemotherapy, in a trial with Capecitabine [82]. However, recommendations on which type of chemotherapy is to be preferred remain inconsistent in literature. Most of the recent studies used Gemcitabine or 5-FU as adjuvant chemotherapy, neoadjuvant induction therapy, or as first-line therapy for unresectable perihilar cholangiocarcinoma [82-88]

3 Question

This study aims to assess the optimal curative intended surgical approach in patients with PHC and lymph node metastases with regards to oncologic outcomes including overall survival and disease-free survival. This includes the question of whether PHC N+ patients benefit from more extensive and radical resections such as extended right hepatectomy and hilar en bloc resections, or from less radical surgical approaches such as parenchyma-saving left hepatectomy procedures. Furthermore, the effect of the number of examined lymph nodes on long-term survival was assessed.

4 Patients and methods

4.1 Study design

Between 2005 and 2015, 1,913 patients with intra- or extrahepatic cholangiocarcinoma, gallbladder tumors or hepatocellular carcinoma were treated at the Department of Surgery, Campus Charité-Mitte and Campus Virchow Klinikum. After searching for ICD-10 codes in our clinical databases of hospital information system (SAP), the records of all the patients with histologically confirmed cholangiocarcinoma who underwent operative exploration at this hospital were retrospectively reviewed and filtered by PHC.

After accumulating the information from SAP system, our research team excluded patients with palliative intended treatment, distant metastases (M1), liver transplantation, bile duct resection alone, or multivisceral tumor resection.

In total, 231 patients with newly diagnosed and histologically confirmed PHC undergoing major hepatectomy between January 2005 and December 2015 were included in the study. The primary patient outcome parameter was mean overall survival (mOS). This retrospective study was approved by the local ethics committee (EA2/006/16).

4.2 Data sources and collection of information

All data were collected by searching the clinical databases of hospital information system (SAP), the central archives and the German tumor index of deaths. To follow up on patients who were discharged into outpatient care and for whom information on possible tumor recurrence or death were missing, we contacted the primary care physicians.

4.3 Preoperative evaluation and workup

The perioperative evaluation of location and extent of the disease was performed highly individually, but generally included ultrasonography, enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen, endoscopic retrograde cholangiography (ERC) with or without biliary stenting, or percutaneous transhepatic cholangiodrainage (PTCD) if ERC was not feasible. In addition to liver-specific laboratory values and preoperative standard laboratory

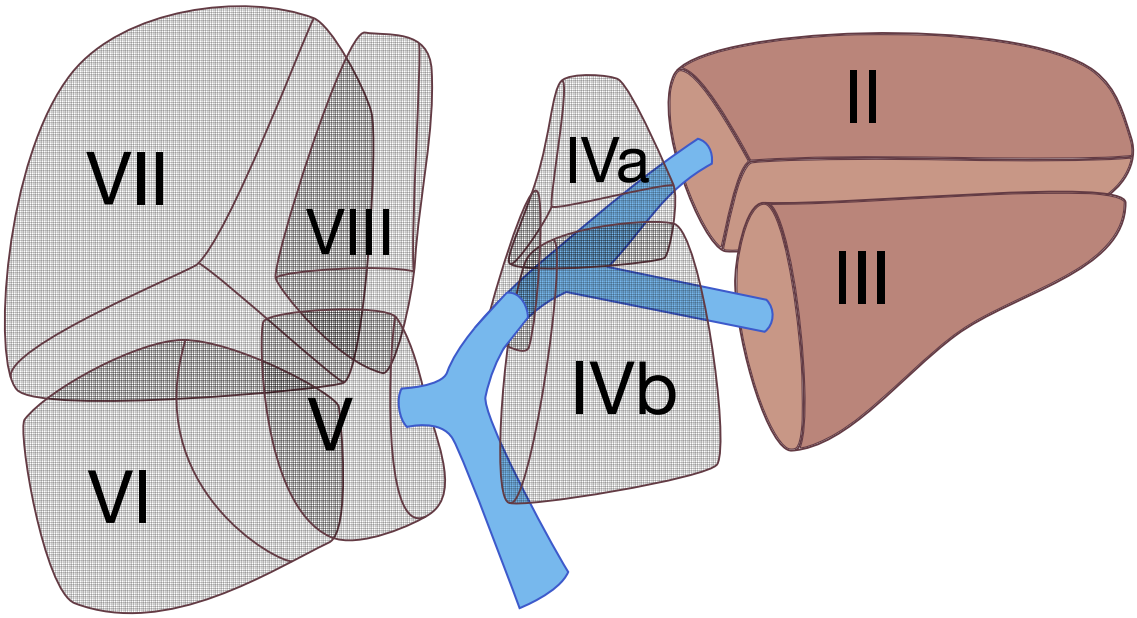
diagnostics, the tumor markers carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) were ideally assessed as well. Furthermore, either diagnostic laparotomy or laparoscopy was conducted whenever patients were suspected to have peritoneal carcinomatosis. A few patients also received diagnostic imaging and interventions at external medical centers before connecting with the Charité hospital for the initial surgery. To ease comparability, we specified textbook outcome (TO) as the non-existence of major complications (i.e. > grade II according to Clavien-Dindo [89]), 90-day mortality, hospital readmission because of complications, and elongated hospital stay (such as <75th percentile).

4.4 Extent of surgery

As radical surgical resection remains the only curative treatment for malignancies of the biliary tract, the gold standards for the treatment of resectable PHC are extended hepatectomy procedures with resection of the extrahepatic bile ducts and complete regional lymphadenectomy. Extrahepatic bile duct resection is no longer an appropriate method as the probability of tumor recurrence is very high. Extended hepatectomies were further differentiated with respect to the side of resection, meaning extended right vs. extended left hepatectomy. Major resections with technical alterations, such as segment-4 preserving variations [90], and portal vein and hepatic artery resection were included but not further distinguished for statistical reasons. Nevertheless, the surgical technique is further specified in our *Patient characteristics* table, listed below. Technical approaches such as standard major hepatectomy vs. en-bloc resection, however, were included in the statistical analysis. Consequently, Extrahepatic bile duct resection alone and multivisceral resections such as hepatoduodenopancreatectomy (HPD) were excluded from the calculations due to lack of comparability between the cohorts. Patients with intrahepatic or distant metastases as well as local peritoneal carcinomatosis, who underwent hepatectomy by individualized conceptions, were also precluded from the analysis. Trisectionectomy, the most radical strategy within the extended liver resections, was defined as resection of 6/8 liver segments and the most frequently conducted in our cohort. **Figure 3** shows an example of the amount of liver tissue (light) that is removed in the course of a trisectionectomy on the right side. Segment 1 is also resected, but not depicted in the present image so as to provide an overview. Some

of our patients were treated with the “no-touch” technique or “en-bloc” resection, first postulated by Neuhaus[13]. This procedure involves an extended hepatectomy (usually a trisectionectomy) on the right side with excision of the extrahepatic bile ducts en-bloc with the portal vein bifurcation and the right hepatic artery.

Figure 3: Right trisectionectomy

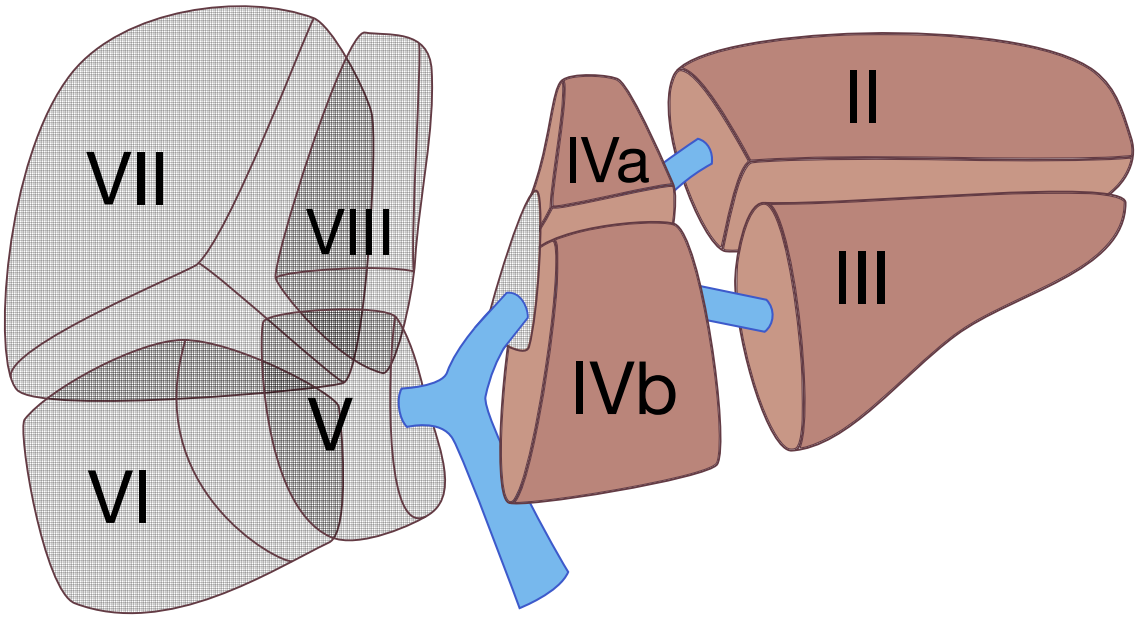


Source: Author‘s drawing; figure created with Inkscape.org

During a hemihepatectomy, only half of the liver tissue is removed, i.e., resection of segments II-IV in a left-sided hemihepatectomy and segment V-VIII in a right-sided hemihepatectomy. In the present study cohort, all procedures were classified as extended hemihepatectomy. Segment 1 was resected in all cases. Additionally, some patients received partial resections of further segments (e.g. parts of segment V in a left-sided hemihepetectomy) or true trisectionectomies. As a modification to right trisectionectomy, parts of segment 4 can be preserved [90]. The main reason for segment-4 preserving variations was to increase the future liver remnant in selected patients [90]. This type of procedure has proven to maintain the oncological standard. In this approach, the anterior parenchymal resection line begins between segment 4a on the left and segment 8 on the right, before turning to the left until reaching perpendicularly between the left medial (segment 4b) and the left lateral (segment 3)

section, resulting in a partial resection of 4a and even more of 4b in addition to the hemihepatectomy.
Furthermore, portal vein resections were performed in some cases, while the resection and reconstruction of the contralateral hepatic artery was rarely performed.

Figure 4: Extended right hepatectomy



Source: Author‘s drawing; figure created with Inkscape.org

The light liver tissue in **Figure 4** represents the resected liver segments during a hemihepatectomy on the right side with additional segment 1 resection.

All patients in our cohort underwent dissection of regional lymph nodes at the liver hilum and peripancreatic. The portal vein and/or, in selected cases, the hepatic artery were resected and reconstructed if a macroscopic vascular invasion was suspected during surgery. The nerve plexus or connective tissue around the vessel was sampled in conjunction with regional lymph nodes for the assessment of perineural sheath status and the lymphovascular status.

4.5 Histopathological evaluation

The assessment of bile duct margins was done intraoperatively by frozen section. For the pathological examination, a negative margin (R0) was defined as a microscopically tumor-free margin, an R1 margin was defined as a microscopically positive margin, and an R2 margin was declared as a macroscopically positive margin.

Pathology reports were reviewed to determine tumor histological grade, margin status, and the presence of microvascular, lymphovascular and perineural invasion. Tumors were staged using the tumor-node-metastasis (TNM) classification and the UICC stage classification of Malignant Tumors of the International Union Against Cancer (8th edition, 2016) for proximal extrahepatic bile duct cancer [91].

4.6 Postoperative course

Patients were routinely admitted to the intensive care unit postoperatively. LiMAx liver function tests were carried out as clinically indicated. Postoperative complications within 90 days were defined and graded according to the validated Clavien-Dindo classification system[92]. Morbidity was defined as major Clavien-Dindo complications (CD 3-4). Postoperative mortality was defined as death as an inpatient, and additionally, 30- and 90-day mortality (i.e. death within 30- and 90 days after surgery, respectively) were reported.

4.7 Adjuvant treatment

Due to the unclear benefit of adjuvant treatment for PHC during the period the study data was collected, patients did not routinely receive adjuvant radiotherapy or chemotherapy, but after discussing each case at the interdisciplinary tumor board, the tendency has been to recommend a Gemcitabine (GEM), cisplatin and/or fluorouracil (as single agents or in combination) based chemotherapy in the last few years. Nowadays there is a tendency towards routine application of adjuvant chemotherapy due to new study results from the BILCAP phase III trial [82] and other studies [93,94].

4.8 Postoperative long-term follow-up

Patients were followed regularly in the outpatient clinic of the department of hematology and oncology at Charité Campus Virchow Klinikum or Campus Charité-Mitte Klinikum, or in external outpatient clinics. During routine follow-up checks, clinical examinations were performed, and tumor markers including CEA and CA19-9 as well as liver function were checked. Furthermore, radiological follow-up examinations including abdominal ultrasound, CT and/or MRI were carried out regularly. Additionally, it was noted whether the patient received adjuvant therapy. If the patient died during the follow-up period, we also tried to record whether or not it was a tumor-related death, mainly by using the German tumor index of deaths. The median follow-up period for resected patients was 23 months (range, 1-134 months) with a follow-up rate of 100%.

4.9 Statistical analysis

Statistical calculations were performed using SPSS, version 24.0 (IBM Corp., Armonk, NY, USA). R Studio Version 1.2.5033 (R Studio, Boston, MA, USA) was used for propensity score matching analysis. Results were considered significant when the p value was smaller than 0.05. Continuous parameters were displayed as median and range, and, if necessary, also as mean. Counts and proportions are indicated for categorical variables. Continuous variables were examined using the non-parametric Wilcoxon rank-sum test and the Pearson $\chi 2$ test was applied for the categorical variables. The Kaplan-Meier method was used for evaluating survival probabilities and the likeliness of initial recurrence; the results were compared using the log-rank test. For instance, 1-year, 3-year and 5-year overall survival were analysed using the Kaplan-Meier method and then compared using the log-rank test. The results were displayed as cumulative percentages at the end of each year. Overall survival (OS, in months) was measured from the date of surgery to the date of death or date of last follow-up. Disease-free survival (DFS, in months) was measured from the date of surgery to the date of recurrence. The Cox proportional hazards regression model with the forward conditional calculating method were used to determine independent predictors of outcome, using survival as the dependent variable and factors significant ($p<0.10$) on univariate analysis as covariates. The

results of the Cox regression are listed as hazard ratio (HR) and 95% confidence interval (95% CI). In addition, patient characteristics within the subgroup of patients with lymph node metastases (N+) were compared according to the side of hepatic resection. Discriminating factors, including age, L status and T stage were integrated into a multivariate propensity score matching analysis. Subsequently, a score was created in a logistic regression and patients were matched with a caliper of 0.20 through nearest neighbor matching.

4.9.1 Descriptive statistics

The following data were reviewed in the progress of describing the study population and finding characteristic parameters within the subgroups:

(1) **Preoperative clinical factors**: Gender, age, BMI, comorbidities and risk factors in anamnesis (preoperative cholangitis, cardiac/cardiovascular comorbidities, pulmonic comorbidities, renal comorbidities, metabolic comorbidities, Diabetes, Charlson index, other carcinoma in anamnesis, alcohol abuse in anamnesis, smoking in anamnesis, ASA score and earlier abdominal operation (e.g. ERCP with stenting, PVE) in anamnesis);
(2) **Preoperative treatment-related factors**: Preoperative diagnostic laparoscopy, preoperative drainage or stenting, preoperative portal vein embolization (PVE);
(3) **Preoperative diagnostic parameters**: Bilirubin, CA19-9, ALT, ALST, GGT, LiMAx, Bismuth-Corlette classification, tumor size on imaging (CT/MRI);
(4) **Resection-related factors**: Date of resection (before vs. after 2010), side of resection, surgical approach, portal vein resection, resection margin, intraoperative blood loss, length of operation;
(5) **Tumor characteristics**: Lymph node involvement, number of lymph nodes resected, tumor differentiation, vascular invasion, lymphovascular invasion, perineural sheath infiltration, grade of fibrosis/cirrhosis (Desmet/Scheuer score[95]), metastases, T stage, UICC stage;
(6) **Parameters regarding the postoperative course**: Duration of hospital stay, adjuvant chemotherapy, duration of stay in intensive care unit, antibiotics needed during ICU stay, transfusion of RBC concentrate/FFP, Bilirubin, ALT, AST, GGT,

LiMAx, grade of postoperative complications according to Clavien-Dindo classification,[92] postoperative morbidity, 30-day and 90-day mortality, hospital readmission, textbook outcome;

(7) **Recurrence-related parameters**: recurrence yes/no, location of recurrence, treatment of recurrence.

5 Results

5.1 Patient characteristics

Two hundred and thirty-one patients underwent major hepatectomy for PHC between 2005 and 2015 and met the inclusion criteria. The mean age was 65 years (range, 33-83), with the male gender predominating (139 patients). Only 11% of the patients collectively were without comorbidities. Thirty-nine percent of the patients presented with preoperative cholangitis. Most of the patients (89%) had comorbidities – in descending order: 55% with cardiovascular disease, 36% with metabolic disease (including 15% with diabetes), 14% had been treated for another tumor entity in their earlier history, 11% with pulmonic disease and 6% with renal disease. Estimated 1-year mortality rates according to the Charlson index [96-98] were 12% for 157 patients (0 points), 26% for 64 patients (1-2 points), 52% for 8 patients and 85% for 2 patients, respectively. Only 17% (n = 36) of the patient collective presented with abuse of alcohol and 29% with earlier or persistent smoking in their anamnesis. The median body mass index (BMI) was at the border to pre-obesity (25), but with great range (18-41). Classified according to the American Society of Anesthesiologists Score (ASA score), more than half of the patients (56%, n = 130) suffered from mild systemic disease (ASA 2), 37 % (n = 85) of the patients had a severe systemic disease before the operation (ASA 3), and four patients (2%) suffered from a severe systemic disease that was a constant threat to life (ASA 4). In 74% (n = 169) of the patient histories we found a previous abdominal operation or intervention, which is important because of possible adhesions caused by the operation that limit future access paths. **Table 2** gives an overview of the anamnestic information prior to the operation.

Table 2: Patient characteristics

Characteristic	n	%	Median	Range
All patients	231	100		
Gender				
Female	92	40		
Male	139	60		
Age			65	33-83
BMI			25	16-41
Comorbidities				
No	26	11		
Yes	205	89		
Preoperative cholangitis				
No	141	61		
Yes	89	39		
Cardiovascular				
No	103	45		
Yes	128	55		
Pulmonic				
No	206	89		
Yes	25	11		
Renal				
No	217	94		
Yes	14	6		
Metabolic				
No	148	64		
Yes	83	36		
Diabetes mellitus				
No	197	85		
Yes	34	15		
Charlson Index				
0	175	68		
1-2	64	28		
3-4	8	3		
≥5	2	1		
Other preoperative carcinoma				
No	198	86		
Yes	33	14		
Alcohol abuse in anamnesis				
No	181	83		
Yes	36	17		
Smoking in anamnesis				
No	152	71		
Yes	61	29		
ASA score				
1	12	5		
2	130	56		
3	85	37		
4	4	2		

5.2 Preoperative evaluation and workup

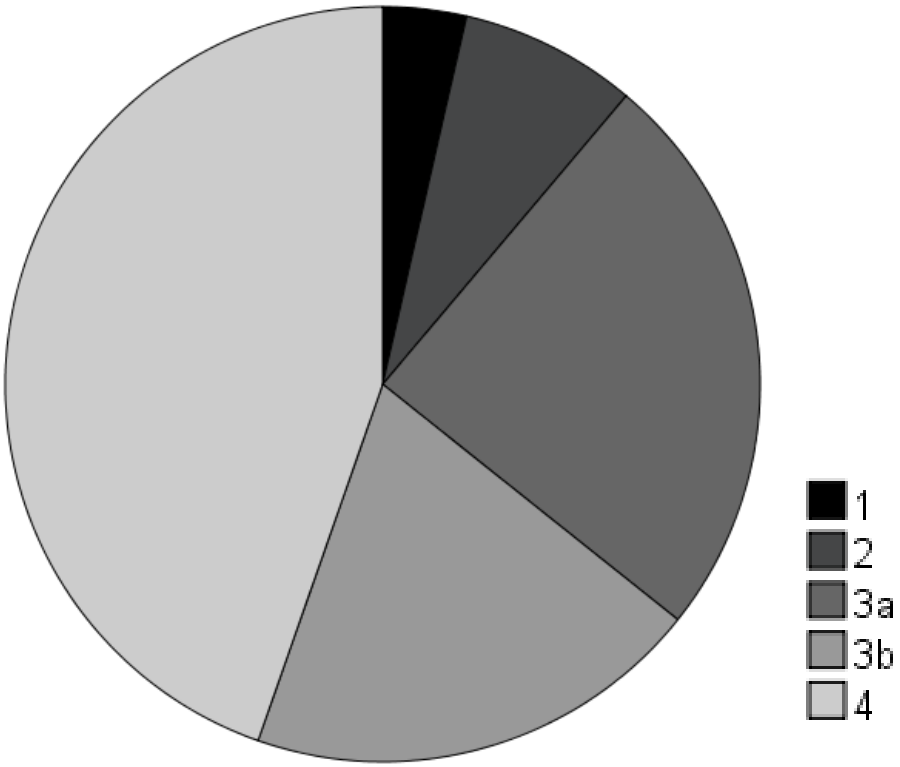
At the Department of Surgery at Campus Charité-Mitte and Campus Virchow Klinikum, endoscopic biliary drainage (EBD) was preferred and carried out in 62% of patients, but percutaneous transhepatic biliary drainage (PTBD) was performed when EBD was not successful (9%). Thirteen percent of the patients received both EBD and PTBD. Sixteen percent of the patient collective (n = 36) received no biliary decompression. To enlarge the future liver remnant and to reduce the risk of postoperative liver failure, nearly half of the patients (43%) received portal vein embolization (PVE). Preoperative diagnostic laparoscopy was performed whenever curative intended respectability was not certain after preoperative imaging and was performed in 16 patients (7%). **Table 3** provides an overview of the preoperative workup including relevant laboratory and LiMAx (maximal liver function capacity based on ^{13}C-Methacetin) liver function test results.

Table 3: Preoperative workup

Characteristic	n	%	Median	Range
Preoperative diagnostic laparoscopy				
No	214	93		
Yes	16	7		
Drainage or stenting preoperative				
None	36	16		
ERCP+ stent	138	62		
PTCD	20	9		
Both	29	13		
PVE preoperative				
No	130	57		
Yes	100	43		
Bilirubin [mg/dl]	215	100	1	0.2-41
<2 mg/dl	129	60		
≥2 mg/dl	86	40		
CA-19-9 [kU/l]			63	1-32670
<100 kU/l	80	62		
≥100 kU/l	49	38		
ALT [U/l]	184		71	9-924
AST [U/l]	218		60	15-2010
GGT [U/l]	211		461	27-14872
LiMAx [µg/kg/h]	141		373	165-1228
Tumor size on imaging (CT/MRI) [cm]	89		2.7	0.5-10.2

Patients were assessed preoperatively according to the Bismuth-Corlette[54] (BC) classification: In 4% of the cases (n = 8), the tumor was located below the confluence of the left and right hepatic duct (type I). In 7% of the cases (n = 17), the tumor reached the confluence without involving the hepatic ducts (type II). In 24% of the cases (n = 55), the tumor infiltrated the right- (type IIIa) and in 19% of cases (n = 44) the left hepatic duct (type IIIb). However, in most of the cases (43%, n = 100) the tumor involved both second-order intrahepatic bile ducts (type IV). **Figure 5** shows the distribution of tumor location by Bismuth-Corlette.

Figure 5: Distribution of tumor location by Bismuth-Corlette classification



5.3 Tumor characteristics

The median macroscopic tumor diameter was 3 cm (range 0-9 cm, **Table 5**). Most of the tumors were moderately-differentiated G2 (153 patients - 67%), while 11 patients had well-differentiated G1 (5%) and 63 patients had poorly differentiated G3 (28%). Lymph node infiltration was classified according to the 8th edition AJCC System[99]. In 122 cases (53%), no lymph nodes were involved. One hundred and nine patients

(47%) had histopathologically confirmed local lymph node metastases (N+). Regional lymph node metastases included lymph nodes along the cystic duct, common bile duct, hepatic artery and portal vein. The N+ patient cohort was further divided into two subgroups: First, the N1 subgroup with one to three positive lymph nodes and second, the N2 subgroup with four or more positive lymph nodes. Lymph node-positive patients tended to show features of more advanced tumors, including microvascular invasion, histopathological grading, perineural sheath infiltration, L status, T stage and CA 19-9 levels.

In most of the cases (80%), no vascular invasion (V0) was observed, yet in 20% microvascular invasion was observed. Perineural invasion was observed in 164 patients (89%), while perineural infiltration was clearly absent in only 11% of the cases. The distribution of lymphovascular invasion was rather balanced with lymphovascular invasion (L0) non-existent in 54% and present in 46% of the cases. A negative resection margin (R0) was achieved in more than half of the cases (68%). In 32% of the operations, a microscopic infiltration of the resection margin (R1) remained. A macroscopic (R2) tumor invasion of the resection margin was not reported. Among the reports in which fibrosis/cirrhosis was documented, there were 31 cases with low-grade fibrosis (F1), 94 cases with middle-grade fibrosis (F2), 20 cases with high-grade fibrosis (F3), and 8 cases with liver cirrhosis (F4) (classification according to Desmet/Scheuer score [95]). As expected, most of our patients were diagnosed with a locally advanced tumor stage. As per the AJCC 8th edition staging system [99], our study included 78 patients (34%) with a T3 tumor stage, 67 patients with a T2b stage, 63 patients with a T2a stage, 16 cases with a T1 stage and 7 cases with a T4 stage. In descending order of frequency, the UICC stages present according to AJCC 8th edition staging system were: Stage IIIb (45%), stage II (34%), stage IIIa (13%), stage IVa (3%), stage I (4%) and stage IVb (0%).

Table 4: Tumor characteristics

Characteristic	n	%
Tumor size by pathology		
<3 cm	87	49
≥3 cm	89	51
Tumor differentiation		
G1	11	5
G2	153	67
G3	63	28
Lymph node status		
N0	122	53
N+	109	47
N1 (<4 positive)	86	79
N2 (≥4 positive)	22	20
Microvascular invasion		
V0	160	80
V1	41	20
Perineural sheath invasion		
Pn0	20	11
Pn1	164	89
Lymphovascular invasion		
L0	106	54
L1	89	46
Resection margin		
R0	154	68
R1	73	32
Grade of fibrosis/ cirrhosis (Desmet/Scheuer score) [95]	188	100
F0	35	19
F1	31	17
F2	94	50
F3	20	11
F4	8	4
T Stage – AJCC 8th edition [99]		
T1	16	7
T2a	63	27
T2b	67	29
T3	78	34
T4	7	3
UICC Stage – AJCC 8th edition[99]		
I	10	4
II	79	34
IIIa	31	13
IIIb	104	45
IVa	7	3
IVb	0	0

5.4 Surgical approach and postoperative course

In two-thirds of all the patients (63%), extended right hepatectomy variation (3%) or right trisectionectomy (60%) were performed, of which 77% were performed as a formal hilar en bloc resection **(Table 6)**. Resections of the left hepatic side were carried out less often, specifically, extended left hepatectomy variation in 7% and left trisectionectomy in 31% of the cases. As expected, the Bismuth-Corlette classification did not correlate with the extent of surgery and thus cannot be a reliable predicting parameter for long-term survival. The surgical procedures in relation to the Bismuth-Corlette classification are shown in **Table 7**.

Around half of the patients were resected using the hilar en bloc technique (52%)[13]. The number of operations after 2010 increased by nearly one quarter (24%) in comparison to the first half of the study. Vascular resection and reconstruction of the portal vein were conducted in 136 (59%) cases. Median retention time at the intensive care unit (ICU stay) was 4 days (range, 2-123). In most cases, no packed red cells were needed (RBC concentrate), and the maximum amount of transfused erythrocyte concentrate was 9 packages. Fresh frozen plasma (FFP) was often needed to improve blood coagulation (median: 4 bags of FFP).

204 patients sustained light or severe postoperative complications within 90 days, including in descending order: 56 patients endured bile leakage, 52 pleural effusion, 47 liver failure, 39 kidney failure, 30 postoperative cholangitis, 28 anastomotic complications, 24 secondary bleeding, 21 biloma, 21 cardiac complications, 20 pneumonia, 20 portal vein thrombosis, 15 intraabdominal abscess, 6 pancreatitis, and 4 patients developed a pancreas fistula.

After surgery the morbidity amounted to 61% including patients with complications of grades 3-5 according to Clavien-Dindo classification [89]. Forty-eight (21%) patients had complications after discharge from the hospital and had to be readmitted for treatment. Adjuvant chemotherapy, radiation or phototherapy were not routinely applied due to the lack of evidence of benefit at present. Only 39 patients received adjuvant chemotherapy.

Table 5: Treatment-related characteristics and postoperative course

Characteristic	n	%	Median	Range
Date of resection				
Post 2010	128	55		
Pre 2010	103	45		
Resection side				
Extended left hepatectomy	86	37		
Extended left hepatectomy variation	15	7		
Left trisectionectomy	71	31		
Extended right hepatectomy	145	63		
Extended right hepatectomy variation	6	3		
Right trisectionectomy	139	60		
Surgical approach				
Standard major hepatectomy	111	48		
Hilar en bloc resection	120	52		
Extended right hepatectomy	4	7		
Right trisectionectomy	116	97		
Portal vein resection				
No	95	41		
Yes	136	59		
Length of operation [min]			375	187-799
<375 min	110	49		
≥375 min	114	51		
Intraoperative blood loss [ml]			800	250-2000
Hospital stay			23	7-213
Adjuvant chemotherapy				
Yes	39	18		
No	182	82		
Transfusion of RBC concentrate [bags]			0	0-9
<2 bags	173	76		
≥2 bags	54	24		
Transfusion of FFP [bags]			4	0-41
<2 bags	52	23		
≥2 bags	178	77		
ICU stay [days]			4	2-123
<4 days	107	47		
≥4 days	121	53		
Antibiotics during ICU stay				
No	113	49		
Yes	116	51		
Bilirubin [mg/dl]	230		3	0.57-126
ALT [U/l]	231		279	25-6972
AST [U/l]	231		334	27-8618
GGT [U/l]	230		343	13-2252
LiMAx [µg/kg/h**]**	90		111	16-836
Complications within 90 days				
No	27	12		

Yes	204	88
Grade of complications (Clavien-Dindo[89])		
No complications	28	12
I	11	5
II	51	22
IIIa	62	27
IIIb	41	18
IVa	6	3
IVb	1	0
V	31	12
30-day mortality	16	7
90-day mortality	29	13
Hospital readmission	48	21
Adjuvant chemotherapy		
No	182	82
Yes	39	18

Table 6: Bismuth-Corlette classification and surgical approach

Bismuth-Corlette classification	Number of patients n (%) n=224	n (%) Surgical approach
Type I/II	25 (11%)	• 16 (64%) Right trisectionectomy • 5 (20%) Left trisectionectomy • 3 (12%) Extended right hepatectomy • 1 (4%) Extended left hepatectomy
Type IIIa	55 (25%)	• 49 (89%) Right trisectionectomy • 4 (7%) Left trisectionectomy • 1 (2%) Extended right hepatectomy • 1 (2%) Extended left hepatectomy
Type IIIb	44 (20%)	• 12 (27%) Right trisectionectomy • 26 (59%) Left trisectionectomy • 6 (14%) Extended left hepatectomy
Type IV	100 (45%)	• 58 (58%) Right trisectionectomy • 35 (35%) Left trisectionectomy • 2 (2%) Extended right hepatectomy • 5 (5%) Extended left hepatectomy

5.5 Recurrence

The tumor recurrence rate after the operation was 32 percent (73 cases, **Table 8**). The PHC relapsed most often in the liver (41 times), while it relapsed in the peritoneum 21 times, in the lung 11 times and 1 time in the bones. If recurrence was diagnosed, only 18% of cases were treated with tumor resection, while 44% received chemotherapy, 14% received radiation, 11% were treated symptomatically with a bypass and 22% received only best supportive care.

Table 7: Recurrence

Characteristic	n	%
Recurrence		
No	158	68
Yes	73	32
Location of recurrence	73	100
Liver	41	56
Peritoneum	21	29
Lung	11	15
Bones	1	1
Resection of recurrence	73	
No	60	82
Yes	13	18
Recurrence and other therapy	73	
Chemotherapy	32	44
Radiation	10	14
Bypass	8	11
Best supportive care	16	22

5.6 Survival analysis

5.6.1 Surgical approaches and postoperative morbidity and mortality according to lymph node status

Major postoperative complications, as defined by Clavien-Dindo IIIa – V, appeared in 61% of all patients, with significantly more complications being noted after extended right hepatectomy (67%) than after extended left hepatectomy (33%, p = 0.048). Thirty-day and 90-day mortality were 7% and 13%, respectively. Both 30-day (11% vs. 7%, p = 0.001) and 90-day mortality (18% vs. 4%, p=0.001) were significantly higher after extended right hepatectomy, when compared to extended left hepatectomy. Notably, major complications (70% vs. 53%, p = 0.011) were seen more frequently and 90-day mortality (20% vs. 6%, p = 0.001) was significantly higher among lymph node-positive patients, when compared to lymph node-negative patients (all $p < 0.05$, **Table 9**). Among the nodal positive cohort, if they underwent extended right hepatectomy, there was also a tendency toward an increased percentage of major complications (75% vs. 61%, p = 0.126) and a significantly

higher 30-day mortality (16% vs. 0%, p = 0.010) and 90-day mortality (27% vs. 8%, p = 0.019), respectively. Of note, there were no significant discrepancies between the N0 and N+ cohorts regarding the patient characteristics. Age (p = 0.424), BMI (p = 0.492), gender (p = 0.704) and ASA score (p = 0.201) were rather homogeneous between the two cohorts. Discriminating factors were only found among the tumor-related characteristics: There was a clear tendency toward locally advanced T stages (p = 0.009), UICC stages (p < 0.001), microvascular invasion (p = 0.020), lymphovascular infiltration (p <0.001), perineural sheath infiltration (p = 0.046), higher histopathological grades (p = 0.030), and greater CA 19-9 levels (p = 0.002) for the lymph node-positive cohort, as compared to the N0 patients. Regarding treatment-related characteristics, there were no significant discrepancies affecting the side of resection (p = 0.515) or the surgical approach (p = 0.248). Solely the adjuvant chemotherapy was conducted more often among the N+ cohort, albeit unsurprisingly.

Table 8: Patient and tumor characteristics according to lymph node status

	N0 n = 122	N+ n = 109	*P* value
Age *	66 (34-83)	64 (33-83)	0.424
BMI *	24.2 (18-38)	24.8 (16-41)	0.491
Gender (male) **	72 (59)	67 (62)	0.704
ASA score **			0.201
1	6 (5)	6 (6)	
2	70 (57)	60 (55)	
3	46 (38)	39 (36)	
4	0 (0)	4 (4)	
Bismuth-Corlette **			0.967
I	5 (4)	3 (3)	
II	8 (7)	9 (8)	
IIIa	29 (25)	26 (24)	
IIIb	23 (20)	21 (20)	
IV	51 (44)	49 (45)	
UICC Stage **			<0.001
I	10 (8)	0 (0)	
II	79 (65)	0 (0)	
IIIa	31 (25)	0 (0)	
IIIb	0 (0)	104 (95)	
IVa	2 (2)	5 (5)	
Resection margin **			<0.001
R0	94 (78)	60 (56)	
R1	26 (22)	47 (44)	
Microvascular invasion **			0.020
Yes	15 (14)	26 (63)	

No	91 (86)	69 (73)	
Histopathological grading **			0.030
Grade 1	7 (6)	4 (4)	
Grade 2	90 (74)	63 (60)	
Grade 3	25 (21)	38 (36)	
Perineural sheath infiltration **			0.046
Yes	76 (84)	88 (94)	
No	14 (16)	6 (6)	
Lymphangitis carcinomatosa **			<0.001
Yes	74 (73)	62 (66)	
No	27 (27)	32 (34)	
T Stage **			0.009
1	10 (8)	6 (6)	
2a	43 (35)	20 (18)	
2b	36 (30)	31 (28)	
3	31 (25)	47 (43)	
4	2 (2)	5 (5)	
Resection side **			0.515
Extended left hepatectomy	48 (39)	38 (35)	
Extended left hep. variation	7 (6)	8 (7)	
Left trisectionectomy	41 (34)	30 (38)	
Extended right hepatectomy	74 (61)	71 (65)	
Extended right hep. variation	3 (3)	3 (3)	
Right trisectionectomy	71 (58)	68 (62)	
Surgical approach **			0.248
Standard major hepatectomy	63 (52)	48 (43)	
Hilar en-bloc resection	59 (48)	61 (51)	
Portal vein resection **			0.119
Yes	66 (54)	70 (64)	
No	56 (46)	39 (36)	
Complications (Clavien-Dindo) **			0.018
None	18 (15)	10 (9)	
I	10 (8)	1 (1)	
II	29 (23)	22 (20)	
IIIa	33 (27)	29 (27)	
IIIb	19 (16)	22 (20)	
IVa	3 (3)	3 (3)	
IVb	1 (1)	0 (0)	
V	9 (7)	22 (20)	
CA 19-9 (kU/l) *	34.4 (1-32670)	176 (1-23049)	0.002
ICU stay (days) *	3 (2-123)	5 (2-111)	0.016
Hospital stay (days) *	22 (7-185)	26 (9-213)	0.241
90-day mortality **	7 (6)	22 (20)	0.001
Adjuvant Chemotherapy			0.002
Yes	12 (10)	76 (74)	
No	106 (90)	27 (26)	
Recurrence / Death **	82 (67)	94 (86)	0.001

* Data is presented as median and range

** Data is presented as count and proportions (%)

5.6.2 Tumor-free margins after extended right and left hepatectomy

Taking into account the high 90-day mortality after extended right hepatectomy of nearly one-third among the lymph node-positive cohort, we pursued considerations as to whether the postulated benefits of locally aggressive extended right hepatectomy are also valid for lymph node-positive patients. Between the two lymph node subgroups N0 and N+, microscopically tumor-free margins were less commonly seen in lymph node-positive patients (R0, 22% vs. 44%, $p < 0.001$). In our study, tumor-free resection margins (R0) could be obtained in 68% of all patients, with a tendency towards higher R0 rates after right hepatectomy, as compared to left hepatectomy, which was short of statistical significance (R0, 72% vs. 62%, $p = 0.147$; **Table 9**). In lymph node-negative patients, extended right hepatectomy was significantly superior to extended left hepatectomy in terms of microscopically free margins (N0, extended right hepatectomy: 86% vs. extended left hepatectomy: 66%, $p = 0.008$). However, when considering only lymph node-positive patients, there were no differences between right and left hepatectomy with regards to R status (N+, extended right hepatectomy: 55% vs. extended left hepatectomy: 58%, $p = 0.778$; **Table 10**). Furthermore, in lymph node-negative patients (N0), microscopically tumor-free margins were more likely achieved when right-sided resections were performed as hilar en-bloc resection (N0, hilar en-bloc resection: 90% vs. standard major hepatectomy: 67%, $p = 0.003$). Once again, this did not apply to the subset of nodal positive patients, who obviously do not benefit from an expansion in local aggressiveness (N1, hilar en-bloc resection and R0: 55% vs. standard major hepatectomy and R0: 57%, $p = 0.800$).

Table 9: Resection margin status according to surgical approach and lymph node status

All patients (N0/N+) patients			
	R0 n = 154	R1 n = 72	*P* value
Resection side			0.147
Extended left hepatectomy	53 (62)	32 (38)	
Extended right hepatectomy	101 (72)	40 (28)	
Surgical approach			0.134
Standard major hepatectomy	68 (63)	40 (37)	
Hilar en-bloc resection	86 (72)	33 (28)	
Portal vein resection			0.485
Yes	94 (70)	41 (30)	
No	60 (65)	32 (35)	

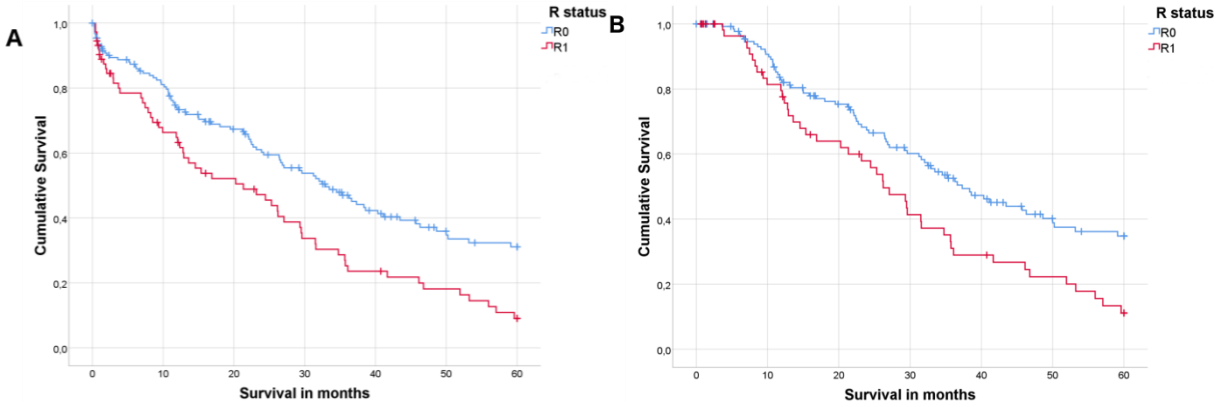
N0 patients			
	R0 n = 94	R1 n = 26	*P* value
Resection side			0.008
Extended left hepatectomy	31 (66)	16 (34)	
Extended right hepatectomy	63 (86)	10 (14)	
Surgical approach			0.003
Standard major hepatectomy	41 (67)	20 (33)	
Hilar en-bloc resection	53 (90)	6 (10)	
Portal vein resection			0.018
Yes	57 (86)	9 (14)	
No	37 (69)	17 (31)	

N+ patients			
	R0 n = 60	R1 n = 47	*P* value
Resection side			0.778
Extended left hepatectomy	22 (58)	16 (42)	
Extended right hepatectomy	38 (55)	31 (45)	
Surgical approach			0.800
Standard major hepatectomy	27 (57)	20 (43)	
Hilar en-bloc resection	33 (55)	27 (45)	
Portal vein resection			0.491
Yes	37 (54)	32 (46)	
No	23 (61)	15 (40)	

5.6.3 Survival in lymph node-positive patients according to resection margin

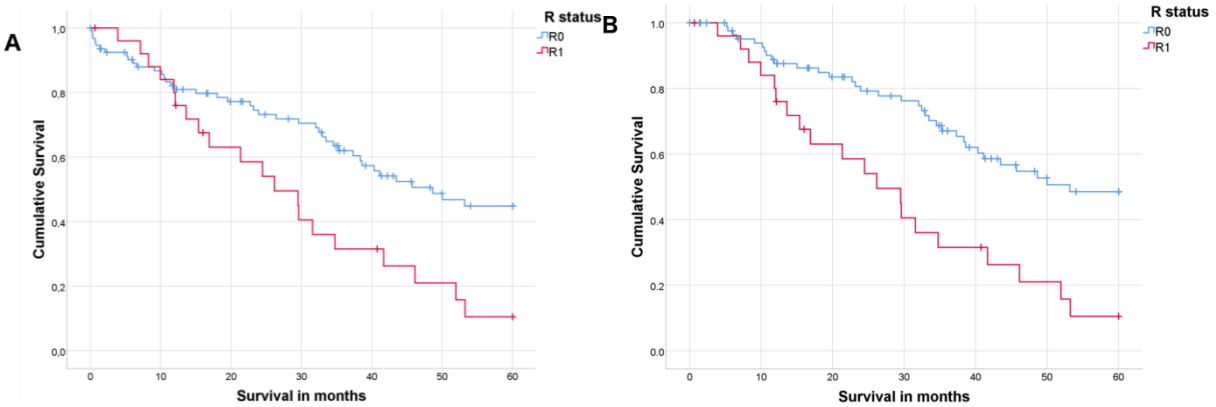
As outlined before, the superiority of extended right hepatectomy with local aggressiveness as its outstanding characteristic is evidently restricted to lymph node negative patients. Therefore, we consequently focused on analyzing overall survival (OS) and disease-free survival (DFS) according to the resection margin in lymph node-positive patients. Within the whole cohort, irrespective of the lymph node status, mean overall survival (mOS) was significantly superior when microscopically tumor-free resection margins (R0) could be achieved (N0/N+: 49.4 vs. 27.2 months, p = 0.001, **Figure 6A;** excluding 90-day mortality: 55.1 vs. 33.1 months, p = 0.002, **Figure 6B**). Similar results were found within the cohort of lymph node-negative patients (N0: 63.8 vs. 33.7 months, p = 0.006, **Figure 7A;** excluding 90-day mortality: 68.9 vs. 33.7 months, p = 0.001, **Figure 7B**).

Figure 6: Five-year survival according to resection margin, irrespective of lymph node status



Legend: Kaplan-Meier curve of overall survival of all resected patients with PHC according to R status, with (A) and without 90-day mortality (B).

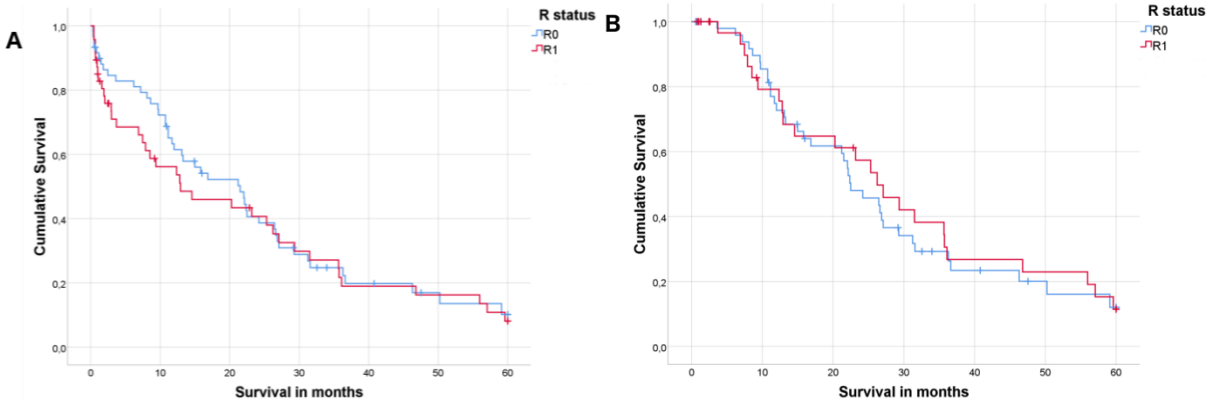
Figure 7: Five-year survival according to resection margin for lymph node-negative patients



Legend: Kaplan-Meier curve of overall survival of N0 patients according to R status, with (A) and without 90-day mortality (B).

Within the lymph node-positive cohort (N+), however, there were no equivalent differences between negative (R0) and positive resection margin (R1) detected (mOS, 25.0 vs. 23.2 months, p = 0.625, **Figure 8A;** excluding 90-day mortality: 29.4 vs. 32.1 months, p = 0.715, **Figure 8B**).

Figure 8: Five-year survival according to resection margin for lymph node-positive patients

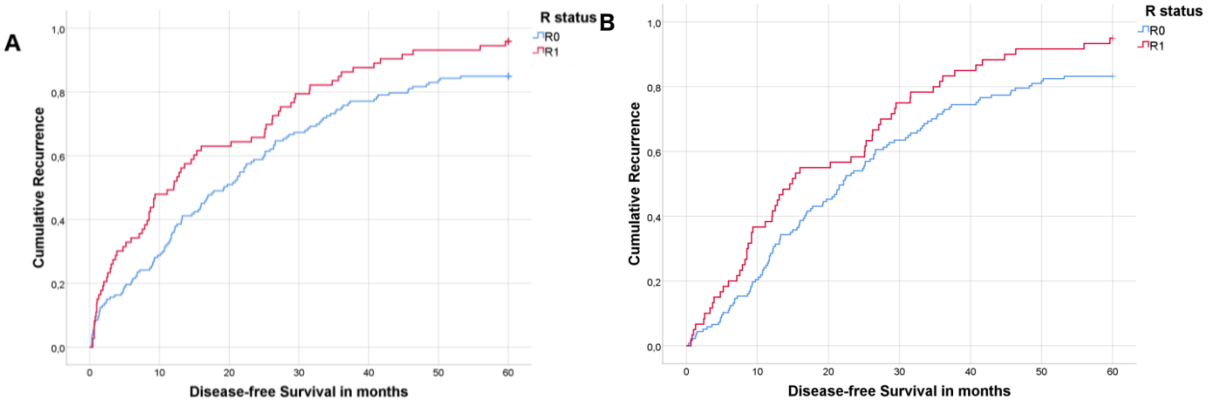


Legend: Kaplan-Meier curve of overall survival of N+ patients according to R status, with (A) and without 90-day mortality (B).

Consistent with the results for OS, disease-free survival (DFS) was significantly higher in patients, irrespective of the lymph node status, when microscopically tumor-free margins could be achieved (N0/N+: 40.8 vs. 22.0 months, p= 0.001, **Figure 9A;** excluding 90-day mortality: 45.5 vs. 26.7 months, p = 0.005, **Figure 9B**). Similar

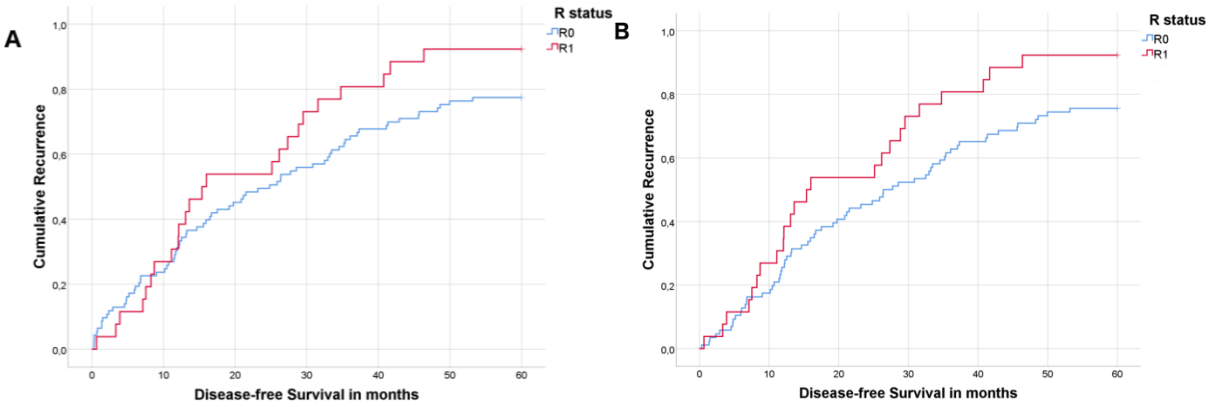
results were found within the cohort of lymph node-negative patients (N0: 53.5 vs. 30.3 months, p = 0.043, **Figure 10A;** excluding 90-day mortality: 57.8 vs. 30.3 months, p = 0.009, **Figure 10B**).

Figure 9: Five-year DFS according to resection margin, irrespective of lymph node status



Legend: Kaplan-Meier curve of disease-free survival of all resected patients with PHC according to R status, with (A) and without 90-day mortality (B).

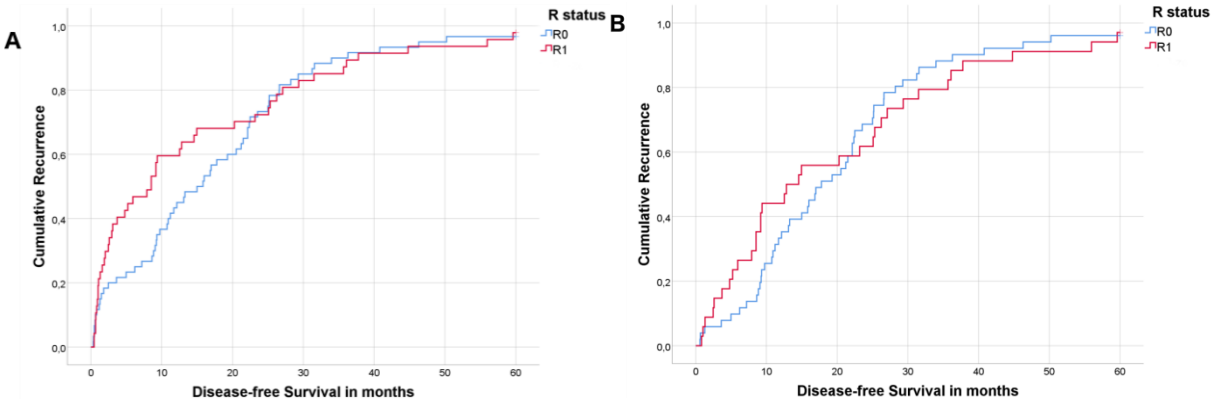
Figure 10: Five-year DFS according to resection margin for lymph node-negative patients



Legend: Kaplan-Meier curve of disease-free survival of N0 patients according to R status, with (A) and without 90-day mortality (B).

Once again, within the subgroup of lymph node metastases (N+), disease-free survival (DFS) did not differ significantly between patients with negative and positive resection margins, respectively (R0: 19.8 vs. R1: 17.6 months, p = 0.537, **Figure 11A;** excluding 90-day mortality: 23.2 vs. 24.2 months, p = 0.853, **Figure 11B**).

Figure 11: Five-year DFS according to resection margin for lymph node-positive patients



Legend: Kaplan-Meier curve of disease-free survival of N+ patients according to R status, with (A) and without 90-day mortality (B).

The cumulative 1-year, 3-year, and 5-year survival rates and DFS rates according to N- and R status are illustrated in **Table 11**. One-year survival rates were similar regarding the resection margin status (R status), but differed significantly between the nodal status subgroups (N0/R0: 82% and N0/R1: 81% vs. N+/R0: 65% and N+R1: 60%; 1-year OS according to N-status: p = 0.000). However, the differences between 5-year survival rates of patient subsets were minor, with outstanding percentages only within patients with negative resection margin and negative lymph node status (N0/R0: 56%, N0/R1: 23%, N+/R0: 23%, N+/R1: 21%). Five-year DFS rates showed a similar trend, with great discrepancies regarding the lymph node status within the R0-group (N0/R0: 23% vs. N+/R0: 3%).

Table 10: Cumulative 1-year, 3-year, and 5-year survival rates and disease-free survival rates according to N status and R status

	All patients (N0 and N+) N = 231	N0 n = 122	N+ n = 109
R0-status			
1-year survival rate	75%	82%	65%
3-year survival rate	53%	67%	32%
5-year survival rate	44%	56%	23%
1-year disease-free survival rate	64%	69%	57%
3-year disease-free survival rate	26%	36%	10%
5-year disease-free survival rate	16%	23%	3%
R1-status			
1-year survival rate	67%	81%	60%
3-year survival rate	34%	39%	32%
5-year survival rate	22%	23%	21%
1-year disease-free survival rate	51%	69%	40%
3-year disease-free survival rate	15%	19%	13%
5-year disease-free survival rate	4%	8%	2%

5.6.4 Long-term survival in lymph node-positive patients according to resection side

In accordance with the calculations outlined previously, nodal positive patients apparently do not benefit from of obtaining microscopically tumor-free margins. For this reason, we then investigated whether this subset of patients with lymph node metastases might benefit from less radical concepts that are accepted to be associated with lower postoperative morbidity.

Extended left hepatectomy had a lower morbidity (**Table 12**), as compared to extended right-sided resections within the N+ subgroup, with a shorter median ICU stay (N+/left hepatectomy: 2.5 days vs. N+/right hepatectomy: 6 days, p = 0.001) and minor 90-day mortality (N+/left hepatectomy: 8% vs. N+/right hepatectomy: 27%, p = 0.019).

Table 11: Patient characteristics according to resection side

	All N+ patients n=109	Extended right hepatectomy n = 71	Extended left hepatectomy n = 38	*P* value
Age *	64 (33-83)	64 (38-83)	65.5 (33-83)	0.552
BMI *	24.8 (16-41)	24.0 (16-41)	25.6 (19-37)	0.098
Gender (male) **	67 (62)	45 (63)	22 (58)	0.575
ASA score **				0.532
1	6 (6)	5 (7)	1 (3)	
2	60 (55)	41 (58)	19 (50)	
3	39 (36)	23 (32)	16 (42)	
4	4 (4)	2 (3)	2 (5)	
Bismuth-Corlette **				<0.001
I	3 (3)	2 (3)	1 (3)	
II	9 (8)	7 (10)	2 (5)	
IIIa	26 (24)	24 (34)	2 (5)	
IIIb	21 (19)	6 (9)	15 (40)	
IV	49 (45)	31 (44)	18 (47)	
UICC Stage **				0.030
I	0 (0)	0 (0)	0 (0)	
II	0 (0)	0 (0)	0 (0)	
IIIa	0 (0)	0 (0)	0 (0)	
IIIb	104 (95)	70 (99)	34 (90)	
IVa	5 (5)	1 (1)	4 (11)	
IVb	0 (0)	0 (0)	0 (0)	
Resection margin **				0.778
R0	60 (56)	38 (55)	22 (58)	
R1	47 (44)	31 (45)	16 (42)	
Microvascular invasion **				0.883
Yes	26 (63)	17 (28)	9 (27)	
No	69 (73)	44 (72)	25 (74)	
Histopathological grading **				0.121
Grade 1	4 (4)	1 (2)	3 (8)	
Grade 2	63 (60)	38 (57)	25 (66)	
Grade 3	38 (36)	28 (42)	10 (26)	
Perineural sheath infiltration **				0.083
Yes	88 (94)	58 (91)	30 (100)	
No	6 (6)	6 (9)	0 (0)	
Lymphangitis carcinomatosa **				0.111
Yes	62 (66)	45 (73)	18 (56)	
No	32 (34)	17 (27)	14 (47)	
T Stage **				0.009
1	6 (6)	3 (4)	3 (8)	
2a	20 (18)	15 (21)	5 (13)	
2b	31 (28)	15 (21)	16 (42)	
3	47 (43)	37 (52)	10 (26)	
4	5 (5)	1 (1)	4 (11)	
Surgical approach **				

Standard major hepatectomy	48 (44)	10 (14)	38 (100)	<0.001
Hilar en bloc resection	61 (57)	61 (86)	0 (0)	
Portal vein resection **				<0.001
Yes	70 (64)	63 (89)	7 (18)	
No	39 (36)	8 (11)	31 (82)	
Complications (Clavien-Dindo) **				
None	10 (9)	5 (7)	5 (13)	0.118
I	1 (1)	1 (1)	0 (0)	
II	22 (20)	12 (17)	10 (26)	
IIIa	29 (27)	19 (27)	10 (26)	
IIIb	22 (20)	12 (17)	10 (26)	
IVa	3 (3)	2 (3)	1 (3)	
IVb	0 (0)	0 (0)	0 (0)	
V	22 (20)	20 (28)	2 (5)	
CA 19-9 (kU/l) *	176 (1-23049)	204 (1-10633)	81 (1-23049)	0.229
ICU stay (days) *	5 (2-111)	6 (2-111)	2.5 (2-32)	0.001
Hospital stay (days) *	26 (9-213)	28 (10-148)	21.5 (9-213)	0.355
90-day mortality **	22 (20)	19 (27)	3 (8)	0.019
Hospital readmission **	21 (19)	10 (14)	11 (28)	0.077
Textbook outcome ***				0.329
Yes	25 (23)	14 (20)	11 (28)	
No	84 (77)	56 (80)	28 (72)	
Adjuvant chemotherapy **				0.022
Yes	27 (27)	13 (19)	14 (40)	
No	76 (74)	55 (81)	21 (60)	
Recurrence / death **	94 (86)	65 (92)	29 (76)	0.028

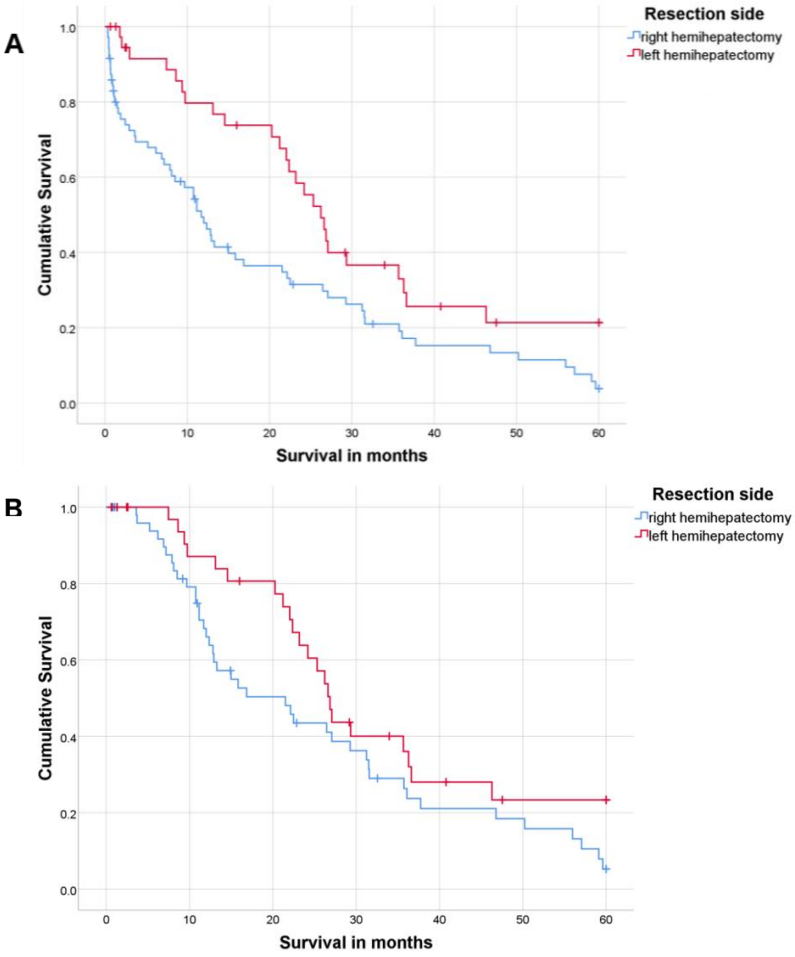
* Data is presented as median and range, ** Data is presented as count and proportions (%),

*** Textbook outcome = no hospital readmission, no 90-day mortality, no major complications (> Clavien-Dindo grade 2), hospital stay <40 days (75^{th} percentile)

Within the whole patient cohort, the mOS was 41.4 months (median OS was 29.3 months), wherein the survival of lymph node-negative patients was significantly better than the survival of the subgroup with lymph node metastases (N0, 56.4 months vs. N+, 24.4 months, $p < 0.001$). The cumulative 1-year, 3-year, and 5-year survival rates of all patients (N0/N+) were 72% (N0: 82%, N+: 62%), 48% (N0: 62%, N+: 32%), and 36% (N0: 49%, N+: 22%), respectively. For all patients, the mean DFS was 34.4 months (median DFS was 22.1 months). Once more, the DFS of N0 patients was significantly higher compared to N+ patients (48.3 months vs. 18.9 months, $p < 0.001$). The cumulative 1-year, 3-year, and 5-year DFS rates were 60% (N0: 69%, N+ 50%), 22% (N0: 32%, N+: 11%), and 12% (N0: 20%, N+: 3%), respectively. Of particular note was the statistical analysis of cumulative 1-year, 3-

year, and 5-year survival in the subset of lymph node-positive patients after extended right vs. extended left hepatectomy, reaching significance for 1-year and 5-year (52% and 82% (p = 0.002), 27% and 42% (p = 0.102), 16% and 34% (p = 0.025), respectively, **Figure 12A**). Extended left hepatectomy was associated with improved mOS when compared to extended right hepatectomy within the N+ subgroup (32.9 months vs. 19.6 months, p = 0.008, **Figure 12A**; excluding 90-day mortality: p = 0.089, **Figure 12B**). This indicates that patients with positive lymph nodes do not benefit from the excessive right-sided resection. After five years, the liver-sparing extended left hepatectomy seems to be sufficient. **Figure 12B** shows the survival curve excluding 90-day mortality, revealing that the effect is not only due to higher postoperative mortality after extensive right-sided resection.

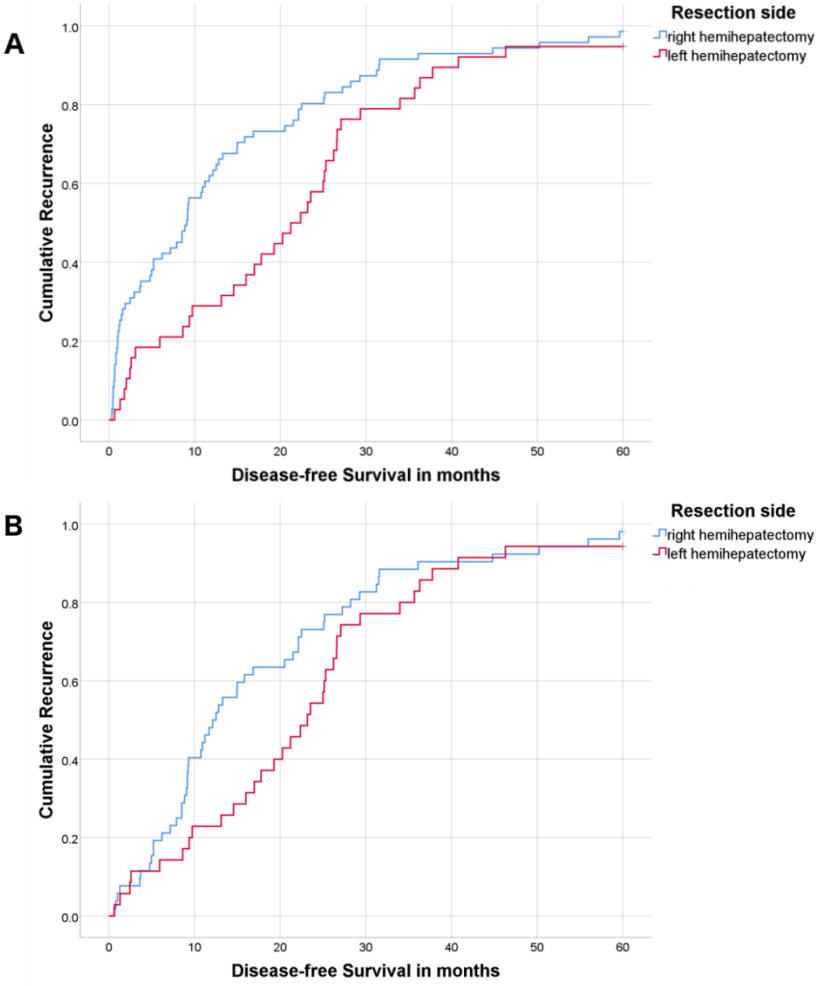
Figure 12: Cumulative 1-year, 3-year, and 5-year survival after extended right and left hepatectomy for lymph node-positive patients



Legend: Kaplan-Meier curve of overall survival of N+ patients according to the side of the hepatic resection, with (A) and without 90-day mortality (B).

The cumulative 1-year, 3-year, and 5-year DFS in lymph node-positive patients for right and left extended hepatetcomy were 38% and 71% (p = 0.001), 9% and 16% (p = 0.243), and 1% and 5% (p = 0.241), respectively (**Figure 13A**). Within the N+ subgroup, extended left hepatectomy was associated with improved DFS when compared to extended right hepatectomy (25.9 months vs. 14.9 months, p = 0.003, **Figure 13A**). **Figure 13B** visualizes the DFS excluding 90-day mortality, showing many overlaps between the two lines after three years of disease-free survival (p = 0.041).

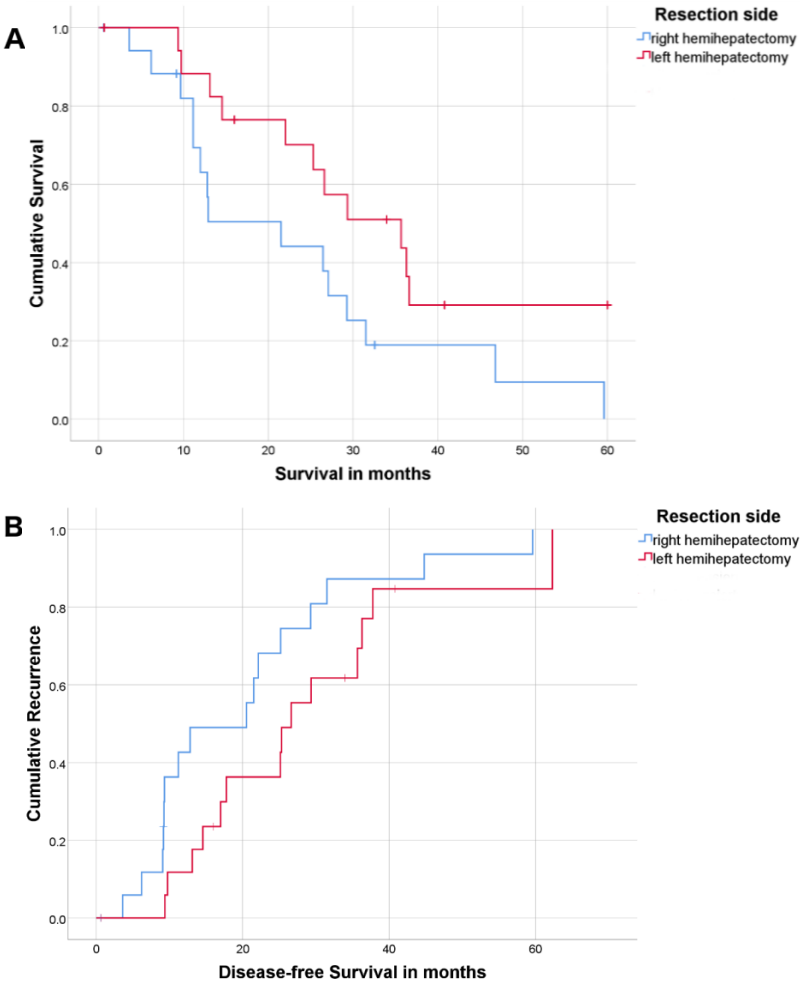
Figure 13: Cumulative 1-year, 3-year, and 5-year disease-free survival after extended right and left hepatectomy for lymph node-positive patients



Legend: Kaplan Meier curve of disease-free survival of N+ patients according to side of hepatic resection, with (A) and without 90-day mortality (B).

The long-term outcome in lymph node-positive patients undergoing extended left-sided resections was superior compared to extended right-sided resections (5-year overall survival 34% vs. 16%, respectively, p = 0.025). After excluding 90-day mortality, the benefits of left-sided resection on overall survival (OS) and DFS were still evident, but short of statistical significance. After propensity score matching for T stage and L status, the difference between right-sided and left-sided hepatectomy with regard to OS and DFS showed significance (p= 0.039, **Figure 14A;** p = 0.085, **Figure 14B**). Of note, patients undergoing extended left hepatectomy were also more likely to receive adjuvant chemotherapy (p = 0.022).

Figure 14: OS and DFS lymph node-positive patients after extended right and left hepatectomy, excluding 90-day mortality, after propensity score matching for T stage and L status

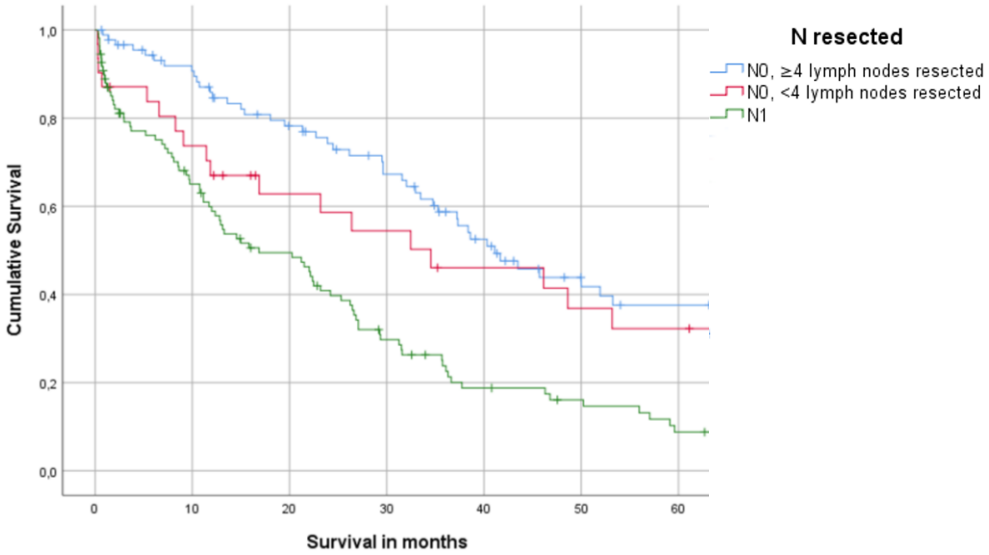


Legend: Kaplan-Meier curve of overall survival (A) and disease-free survival (B) after propensity score matching of N+ patients according to the side of the hepatic resection, without 90-day mortality.

5.6.5 Survival according to number of lymph nodes resected

In accordance with recent studies [21,22,76] which reported that the total number of lymph nodes examined (TNLE) seemed to influence the outcome after the operation, and to accurately stage a tumor, at least four or five lymph nodes needed to be resected, and this parameter was included in the calculation. Among the N0 group, at least four lymph nodes were resected in 90 cases (74%), and less than four in 31 patients (26%). The median and mean numbers of lymph nodes resected were 6 and 7, respectively. Log-rank test showed significance regarding the number of lymph nodes resected (cut-off = 4) for the whole cohort (N0 and N+), especially within the first 40 months (**Figure 15, Table 13**).

Figure 15: Overall survival according to number of lymph nodes resected



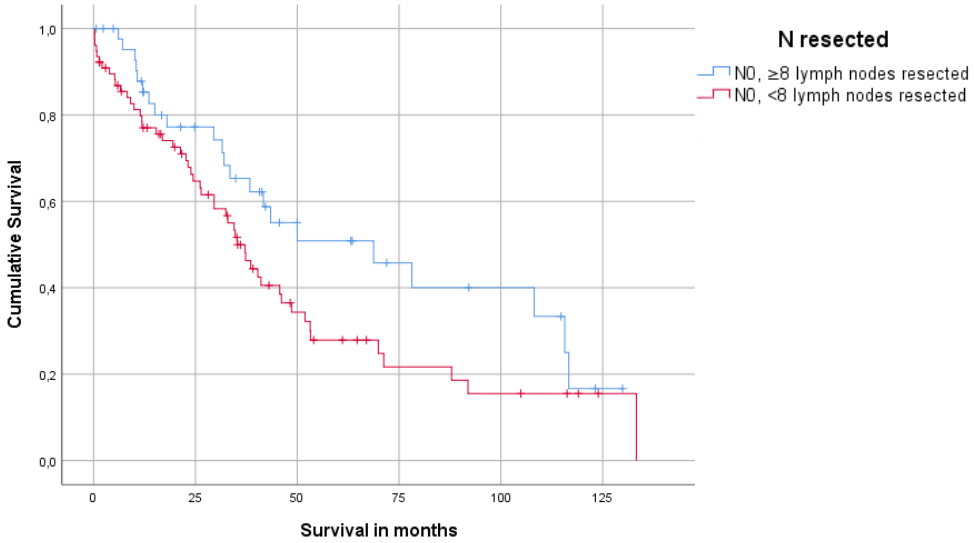
Legend: Kaplan-Meier curve of overall survival of all resected patients with perihilar cholangiocarcinoma according to the number of lymph nodes resected, cut-off=4.

Table 12: Overall survival according to number of lymph nodes resected

All patients (N0/N+) patients			
	n=231 n	Mean OS [months]	*P* value
N0, ≥4 lymph nodes resected	90	58.3	0.000
N0, <4 lymph nodes resected	31	49.8	
N1	109	24.4	

When only considering the N0 resected patients, however, the results were not significant (cut-off 3: p = 0.625; cut-off 4: p = 0.363; cut-off 5: p = 0.675; cut-off 6: p = 0.996; cut-off 7: p = 0.516; cut-off 8: p = 0.066; cut-off 9: p=0.371). The only cut-off nearly reaching significance was *8* (p=0.066, **Figure 16**), suggesting that with an examination of 8 lymph nodes, there is a significant higher chance of finding N+ patients within the N0 subgroup.

Figure 16: Overall survival according to number of lymph nodes resected for lymph node-negative patients, cut-off = 8



Legend: Kaplan-Meier curve of overall survival of all resected patients with perihilar cholangiocarcinoma without lymph node metastases (N0) according to the number of lymph nodes resected, cut-off = 8.

5.6.6 Prognostic factors determining long-term survival

When analyzing overall survival by taking into account examined prognostic factors from literature and using univariate Cox regression, the analysis revealed that T stage < 3, histopathological grading, N status, R status, L status, and V status were variables of prognostic significance within the whole cohort (p < 0.10). By contrast, age, gender, BMI, Bismuth-Corlette classification >II, Pn status, adjuvant chemotherapy and CA 19-9 levels did not reach significance. All parameters showing significance (p < 0.10) in univariate analysis were included in multivariate analysis. Consequently, R, N, and V status were found to be independent prognostic factors for overall survival (**Table 14**). The univariate Cox regression involving only lymph

node-negative patients also revealed that T stage < 3, R status and V status were of prognostic value ($p < 0.05$). Multivariate analysis, however, revealed R status to be the only independent variable with prognostic significance in N0 patients ($p = 0.037$, **Table 14**). Different results were revealed in calculations within the lymph node-positive cohort. In univariate analysis, histopathological grading, V status, and adjuvant chemotherapy were associated with significantly prolonged overall survival (OS). The resection margin, however, did not seem to play any major role within the N+ subgroup, not being independently associated with overall survival ($p = 0.626$). Instead, adjuvant chemotherapy was strongly associated with superior OS both in univariate and multivariate analysis, leading to a death rate more than twice as high when no chemotherapy was given (HR = 2.635, $p = 0.002$). Additionally, multivariate Cox regression showed also that grading was independently associated with OS in those patients.

Table 13: Univariate and multivariate analysis of factors influencing overall survival in all resected patients (N0 and N+), patients with N0- and N+ status, respectively

All patients (N0 and N+)				
Variable	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Age	1.013 (0.997-1.029)	0.118		
Gender (male)	1.265 (0.916-1.747)	0.153		
Body mass index	1.022 (0.980-1.066)	0.303		
Bismuth-Corlette > II	0.836 (0.504-1.386)	0.488		
T Stage <3	0.629 (0.460-0.862)	0.004	0.738 (0.485-1.123)	0.156
N Status (N0)	0.403 (0.291-0.557)	<0.001	0.444 (0.294-0.669)	<0.001
Resection margin (R0)	0.568 (0.411-0.786)	0.001	0.628 (0.411-0.959)	0.031
Histopathological grading				
G1	Reference	0.051	Reference	0.311
G2	0.429 (0.183-1.005)	0.051	0.473 (0.158-1.415)	0.181
G3	0.708 (0.500-1.000)	0.050	0.963 (0.607-1.528)	0.874
Perineural sheath infiltration (Pn1)	0.744 (0.363-1.525)	0.419		
Lymphovascular invasion (L0)	0.658 (0.464-0.931)	0.018	1.234 (0.742-2.052)	0.824
Microvascular invasion (V0)	0.503 (0.336-0.752)	0.001	0.491 (0.299-0.807)	0.005
No adjuvant chemotherapy	0.846 (0.541-1.324)	0.464		
Carbohydrate antigen 19-9 (U/ml)	1.000 (1.000-1.000)	0.897		

N0 patients				
Variable	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Age	1.019 (0.995-1.044)	0.128		
Gender (male)	1.350 (0.830-2.196)	0.227		
Body mass index	1.046 (0.979-1.118)	0.184		
Bismuth-Corlette > II	0.738 (0.336-1.620)	0.449		
T Stage <3	0.608 (0.375-0.985)	0.043	0.728 (0.393-1.349)	0.313
Resection margin (R0)	0.493 (0.294-0.826)	0.007	0.504 (0.264-0.959)	0.037
Histopathological Grading				
G1	Reference	0.300		
G2	0.556 (0.162-1.903)	0.350		
G3	0.663 (0.385-1.143)	0.139		
Perineural sheath infiltration (Pn1)	0.719 (0.258-2.005)	0.529		
Lymphovascular invasion (L0)	0.950 (0.512-1.762)	0.871		
Microvascular invasion (V0)	0.465 (0.242-0.894)	0.022	0.642 (0.309-1.333)	0.234
No adjuvant chemotherapy	0.708 (0.319-1.572)	0.396		
Carbohydrate antigen 19-9 (U/ml)	1.000 (1.000-1.000)	0.832		

N+ patients				
Variable	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Age	1.016 (0.994-1.039)	0.148		
Gender (male)	1.226 (0.794-1.894)	0.358		
Body mass index	0.969 (0.501-1.872)	0.924		
Bismuth-Corlette > II	1.179 (0.580-2.393)	0.649		
T Stage <3	0.891 (0.584-1.361)	0.594		
Resection margin (R0)	0.898 (0.584-1.382)	0.626		
Histopathological grading				
G1	Reference	0.132	Reference	0.105
G2	0.309 (0.093-1.028)	0.055	0.214 (0.049-0.937)	0.041
G3	1.043 (0.661-1.646	0.855	1.025 (0.609-1.727)	0.925
Perineural sheath infiltration (Pn1)	1.392 (0.502-3.862)	0.525		
Lymphovascular invasion (L0)	0.914 (0.560-1.491)	0.719		
Microvascular invasion (V0)	0.635 (0.380-1.061)	0.083	0.398 (0.212-0.748)	0.127
No adjuvant chemotherapy	2.227 (1.284-3.863)	0.004	2.635 (1.413-4.917)	0.002
Carbohydrate antigen 19-9 (U/ml)	1.000 (1.000-1.000)	0.112		

5.6.7 Survival summary

The median follow-up was 23 months (range, 1-134 months). The overall 1-year, 3-year, and 5-year survival rates were 72% (N0: 82%, N+: 62%), 48% (N0: 62%, N+: 32%), and 36% (N0: 49%, N+: 22%), with a mean overall survival of 41.4 months (N0, 56.4 vs. N+, 24.4 months), respectively. Mean disease-free survival (DFS) was 34.4 months (N0-patients: 48.3 months vs. N+-patients: 18.9 months), and the cumulative 1-year, 3-year, and 5-year DFS rates were 60% (N0: 69%, N+ 50%), 22% (N0: 32%, N+: 11%), and 12% (N0: 20%, N+: 3%), respectively. At the end of the follow-up period, 71 patients (31%) were still alive.

Among lymph node-positive patients, major complications were seen more frequently and 90-day mortality was significantly higher, when compared to lymph node-negative patients (all $p < 0.05$). Among the nodal positive cohort, there was also a tendency toward an increased percentage of major complications ($p = 0.126$) and a significantly higher 30-day mortality ($p = 0.010$) and 90-day mortality ($p = 0.019$), respectively, if they underwent extended right hepatectomy.

Between the two lymph node subgroups N0 and N+, microscopically tumor-free margins were less commonly seen in lymph node-positive patients ($p < 0.001$).

Furthermore, within the lymph node-positive cohort, there were no differences between extended right and left hepatectomy with regards to R status ($p = 0.778$). The subset of N+ patients did not benefit from an expansion in local aggressiveness, i.e., hilar en-bloc resection and/or portal vein resection, in terms of a tumor-free resection margin (all $p > 0.05$).

When comparing the mOS within the lymph node-positive cohort (N+), there were no significant differences between negative (R0) and positive resection margin (R1) detected ($p = 0.625$). Additionally, the disease-free survival (DFS) did not differ significantly between negative and positive resection margin within the N+ subgroup ($p = 0.537$).

The mOS of lymph node-negative patients was significantly better than the survival of the subgroup with lymph node metastases ($p < 0.001$).

The 1-year and 5-year survival rates in the subset of lymph node-positive patients after extended right vs. extended left hepatectomy reached significance (52% vs. 82%, $p = 0.002$ and 16% vs. 34%, $p = 0.025$, respectively).

As expected, extended left hepatectomy had a lower morbidity, as compared to extended right-sided resections within the N+ subgroup, with a shorter median ICU stay ($p = 0.001$) and minor 90-day mortality ($p = 0.019$).

Multivariate analysis revealed adjuvant chemotherapy ($p = 0.002$) to be associated with significantly prolonged overall survival (OS) in N+ patients. The resection margin, however, did not seem to play any major role within the N+ subgroup, not being independently associated with overall survival ($p = 0.626$ on univariate analysis).

6 Discussion

At this point, the only curative treatment of perihilar cholangiocarcinoma is major hepatectomy aiming to achieve microscopically tumor-free margins. The surgical approach is often determined by the specific tumor pattern with intraductal and periductal-infiltrating growth, the degree to which the vessels or the lymph system are affected, and of course, the future liver remnant. It is dependent not only on the extent of surgery but also on the liver tissue and its grade of fibrosis. Nevertheless, Neuhaus et al. showed that extended hepatectomy on the right side should be favored whenever technically feasible with regard to the future liver remnant as this approach has proven to provide oncological radicality with outstanding long-term survival [13]. The preferable operative technique in this regard should be the hilar en-bloc resection – a right trisectionectomy with resection of the extrahepatic bile ducts en bloc with the portal vein bifurcation and the right hepatic artery [13,74]. By contrast, left-sided resections are accompanied by oncological compromises due to the anatomical proximity of the right hepatic artery and the tumor-bearing field. However, the postoperative morbidity and mortality of the more extensive right sided hepatectomies exceed left-sided hepatectomies [20]. Consequently, patients must be identified who do not benefit from extensive surgery regarding long-term survival. A strong parameter associated with a significantly poorer prognosis after an operation, and often present in patients with perihilar cholangiocarcinoma, is the presence of lymphatic metastases [21-24]. A positive lymph node status is also regarded as a contraindication for liver transplantation (e.g., pro-duct002 trial, DRKS00013276). By contrast, the lymph node status does not change the surgical strategy in liver resection [25,26]. This topic has not yet been examined in detail in the current literature. Thus, this is the first study aiming to investigate whether PHC N+ patients really benefit from more extensive resections such as extended right hepatectomy and hilar en bloc resections, or whether less radical surgical approaches, in particular left-sided hepatectomies, are more appropriate for this subset of patients. In order to make the singularity and implications of the results clear, the discussion is based on the methodical approach, i.e., step by step.

6.1 Survival after hepatectomy for the whole patient collective

In the present study, median overall survival was 29.3 months and median disease-free survival (DFS) was 22.1 months, respectively. Median OS was comparable to that of previous studies, ranging from 26-32 months [1-5]. Median DFS however was slightly above the reported time period of other studies, ranging from 17-18 months [1-5]. The overall 1-year, 3-year, and 5-year survival rates were 72%, 48%, and 36%, in line with results of previous studies (OS rates at 1, 3, and 5 years were 60-84%, 37-46%, and 20-32%, respectively [1-5]). OS and DFS of lymph node-negative patients were significantly better than the survival of the subgroup with lymph node metastases, which is in accordance with previous studies [60].

6.2 Prognostic factors after hepatectomy for the whole patient collective

Known factors reducing long-term survival for PHC after curative intended resection are a positive lymph node status, microvascular invasion, histologically less differentiated tumors, positive resection margins, perineural sheath infiltration and high T-category (T3 and T4) [3,24,60,74,76,100-104]. Other factors are discussed controversially in the literature, such as preoperative CA 19-9 levels [60,105,106]. Adjuvant chemotherapy is considered a positive prognostic factor regarding long-term survival in PHC [2,62,82].

Numerous results from preceding studies were confirmed by our matching results. In the present trial, univariate analysis revealed that T stage < 3, histologically better differentiated tumors (<G2), negative lymph node status (N0), negative resection margin (R0), no lymphovascular invasion (L0), and no microvascular invasion (V0) status were favorable variables of prognostic significance within the whole cohort. By contrast, age, gender, BMI, Bismuth-Corlette classification >II, Pn status, adjuvant chemotherapy and CA 19-9 levels did not reach significance. In multivariate analysis, only R, N, and V status were found to be independent prognostic factors for overall survival. R and N status are very important factors influencing long-term survival that are reported homogeneously in literature [60,107]. Perineural sheath invasion did not reach significance in this study, despite being an independent prognostic factor in previous studies [108]. The unequal distribution of Pn status (Pn0 = 11% vs. Pn1 = 89%) might be a reason for the lack of statistical significance in the present study.

6.2.1 Number of lymph nodes to be examined for the definition of N status

In general, in order to determine the lymph node status properly, the current recommendation is the sampling of at least four or five lymph nodes [21,76]. In our study, there was a considerable difference regarding overall survival in N0 patients when more or less than eight lymph nodes were resected, favoring patients with a larger number of lymph nodes resected. This indicates that by examining less than eight lymph nodes, there is still a chance of missing N+ patients. Therefore, an approximate number of lymph nodes to be evaluated in postoperative histopathology could be eight, which is more than was demanded in previous studies [21,76].

6.3 Postoperative morbidity and mortality

The outstanding feature of our patient collective was the high rate of locally advanced stages. The most commonly recorded were Bismuth IV tumors infiltrating both the right and left hepatic ducts and the subsegments (45%), and tumor-bearing lymph nodes were detected in almost half of the patients (47%). After surgery the morbidity of 61%, including patients with complications of grades 3-5 according to Clavien-Dindo classification,[89] was rather high but comparable to the outcomes of other studies [17,109-111]. However, the period of time in which postoperative complications are recorded varies strongly between the studies. In the present study, all complications within 90 days after surgery were recorded, whereas in other studies only complications during hospitalization were recorded [109,110,112]. Overall postoperative (90-day) mortality was 13% in this study, which corresponds to the mortality rates of a recently published multicenter study with a 12% mortality without portal vein embolization and a 18% mortality after portal vein embolization [113]. However, there are also better results to be found in the literature – for instance, Nagino et al. published several studies in Japan with mortality rates with a range of 2 to 5% [114-116], which is markedly lower than the numbers in our study. Nevertheless, comparisons regarding mortality rates between Eastern and Western centers are problematic due to the substantial discrepancies in patient features such as age, comorbidities and tumor stage [117]. One reason for the high postoperative morbidity and mortality rate in our study could be the great amount of right trisectionectomies (60% of all resections). Right triscetionectomies associate with a significant reduction of liver parenchyma, which can lead to critically low liver remnant volumes, increasing

the risk of postoperative liver failure and the morbidity and mortality rate in general [118,119]. The rate of postoperative liver failure in the present study was 20% (n=47), which is much higher than in other previous studies [120]. Within the subgroup of right trisectionectomies, the percentage of postoperative liver failure was even higher (30%, n=42). However, in the comparable studies, the percentage of trisectionectomies much was lower [116,120]. For instance, Igami et al. reported a low rate of postoperative liver failure (6%, n=18), but the percentage of right trisectionectomies was only 5% (n=14) and left trisectionectomies were only 22% (n=65) [120]. Nagino et al. reported a comparably high amount of postoperative liver failure between 2006 and 2010 of 40%, but the percentage of right trisectionectomies was only 11% (n=23) and left trisectionectomies were 30% (n=65) [116]. The great discrepancies regarding postoperative liver failure in the literature could be due to heterogeneous definitions of this complication as well as heterogeneities regarding patient characteristics [121].

6.3.1 Preoperative evaluation and workup as resource for reducing postoperative mortality

The high percentage of major complications emphasizes the necessity of preoperative management and monitoring not only during hospitalization, but also after discharge from the hospital. Hepatobiliary decompression can improve the performance status before major hepatectomy, but is controversially discussed because of intervention-related complications [122-124]. On the one hand, a persistent obstruction of the hepatobiliary ducts can cause liver failure, subphrenic abscesses from biliary fistulae, hemorrhages and sepsis, and can therefore lead to higher postoperative morbidity and mortality [125,126]. On the other hand, there is only evidence for reduction of postoperative morbidity in literature - mortality rates could not be reduced significantly through hepatobiliary drainage or stenting before curative intended resection for PHC [123]. A compromise could be performing biliary drainage routinely only in patients with proximal biliary obstruction, as postulated by Iacono et al. and van der Gaag et al., [125,126] or selecting patients according to their individual risk for postoperative complications. They also suggest that biliary drainage in jaundiced patients should be planned on the basis of multidisciplinary discussion and should be recommended in patients with long-standing jaundice, cholangitis, renal

failure, malnourishment, or indications for neoadjuvant chemotherapy [125,126]. In order to reduce the risk of postoperative liver failure, Charité – Universitätsmedizin has introduced the LiMAx test (maximal liver function capacity based on ^{13}C-Methacetin) as a preoperative algorithm for estimating liver capacity, and thereby could reduce morbidity and mortality after liver resection [127]. The LiMAx test was also routinely implemented in the present study (n = 141), sometimes twice, before and after portal vein embolization (PVE). PVE is a method for inducing liver hypertrophy before trisectionectomies and is considered as a safe and efficient standard treatment, superior to hepatic artery embolization (HAE) [128-130]. It allows for major hepatectomies in a patient group with advanced PHC and inadequate future liver remnant (FLR).

6.4 Right versus left-sided resection for the whole patient collective and the impact of resection margins

In the present study, two-thirds of all patients (63%) received extended right hepatectomy variation (3%) or right trisectionectomy (60%), of which 77% were performed as a formal hilar en-bloc resection. Resections of the left hepatic side were carried out as extended left hepatectomy variation in 7% of the cases and as left trisectionectomy in 31%. The outstanding long-term survival of surgical radicality, postulated by Neuhaus et al., [13,74] was confirmed in the present study when considering both N0 and N+ patients. MOS was significantly superior when microscopically tumor-free resection margins (R0) could be achieved (N0/N+: 49.4 vs. 27.2 months, p = 0.001), indicating that a more radical surgical approach leads to a better prognosis. Resection margin was the only parameter both influenced by surgical therapy and having a significant impact on long-term survival on multivariate analysis. The importance of negative resection margins on long-term survival is supported by other studies, reporting 5-year survival rates of 11-67% after R0 resections for PHC [13,16,101,102,114,116,121,131], but only 5-year survival rates of 0-35% after R1-resections [102,104,121,132]. According to Neuhaus et al., extended resections, especially right trisectionectomies, result in the highest rate of R0 resections and combined with portal vein resection should be the oncological standard in resectable PHC [74,133]. However, when considering the whole cohort (all N stages), the resection side did not have significant influence on the resection margin in our study. In our

study, tumor-free resection margins (R0) were be achieved in 68% of all patients, with a tendency towards higher R0 rates after right hepatectomy, as compared to left hepatectomy, but this was short of statistical significance. Furthermore, major postoperative complications (Clavien-Dindo IIIa–V) appeared in 61% of all patients, with significantly more complications being noted after extended right hepatectomy (67%) than after extended left hepatectomy (33%). Both 30-day (11% vs. 7%, p = 0.001) and 90-day mortality (18% vs. 4%, p=0.001) were significantly higher after extended right hepatectomy, when compared to extended left hepatectomy, which is in accordance with previous studies [20]. In general, trisectionectomies are accompanied by high morbidity rates of 27-59% [13,102,114,115,134], which is in line with the high morbidity rates of the present study. Nevertheless, they are favored by many authors because of the outstanding long-term results achieved by oncological radicality, with 5-year survival rates of 32-64% [13,102,114,115,134] in the literature, and a 5-year OS of 36% in the present study. However, the choice of the preferred resection side in central tumors is not consistent in literature – opponents are calling for less radical approaches with reduced rates of complications [118,135]. Which side of resection should be favored – right or left hepatectomy – is the subject matter of current controversies, with a clear tendency towards right hepatectomies. From an oncological point of view, right trisectionectomies have clear advantages. First, PHC are usually located near the right hepatic artery due to anatomical reasons, while the left hepatic artery is located distant from the common bile duct and hilar bile duct confluence. Second, the right hepatic bile duct ramifies into multiple intrahepatic bile ducts immediately after the bifurcation. Third, the portal vein also ramifies into the second-order branches immediately at the right side. Fourth, the right part of the caudate lobe cannot easily be discriminated from the right hepatic lobe, but the left-sided caudate lobe can be easily removed from the left hepatic lobe. Therefore, it has been postulated that the radical right-sided hepatectomy should be favored for PHC in order to achieve a curative resection. Some authors advocate right hepatectomies for all PHC except for tumors located predominantly on the left hepatic side, e.g., involving the left hepatic duct and/or involving the left portal vein and the left hepatic artery [136-140].

6.4.1 Survival after right versus left-sided resection for N0 patients

In the N0 group, right-sided resections were affiliated with a significantly higher probability of R0 margins compared to left-sided resections (86% and 66%, respectively, p = 0.008). In particular, when the hilar en-bloc or “no-touch“ technique [13] was implemented, the oncological benefits of extended right hepatectomy were even more obvious, but only among N0 patients. This result is significant as microscopically tumor-free resection margins were found to be the only independent prognostic factor (p = 0.037) that can be influenced by the surgical approach for N0 patients. Correspondingly, N0 patients may genuinely benefit the most from the locally aggressive surgical strategies, at least from a conceptual oncological perspective.

6.5 Recurrence pattern and therapy for PHC

In the present study, the tumor recurrence rate after surgery was 32% (73 cases). A multi-institutional study from 2018 by Zhang et al. reported a recurrence rate of 44% [141]. These numbers are only partially comparable as they always depend on the length of the follow-up. Mean DFS was 34.4 months (N0-patients: 48.3 months vs. N+-patients: 18.9 months), and PHC relapsed most often locally in the liver (56%) and second most frequently in the peritoneum (29%) in the present study. This recurrence pattern emphasizes the need for abdominal imaging in routine follow-up checks. At Charité – Universätitsmedizin Berlin routine follow-up examinations include abdominal ultrasound, CT and/or MRI. Other less frequent and distant locations of tumor recurrence were the lung (15%) and bones (1%). According to Zhang et al., early recurrence, defined as recurrence that occurs within the first 2.5 years, is more likely present as distant disease [141]. In our study, mean time to recurrence for patients with recurrence in the lung was 13 months and for patients with recurrence in the bones 16 months, whereas for patients with recurrence in the liver mean DFS was 18 months and in patients with peritoneal recurrence mean DFS was 21 months. However, these results must be treated with caution, as the case number of recurrence was small in the present study and in some cases, local and distant recurrence was detected at the same time. In the present study, most of the patients with recurrence of PHC (44%) received palliative chemotherapy. This

approach is the current standard. In particular, the use of gemcitabine in the treatment

of metastatic PHC has been increasingly recognized. In 2010, Valle et al. showed in a phase III (ABC-02) study of 410 patients with locally advanced or metastatic biliary tract cancers that treatment with gemcitabine plus cisplatin was associated with a survival advantage over gemcitabine alone and without additional toxicity [66]. Follow-up studies using the same therapy regimen have validated these results [142,143]. Advances in understanding the molecular patterns of PHC have enabled new therapies targeting key molecular pathways, e.g., EGFR inhibitors. However, subsequent randomized trials could not confirm the clinical benefit [144,145].

6.6 Specifics of N+ patients

In the present study, the mOS survival of lymph node-positive patients was significantly worse than the survival of the subgroup without lymph node metastases (N+, 24.4 months vs. N0, 56.4 months), in line with previous studies [21-24]. Also, the DFS of N+ patients was significantly shorter compared to N0 patients (N+, 18.9 months vs. N0, 48.3 months).

6.6.1 Right- versus left-sided resection for N+ patients

However, given the outcome of the present study, the current standards of surgical therapy are not suitable for N+ patients, as they do not benefit from extended right hepatectomy. There was a tendency towards an increased percentage of major complications and a significantly higher 30-day mortality ($p = 0.010$) and 90-day mortality ($p = 0.019$), respectively, if they underwent extended right hepatectomy. Additionally, the median ICU stay was significantly longer after extended right hepatectomy. Interestingly, as opposed to the N0 group, right hepatectomy did not associate with an increased percentage of tumor-free resection margins when compared to left hepatectomy. As a consequence, more radical surgical approaches such as portal vein resection and hilar en bloc resections did not result in improved R0 rates either.

Of note, extended left hepatectomy was associated with improved OS and DFS when compared to extended right hepatectomy ($p = 0.008$ and $p = 0.003$). Of particular note was the statistical analysis of cumulative 1-year and 5-year survival in N+

patients after extended right vs. extended left hepatectomy reaching significance (52% vs. 82% and 16% vs. 34%, respectively). After excluding 90-day mortality, the benefits of left-sided resection on OS and DFS were still evident but short of statistical significance. After propensity score matching for T stage and L status, the difference between right-sided and left-sided hepatectomy with regard to OS and DFS showed statistical significance. This indicates that in N+ patients, whenever technically feasible, liver-sparing left-sided resections appear to be the preferable surgical approach, achieving better long-term survival rates. Literature for comparison is difficult to find, as the other studies focusing on nodal positive patients usually address the fundamental question whether these patients are eligible for curative-intent resection or not, but not the extent of resection [146]. Other studies focused on the extent of surgery, but did not address N+ patients specifically [13,74,114]. One of these studies noted, however, that despite a high rate of right trisectionectomies, significantly less R0 resections were performed in N+ patients, when compared to N0 patients [74]. Many studies also focus on the number of lymph nodes to be retrieved for assessing the nodal status [147,148].

6.6.2 Survival according to resection margin for N+ patients

When comparing the mOS within the lymph node-positive cohort (N+), there were no significant differences between negative (R0) and positive resection margin (R1) detected ($p = 0.625$). Also, the DFS did not differ significantly between R0 and R1 patients within the N+ subgroup ($p = 0.537$). Consequently, the resection margin seems to be of minor importance within N+ patients, as opposed to other factors such as the possibility of receiving adjuvant chemotherapy.

Furthermore, a negative resection margin could not be achieved through expansion in local aggressiveness in the present study. Neither the side of hepatectomy nor the performance of hilar en-bloc resection or portal vein resection had a significant influence on R status in univariate analysis. In accordance with those results, some authors also report compromised circumferential clearance of the resection margin despite extended hepatectomy and vascular resection [149]. Other studies postulate that right trisectionectomies, especially when combined with portal vein resection, increase the rate of R0 resections [74,133]. Some studies that did not specify the extent

of surgery found significant superiority of right-sided hepatectomies when compared to left-sided hepatectomies regarding the resection margin [150].

6.6.3 Postoperative morbidity and mortality in N+ patients

Of note, major complications were seen more frequently and 90-day mortality was significantly higher among lymph node-positive patients, when compared to lymph node-negative patients. Patients with infiltrated lymph nodes were characterized by advanced-stage tumor biological features, such as significantly higher UICC stages, higher proportions of microvascular invasion, histologically less differentiated tumors, more perineural sheath infiltration and higher T stages. The extent that those attributes are responsible for higher morbidity and mortality in patients with positive lymph node status, and if so, why, is not yet clear. High UICC stages are a known risk factor for OS, but not for postoperative morbidity and mortality [151]. Also some studies report histopathological grading as an independent prognostic factor for OS, but not for postoperative morbidity/mortality [152]. As the advanced-stage tumor biological features are associated with the necessity of extensive resections, this might, however, be a reason for the higher rate of major postoperative complications and postoperative mortality. Regarding microvascular invasion as a potential risk factor for postoperative mortality, the concomitant factor *vascular resection* is known to increase the risk of perioperative mortality significantly [153]. Other well known risk-factors such as the ASA score did not differ significantly within the subgroups ($p = 0.201$). ASA score levels >3 are associated with a higher risk or postoperative morbidity and mortality after hepatectomy [119]. Other well-known risk factors for complications and early mortality after liver resection are prior damage of the liver (e.g. fibrosis, steatosis, preoperative AST elevation ascites), the extent of resection, the length of operation and the intraoperative blood loss [20,119,154].

6.6.4 Adjuvant chemotherapy for N+ patients

In conclusion, the resection margin seems to be of minor importance within N+ patients. By contrast, major complications seem to have a high impact regarding therapy strategies in N+ patients. Of note, multivariate analysis for long-term survival revealed adjuvant chemotherapy ($p = 0.002$) to be the only independent prognostic factor for OS in N+ patients that can be influenced by therapy. Therefore, future

efforts should focus on reducing postoperative complications in order to enable adjuvant chemotherapy in these patients. As there was a decreased percentage of major complications and a significantly lower 30-day and 90-day mortality if N+ patients underwent extended left hepatectomy, left-sided resections should be preferred. Regarding postoperative chemotherapy, the BILCAP study underlines our results, despite them being short of statistical significance, showing that patients with lymph node infiltration might benefit most from adjuvant chemotherapy with Capecitabine [82]. Given the outcome that N+ patients do not benefit from the most radical therapy but more from parenchyma-preserving resections (i.e. left hepatectomy), the next question to investigate could be whether N+ patients benefit from surgery at all, or whether chemotherapy alone could be enough therapy. Palliative chemotherapy alone, for locally advanced or metastatic cholangiocarcinoma, usually allows a median overall survival of around 8-12 months [88,142,144,155-157]. In contrast, in our subgroup with lymph node metastases and positive resection margins, mean overall survival was about twice as long as generally observed after palliative chemotherapy (mean OS for N+, 24.4 months), confirming the requirement of surgery in curative intended therapy.

In the present cohort study, the most common chemotherapeutic agents for adjuvant therapy were either gemcitabine or fluorouracil (5-FU), alone or in combination. Which type of chemotherapy is to be preferred remains inconsistent in literature. Most of the recent studies also used gemcitabine or 5-FU as adjuvant chemotherapy, neoadjuvant induction therapy, or as first-line therapy for unresectable perihilar cholangiocarcinoma [82-88]. Of note, patients undergoing extended left hepatectomy were more likely to receive adjuvant chemotherapy ($p = 0.022$) in the present study.

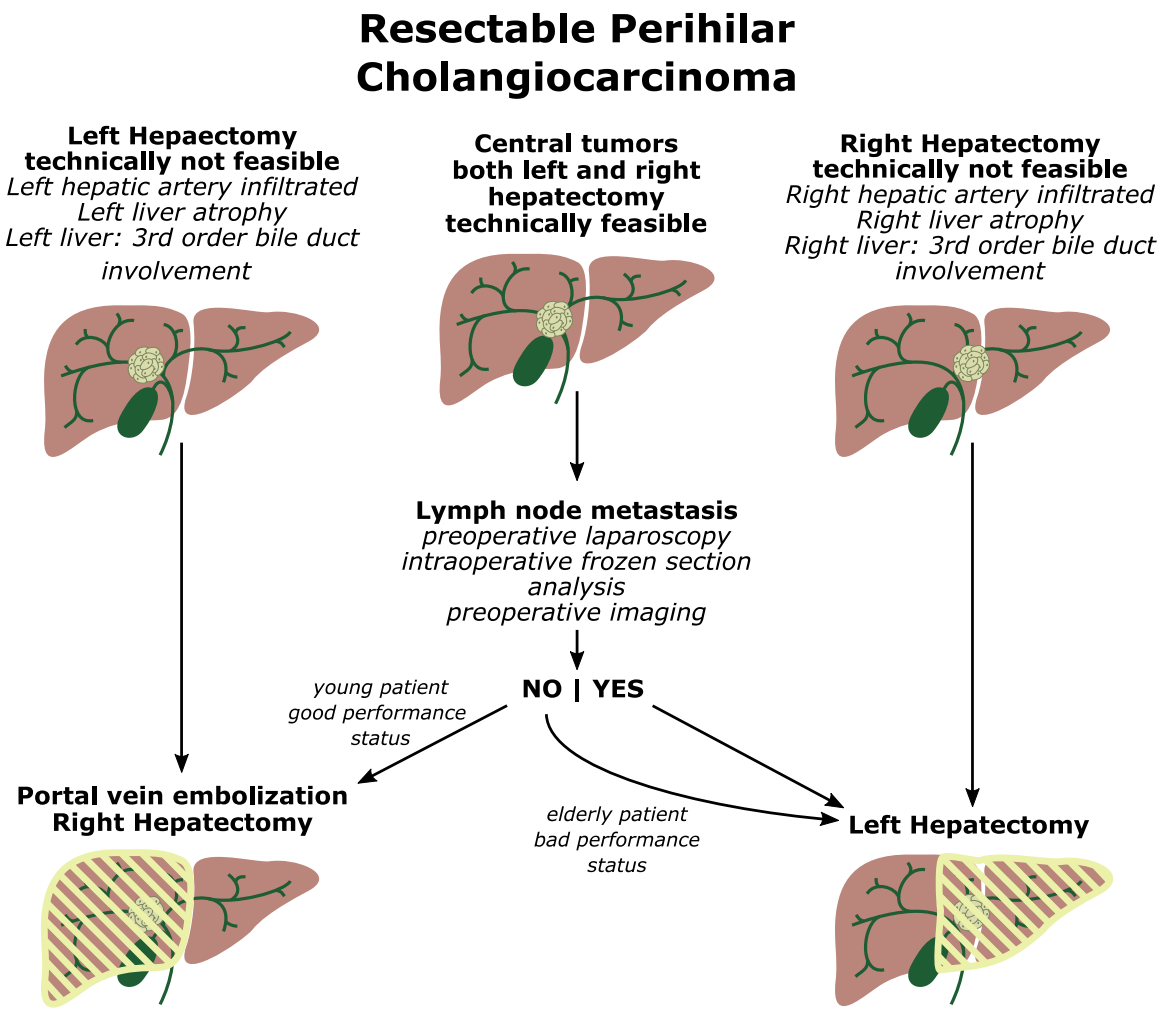
There are also studies decreasing the effect and importance of adjuvant chemotherapy on OS; a meta-analysis of randomized clinical trials of Messina et al. showed that adjuvant chemotherapy for resected biliary tract cancer only improved DFS but had no effect on OS in N+ patients [158]. Nevertheless, after resection of N+ patients with PHC, chemotherapy should be offered to patients according to the expert consensus statement of Mansour et al. [159].

6.7 Suggested therapy algorithm in resectable PHC

In conclusion, it can be said that the established surgical approaches are less appropriate for the subgroup of lymph node-positive patients in terms of both regarding short- and long-term outcome. Indeed, less extensive surgical approaches with less postoperaitve morbidity have shown to be beneficial to this subset of patients with PHC, enabling the possibility of adjuvant chemotherapy [160]. Despite this, the 90-day mortality of 27% among the lymph node-positive cohort after extended hepatectomy on the right side needs to be validated, considering accepted mortality rates in hepatobiliary surgery. Compared to the mortality rate after extended left hepatectomy of only 8%, the more tissue-sparing resection seems to be notably attractive for the subset of lymph node-positive patients. However, major hepatectomy (i.e. left hemihepatectomy being the least radical type of surgical approach right up to right trisectionectomy as most radical one) remains the cornerstone of curative intended therapy in perihilar cholangiocarcinoma, regardless of the lymph node status.

As a consequence to our findings in the present study, we propose a new pathway according to the patient's lymph node status, which is shown in **Figure 17**.

Figure 17: Suggested therapy algorithm in resectable PHC



Source: Author‘s drawing; figure created with Inkscape.org

6.7.1 Preoperative lymph node sampling for N+ patients

We suggest that for patients with central PHC for whom both left and right hepatectomy are technically feasible, lymph node sampling should be carried out before resection. This means that even tumors growing to the right side (Bismuth IIIa) can be potentially resected by left trisectionectomy, providing the right artery and the portal vein are not infiltrated. Conversely, a Bismuth IIIa tumor infiltrating the (sub-) segmental bile ducts and/or the vessels on the right side can only be resected by performing right hepatectomy. The detection of suspicious lymph nodes should be carried out through preoperative imaging by CT or MRI scans. The accuracy of these methods is rather good, but nevertheless has some flaws – Ruys et al. found a

sensitivity of 61% and specificity of 88% in detecting nodal metastases with CT [57]. The assessment of the nodal status could therefore be complemented by preoperative open or laparoscopic sampling of lymph nodes around the coeliac/common hepatic artery, upper pancreatic margin, and retroduodenal lymph nodes; the perihilar region, however, should not be dissected, in order to avoid tumor spreading. A comparable approach can be observed in PHC patients who are scheduled for liver transplantation (e.g., pro-duct002 trial, DRKS00013276). A left hepatectomy should be favoured whenever infiltrated lymph nodes are detected and/or whenever the patient's general condition is bad. However, in physically fit patients with negative lymph node status, we propose right trisectionectomy with hilar en bloc resection as postulated by Neuhaus et al. [13] (**Figure 17**).

6.8 Limitations

6.8.1 Data collection

This study includes data from a single center, and even though the department of visceral surgery at Charité – Universitätsmedizin Berlin, Campus Virchow or Campus Mitte, represents a highly-specialized department for this tumor entity that also treats patients from abroad, a potential selection bias is inevitable, as we mainly admit patients in advanced tumor stages to our hospital. Due to the late transition from analog data archiving to digitalization, we were reliant on the diligent collection of discharge letters, personal data, and operation reports in our local repositories, especially in surgeries from the early time period. If patients came from abroad and did not participate in follow-ups at our clinic, or took an ambulance that did not keep in touch with our doctors, it was difficult to track the recurrence rate and adjuvant therapy.

6.8.2 Epidemiologic factors

The retrospective cohort study design is accompanied by obvious disadvantages as it can only assess the exposures determined at the beginning of the study, i.e., questionnaires about the consumption of alcohol or the parameter "smoking", were not prospectively collected.

6.8.3 Adjuvant treatment

Although surgical resection remains the treatment of choice for curative intended therapy for PHC, adjuvant chemotherapy is accepted to be an important component of the current therapy regime. In early cases of the present study, however, there was no standardized implementation of adjuvant chemotherapy and it therefore needs to be mentioned as a clear shortcoming of the present study.

6.8.4 Study design

As our study is a retrospective cohort study, it clearly has the advantage of yielding results from presently collectible data compared with forward studies that require the future observation of patients over an extended period. For rare diseases such as hilar cholangiocarcinoma, retrospective cohort studies are a common and less time-intensive alternative to prospective multicenter studies. Future prospective analyses focusing on the surgical approach with regards to the patient's lymph node status should be performed to strengthen the results found in the present study.

A clear advantage of the present study, however,

is the large number of patients included. As PHC is a rare tumor entity, comparable single-center studies deal with lower numbers of patients. Furthermore, the large database with numerous variables needs to be highlighted as an advantage. So far, the present study is the first to destinctly investigate the surgical and therapeutical situation of N+ patients.

7 Summary

In conclusion, major hepatectomy remains the mainstay for curatively intended treatment in PHC irrespective of the patient's lymph node status. In the present retrospective cohort study, the data of 231 patients with PHC undergoing curative intended major hepatectomy were analysed. The rather high postoperative morbidity and mortality can be explained by a high proportion of right trisectionectomies in the present cohort.

In lymph node-negative patients, however, this negative effect could be outweighed by the higher probability of R0 margins after extended right hepatectomy and its favourable influence on long-term survival.

By contrast, in lymph node-positive patients, this favourable effect of extensive right hepatectomy was not evident. Interestingly, as opposed to N0 patients, there were no differences between extended right and left hepatectomy procedures with regards to the proportion of patients who had R0 resections. Furthermore, R status did not significantly impact long-term survival in this subset of patients. Analysis of cumulative 5-year survival in N+ patients after extended right vs. extended left hepatectomy showed the significant benefit of the liver-sparing extended left hepatectomy on long-term survival (5-year survival rate of 16% vs. 34%). Multivariate analysis exposed adjuvant chemotherapy to be the only independent prognostic factor for OS in N+ patients that can be influenced by therapy. Consequently, patients with nodal disease might benefit most from less aggressive surgical approaches, as this is accompanied by a low morbidity, and the opportunity for improved survival benefits provided by multimodal therapy, in particular adjuvant chemotherapy. Diagnostic lymph node sampling might help to identify patients who really benefit from locally aggressive approaches such as extended right hepatectomy.

8 References

1. Baton O, Azoulay D, Adam DV, Castaing D. Major hepatectomy for hilar cholangiocarcinoma type 3 and 4: prognostic factors and longterm outcomes. J Am Coll Surg 2007;204:250-60.
2. Dumitrascu T, Chirita D, Ionescu M, Popescu I. Resection for hilar cholangiocarcinoma: analysis of prognostic factors and the impact of systemic inflammation on long-term outcome. J Gastrointest Surg 2013;17:913-24.
3. Hu HJ, Mao H, Shrestha A, Tan YQ, Ma WJ, Yang Q, Wang JK, Cheng NS, Li FY. Prognostic factors and long-term outcomes of hilar cholangiocarcinoma: A single-institution experience in China. World J Gastroenterol 2016;22:2601-10.
4. Kimura N, Young AL, Toyoki Y, Wyatt JI, Toogood GJ, Hidalgo E, Prasad KR, Kudo D, Ishido K, Hakamada K, Lodge JPA. Radical operation for hilar cholangiocarcinoma in comparable Eastern and Western centers: Outcome analysis and prognostic factors. Surgery 2017;162:500-14.
5. Li H, Qin Y, Cui Y, Chen H, Hao X, Li Q. Analysis of the surgical outcome and prognostic factors for hilar cholangiocarcinoma: a Chinese experience. Dig Surg 2011;28:226-31.
6. Chaiteerakij R, Harmsen WS, Marrero CR, Aboelsoud MM, Ndzengue A, Kaiya J, Therneau TM, Sanchez W, Gores GJ, Roberts LR. A new clinically based staging system for perihilar cholangiocarcinoma. Am J Gastroenterol 2014;109:1881-90.
7. Nakeeb A, Tran KQ, Black MJ, Erickson BA, Ritch PS, Quebbeman EJ, Wilson SD, Demeure MJ, Rilling WS, Dua KS, Pitt HA. Improved survival in resected biliary malignancies. Surgery 2002;132:555-63; discission 63-4.
8. Ethun CG, Lopez-Aguiar AG, Anderson DJ, Adams AB, Fields RC, Doyle MB, Chapman WC, Krasnick BA, Weber SM, Mezrich JD, Salem A, Pawlik TM, Poultsides G, Tran TB, Idrees K, Isom CA, Martin RCG, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Cardona K, Maithel SK. Transplantation Versus Resection for Hilar Cholangiocarcinoma: An Argument for Shifting Treatment Paradigms for Resectable Disease. Ann Surg 2018;267:797-805.
9. Cillo U, Fondevila C, Donadon M, Gringeri E, Mocchegiani F, Schlitt HJ, Ijzermans JNM, Vivarelli M, Zieniewicz K, Olde Damink SWM, Groot Koerkamp B. Surgery for cholangiocarcinoma. Liver Int 2019;39 Suppl 1:143-55.
10. Rassam F, Roos E, van Lienden KP, van Hooft JE, Klumpen HJ, van Tienhoven G, Bennink RJ, Engelbrecht MR, Schoorlemmer A, Beuers UHW, Verheij J, Besselink MG, Busch OR, van Gulik TM. Modern work-up and extended resection in perihilar cholangiocarcinoma: the AMC experience. Langenbecks Arch Surg 2018;403:289-307.
11. Dondossola D, Ghidini M, Grossi F, Rossi G, Foschi D. Practical review for diagnosis and clinical management of perihilar cholangiocarcinoma. World J Gastroenterol 2020;26:3542-61.
12. Seehofer D, Kamphues C, Neuhaus P. [Resection of Klatskin tumors]. Chirurg 2012;83:221-8.
13. Neuhaus P, Thelen A, Jonas S, Puhl G, Denecke T, Veltzke-Schlieker W, Seehofer D. Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. Ann Surg Oncol 2012;19:1602-8.

14. Nagino M, Kamiya J, Arai T, Nishio H, Ebata T, Nimura Y. "Anatomic" right hepatic trisectionectomy (extended right hepatectomy) with caudate lobectomy for hilar cholangiocarcinoma. Ann Surg 2006;243:28-32.
15. Jonas S, Benckert C, Thelen A, Lopez-Hanninen E, Rosch T, Neuhaus P. Radical surgery for hilar cholangiocarcinoma. Eur J Surg Oncol 2008;34:263-71.
16. Nuzzo G, Giuliante F, Ardito F, Giovannini I, Aldrighetti L, Belli G, Bresadola F, Calise F, Dalla Valle R, D'Amico DF, Gennari L, Giulini SM, Guglielmi A, Jovine E, Pellicci R, Pernthaler H, Pinna AD, Puleo S, Torzilli G, Capussotti L, Cillo U, Ercolani G, Ferrucci M, Mastrangelo L, Portolani N, Pulitanò C, Ribero D, Ruzzenente A, Scuderi V, Federico B, Association ICotIH-P-B. Improvement in perioperative and long-term outcome after surgical treatment of hilar cholangiocarcinoma: results of an Italian multicenter analysis of 440 patients. Arch Surg 2012;147:26-34.
17. Gerhards MF, van Gulik TM, de Wit LT, Obertop H, Gouma DJ. Evaluation of morbidity and mortality after resection for hilar cholangiocarcinoma--a single center experience. Surgery 2000;127:395-404.
18. Molina V, Sampson J, Ferrer J, Díaz A, Ayuso JR, Sánchez-Cabús S, Fuster J, García-Valdecasas JC. Surgical treatment of perihilar cholangiocarcinoma: early results of en bloc portal vein resection. Langenbecks Arch Surg 2017;402:95-104.
19. Olthof PB, Coelen RJS, Wiggers JK, Groot Koerkamp B, Malago M, Hernandez-Alejandro R, Topp SA, Vivarelli M, Aldrighetti LA, Robles Campos R, Oldhafer KJ, Jarnagin WR, van Gulik TM. High mortality after ALPPS for perihilar cholangiocarcinoma: case-control analysis including the first series from the international ALPPS registry. HPB (Oxford) 2017;19:381-7.
20. Bednarsch J, Czigany Z, Lurje I, Tacke F, Strnad P, Ulmer TF, Gaisa NT, Bruners P, Neumann UP, Lurje G. Left- versus right-sided hepatectomy with hilar en-bloc resection in perihilar cholangiocarcinoma. HPB (Oxford) 2020;22:437-44.
21. Bagante F, Tran T, Spolverato G, Ruzzenente A, Buttner S, Ethun CG, Groot Koerkamp B, Conci S, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Vitiello G, JN IJ, Maithel SK, Poultsides G, Guglielmi A, Pawlik TM. Perihilar Cholangiocarcinoma: Number of Nodes Examined and Optimal Lymph Node Prognostic Scheme. J Am Coll Surg 2016;222:750-9.e2.
22. Guglielmi A, Ruzzenente A, Campagnaro T, Pachera S, Conci S, Valdegamberi A, Sandri M, Iacono C. Prognostic significance of lymph node ratio after resection of peri-hilar cholangiocarcinoma. HPB (Oxford) 2011;13:240-5.
23. Tang Z, Yang Y, Zhao Z, Wei K, Meng W, Li X. The clinicopathological factors associated with prognosis of patients with resectable perihilar cholangiocarcinoma: A systematic review and meta-analysis. Medicine (Baltimore) 2018;97:e11999.
24. Groot Koerkamp B, Wiggers JK, Gonen M, Doussot A, Allen PJ, Besselink MG, Blumgart LH, Busch OR, D'Angelica MI, DeMatteo RP, Gouma DJ, Kingham TP, van Gulik TM, Jarnagin WR. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. Ann Oncol 2015;26:1930-5.
25. Sano T, Shimizu Y, Senda Y, Kinoshita T, Nimura Y. Assessing resectability in cholangiocarcinoma. Hepat Oncol 2014;1:39-51.
26. Schulick RD. Criteria of unresectability and the decision-making process. HPB (Oxford) 2008;10:122-5.
27. Sharp GB, Cologne JB, Fukuhara T, Itakura H, Yamamoto M, Tokuoka S. Temporal changes in liver cancer incidence rates in Japan: accounting for death

certificate inaccuracies and improving diagnostic techniques. Int J Cancer 2001;93:751-8.
28. Schönemann T. Universitätsklinikum Hamburg-Eppendorf. UKE-Forscher leiten internationale Studie zur Behandlung von Gallengangskrebs. In: Trowitzsch C, ed. Krebs-Nachrichten. online: cura:medial UG (haftungsbeschränkt); 2014:13.
29. Charbel H, Al-Kawas FH. Cholangiocarcinoma: epidemiology, risk factors, pathogenesis, and diagnosis. Curr Gastroenterol Rep 2011;13:182-7.
30. Tannapfel A, Wittekind C. [Anatomy and pathology of intrahepatic and extrahepatic bile duct tumors]. Der Pathologe 2001;22:114-23.
31. Keith D Lillemoe MD. Klatskin tumors. Munich: W. Zuckschwerdt Verlag GmbH.; 2001.
32. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 2011;8:512-22.
33. Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, Hruban RH, Lillemoe KD, Yeo CJ, Cameron JL. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463-73; discussion 73-5.
34. Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. Am J Gastroenterol 2004;99:523-6.
35. Nashan B, Schlitt HJ, Tusch G, Oldhafer KJ, Ringe B, Wagner S, Pichlmayr R. Biliary malignancies in primary sclerosing cholangitis: timing for liver transplantation. Hepatology 1996;23:1105-11.
36. Boberg KM, Bergquist A, Mitchell S, Pares A, Rosina F, Broome U, Chapman R, Fausa O, Egeland T, Rocca G, Schrumpf E. Cholangiocarcinoma in primary sclerosing cholangitis: risk factors and clinical presentation. Scand J Gastroenterol 2002;37:1205-11.
37. de Vries JS, de Vries S, Aronson DC, Bosman DK, Rauws EA, Bosma A, Heij HA, Gouma DJ, van Gulik TM. Choledochal cysts: age of presentation, symptoms, and late complications related to Todani's classification. J Pediatr Surg 2002;37:1568-73.
38. Soreide K, Soreide JA. Bile duct cyst as precursor to biliary tract cancer. Ann Surg Oncol 2007;14:1200-11.
39. Miyazaki M, Takada T, Miyakawa S, Tsukada K, Nagino M, Kondo S, Furuse J, Saito H, Tsuyuguchi T, Chijiiwa K, Kimura F, Yoshitomi H, Nozawa S, Yoshida M, Wada K, Amano H, Miura F. Risk factors for biliary tract and ampullary carcinomas and prophylactic surgery for these factors. J Hepatobiliary Pancreat Surg 2008;15:15-24.
40. Stromberg C, Luo J, Enochsson L, Arnelo U, Nilsson M. Endoscopic sphincterotomy and risk of malignancy in the bile ducts, liver, and pancreas. Clin Gastroenterol Hepatol 2008;6:1049-53.
41. Kim HG, Han J, Kim MH, Cho KH, Shin IH, Kim GH, Kim JS, Kim JB, Kim TN, Kim TH, Kim TH, Kim JW, Ryu JK, Moon YS, Moon JH, Park SJ, Park CG, Bang SJ, Yang CH, Yoo KS, Yoo BM, Lee KT, Lee DK, Lee BS, Lee SS, Lee SO, Lee WJ, Cho CM, Joo YE, Cheon GJ, Choi YW, Chung JB, Yoon YB. Prevalence of clonorchiasis in patients with gastrointestinal disease: a Korean nationwide multicenter survey. World J Gastroenterol 2009;15:86-94.
42. Poomphakwaen K, Promthet S, Kamsa-Ard S, Vatanasapt P, Chaveepojnkamjorn W, Klaewkla J, Sujirarat D, Pichainarong N. Risk factors for

cholangiocarcinoma in Khon Kaen, Thailand: a nested case-control study. Asian Pac J Cancer Prev 2009;10:251-8.
43. Sahani D, Prasad SR, Tannabe KK, Hahn PF, Mueller PR, Saini S. Thorotrast-induced cholangiocarcinoma: case report. Abdom Imaging 2003;28:72-4.
44. Lipshutz GS, Brennan TV, Warren RS. Thorotrast-induced liver neoplasia: a collective review. J Am Coll Surg 2002;195:713-8.
45. Lazaridis KN, Gores GJ. Cholangiocarcinoma. Gastroenterology 2005;128:1655-67.
46. Okuda K, Nakanuma Y, Miyazaki M. Cholangiocarcinoma: recent progress. Part 1: epidemiology and etiology. J Gastroenterol Hepatol 2002;17:1049-55.
47. Wu TT, Levy M, Correa AM, Rosen CB, Abraham SC. Biliary intraepithelial neoplasia in patients without chronic biliary disease: analysis of liver explants with alcoholic cirrhosis, hepatitis C infection, and noncirrhotic liver diseases. Cancer 2009;115:4564-75.
48. Ben-Menachem T. Risk factors for cholangiocarcinoma. Eur J Gastroenterol Hepatol 2007;19:615-7.
49. Sorensen HT, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, Linet M, Trichopoulos D, Vilstrup H, Olsen J. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. Hepatology 1998;28:921-5.
50. Shaib YH, El-Serag HB, Nooka AK, Thomas M, Brown TD, Patt YZ, Hassan MM. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a hospital-based case-control study. Am J Gastroenterol 2007;102:1016-21.
51. El-Serag HB, Engels EA, Landgren O, Chiao E, Henderson L, Amaratunge HC, Giordano TP. Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: A population-based study of U.S. veterans. Hepatology 2009;49:116-23.
52. Tocchi A, Mazzoni G, Liotta G, Lepre L, Cassini D, Miccini M. Late development of bile duct cancer in patients who had biliary-enteric drainage for benign disease: a follow-up study of more than 1,000 patients. Ann Surg 2001;234:210-4.
53. Jarnagin WR, Bowne W, Klimstra DS, Ben-Porat L, Roggin K, Cymes K, Fong Y, DeMatteo RP, D'Angelica M, Koea J, Blumgart LH. Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. Ann Surg 2005;241:703-12; discussion 12-4.
54. Paul A, Kaiser GM, Molmenti EP, Schroeder T, Vernadakis S, Oezcelik A, Baba HA, Cicinnati VR, Sotiropoulos GC. Klatskin tumors and the accuracy of the Bismuth-Corlette classification. Am Surg 2011;77:1695-9.
55. Kwon W, Jang JY, Chang YR, Jung W, Kang MJ, Kim SW. Suggestions for improving perihilar cholangiocarcinoma staging based on an evaluation of the seventh edition AJCC system. J Gastrointest Surg 2015;19:666-74.
56. Gaspersz MP, Buettner S, van Vugt JLA, de Jonge J, Polak WG, Doukas M, Ijzermans JNM, Koerkamp BG, Willemssen F. Evaluation of the New American Joint Committee on Cancer Staging Manual 8th Edition for Perihilar Cholangiocarcinoma. J Gastrointest Surg 2020;24:1612-8.
57. Ruys AT, van Beem BE, Engelbrecht MR, Bipat S, Stoker J, Van Gulik TM. Radiological staging in patients with hilar cholangiocarcinoma: a systematic review and meta-analysis. Br J Radiol 2012;85:1255-62.
58. Anderson CD, Rice MH, Pinson CW, Chapman WC, Chari RS, Delbeke D. Fluorodeoxyglucose PET imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma. J Gastrointest Surg 2004;8:90-7.

59. Lorenz JM. Management of Malignant Biliary Obstruction. Seminars in interventional radiology 2016;33:259-67.
60. Bird NTE, McKenna A, Dodd J, Poston G, Jones R, Malik H. Meta-analysis of prognostic factors for overall survival in patients with resected hilar cholangiocarcinoma. Br J Surg 2018.
61. Weber A, Landrock S, Schneider J, Stangl M, Neu B, Born P, Classen M, Rosch T, Schmid RM, Prinz C. Long-term outcome and prognostic factors of patients with hilar cholangiocarcinoma. World J Gastroenterol 2007;13:1422-6.
62. Murakami Y, Uemura K, Sudo T, Hashimoto Y, Nakashima A, Kondo N, Sakabe R, Ohge H, Sueda T. Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma. Ann Surg Oncol 2011;18:651-8.
63. Kobayashi A, Miwa S, Nakata T, Miyagawa S. Disease recurrence patterns after R0 resection of hilar cholangiocarcinoma. Br J Surg 2010;97:56-64.
64. [Gallenwegsleiden]. Leberzentrum der Charité – Universitätsmedizin Berlin, 2018. (Accessed January 11th, 2018, at https://leberzentrum.charite.de/leistungen/therapie/hepatologische_und_gastroenterologische_therapieverfahren/gallenwegsleiden/.)
65. Benson AB, 3rd, D'Angelica MI, Abrams TA, Are C, Bloomston PM, Chang DT, Clary BM, Covey AM, Ensminger WD, Iyer R, Kelley RK, Linehan D, Malafa MP, Meranze SG, Park JO, Pawlik T, Posey JA, Scaife C, Schefter T, Sigurdson ER, Tian GG, Vauthey JN, Venook AP, Yen Y, Zhu AX, Hoffmann KG, McMillian NR, Sundar H. Hepatobiliary cancers, version 2.2014. J Natl Compr Canc Netw 2014;12:1152-82.
66. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-81.
67. [Radiofrequenzablation (RFA) zur Behandlung von Lebertumoren]. Leberzentrum der Charité – Universitätsmedizin Berlin, 2018. (Accessed January 11th, 2018, at https://leberzentrum.charite.de/leistungen/therapie/radiologische_therapieverfahren/rfa/.)
68. Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, Rosen CB. Liver transplantation for unresectable perihilar cholangiocarcinoma. Semin Liver Dis 2004;24:201-7.
69. Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, Botha JF, Mezrich JD, Chapman WC, Schwartz JJ, Hong JC, Emond JC, Jeon H, Rosen CB, Gores GJ, Heimbach JK. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology 2012;143:88-98.e3; quiz e14.
70. Coelen RJS, Ruys AT, Besselink MGH, Busch ORC, van Gulik TM. Diagnostic accuracy of staging laparoscopy for detecting metastasized or locally advanced perihilar cholangiocarcinoma: a systematic review and meta-analysis. Surg Endosc 2016;30:4163-73.
71. Ahrendt SA, Nakeeb A, Pitt HA. Cholangiocarcinoma. Clin Liver Dis 2001;5:191-218.
72. Mizuno T, Ebata T, Nagino M. Advanced hilar cholangiocarcinoma: An aggressive surgical approach for the treatment of advanced hilar cholangiocarcinoma: Perioperative management, extended procedures, and multidisciplinary approaches. Surg Oncol 2020;33:201-6.

73. Nagino M. Surgical Treatment of Perihilar Cholangiocarcinoma: Resection or Transplant? Ann Surg 2018;267:806-7.
74. Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, Wex C, Lobeck H, Hintze R. Extended resections for hilar cholangiocarcinoma. Ann Surg 1999;230:808-18; discussion 19.
75. [Chirurgische Therapieverfahren]. Leberzentrum der Charité – Universitätsmedizin Berlin, 2018. (Accessed January 11th, 2018, at https://leberzentrum.charite.de/leistungen/therapie/chirurgische_therapieverfahren/.)
76. Aoba T, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y, Nagino M. Assessment of nodal status for perihilar cholangiocarcinoma: location, number, or ratio of involved nodes. Ann Surg 2013;257:718-25.
77. Shinohara K, Ebata T, Shimoyama Y, Mizuno T, Yokoyama Y, Yamaguchi J, Onoe S, Watanabe N, Nagino M. A Study on Radial Margin Status in Resected Perihilar Cholangiocarcinoma. Ann Surg 2019.
78. Sweigert PJ, Eguia E, Baker MS, Paredes AZ, Tsilimigras DI, Dillhoff M, Ejaz A, Cloyd J, Tsung A, Pawlik TM. Assessment of textbook oncologic outcomes following pancreaticoduodenectomy for pancreatic adenocarcinoma. J Surg Oncol 2020;121:936-44.
79. Tsilimigras DI, Sahara K, Moris D, Mehta R, Paredes AZ, Ratti F, Marques HP, Soubrane O, Lam V, Poultsides GA, Popescu I, Alexandrescu S, Martel G, Workneh A, Guglielmi A, Hugh T, Aldrighetti L, Weiss M, Bauer TW, Maithel SK, Pulitano C, Shen F, Koerkamp BG, Endo I, Pawlik TM. Assessing Textbook Outcomes Following Liver Surgery for Primary Liver Cancer Over a 12-Year Time Period at Major Hepatobiliary Centers. Ann Surg Oncol 2020;27:3318-27.
80. Mehta R, Paredes AZ, Tsilimigras DI, Moro A, Sahara K, Farooq A, Dillhoff M, Cloyd JM, Tsung A, Ejaz A, Pawlik TM. Influence of hospital teaching status on the chance to achieve a textbook outcome after hepatopancreatic surgery for cancer among Medicare beneficiaries. Surgery 2020;168:92-100.
81. van Roessel S, Mackay TM, van Dieren S, van der Schelling GP, Nieuwenhuijs VB, Bosscha K, van der Harst E, van Dam RM, Liem MSL, Festen S, Stommel MWJ, Roos D, Wit F, Molenaar IQ, de Meijer VE, Kazemier G, de Hingh I, van Santvoort HC, Bonsing BA, Busch OR, Groot Koerkamp B, Besselink MG, Dutch Pancreatic Cancer G. Textbook Outcome: Nationwide Analysis of a Novel Quality Measure in Pancreatic Surgery. Ann Surg 2020;271:155-62.
82. Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, Anthony A, Corrie P, Falk S, Finch-Jones M, Wasan H, Ross P, Wall L, Wadsley J, Evans JTR, Stocken D, Praseedom R, Ma YT, Davidson B, Neoptolemos JP, Iveson T, Raftery J, Zhu S, Cunningham D, Garden OJ, Stubbs C, Valle JW, Bridgewater J, group Bs. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol 2019;20:663-73.
83. Nakeeb A, Pitt HA. Radiation therapy, chemotherapy and chemoradiation in hilar cholangiocarcinoma. HPB (Oxford) 2005;7:278-82.
84. Bisello S, Buwenge M, Palloni A, Autorino R, Cellini F, Macchia G, Deodato F, Cilla S, Brandi G, Tagliaferri L, Cammelli S, Valentini V, Morganti AG, Mattiucci GC. Radiotherapy or Chemoradiation in Unresectable Biliary Cancer: A Retrospective Study. Anticancer Res 2019;39:3095-100.
85. Li H, Zhang ZY, Zhou ZQ, Guan J, Tong DN, Zhou GW. Combined gemcitabine and S-1 chemotherapy for treating unresectable hilar

cholangiocarcinoma: a randomized open-label clinical trial. Oncotarget 2016;7:26888-97.
86. Morine Y, Shimada M, Ikemoto T, Arakawa Y, Iwahashi S, Saito YU, Yamada S, Imura S. Effect of Adjuvant Gemcitabine Combined with Low-dose 5-Fluorouracil and Cisplatin Chemotherapy for Advanced Biliary Carcinoma. Anticancer Res 2017;37:6421-8.
87. Belkouz A, Nooijen LE, Riady H, Franken LC, van Oijen MGH, Punt CJA, Erdmann JI, Klümpen HJ. Efficacy and safety of systemic induction therapy in initially unresectable locally advanced intrahepatic and perihilar cholangiocarcinoma: A systematic review. Cancer Treat Rev 2020;91:102110.
88. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J, Investigators ABCT. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-81.
89. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
90. Jonas S, Krenzien F, Atanasov G, Hau HM, Gawlitza M, Moche M, Wiltberger G, Pratschke J, Schmelzle M. Hilar en bloc resection for hilar cholangiocarcinoma in patients with limited liver capacities-preserving parts of liver segment 4. Eur Surg 2018;50:22-9.
91. IUA C. TNM Classification of Malignant Tumors. 8th edition ed. New York: Wiley-Liss 2018.
92. Hiess M, Ponholzer A, Lamche M, Schramek P, Seitz C. [The Clavien-Dindo classification of complications used for radical prostatectomy]. Wien Med Wochenschr 2014;164:297-301.
93. Ghidini M, Pizzo C, Botticelli A, Hahne JC, Passalacqua R, Tomasello G, Petrelli F. Biliary tract cancer: current challenges and future prospects. Cancer Manag Res 2019;11:379-88.
94. Belkouz A, Wilmink JW, Haj Mohammad N, Hagendoorn J, de Vos-Geelen J, Dejong CHC, Homs MYV, Groot Koerkamp B, van Gulik TM, van Oijen MGH, Punt CJA, Klümpen H. Advances in adjuvant therapy of biliary tract cancer: an overview of current clinical evidence based on phase II and III trials. Crit Rev Oncol Hematol 2020;151:102975.
95. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513-20.
96. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173:676-82.
97. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
98. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.
99. Amin MB ES, Greene FL, et al. Perihilar Bile Ducts. In: Amin MB, Edge S, Greene F, et al., eds. AJCC Cancer Staging Manual 8th ed. New York: Springer International Publishing; 2017:311-6.

100. Kimbrough CW, Cloyd JM, Pawlik TM. Surgical approaches for the treatment of perihilar cholangiocarcinoma. Expert Rev Anticancer Ther 2018;18:673-83.
101. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BJ, Youssef BM, Klimstra D, Blumgart LH. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507-17; discussion 17-9.
102. Seyama Y, Kubota K, Sano K, Noie T, Takayama T, Kosuge T, Makuuchi M. Long-term outcome of extended hemihepatectomy for hilar bile duct cancer with no mortality and high survival rate. Ann Surg 2003;238:73-83.
103. Murakami Y, Uemura K, Sudo T, Hashimoto Y, Kondo N, Nakagawa N, Muto T, Sasaki H, Urabe K, Sueda T. Perineural invasion in extrahepatic cholangiocarcinoma: prognostic impact and treatment strategies. J Gastrointest Surg 2013;17:1429-39.
104. Endo I, House MG, Klimstra DS, Gönen M, D'Angelica M, Dematteo RP, Fong Y, Blumgart LH, Jarnagin WR. Clinical significance of intraoperative bile duct margin assessment for hilar cholangiocarcinoma. Ann Surg Oncol 2008;15:2104-12.
105. Abd ElWahab M, El Nakeeb A, El Hanafy E, Sultan AM, Elghawalby A, Askr W, Ali M, Abd El Gawad M, Salah T. Predictors of long term survival after hepatic resection for hilar cholangiocarcinoma: A retrospective study of 5-year survivors. World J Gastrointest Surg 2016;8:436-43.
106. Kondo N, Murakami Y, Uemura K, Sudo T, Hashimoto Y, Sasaki H, Sueda T. Elevated perioperative serum CA 19-9 levels are independent predictors of poor survival in patients with resectable cholangiocarcinoma. J Surg Oncol 2014;110:422-9.
107. Groot Koerkamp B, Fong Y. Outcomes in biliary malignancy. J Surg Oncol 2014;110:585-91.
108. Shirai K, Ebata T, Oda K, Nishio H, Nagasaka T, Nimura Y, Nagino M. Perineural invasion is a prognostic factor in intrahepatic cholangiocarcinoma. World J Surg 2008;32:2395-402.
109. Dinant S, Gerhards MF, Rauws EA, Busch OR, Gouma DJ, van Gulik TM. Improved outcome of resection of hilar cholangiocarcinoma (Klatskin tumor). Ann Surg Oncol 2006;13:872-80.
110. Hirano S, Kondo S, Tanaka E, Shichinohe T, Tsuchikawa T, Kato K, Matsumoto J, Kawasaki R. Outcome of surgical treatment of hilar cholangiocarcinoma: a special reference to postoperative morbidity and mortality. J Hepatobiliary Pancreat Sci 2010;17:455-62.
111. Su CH, Tsay SH, Wu CC, Shyr YM, King KL, Lee CH, Lui WY, Liu TJ, P'Eng F K. Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. Ann Surg 1996;223:384-94.
112. Sano T, Shimada K, Sakamoto Y, Yamamoto J, Yamasaki S, Kosuge T. One hundred two consecutive hepatobiliary resections for perihilar cholangiocarcinoma with zero mortality. Ann Surg 2006;244:240-7.
113. Olthof PB, Aldrighetti L, Alikhanov R, Cescon M, Groot Koerkamp B, Jarnagin WR, Nadalin S, Pratschke J, Schmelze M, Sparrelid E, Lang H, Guglielmi A, van Gulik TM, Perihilar Cholangiocarcinoma Collaboration G. Portal Vein Embolization is Associated with Reduced Liver Failure and Mortality in High-Risk Resections for Perihilar Cholangiocarcinoma. Ann Surg Oncol 2020;27:2311-8.
114. Ebata T, Mizuno T, Yokoyama Y, Igami T, Sugawara G, Nagino M. Surgical resection for Bismuth type IV perihilar cholangiocarcinoma. Br J Surg 2018;105:829-38.

115. Matsumoto N, Ebata T, Yokoyama Y, Igami T, Sugawara G, Shimoyama Y, Nagino M. Role of anatomical right hepatic trisectionectomy for perihilar cholangiocarcinoma. Br J Surg 2014;101:261-8.
116. Nagino M, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. Ann Surg 2013;258:129-40.
117. Olthof PB, Miyasaka M, Koerkamp BG, Wiggers JK, Jarnagin WR, Noji T, Hirano S, van Gulik TM. A comparison of treatment and outcomes of perihilar cholangiocarcinoma between Eastern and Western centers. HPB (Oxford) 2019;21:345-51.
118. Xiang S, Lau WY, Chen XP. Hilar cholangiocarcinoma: controversies on the extent of surgical resection aiming at cure. Int J Colorectal Dis 2015;30:159-71.
119. Heise M, Jandt K, Rauchfuss F, Settmacher U. [Management of complications after liver resection]. Zentralbl Chir 2010;135:112-20.
120. Igami T, Nishio H, Ebata T, Yokoyama Y, Sugawara G, Nimura Y, Nagino M. Surgical treatment of hilar cholangiocarcinoma in the "new era": the Nagoya University experience. J Hepatobiliary Pancreat Sci 2010;17:449-54.
121. Abbas S, Sandroussi C. Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. HPB (Oxford) 2013;15:492-503.
122. Sewnath ME, Karsten TM, Prins MH, Rauws EJ, Obertop H, Gouma DJ. A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. Ann Surg 2002;236:17-27.
123. Moole H, Bechtold M, Puli SR. Efficacy of preoperative biliary drainage in malignant obstructive jaundice: a meta-analysis and systematic review. World J Surg Oncol 2016;14:182.
124. Fang Y, Gurusamy KS, Wang Q, Davidson BR, Lin H, Xie X, Wang C. Meta-analysis of randomized clinical trials on safety and efficacy of biliary drainage before surgery for obstructive jaundice. Br J Surg 2013;100:1589-96.
125. Iacono C, Ruzzenente A, Campagnaro T, Bortolasi L, Valdegamberi A, Guglielmi A. Role of preoperative biliary drainage in jaundiced patients who are candidates for pancreatoduodenectomy or hepatic resection: highlights and drawbacks. Ann Surg 2013;257:191-204.
126. van der Gaag NA, Kloek JJ, de Castro SM, Busch OR, van Gulik TM, Gouma DJ. Preoperative biliary drainage in patients with obstructive jaundice: history and current status. J Gastrointest Surg 2009;13:814-20.
127. Jara M, Reese T, Malinowski M, Valle E, Seehofer D, Puhl G, Neuhaus P, Pratschke J, Stockmann M. Reductions in post-hepatectomy liver failure and related mortality after implementation of the LiMAx algorithm in preoperative work-up: a single-centre analysis of 1170 hepatectomies of one or more segments. HPB (Oxford) 2015;17:651-8.
128. Denecke T, Seehofer D, Steffen IG, Grieser C, Stelter L, Schnapauff D, Rothe JH, Weigelt A, Pech M, Langrehr J, Podrabsky P, Neuhaus P, Hänninen EL. Arterial versus portal venous embolization for induction of hepatic hypertrophy before extended right hemihepatectomy in hilar cholangiocarcinomas: a prospective randomized study. J Vasc Interv Radiol 2011;22:1254-62.
129. Glantzounis GK, Tokidis E, Basourakos SP, Ntzani EE, Lianos GD, Pentheroudakis G. The role of portal vein embolization in the surgical management

of primary hepatobiliary cancers. A systematic review. Eur J Surg Oncol 2017;43:32-41.
130. Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nagino M. Portal vein embolization before extended hepatectomy for biliary cancer: current technique and review of 494 consecutive embolizations. Dig Surg 2012;29:23-9.
131. Rea DJ, Munoz-Juarez M, Farnell MB, Donohue JH, Que FG, Crownhart B, Larson D, Nagorney DM. Major hepatic resection for hilar cholangiocarcinoma: analysis of 46 patients. Arch Surg 2004;139:514-23; discussion 23-5.
132. Lee SG, Song GW, Hwang S, Ha TY, Moon DB, Jung DH, Kim KH, Ahn CS, Kim MH, Lee SK, Sung KB, Ko GY. Surgical treatment of hilar cholangiocarcinoma in the new era: the Asan experience. J Hepatobiliary Pancreat Sci 2010;17:476-89.
133. Neuhaus P, Jonas S, Settmacher U, Thelen A, Benckert C, Lopez-Hänninen E, Hintze RE. Surgical management of proximal bile duct cancer: extended right lobe resection increases resectability and radicality. Langenbecks Arch Surg 2003;388:194-200.
134. Natsume S, Ebata T, Yokoyama Y, Igami T, Sugawara G, Shimoyama Y, Nagino M. Clinical significance of left trisectionectomy for perihilar cholangiocarcinoma: an appraisal and comparison with left hepatectomy. Ann Surg 2012;255:754-62.
135. van Gulik TM, Ruys AT, Busch OR, Rauws EA, Gouma DJ. Extent of liver resection for hilar cholangiocarcinoma (Klatskin tumor): how much is enough? Dig Surg 2011;28:141-7.
136. Miyazaki M, Kimura F, Shimizu H, Yoshidome H, Otuka M, Kato A, Yoshitomi H, Furukawa K, Takeuchi D, Takayashiki T, Suda K, Takano S. One hundred seven consecutive surgical resections for hilar cholangiocarcinoma of Bismuth types II, III, IV between 2001 and 2008. J Hepatobiliary Pancreat Sci 2010;17:470-5.
137. Paik KY, Choi DW, Chung JC, Kang KT, Kim SB. Improved survival following right trisectionectomy with caudate lobectomy without operative mortality: surgical treatment for hilar cholangiocarcinoma. J Gastrointest Surg 2008;12:1268-74.
138. Kondo S, Hirano S, Ambo Y, Tanaka E, Okushiba S, Morikawa T, Katoh H. Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins: results of a prospective study. Ann Surg 2004;240:95-101.
139. Hirano S, Tanaka E, Shichinohe T, Suzuki O, Hazama K, Kitagami H, Okamura K, Yano T, Kondo S. Treatment strategy for hilar cholangiocarcinoma, with special reference to the limits of ductal resection in right-sided hepatectomies. J Hepatobiliary Pancreat Surg 2007;14:429-33.
140. Nagino M. Perihilar cholangiocarcinoma: a surgeon's viewpoint on current topics. J Gastroenterol 2012;47:1165-76.
141. Zhang XF, Beal EW, Chakedis J, Chen Q, Lv Y, Ethun CG, Salem A, Weber SM, Tran T, Poultsides G, Son AY, Hatzaras I, Jin L, Fields RC, Buettner S, Scoggins C, Martin RCG, Isom CA, Idrees K, Mogal HD, Shen P, Maithel SK, Schmidt CR, Pawlik TM. Defining Early Recurrence of Hilar Cholangiocarcinoma After Curative-intent Surgery: A Multi-institutional Study from the US Extrahepatic Biliary Malignancy Consortium. World J Surg 2018;42:2919-29.
142. Valle JW, Furuse J, Jitlal M, Beare S, Mizuno N, Wasan H, Bridgewater J, Okusaka T. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. Ann Oncol 2014;25:391-8.

143. Agarwal R, Sendilnathan A, Siddiqi NI, Gulati S, Ghose A, Xie C, Olowokure OO. Advanced biliary tract cancer: clinical outcomes with ABC-02 regimen and analysis of prognostic factors in a tertiary care center in the United States. J Gastrointest Oncol 2016;7:996-1003.
144. Malka D, Cervera P, Foulon S, Trarbach T, de la Fouchardière C, Boucher E, Fartoux L, Faivre S, Blanc JF, Viret F, Assenat E, Seufferlein T, Herrmann T, Grenier J, Hammel P, Dollinger M, André T, Hahn P, Heinemann V, Rousseau V, Ducreux M, Pignon JP, Wendum D, Rosmorduc O, Greten TF. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. Lancet Oncol 2014;15:819-28.
145. Chen JS, Hsu C, Chiang NJ, Tsai CS, Tsou HH, Huang SF, Bai LY, Chang IC, Shiah HS, Ho CL, Yen CJ, Lee KD, Chiu CF, Rau KM, Yu MS, Yang Y, Hsieh RK, Chang JY, Shan YS, Chao Y, Chen LT. A KRAS mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in combination with cetuximab in advanced biliary tract cancer. Ann Oncol 2015;26:943-9.
146. Buettner S, van Vugt JLA, Gaspersz MP, Coelen RJS, Roos E, Labeur TA, Margonis GA, Ethun CG, Maithel SK, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick BA, Weber SM, Salem A, Martin RCG, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, JNM IJ, van Gulik TM, Pawlik TM, Groot Koerkamp B. Survival after resection of perihilar cholangiocarcinoma in patients with lymph node metastases. HPB (Oxford) 2017;19:735-40.
147. Mao K, Liu J, Sun J, Zhang J, Chen J, Pawlik TM, Jacobs LK, Xiao Z, Wang J. Patterns and prognostic value of lymph node dissection for resected perihilar cholangiocarcinoma. J Gastroenterol Hepatol 2016;31:417-26.
148. Kambakamba P, Linecker M, Slankamenac K, DeOliveira ML. Lymph node dissection in resectable perihilar cholangiocarcinoma: a systematic review. Am J Surg 2015;210:694-701.
149. Govil S, Reddy MS, Rela M. Surgical resection techniques for locally advanced hilar cholangiocarcinoma. Langenbecks Arch Surg 2014;399:707-16.
150. Shinohara K, Ebata T, Shimoyama Y, Mizuno T, Yokoyama Y, Yamaguchi J, Onoe S, Watanabe N, Nagino M. A Study on Radial Margin Status in Resected Perihilar Cholangiocarcinoma. Ann Surg 2021;273:572-8.
151. Juntermanns B, Kaiser GM, Reis H, Gries S, Kasper S, Paul A, Canbay A, Fingas CD. Long-term Survival after resection for perihilar cholangiocarcinoma: Impact of UICC staging and surgical procedure. Turk J Gastroenterol 2019;30:454-60.
152. Unno M, Katayose Y, Rikiyama T, Yoshida H, Yamamoto K, Morikawa T, Hayashi H, Motoi F, Egawa S. Major hepatectomy for perihilar cholangiocarcinoma. J Hepatobiliary Pancreat Sci 2010;17:463-9.
153. Higuchi R, Yazawa T, Uemura S, Izumo W, Ota T, Kiyohara K, Furukawa T, Egawa H, Yamamoto M. Surgical Outcomes for Perihilar Cholangiocarcinoma with Vascular Invasion. J Gastrointest Surg 2019;23:1443-53.
154. Golse N, Nunez J, Mazzotta A, Cano L, Bergeat D, Sulpice L, Jeddou H, Abdelrafee A, Sa Cunha A, Cherqui D, Adam R, Boudjema K, Vibert E. Personalized Preoperative Nomograms Predicting Postoperative Risks after Resection of Perihilar Cholangiocarcinoma. World J Surg 2020;44:3449-60.
155. Massironi S, Pilla L, Elvevi A, Longarini R, Rossi RE, Bidoli P, Invernizzi P. New and Emerging Systemic Therapeutic Options for Advanced Cholangiocarcinoma. Cells 2020;9.

156. Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, Nagino M, Kondo S, Nagaoka S, Funai J, Koshiji M, Nambu Y, Furuse J, Miyazaki M, Nimura Y. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 2010;103:469-74.
157. Lee J, Park SH, Chang HM, Kim JS, Choi HJ, Lee MA, Jang JS, Jeung HC, Kang JH, Lee HW, Shin DB, Kang HJ, Sun JM, Park JO, Park YS, Kang WK, Lim HY. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2012;13:181-8.
158. Messina C, Merz V, Frisinghelli M, Trentin C, Grego E, Veccia A, Salati M, Messina M, Carnaghi C, Caffo O. Adjuvant chemotherapy in resected bile duct cancer: A systematic review and meta-analysis of randomized trials. Crit Rev Oncol Hematol 2019;143:124-9.
159. Mansour JC, Aloia TA, Crane CH, Heimbach JK, Nagino M, Vauthey JN. Hilar cholangiocarcinoma: expert consensus statement. HPB (Oxford) 2015;17:691-9.
160. Chauhan A, House MG, Pitt HA, Nakeeb A, Howard TJ, Zyromski NJ, Schmidt CM, Ball CG, Lillemoe KD. Post-operative morbidity results in decreased long-term survival after resection for hilar cholangiocarcinoma. HPB (Oxford) 2011;13:139-47.

9 Appendix

9.1 Statutory declaration (Eidesstattliche Versicherung)

„Ich, Alexa Christina Mieg, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema „Ein maßgeschneidertes Vorgehen bei perihilärem Gallengangskarzinom und positivem Lymphknotenstatus“/ „A tailored approach in lymph node positive 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.“

Datum Unterschrift

9.2 Curriculum vitae

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

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