Aus der Universitätsklinik für Allgemeine, Viszeral- und Transplantationschirurgie Tübingen

Associated Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) for Cholangiocarcinoma: a single center experience.

Inaugural-Dissertation

zur Erlangung

des Doktorgrades der Medizin

der Medizinischen Fakultät

der Eberhard Karls Universität

zu Tübingen

vorgelegt von

Capobianco, Ivan

Promotionsjahr

2021

Dekan: Professor Dr. B. Pichler

1. Berichterstatter: Professor Dr. S. Nadalin
2. Berichterstatter: Professor Dr. R. R. Plentz

Tag der Disputation: 13.01.2021

SUMMARY

Abbreviations

99mTc-GSA: 99mTc-Galactosyl Serum Albumin Scintigraphy

AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control

ALPPS: Associating Liver Partition and Portal vein ligation for Staged hepatectomy

ALPPS-RS 1 or 2: ALPPS Risk Score before Stage 1 or before Stage 2

ASA: American Society of Anesthesiologists

BD: Biliary Drainage

BDA: BilioDigestive Anastomosis

BMI: Body Mass Index

BSA: Body Surface Area

CASH: Chemotherapy Associated SteatoHepatitis

CCA: CholangioCArcinoma

CHD: Common Hepatic Duct

CHE: cholinesterase

CRLM: ColoRectal Liver Metastasis

CT: ComputerTomography

dCCA: Distal CholangioCarcinoma

DFS: Disease-Free Survival

E-AHPBA: European-African Hepato-Pancreato-Biliary Association

eLVD: extended Liver Venous Deprivation

ERCP: Endoscopic Retrograde CholangioPancreatography

Fig.: Figure

FLR/BW: FLR Volume to Body Weight ratio

FLR/TLV: FLR to Total Liver Volume

FLR: Future Liver Remnant

FUP: Follow-Up

HA: Hepatic Artery

HAT: Hepatic Artery Thrombosis

HPB-Surgery: Hepato-Pacreato-Biliary Surgery

HBS: HepatoBiliary Scintigraphy

HCC: HepatoCellular Carcinoma

HIDA: 99mTc-Mebrofenin Hepatobiliary Scintigraphy

HVE: Hepatic Vein Embolization

iCCA: Intrahepatic CholagioCArcinoma

ICG: Indocyanine green Clearance Test

ICU: Intensive Care Unit

IHPB: International Hepato-Pancreato-Biliary association

IOUS: IntraOperative UltraSound

IPN: Intraductal Papillary Neoplasm

KGR: Kinetic Growth Rate

LHA: Left Hepatic Artery

LHD: left hepatic (or bile) duct

LiMAx: 13C-Methacetin Breath Test

LPV: Left Portal Vein

M&M: Morbidity and Mortality

MELD(-Score): Model for End-stage Liver Disease (-Score)

MHV: Middle Hepatic Vein

MRI: Magnetic Resonance Imaging

MVG: Median Volume Gain

MWA: MicroWave Ablation

OS: Overall Survival

p-ALPPS: partial ALPPS

pFLRF: predicted Future Liver Remnant Function

phCCA: PeriHilar CholangioCArcinoma

PHLF: Post-Hepatectomy Liver Failure

PIPAC: Pressurized IntraPeritoneal Aerosol Chemotherapy

POD: PostOperative Day

PTCD: Percutaneous Transhepatic Cholangiography Drainage

PV: Portal Vein

PVE: Portal Vein Embolization

PVL: Portal Vein Ligation

PVO: Portal Vein Occlusion

PVP: Portal Vein Pressure

PVT: Portal Vein Thrombosis

RALPPS: Radiofrequency-assisted ALPPS

RCT: Randomized Control Trial

RFA: RadioFrequency Ablation

RHA: Right Hepatic Artery

RHD: Right Hepatic (or bile) Duct

RPV: Right Portal Vein

sFLR: standardized Future Liver Remnant

SIRT: Selective Internal RadioTherapy

SOP: Standard Operating Procedures

sTLV: standardized Total Liver Volume

TLV: Total Liver Volume

TSH: Two-Stage Hepatectomy

1 INTRODUCTION

1.1 CHOLANGIOCARCINOMA (CCA) - AN OVERVIEW

Cholangiocarcinoma (CCA) remains a major challenge among liver tumors. It is defined as a tumor that arises from bile ducts.

1.1.1 Anatomical classification

Based on location, it can be classified into intrahepatic (iCCA), perihilar (phCCA) and distal cholangiocarcinoma (dCCA). From a surgical point of view, the first two involve the liver, while the last one is mostly isolated or involves the pancreas, therefore only the first two will be discussed here.

phCCA can be further anatomically classified according to the Bismuth-Corlette classification (see Fig. 1). It differentiates four types of tumor by focusing on bile duct invasion (1, 2).

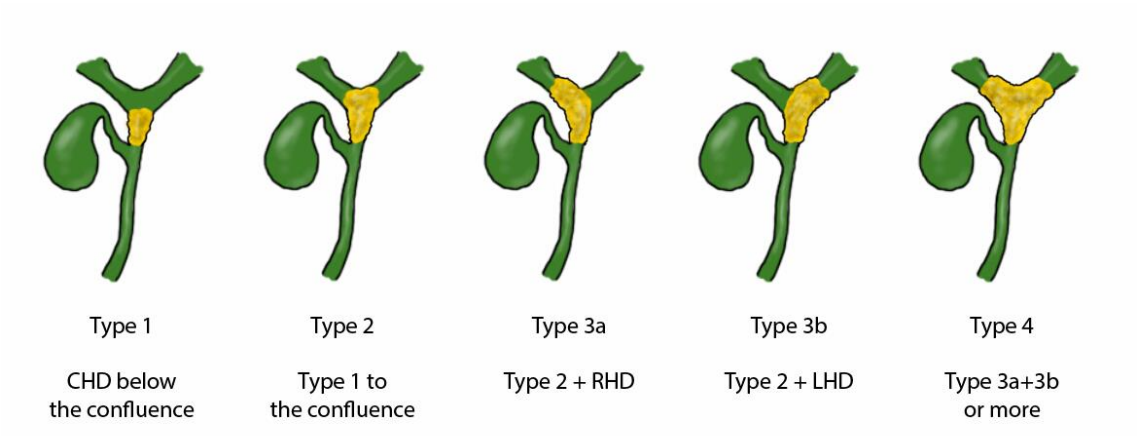


Figure 1 - *The Bismuth-Corlette classification for phCCA. CHD: Common Hepatic Duct; LHD: main Left Hepatic Duct; phCCA: perihilar Cholangiocarcinoma; RHD: main Right Hepatic Duct.*

1.1.2 Etiology

CCA develops in a context of chronic inflammation, with many different known genetic or epigenetic risk factors causing chronic liver disease (see Table 1) (1, 3). In Western countries, however, a specific cause can only be identified in about 50% of cases (3, 4).

	Strong association	***Weak or moderate association***
Risk factors for CCA	• Bile duct cysts • Caroli's disease • PSC/Cholangitis • Hepatolithiasis* • Cholelithiasis/ choledocholithiasis • Cirrhosis • HBV* • HCV* • Opisthorchis viverrini • Clonorchis sinensis • NAFLD/NASH • Thorotrast • 1,2-dichloropropane • Asbestos*	• Hemochromatosis • IBD • Chronic pancreatitis** • Duodenal/gastric ulcer • Diabetes type II • Obesity • Alcohol • Cigarette smoking

Table 1 - *Risk factors associated with CCA. *strong association only for iCCA; ** weak association for iCCA but strong for extrahepatic CCA (including phCCA and dCCA). Table adapted from Khan et al. (3). CCA: Cholangiocarcinoma; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; IBD: Inflammatory Bowel Diseases; NAFLD/NASH: Non-Alcoholic Fatty Liver Disease / Non-Alcoholic Steatohepatitis; PSC: Primary Sclerosing Cholangitis.*

1.1.3 Epidemiology

The distribution of CCA varies widely worldwide, reflecting a different distribution of risk factors, with an incidence ranging from 0.3-3.4 per 100,000 inhabitants in Western countries to 3.1-15 per 100,000 in Asian countries (with a peak of 85 per 100,000 reported in North East Thailand!)(3).

phCCA represents 50-70% of all CCAs, while iCCA represents 10% (1, 4-6). However, an increasing incidence of iCCA has been repeatedly reported in recent decades (3, 7-9).

1.1.4 Diagnosis and Therapy

The diagnosis of CCA, both for iCCA and phCCA, is often late, mainly due to lack of symptoms in the early stages, and proper preoperative staging is challenging.

To date, no systemic therapy has demonstrated clear efficacy (10, 11) and surgery, if radical resection is possible, remains the only curative option (12).

1.1.5 Overall Survival

Median Overall Survival (OS) after surgery for both phCCA and iCCA is about 20-45 months (11, 13-17) with 1-, 3- and 5- year OS rates of 80-86%, 50-60% and 15-60% for iCCA and 70-80%, 27-42% and 13-40% (11, 17-25) for phCCA respectively (see Fig. 2).

These results vary depending on the type and size of the tumor, biology, localization, vascular and perineural invasion, nodal involvement, comorbidities, type of surgery and related complications (11, 16, 21). In advanced stages, 5-year survival falls below 25% (20, 26).

Unfortunately, about half of the patients are not resectable at the time of laparotomy due to an advanced disease not previously detected (27). Untreated CCA, whether phCCA or iCCA, is rapidly fatal with a median survival rate of 5-12 months (13, 16, 17, 28, 29) (see Fig. 2).

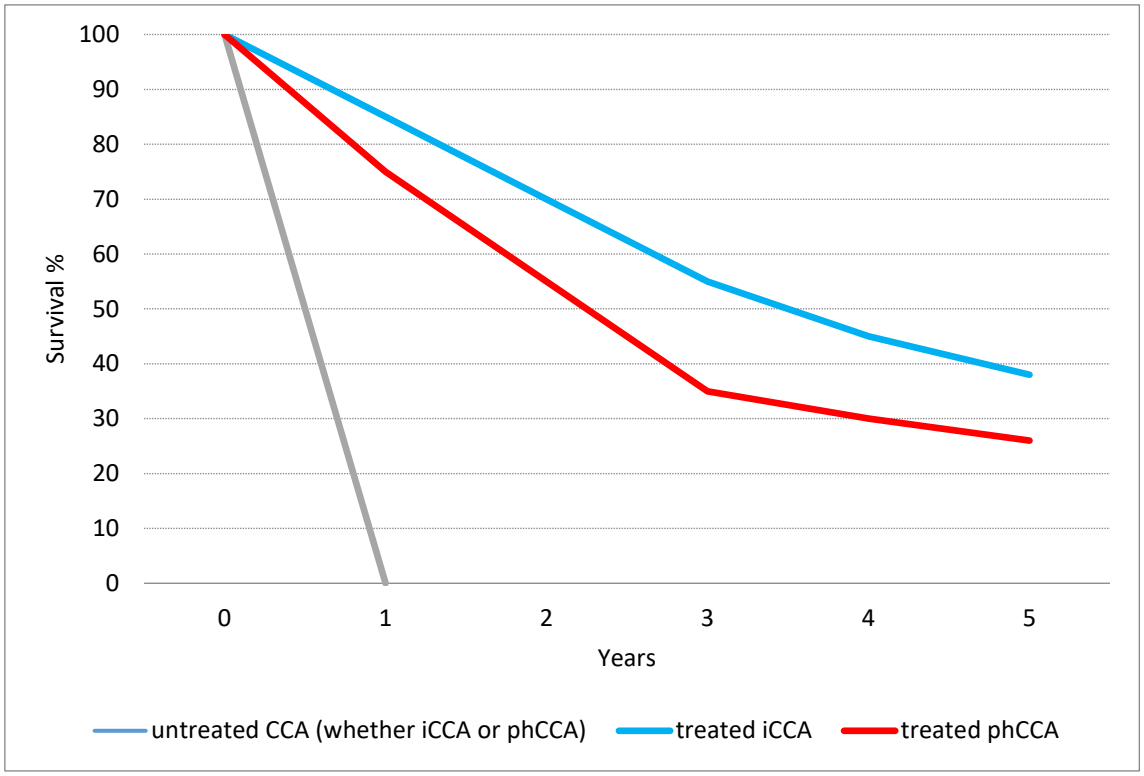


Figure 2 - *Overall survival curves of surgically treated iCCA and phCCA, as well as untreated CCA (whether iCCA or phCCA), based on literature data. CCA: cholangiocarcinoma; iCCA: intrahepatic cholangiocarcinoma; phCCA: perihilar cholangiocarcinoma.*

1.1.6 Surgery and complications

On the other hand, most patients undergoing surgery, particularly those with phCCA, require an extended liver resection, defined as resection of 5 or more liver segments according to the Brisbane's classification (see Fig. 3)(1, 30).

This type of resections are associated with a major morbidity (defined as ≥ IIIa according to Dindo-Clavien classification (31)) ranging from 17% to 66% and a mortality rate ranging from 5 to 16% (32-36).

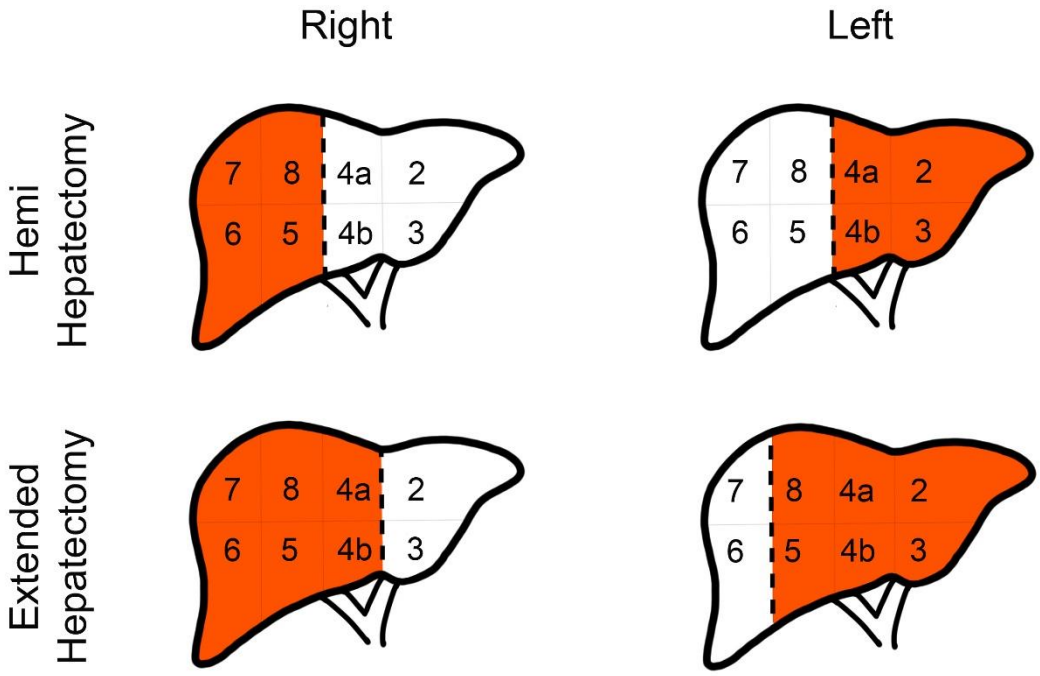


Figure 3 - *Representation of major hepatectomy (right and left hemihepatectomy) and extended hepatectomy (right and left) according to Brisbane's classification (30).*

An insufficient liver remnant after resection (also known as Future Liver Remnant, FLR), either in volume or quality, is a main limit to surgery due to the risk of Post-Hepatectomy Liver Failure (PHLF) and patient mortality (see chapter 1.2 Post-Hepatectomy Liver Failure (PHLF)). PHLF rates are reported up to 35% (37, 38). Mortality in case of PHLF is reported to be over 60% (39).

As mentioned earlier, however, in many cases major hepatectomy is the only therapeutic option for the CCA patient.

Particularly in the case of extended hepatectomy, clinical success depends on the ability of the remnant liver to regenerate through hypertrophy. The regenerative capacity of the liver is a complex interaction between liver condition and pathology, general conditions of the patient and type of augmentation technique used (see Fig. 4). As a result, the clinician is often caught between deciding to give the patient a chance, with a high risk of failure, or to throw in the towel.

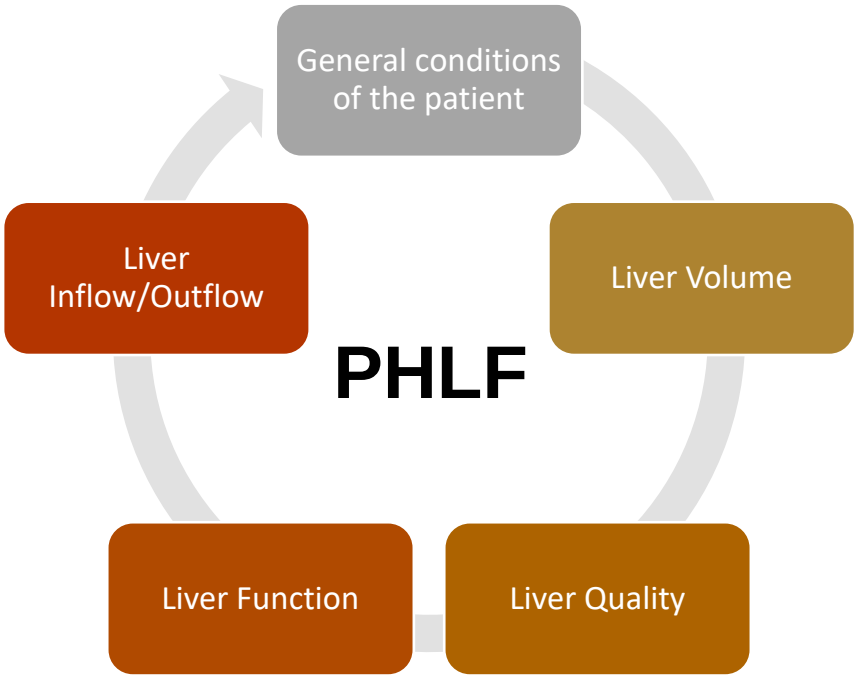


Figure 4 – *The 5 main factors influencing Post-Hepatectomy Liver Failure (PHLF).*

1.1.7 Augmentation Techniques

Novel techniques have been developed to increase the FLR before resection, trying to avoiding a futile outcome and to expand the pool of possible treated patients (see chapter 1.3 Augmentation Techniques).

Currently the gold standard in CCA is the portal vein embolization (PVE) which achieves sufficient hypertrophy of the FLR in about 3-4 weeks after intervention (40). However, a dropout of almost 23% has also been observed in CCA after PVE, mainly due to disease progression (40-42).

Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) is a new surgical augmentation technique introduced in 2007 and consists of a two-stage hepatectomy with right portal vein ligation and parenchymal transection during the first stage, and finalization of the resection

after FLR hypertrophy, usually within two weeks after Stage 1 (see chapter 1.4 ALPPS)(34). The FLR growth rate of this novel technique exceeds any other procedure and opens up the possibility of extended resections with the lowest risk of dropout (34).

However, the high post-operative morbidity (56-73%) and mortality (11-14%) initially reported have led to a fervent debate around the world (34). Following the general consideration, ALPPS is a relative safe and accepted surgical procedure when performed in colorectal liver metastasis (CRLM) (43, 44) but remains controversial for other type of tumors, especially CCA (45, 46). A recent matched control study comparing ALPPS with standard major liver resection for phCCA concluded that ALPPS is not recommended in these high-risk patients (47).

In addition, little is known about long-term oncological results in patients undergoing ALPPS and in particular in patients with CCA.

1.1.8 Aim

This study reviews our single center experience with ALPPS applied to extended hepatectomy (i.e. right trisectionectomy) with the aim of investigating short and long-term outcomes in patients with phCCA and iCCA.

The first part of this Introduction is dedicated to Post-Hepatectomy Liver Failure (PHLF) (see chapter 1.2 Post-Hepatectomy Liver Failure (PHLF)) and augmentation techniques (see chapter 1.3 Augmentation Techniques), the second part presents in particular the ALPPS procedure, its characteristics as well as the perioperative assessment and management of the patient and the liver (see chapter 1.4 ALPPS).

1.2 POST-HEPATECTOMY LIVER FAILURE (PHLF)

According to the International Study Group of Liver Surgery (ISGLS), PHLF is defined as "*a post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5*" (48).

Clinically, patients may present from mild liver failure (Grade A) to multiorgan failure requiring of intensive care (Grade C) (see Table 2).

The PHLF can be alternatively reported using:

- the "50-50" criteria, defined as prothrombin time <50% and serum bilirubin >50 micromol/L on postoperative (POD) day 5 (49)
- the postoperative peak bilirubin > 7 mg/dl proposed by Mullen, but applicable only in non-cirrhotic and non-cholestatic patients (50).

Grade	*Clinical description*	*Treatment*	*Diagnosis*	*Clinical symptoms*	*Location for care*
A	Deterioration in liver function	None	• UOP > 0,5 mL/kg/h • BUN < 150 mg/dl • >90% O2 saturation • INR <1,5	None	Surgical ward
B	Deviation from expected post-operative course without requirement for invasive procedures	Non-invasive: fresh frozen plasma; albumin; diuretics; non-invasive ventilatory support; abdominal ultrasound; CT scan	• UOP ≤ 0,5 mL/kg/h • BUN < 150 mg/dl • <90% O2 saturation despite O2 supplementation • INR ≥1,5 <2	• Ascites • Weight gain • Mild respiratory insufficiency • Confusion • Encephalopathy	IMC or ICU
C	Multi-system failure requiring invasive treatment	Invasive: hemodialysis; intubation; extracorporeal liver support; salvage hepatectomy; vasopressor; glucose; ICP monitor	• UOP ≤ 0,5 mL/kg/h • BUN ≥ 150 mg/dl • ≤85% O2 saturation despite high fraction of inspired oxygen support • INR ≥ 2	• Renal failure • Hemodynamic Instability • Respiratory failure • Large-volume ascites • Encephalopathy	ICU

Table 2 – *ISGLS definition and grading of PHLF (48). BUN: Blood Urea Nitrogen test; IMC: InterMediate Care unit; ICU: Intensive Care Unit; INR: International Normalized Ratio; UOP: Urine Output.*

1.3 AUGMENTATION TECHNIQUES

As introduced above, to improve surgical resectability and reduce PHLF, augmentation procedures have been developed to increase the volume and function of the FLR.

They are recommended in patients with marginally resectable or primarily non-resectable locally advanced liver tumors of any origin, which have shown insufficient FLR either in volume or quality in the preoperative workup (see chapter 1.4.3 Preoperative Workup).

Currently, these include portal vein embolization (PVE) and ligature (PVL), extended liver venous deprivation (eLVD), two-stage hepatectomy (TSH), and Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS). The latter will be discussed in the chapter 1.4 ALPPS.

Before presenting each procedure in detail with the specific potentials of hypertrophy and the associated morbidity and mortality rates, pathophysiological considerations of liver regeneration are described.

1.3.1 Pathophysiology of liver regeneration

The pathophysiology of liver regeneration after portal obstruction and/or hepatectomy is a complex process involving mainly vascular flow (shear stress), buffer response and release of cytokines and other inflammations factors. Each augmentation technique is based on one or more of the following pathways.

It has been shown that in minor liver resections, the contribution to liver regeneration comes from cellular hypertrophy without division, while in extended liver resections, most, but not all, of the initially hypertrophied cells later proliferate (see Fig. 5)(51).

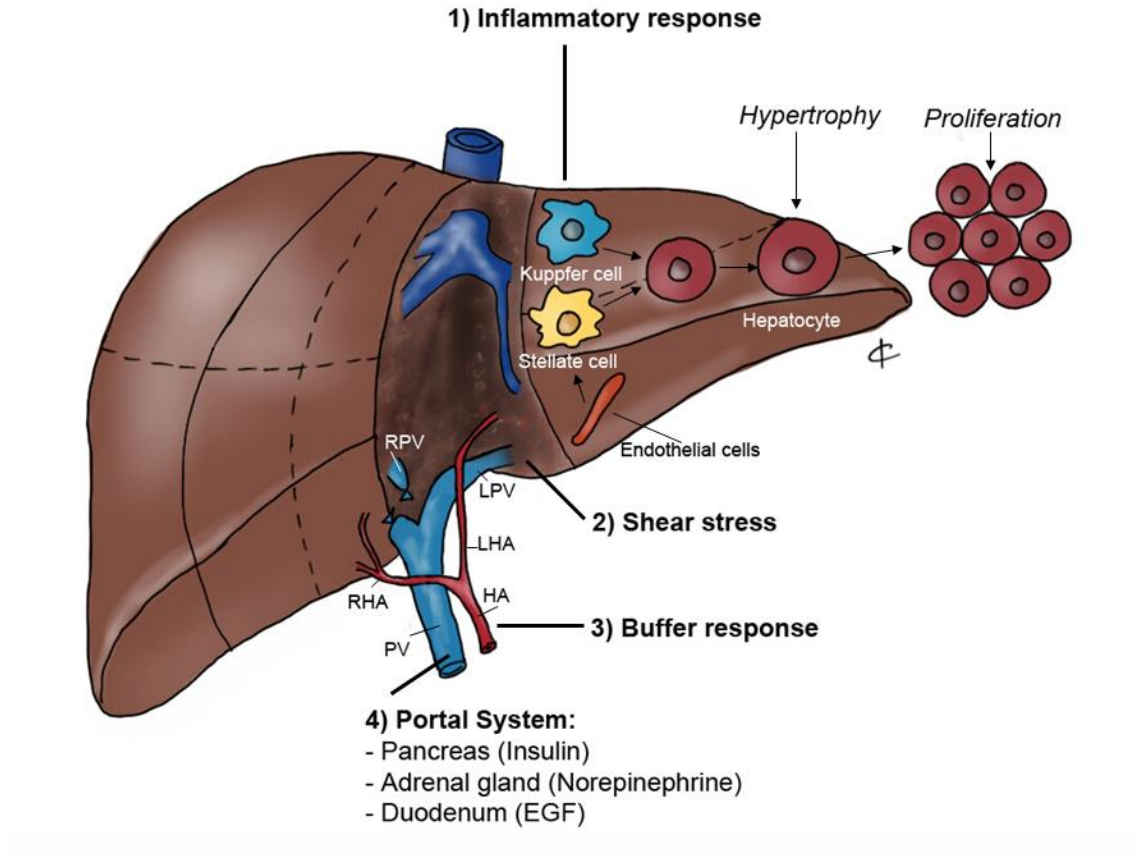


Figure 5 – *Pathways of liver regeneration: 1) inflammatory response, 2) shear stress, 3) buffer response and 4) hepatotrophic factors coming from the portal system. HA: hepatic artery; LHA: left hepatic artery; LPV: left portal vein; PV: portal vein; RHA: right hepatic artery; RPV: right portal vein.*

1.3.1.1 *Inflammatory response and cytokine release*

An acute liver injury, such as a parenchyma transection, triggers an inflammatory response and cytokine release. Many stimulating factors have been identified. Mainly, an early response of the innate immune system, an increase of interleukin (IL)-6, tumor necrosis factor (TNF)-α and cytokine-induced neutrophil chemoattractant (CINC)-1 activate the IL-6-TNF-α-STAT3-pathway and induce liver hypertrophy (52-55). In addition, the activation of Kupffer cells and the release of Vascular Endothelial Growth Factor (VEGF) and interferon gamma (IFNγ) expression has also been detected (56).

The different kinetic of compensatory hypertrophy observed in the various augmentation techniques is attributed to distinct expression in quantity and duration of these factors (52, 57).

In ALPPS an early liver regeneration was shown within 24-48 hours, while in PVL the effect was delayed to 48-72 hours caused by a differential expression of activin and its receptor (58). In a rodent model of ALPPS an increase of IL-6 and TNF-α was observed in the liver tissue already one hour after Stage 1 (53, 59). A hypersecretion of TNF-α leads, however, to apoptosis and irreversible cell damage (37). Therefore, overactivation of inflammatory mediators is not always productive. This partly explains the difference in morbidity and mortality found in different techniques.

1.3.1.2 *Portal hyperflow and shear stress*

Following a portal obstruction, such as in the case of PVE, PVL or partial hepatectomy, there is a sudden increase in portal pressure and flow per gram of tissue in the still portalized liver segments. This generates shear stress on the vascular endothelium (see Fig. 5). Liver sinusoidal endothelial cells (LSECs) are activated to release nitric oxide (NO) and other hepatotrophic factors (such as hepatocyte growth factor (HGF) and transforming growth factor (TGF)α produced from the hepatic stellate cells), which in turn initiates the liver regeneration cascade (60-62).

In addition, the deviation of the portal flow to the FLR causes the redistribution of hepatotrophic factors present in the portal circulation system, such as insulin, norepinephrine and epidermal growth factor (EGF) produced by the pancreas, adrenal glands and duodenum respectively (see Fig. 6)(55).

However, studies on partial graft liver transplantation have shown that an extraordinary increase of the portal vein pressure (PVP) greater than 20 mmHg can damage the liver and cause PHLF even in non-cirrhotic livers (63-66).

Schadde et al. showed that in a group of 15 patients undergoing an ALPPS procedure, portal hyperflow led to an increase in PVP with values that rose from 12 ± 5 mmHg to 18 ± 4 mmHg after ligation of the portal vein and transection of the hepatic parenchyma, and the pressure remained elevated almost up to Stage 2 (67). In addition, Tomassini et al. showed in another cohort of 23 patients that patients with a moderate hemodynamic stress (defined as portal vein pressure (PVP) < 20 mmHg and hepatic to portal vein gradients (HVPG) < 15 mmHg after Stage 1) showed higher FLR regeneration and function that patients above this cutoffs (68).

Finally, the parenchyma partition in ALPPS prevents the formation of collateral during Interstage, as seen on contrary in ex situ angiography on pig model after PVE and PVL (69), which would compromise the effect of portal hyperflow and the redistribution of hepatotrophic factors.

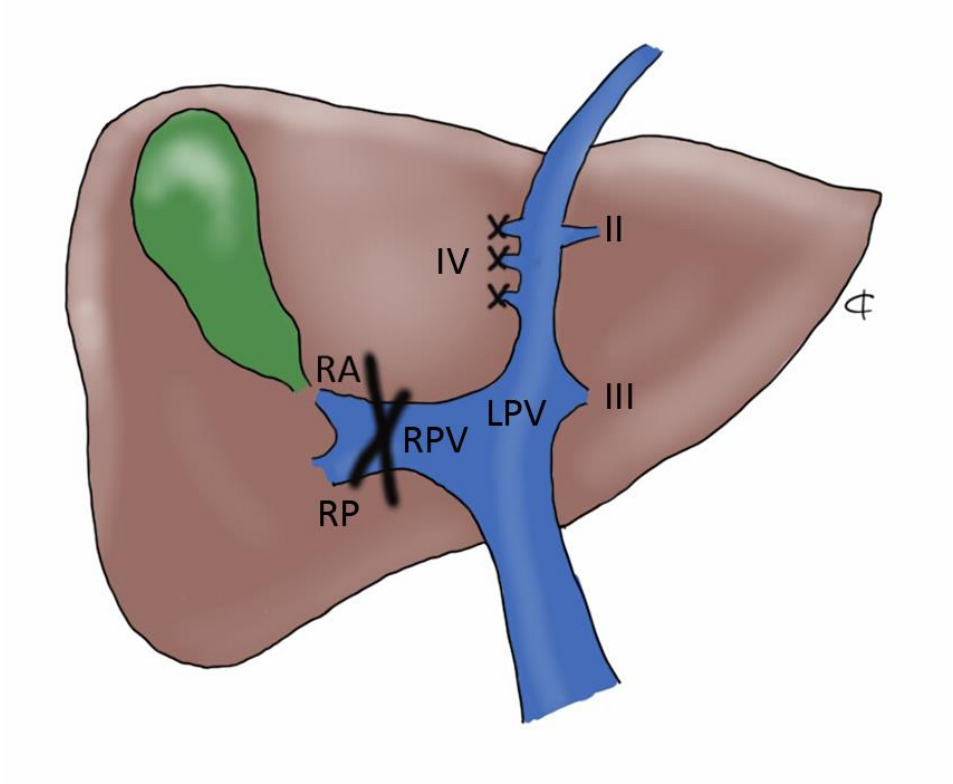


Figure 6 – *Representation of the portal flow situation (e.g. in ALPPS) after obstruction of the right portal vein and the Segment 4-branches: all portal flow is diverted to Segment 2 and 3. II, III, IV: Portal Vein (PV)-branches of Segment II, III and IV LPV: Left PV; RA: right anterior branch of the PV, RP: right posterior branch of the PV; RPV: right PV.*

1.3.1.3 *Buffer response*

The signals activated by hypoxia can also accelerate liver regeneration and contribute to the integrity of sinusoidal morphology (67, 70). Portal hyperflow directed to the FLR causes a reduction in arterial flow in this part of the liver, due to the so-called hepatic arterial buffer response, and induces hypoxia in the FLR (see Fig. 5). In addition, Alvarez et al. demonstrated that hepatic artery clamping increased the PVP during Stage 1 (59, 71).

1.3.1.4 *Role of the deportalized hemiliver*

The role of the deportalized hemiliver is crucial to the success of an augmentation procedure. In fact, while the FLR grows, the deportalized hemiliver acts as a transitory auxiliary liver assisting metabolic, synthetic and detoxifying function for the first and critical week after Stage 1 (72, 73). This knowledge is already applied in liver transplantation in the Auxiliary Partial Orthotopic Liver Transplantation (APOLT) and the recently introduced concept of RAPID (Resection And Partial Liver Segment 2/3 Transplantation With Delayed Total Hepatectomy)(74-77).

If the deportalized hemiliver actively supports the hypertrophy of the FLR by releasing growth factors into the circulation is still under discussion (78, 79).

1.3.2 Portal Vein Embolization (PVE)

Introduced by Makuuchi in the early 1980s (80), embolization of the main branches of the portal vein induces hypertrophy of the remnant liver, due to deviation of the total portal vein flow to the FLR (see chapter 1.3.1

Pathophysiology of liver regeneration)(80, 81). An average increase of the FLR up to 40-50% in 4-8 weeks has been reported (82-87) (see Table 3).

In case of planned right trisectionectomy, additional embolization of Segment 4 PV-branches is mandatory to further improve FLR hypertrophy. However, this approach is technically challenging (88), and the success rate is still underreported (89-91).

Similarly, additional embolization of the ipsilateral hepatic vein may force the growth of the FLR in case of insufficient FLR hypertrophy (see chapter 1.3.4 Extended Liver Venous Deprivation (eLVD))(92, 93).

PVE can be performed using transileocolic or percutaneous (transhepatic), ipsilateral or contralateral approaches (94). The transepathic ipsilateral approach should be preferred to the contralateral approach to avoid a lesion of the FLR (1).

Once the PVE is successfully completed, the resectability of the FLR is reached in more than 70%, with an overall dropout due tumor progress in 23-30% of cases (40, 95). PVE is associated with low morbidity, mostly cholangiosepsis, and almost no mortality (see Table 3)(87, 96-99).

Procedure	***Hypertrophy rate***	***Time period***	***Dropout***	***Morbidity***	***Mortality***
PVE	40-50%	4-8 weeks	23-30%	0-6%*	~4-7%**
PVL	40-50%	4-8 weeks	nr	0-6%*	~3%**
eLVD	~55%	14 days	10-15%	0%*, ***	0%
TSH	27% to 39%	4 weeks	~30%	40%***	6%
ALPPS	61-93%	9-14 days	0-14%	40%***	~10-14%**

Table 3 - *Comparison of different augmentation techniques concerning hypertrophy rate, dropout, morbidity and mortality rate. ALPPS: Associating Liver Partition and Portal vein ligation for Staged hepatectomy; eLVD: extended Liver Venous Deprivation; nr: not reported; PVE: Portal Vein Embolization; PVL: Portal Vein Ligation; TSH: Two-Stage Hepatectomy. * After single procedure / Stage 1 but before resection; **After completed procedure / Stage 2 with hepatic resection; *** major morbidity (defined as ≥ IIIa according to Dindo-Clavien).*

1.3.3 Portal Vein Ligation (PVL)

Portal vein ligation (PVL) is similar to PVE, except that PVL requires a surgical approach. While Capussotti showed that PVL is better than PVE (100) and Broering an inferiority of PVL in inducing hypertrophy (88), the results remain broadly comparable and are much lower than ALPPS in terms of rate and pace of regeneration of FLR (see Table 3)(101, 102).

The morbidity and mortality of the PVL are comparable to the PVE (100-102). Since a laparotomy is necessary, PVL is more demanding for the patient and can cause peritoneal adhesions (100).

On the other hand, PVL can be performed 1) laparoscopically in case of diagnostic laparoscopy (if necessary for the diagnosis and staging of the tumor), 2) simultaneously with surgical exploration, or it can be performed as a 3) rescue procedure in case of insufficient FLR due to unexpected (or undetermined preoperative) poor quality of the parenchyma at exploration or 4) simultaneously with other surgical procedures.

1.3.4 Extended Liver Venous Deprivation (eLVD)

Extended Liver Venous Deprivation (eLVD) consists of simultaneous embolization of the portal vein (PVE) and the ipsilateral hepatic vein (HVE) (103). It is a recent augmentation technique with promising preliminary results in terms of hypertrophy and low morbidity (see Table 3). However, due to its novelty, insufficient data are available.

This concept, introduced by Hwang in 2009 as a rescue from failed PVE in 12 patients, showed a further increase in FLR of 44.2% in 14 days after HVE, with a 12.5% mortality (one patient with phCCA)(103). These data were updated in 2015, after 42 completed patients, mostly with CCA (33 patients with phCCA

and 3 with iCCA), but showed a hypertrophy of 29% after PVE-HVE, and a 3-year survival after resection of 45% (92). Already in this experience, a lower regeneration rate was observed in patients with cirrhosis of the liver.

Recently this concept has been improved with combined, instead of sequential, PVE and right and middle HVE in the same procedure (104, 105). The name Extended liver venous deprivation (eLVD) refers to this latter procedure with simultaneously embolization of the portal and hepatic veins.

The first experience in 10 non-cirrhotic patients (with only one phCCA), showed 53.4% hypertrophy of FLR on day 7 and 64.3% function on day 21, with only 10% dropout, no PHLF or major complications and no mortality (105). Interestingly, another report with similar outcome results (hypertrophy of 40.9% at day 23, 15% dropout, no complications after Stage 1) showed the presence of necrosis of the venous deprived parenchyma. Unfortunately, there are no data reporting the outcome of not resected patients, and if the necrosis lead to other complications (106).

An experience comparing 6 phCCA patients undergoing eLVD with 6 PVE patients showed a median FLR of 58% in 14 days and no adverse events and no mortality in the eLVD group. However, the authors report a dropout of 33% (2 patients) due to extrahepatic progression of the disease (107).

1.3.5 Two-Stage-Hepatectomy (TSH)

Introduced by Bismuth for bilobar CRLM, this two-stage surgical technique consists of one or more liver resections in the FLR at the first-stage and a postponed extended hepatectomy to allow regeneration of the liver (108, 109). Jaeck and colleagues introduced the right PVE or PVL at the first operation to further stimulate hypertrophy (110, 111). In addition, chemotherapy can be performed in the Interstage to reduce the risk of progression (112-114).

The LIGRO Trial, a prospective multicentric RCT, compares TSH with ALPPS and reports an average FLR hypertrophy in the TSH group of 26% in 1 week and up to 39% in 1 month (115). Major morbidity (defined as ≥ IIIa according to Dindo-Clavien) and mortality, respectively 43% and 6,1%, were comparable with the ALPPS group.

TSH allows resection of 20% of patients otherwise unresectable (108, 110, 114, 116), despite a 30% dropout after Stage 1 due to disease progression or insufficient hypertrophy of FLR (113, 114, 117).

It has also been suggested to perform chemotherapy during the Interstage to reduce the risk of progression (112-114).

1.4 ALPPS

Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) is a two-stage surgical procedure (for details see chapters 1.4.2 Operative Technique and 2.4 Surgery) consisting in (84, 118-120):

- Stage 1: occlusion of the portal vein (usually on the right side) and transection of the liver (without removal!) with maintenance of arterial inflow in both hemilivers.
- Stage 2: completion of the hepatectomy with removal of the diseased deportalized liver after adequate volumetric and functional regeneration of the FLR (see Fig. 7).

This technique allows a very fast and unique hypertrophy of the FLR of 61-93% on a median of 9-14 days (119-123). This effect is attributed to a combination of all the growth pathways discussed above (see chapter 1.3.1 Pathophysiology of liver regeneration)(37, 124). ALPPS allows extended liver resection, should reduce the risk of PHLF in a short time and therefore avoids dropout due to tumor growth in the Interstage (115). In fact, the dropout after Stage 1 by ALPPS is observed in 0-15% (115, 121, 125). In addition, ALPPS has been reported to ensure greater radicality. In this context, the achievement of an R0 resection in CRLM was observed in 86-100% of cases (121). Moreover, ALPPS could be applied as rescue option after failed PVE (see chapter 6.1.2.6 Rescue ALPPS)(84).

However, ALPPS is also associated with high morbidity rate and postoperative mortality of almost 10% (124), even higher (up to 48%!) in patients with phCCA (see Table 3 and chapter 4.5 Morbidity and Mortality)(34, 47). Since the indications and surgical techniques are not standardized, ALPPS is still considered at an early stage of development (126).

In addition, there is still a lack of solid long-term results, especially when referring to patients with phCCA. For this reason, ALPPS is actually only

recommended for patients with CRLM and should only be indicated in highly selected patients with HCC and CCA (43-46).

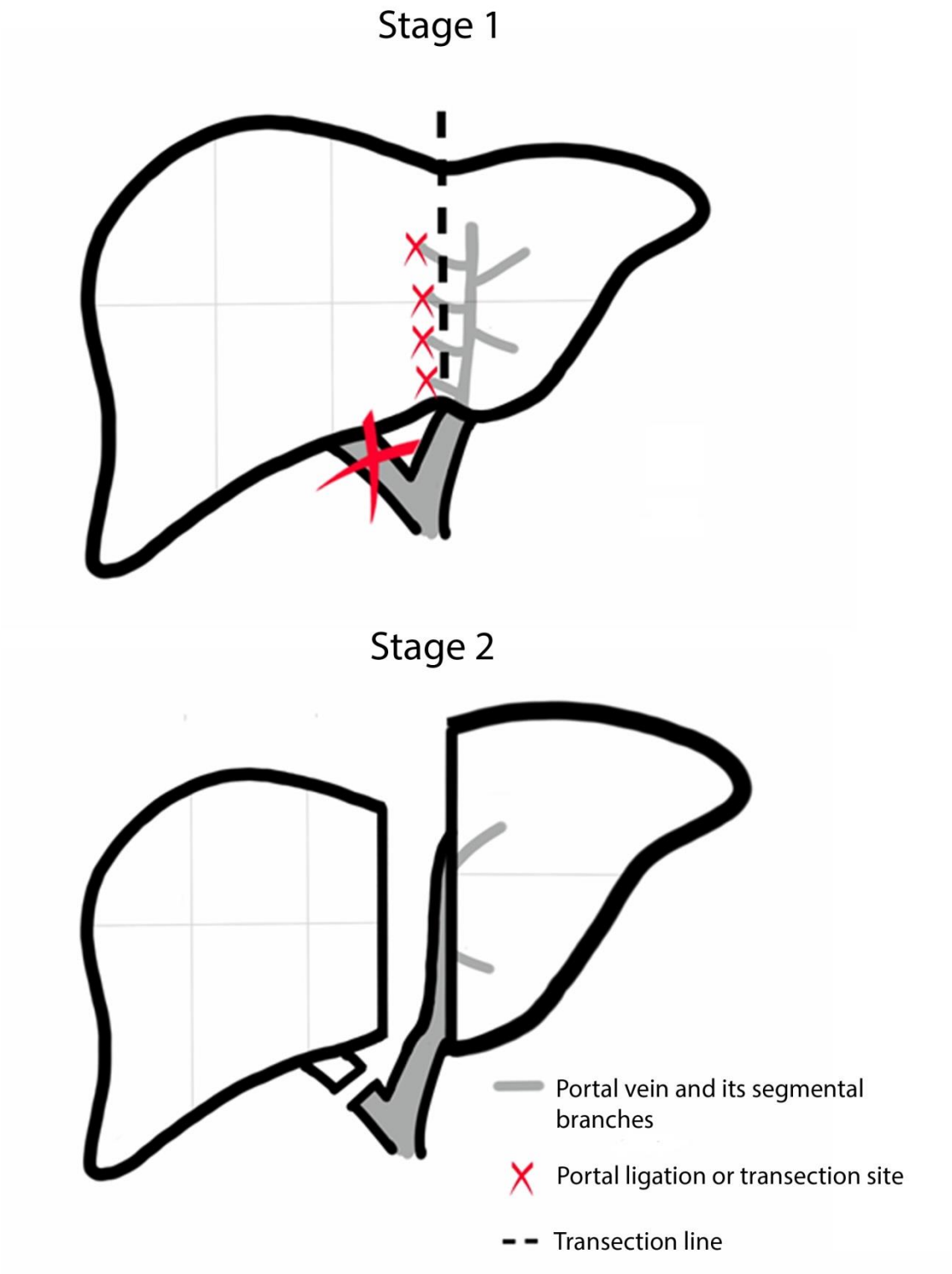


Figure 7 - *Rappresentation of the surgical key points for Stages 1 and 2.*

1.4.1 History of ALPPS

The first case was performed at the University Hospital Regensburg in 2007 in a patient with phCCA. During the liver transection the remnant liver volume appeared too small and a right trisectionectomy too risky (127). As rescue, a ligation of the right portal vein was performed, following the already known concept of PVE and PVL. Surprisingly a control CT scan after 7 days showed a volume gain of over 90% and the procedure could be completed the next day (127).
After that, 3 more cases were made in the same center and, through oral presentations, this strategy spreads first in Germany and Europe. Only in 2011, after the first formal presentation of Baumgart at the 9th Congress of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA Cape Town 2011), did the technique become known worldwide (128).

The first publication arrived in 2011 as a case report (129) and the first multicentric experience was published in 2012 (119). The procedure, until now known as “in-situ-split”, has been renamed in the same issue of Annals of Surgery as ALPPS (130), an acronym that, as already previously explained, stands for “Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy”.
On the wave of the first results, with no or mild PHLF reported, ALPPS spread rapidly around the world (129, 131, 132).

In the same year, the international ALPPS Registry (www.alpps.net) was introduced and the interest in this surgical procedure increased exponentially.
The first report of the Registry, however, described another picture, with high morbidity and mortality (M&M), although 50% of cases were performed with right hemihepatectomy, and criticism shifted to the intolerable postoperative M&M (133, 134).
At the beginning of 2015, the first international meeting on ALPPS was organized in Hamburg and concluded with eight recommendation then highlighted in an consensus paper (see Table 4)(45).

Other international Meetings (i.e. E-AHPB Mainz 2017, IHPB Genf 2018) dedicated one day specifically to ALPPS.

Nr.	***Recommendation***
1	Preserve hepatic inflow and outflow by mean of preoperative knowledge of hepatic anatomy and avoiding unnecessary manipulation of the hilum.
2	No technical variation of the ALPPS transection technique can be recommended as superior.
3	A cholangiogram, bile leak-tests and tagging anatomical structures may be useful.
4	The first CT scan after Stage 1 should be done on days 8 to 10 and repeated weekly for 4 weeks, if sFLR is insufficient. Functional tests may become routine in the future, once convincingly validated.
5	ALPPS can be proposed as personalized treatment strategy in CRLM with high tumor load. Caution in case of ALPPS for HCC and CCA.
6	ALPPS is an option in selected cases with very small FLR or bilobar lesions, as dropout rates seem to be lower compared with PVE or TSH. Ensure top quality PVE using modern embolic materials/Seg IV embolization. In case of failure after PVE, a ‘‘rescue’’ ALPPS can be considered.
7	In case of signs of liver failure (e.g. MELD >10), Stage 2 should be delayed. Patients >60 years are at higher risk of poor outcome, consider longer Interstage.
8	ALPPS in CRLM should only be performed after state-of-the-art neoadjuvant systemic therapy. Tumor progression on chemotherapy is a contraindication for ALPPS. In presence of synchronous CRLM, the liver-first approach can be a good option. Caution to performing synchronous bowel resections during Stage 1.

Table 4 - *Adaptation of the Eight Recommendations from the First International Expert Meeting, 2015 (45). CCA: Cholangiocarcinoma; CRLM: colorectal liver metastases; HCC: Hepatocellular carcinoma: MELD: Model of End stage Liver Disease score; sFLR: standardized Future Liver Remnant.*

Currently, ALPPS is performed in various techniques all over the world, with a main interest in Europe, South America (Argentina and Brazil) and Asia (127, 135). The big exception is North America, with only a few reports from Canada and some centers performing it in the USA (127, 135, 136).

There are actually more than 350 papers dedicated to this procedure. However, the vast majority of them are letters, single center experiences (with a median of 10 patients per paper and heterogeneous cohort with different tumor types) and case reports (135).

As high volume centres also reported about 5 procedures per year (*data from ALPPS Registry,* www.alpps.net), the number of multicentric studies is increasing. Most of them, however, rely on the ALPPS Register, which is based on voluntary data reporting and a trend towards underreporting has already been highlighted (135, 137).

Reviews and Meta-Analysis are also appearing, but are limited by duplication of data, as single-center, multicenter, registry-based studies often report the same patients (135).

Currently, only two randomised controlled trials have been published, among the 11 recorded in clinical trials: a Scandinavian multicentric trial showing the superiority of ALPPS to two-stage hepatectomy (TSH) in terms of feasibility (115), and a British trial (REBIRTH) showing the superiority of Radiofrequency-assisted ALPPS (see chapter 6.1.1.2 Radiofrequency-assisted ALPPS (RALPPS)) to PVE in term of feasibility and hypertrophy of the FLR (42).

ALPPS Milestones

2007 *- First Case (Regensburg)*
2010 *- First Case in Tübingen (Prof. Königsrainer und Prof. Nadalin)(118)*
2011 *- First formal presentation at 9th European-African Hepato-Panreato-Biliary Association Congress (E-AHPBA Cape Town)(128)*
2012 *- First published experience on 3 patients with right hemipatectomy (129)*
2012 *- First Case Series with 25 patients (119)*
2012 *- ALPPS Registry in Zurich (www.alpps.net)*
2012 *- Name ALPPS was proposed (130)*
2015 *- First Meeting (Hamburg)*
2017 *- ALPPS "Update" at E-HPBA (Mainz)*
2018 *- ALPPS "Update" at IHPBA (Genf)*

Table 5 – *The ALPPS Milestones.*

1.4.2 Operative Technique

The first proposed ALPPS procedure consisted of a right trisectionectomy (otherwise known as extended right hemipatectomy (erHH)) with right portal ligation (or dissection) and complete parenchymal transection. This technique, also known as classic-ALPPS and shown in Fig. 7, will be explained in detail in the chapter 2.4 Surgery.

In addition, in recent years, several technical variants have been proposed to reduce operative morbidity and mortality or to extend resectability (138). Among these we remember:

- partial-ALPPS (p-ALPPS), with incomplete transection of the parenchyma (139, 140)

- mini-ALPPS (or PVE-ALPPS), minimizing Stage 1 (combining intraoperative PVE and partial-ALPPS), and a more aggressive Stage 2 (with hylar preparation and completion of parenchymal transection) (139).

- Radiofrequency-assisted ALPPS (RALPPS), using radiofrequency (RFA) to induce parenchymal necrosis along the planed transection line (141, 142).

- Tourniquet-ALPPS, using a Vicryl Tourniquet placed and tightened along the section line (143-145).

- ALPPS applied to other type of hepatectomies with insufficient FLR (i.e. right-ALPPS, left-ALPPS and segmental-ALPPS) (121, 131, 138, 146-150)

- Rescue-ALPPS, in case of failed PVE (59, 86, 131, 151-156).

The technical variants to the classical procedure are described in detail in the Appendix (see chapter 6.1 Technical variants and details).

1.4.3 Preoperative Workup

Preoperative workup is essential in major liver surgery, and particularly in ALPPS, to correctly select the patient, assess the risk, improve settings and plan the operation. It consists of 1) patient assessment and 2) liver assessment.

1.4.3.1 *Patient selection and risk factors*

A correct patient evaluation is always necessary before any major liver procedure to 1) avoid false selection and expose the patient to unnecessary risk as well as, when possible, 2) improve the patient's condition.

Many different risk factors have been analyzed to predict 90-day mortality (124, 137, 157-159). They can be classified in 1) modifiable and non-modifiable or 2) time of appearance (preoperatively, i.e. before Stage 1, or in Interstage, i.e. before Stage 2). They are summarized in Table 6.

Risk Factors	***Preoperative (Before Stage 1)***	***Interstage (Before Stage 2)***
Modifiable (or partly modifiable)	• Cholestasis • Nutritional and physical condition	• Biochemistry parameters (Serum Bilirubin or Creatinin) and MELD-Score • FLR volumetry and functionality
Non- or hardly modifiable	• Age • Tumor Type • Comorbidities • Center experience • FLR quality (fibrosis and cirrhosis) and volumetry	• Complications in Interstage

Table 6 - *Risk factors for 90-days mortality arranged in modifiable and non-modifiable, as well as before Stage 1 and before Stage 2. FLR: Future Liver Remnant.*

Two risk scores are currently available. Both scores predict the 90-day mortality before Stage 1 and before Stage 2.

1. The ALPPS risk score, developed in 2016 by the ALPPS Registry group and several centers outside the ALPPS Registry, and then validated in 2019 in a cohort of subsequent cases (137, 160). It is applicable to all candidate patients.

   The ALPPS Risk Score before Stage 1 (ALPPS-RS 1) is based on: 1) age ≥ 67 and 2) type of tumor; while before Stage 2 (ALPPS-RS 2) on: 1) value of ALPPS-RS 1, 2) Interstage Complication ≥ IIIb and 3) serum bilirubin and 4) creatinine before Stage 2.
2. The newly proposed Risk Score for CRLM was developed specifically on this type of cancer (161).

   The CRLM Risk Score before Stage 1 is based on: 1) age ≥67, 2) FLR/BW ratio <0.40 and 3) if the center is a high volume-center; while before Stage 2 is based on 1) age ≥67 2) FLR/BW ratio <0.40 3) serum bilirubin >50 μmol/L on POD 5 after Stage 1 4) and Interstage morbidity ≥ IIIa.

The predictivity of the two scores, measured by c-statistics, is for ALPPS Risk Score 1 and 2 after validation of 0.64 and 0.77 and for CRLM Risk Score 1 and 2 of 0.70 and 0.72, respectively.

1.4.3.2 *Volumetry*

Several studies have shown that the volumetric assessment of the future liver remnant (FLR) is related to the liver function of the FLR and the risk of PHLF (162).

FLR, defined as the remaining liver volume after completed hepatectomy, could be computed as:

1) percentage of future liver remnant volume to total liver volume (FLR/TLV)
2) future liver remnant volume to body weigh ratio (FLR/BW) (163, 164).

Following intervals have been suggested for a safe hepatectomy (38, 87, 146, 162, 165-172):

1) in patients with a normal liver: FLR/TLV > 25% or FLR/BW > 0,5 %
2) in patients with cholestasis or suspected poor liver quality: FLR/TLV > 30-40% or FLR/BW 0,8 %.

Volumetry can be based on be both CT and MRI (1, 173-176) and can be evaluated either manually, semi-automatically or automatically with software-assisted image postprocessing liver volumetry (SAIP) (177-179). The TLV can be measured analogically or standardized on the BSA (sTLV) (180, 181).

However, interdisciplinary workup between the HPB-surgeon and the radiologist is mandatory to determine the transection line in case of complex resection (e.g. extended left) (182).

1.4.3.3 *Liver Quality*

The performance of the FLR is not only a matter of liver volume, but is directly related to the quality of the liver parenchyma, which in turn is mainly dictated by underlying diseases such as fibrosis, steatosis, cholestasis or cirrhosis (1, 183-186).

1.4.3.3.1 Fibrosis and cirrhosis

Any chronic liver lesion leads to a continuous regeneration of the parenchyma associated with the deposition of fibrous bands and finally ends with cirrhosis of the liver (1, 187, 188). The main consequences are:

- portal hypertension and end stage liver disease due to deposition of fibrous tissue overwhelming the normal parenchyma (6, 187-189).
- intrahepatic direct shunting of portal and arterial blood flow into the hepatic venous outflow with an altered exchange of hepatotrophic factors between hepatic sinuisoids and hepatocytes (6, 49, 188, 190).

- loss of endothelial fenestrations limits the delivery of regeneration factors to the hepatocytes, resulting in an increased risk of PHLF up to 10% and a higher mortality rate (6, 49, 188, 190, 191).

1.4.3.3.2 Steatosis and Steatohepatitis

Steatosis is defined as an accumulation of lipids within the liver cells of more than 5% of the wet weight of the liver.

It is mainly caused by obesity (Non-Alcoholic Fatty Liver Disease, NAFLD), alcohol (Alcoholic Liver Disease, ALD), diabetes mellitus and other toxins (i.e. chemotherapy) (186).

20-40% of the population in Western countries is affected by steatosis, with an even higher prevalence (30-50%) in patients who have undergone chemotherapy (192, 193).

Steatosis decreases hepatic microcirculatory flow causing chronic hypoxia. As a result, there is an intensified inflammatory response due to dysfunction of the Kupffer cells and the damage of the hepatocytes compromises liver regeneration. This situation is called steatohepatitis. This is especially important in case of ischemia-reperfusion injury during surgery.

In these patients an increase in the risk of PHLF of about 15% has been observed, compared to 4% in patients without steatosis (6, 189, 194). In addition, the presence of steatosis is often associated with insulin resistance, which further reduces liver regeneration and increases the rate of post-operative infections (186, 195).

As already mentioned, steatosis and steatohepatitis may also be related to chemotherapy (chemotherapy associated steatohepatitis, CASH). However, there are still conflicting results regarding the type and duration of chemotherapy and whether this affects the postoperative outcome (196-200).

1.4.3.3.3 Cholestasis

The presence of cholestasis is associated with reduced liver regeneration and increased morbidity (particularly PHLF) and mortality by up to 50%, 17% and 13%, respectively, compared to patients without cholestasis (6, 190, 201).

This is mainly due to a decrease in portal venous flow and liver production of proliferation factors, impaired enterohepatic circulation and increased apoptosis (202).

1.4.3.4 *Liver Function*

Volumetric and qualitative assessment of the liver, particularly in high-risk patients, should always be associated with specific assays for liver function. Various methods have been proposed.

Liver function can be assessed globally or segmentally.

A global assessment of liver function can be obtained by means of:

1. blood tests (such as coagulation parameters, proteins, cholinesterase (CHE) (203, 204) and cholestasis parameters)
2. imaging procedures as Indocyanine green clearance test (ICG) (205, 206) or 13C-Methacetin Breath Test (LiMAx) (1, 207).

A segmental liver function can be determined by hepatobiliary scintigraphy (HBS) or MRI as:

1. 99mTc-Galactosyl Serum Albumin Scintigraphy (99mTc-GSA), which shows the uptake capacity of the liver (208);
2. 99mTc-Mebrofenin Hepatobiliary Scintigraphy (HIDA), which shows the excretion capacity of the liver (68, 209-215);
3. MRI with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (gd-eob-dtpa) (216-224).

This tests are discussed in detail in the Appendix (see chapter 6.3 Assessment of Liver Function).

1.4.3.5 *In- and Out-Flow Assessment*

The assessment of In- and Out-Flow is fundamental to avoid the impairment of macro- and microcirculation after surgery and, consequently, PHLF (225-227). It involves not only liver anatomy, but also regional territorial liver mapping, functional volumes and outflow congestion volumes (228, 229).

Three-dimensional Computer-Assisted Surgical Planning (3D-CASP) software, based on information derived from CT and MRI scans, could be useful in determining safely perfused and drained liver volumes and consequently the resection plane (228, 230). In case of extended liver resection, knowing that outflow obstruction could lead to PHLF (225, 226), this technique could provide information on the territory of the middle hepatic vein (227).

Furthermore, it has been clearly demonstrated in hepatic surgery and segmental transplantation that an increase in portal vein pressure (PVP) up to 20 mmHg stimulates liver regeneration (231) but greater than 20 mmHg correlates with PHLF (232). In this latter case, portal vein inflow modulation can be achieved either radiologically (splenic artery embolization), surgically (splenic arterial ligation or splenectomy) or pharmacologically (233). A recent pilot study showed that somatostatin use decreases significantly PVP in patients with PVP > 20 mmHg after hemheipatectomy (234). However, as cirrhosis and high portal pressure are usually a contraindication for ALPPS (see chapter 4.2.2 Liver Quality), there are no reports about this in ALPPS-Literature.

2 MATERIAL AND METHODS

2.1 PLAN AND AIM

A retrospective study was planned to analyze the short and long-term outcomes in all cholangiocarcinoma (CCA) patients who underwent the ALPPS procedure at the Department of General, Visceral and Transplantation Surgery of the University Hospital Tübingen between November 2010 and November 2019.

Ethical consent was obtained from the Ethics Committee of the University Hospital Tübingen (Project No. 680/2018BO2).

Patient demographics, comorbidities, tumor type, surgical details, liver volumetry and quality, perioperative liver function, complications, survival and recurrence of the tumor have been recorded.

Informed consent was obtained for all patients prior to surgery.

2.2 PLANNING OF THE PROCEDURE AND PATIENTS SELECTION

All patients with liver tumors of any origin have been preoperatively discussed at our multidisciplinary tumor board. The evaluation includes abdominal MRI and/or CT scan.

The ALPPS procedure was considered for patients requiring a right trisectionectomy (i.e. extended right hepatectomy) with an insufficient expected Future Remnant Liver (FLR) Volume defined as (166):

- FLR to standardized Total Liver Volume ratio (FLR/TLV) <25% or as FLR to Body Weight Ratio (FLR/BW) < 0,5% in patients with a normal liver;

- FLR/TLV <30% and FLR/BW <0,8% in patients with cholestasis or suspected poor liver quality.

2.3 DEMOGRAPHICS AND COMORBIDITIES

Patient characteristics such as age, weight, height, BMI, BSA (according to the Mosteller's formula (181)) were recorded.

The comorbidity status of the patients was evaluated with the American Society of Anesthesiologists (ASA) physical status (235) and Age-adjusted Charlson Comorbidity Index (ACCI)(236) at Stage 1.

The ALPPS Risk Score (RS) at Stage 1 and 2 was calculated retrospectively (137).

2.4 SURGERY

The procedure, as performed at the University Hospital Tübingen for right trisectionectomy, is described in detail below (118, 119, 166).

2.4.1 Stage 1

Stage 1 consists of:

1. Explorative Laparotomy to determine the extent of the tumor and its resectability.
   An intraabdominal swab is performed for microbiological analysis (118).
2. Intraoperative ultrasound (IOUS) of the liver to:
   a) assess the localization and size of all lesions

b) determine their anatomical relationship to vascular and biliary structures
c) determine the inflow and outflow of the FLR (118, 146).

3. Liver mobilization:
    a) Left liver usually remains untouched. However, to further explore the FLR, mobilization by dissection of the falciform with left triangular, coronary and gastrohepatic ligament can be done at this point.
    b) Mobilization of the right liver, including the right coronary, triangular and hepatocolic ligament, can be perfomed before parenchymal transection, to highlight the posterior line of transection (146, 237).
4. Clean-up of the FLR: if necessary and feasible, a complete resection of the tumor within the FLR can be performed under IOUS control (126, 146).
5. Oncological lymphadenectomy and hilar preparation with identification of the branches of segment IV at origin along the right side of the Rex-Recessus (237).
6. Preparation of the bile ducts (particularly important in case of phCCA, i.e. Bismuth 3a and 4) to achieve a negative surgical margin.
    - After cholecystectomy, the cystic duct is identified and can be prepared for further transcystic exploration of anatomical variations by probing or cholangiography (146), if not prevented by tumor infiltration or previous stenting (as in most in cases of CCA, and phCCA in particular)
7. Portal Vein Occlusion (PVO):
    a) The right branch of the portal vein branch is freed. If there is a separate entry of the right anterior and posterior branches (PV), these are divided separately (118).
    b) The branches of segment IV (237) are dissected along the right side of the Rex-Recessus.

8. The parenchymal dissection (total or almost total) is performed along the falciform ligament anteriorly (or the umbilical fissure posteriorly) up to the level of the inferior vena cava (118, 146, 237).
    a) In case of total transection, the MHV is usually left intact.
    b) Partial transection (p-ALPPS) is defined as 50-80% of the transection surface until intrahepatic detection of MHV (238).
9. A IOUS with Doppler is performed at the end of the operation to determine residual blood flow after parenchymal dissection and confirm the absence of right portal flow (118, 146).
10. An anti-adhesion sheet is applied between the two hemilivers.
11. Placement of closed drainage (usually between the hemilivers at the resection surface and/or in the liver hilum)

2.4.2 Interstage

Postoperatively, patients were initially monitored in intensive care (ICU).

One week after Stage 1 an abdominal CT scan is performed to assess the FLR volume (239). If FLR/TLV and FLR/BW have increased sufficiently, as above defined (see chapter 1.4.3.2 Volumetry), and the patient is in good clinical condition (see chapters 1.4.3.1 Patient selection and risk factors and 4.1 Patient selection) the second step of the procedure is planned. Otherwise, a CT scan was repeated weekly until the above targets were fulfilled.

2.4.3 Stage 2

Stage 2 consists of the following steps:

1. The abdominal cavity is entered using the previous incision (146).
2. Release of inflammatory adhesions (118, 126).

3. An IOUS is performed to control the inflow and outflow of the FLR and to detect growing lesions, which may still be resected (146).
4. In case of p-ALPPS the transection is completed.
5. Identification of the vasculobiliary previously tagged structures and transection of the right hepatic artery, right bile duct and right hepatic vein (118, 146).
6. If not performed during the first step, resection of the bile duct in case of neoplastic involvement of BD bifurcation and creation of a biliodigestive anastomosis (BDA) complete the reconstruction (146).
7. Fixation of the FLR at the diaphragmatic dome and placement of closed drainage (usually in the liver hilum, at the resection surface and/or an ascites drainage) (118, 146, 237).

2.5 PERIOPERATIVE MANAGEMENT

Standard Operating Procedures (SOPs) were introduced at the University Hospital Tübingen in 2016 concerning major liver surgery and the management of patients with liver failure (in particular prevention of PHLF), based on continuous consultation between intensivist and surgeon. These SOPs are summarized in Table 7.

SOP Liver Surgery and PHLF at University Hospital Tübingen

- Daily patient examination (including drainage and signs of encephalopathy)
- Lab tests on POD 1,2, 3 and then every 2 days (or if requested), particularly:
    - Liver/pancreas/renal values
    - Coagulation
    - Inflammation values (CRP and/or procalcitonin (PCT))
    - Albumin
    - Cholinesterase (CHE)
- Ultrasound (US) on POD 0,1,2,3 and then if case of need
- Cardiopulmonary goals:
    - MAP 65-90 mmHg
    - ScvO2 > 70%
    - intravascular normovolemia (cardiac index > 2,5l/min/m^2)
    - Hb > 8mg/dl
    - Thrombocytes > 50.000/µl
- Urine output (UOP) ≥ 0,5 ml/kg/h
- Prevention of thrombosis starting with prophylaxis 6 h postoperative, afterwards depending on patient's risk and coagulation situation
- Antibiotics and antifungal therapy until POD 3, than revaluation based on course, risk factors (i.e. stent) and microbiological findings
- Nutrition: enteral nutrition starting at POD 1 by means of nasogastric-tube
    - Initial phase: 20-25 kcal/kg/d
    - Recovery phase 25-30 kcal/kg/d
    - With high-grand encephalopathy (Grade III+IV): protein restriction
- Prevention of postoperative adynamic ileus with laxative drugs daily starting at POD 1
- Pain control by means of epidural medication or patient-controlled analgesia
- Liver function supportive measures:
    - Vitamin K supplement daily (i.e. Phytomenadione / Konakion 10 mg 1-0-0) until POD 5
    - Prophylaxis of hepatic encephalopathy with oral Lactulose (i.e. Bifiteral 3x20ml), Rifaximin (i.e. Xifaxan 2x 550mg) and avoid Benzodiazepine.
    - Vitamin and trace-element supplementation (i.e. Vitamin B1 und B6, Zinc, eventually Cernevit und Addel)
    - Hypoalbuminemia correction (from <2.5 g/dl)
    - Avoidance of hepatotoxic substances (i.e. Paracetamol and Quinolone antibiotics)
    - Ursodeoxycholic acid (UDCA) daily (i.e. Ursofalk 250 mg 1-0-2)
    - Glucose substitution if insufficient gluconeogenesis present

Table 7 - *Standard Operating Procedure (SOP) for major liver surgery and therefore ALPPS: CRP: C-reactive protein; Hb: hemoglobin; MAP: middle arterial pressure; PHLF: posthepatectomy liver failure; POD: postoperative day; ScvO2: Central venous oxygen saturation.*

2.6 VOLUMETRY

Volumetric measurements applied to CT scans or MRIs were performed prior to surgery and after Stage 1, at POD 7, using analogic image post-processing software (Vitrea R2, Vital Images Inc., Plymouth, Minnesota, USA). In case of insufficient growth, the measurement was repeated with an additional weekly CT scan until sufficient volume was reached. The volume of any FLR lesion was subtracted from the FRL volume estimate.

We evaluated the standardized TLV (sTLV) according to the Vaughtey formula, FLR volume, FLR/TLV, FLR/BW and the Kinetic Growth Rate (KGR). The KGR was calculated as daily volume increase in cc and percentage of FLR (240).

2.7 LIVER QUALITY

Preoperative assessment of liver quality and function using imaging techniques (see chapter 6.2 Assessment of Liver Quality und 6.3 Assessment of Liver Function) was not performed routinely.

The histology was evaluated from the tissue blocks provided after Stage 2. Fibrosis, steatosis, hemochromatosis and cholestasis were recorded. We classified fibrosis and steatosis according to Ishak's Score (241) and Dixon´s classification scale (242) respectively (see Table 8).

Ishak Score	***Fibrosis***
0	No fibrosis
1	Fibrous expansion in some portal areas, with or without short fibrous septa
2	Fibrous expansion in most portal areas, with or without short fibrous septa
3	Fibrous expansion in most portal areas, with occasional portal to portal bridging
4	Fibrous expansion in most portal areas with marked bridging as well as portal-central
5	Marked bridging (portal to portal and/or portal-central) with occasional nodules (incomplete cirrhosis)
6	Cirrhosis, probable or definitive
Dixon Scale	***% of hepatocytes affected from steatosis***
0	No steatosis
1	< 5%
2	5-25%
3	25-75%
4	>75%

Table 8 - *The Ishak Score (241) and Dixon Scale (242) for classification of fibrosis and steatosis, respectively.*

2.8 LIVER FUNCTION

Blood samples for functional evaluation were taken the day before Stage 1, on POD 1, 3, 7 and 10, before Stage 2, and again after Stage 2 on POD 2 1, 3, 7, 10, 14, 30 and 90. These included transaminases, bilirubin, creatinine, INR and cholinesterase (CHE). The overall functional evaluation of the liver was based on MELD-Score and CHE.

2.9 MORBIDITY & MORTALITY

Postoperative complications after Stage 1 and 2 are reported and classified according to the Dindo–Clavien classification (243).

Major complications have been defined as grade ≥ IIIa and severe complications grade ≥ IIIb (see Table 9).

Post-Hepatectomy Liver Failure (PHLF) has been classified according to the International Study Group of Liver Surgery (ISGLS) (see Table 2 in chapter 1.2 Post-Hepatectomy Liver Failure (PHLF))(244).

Mortality has been defined as death during postoperative hospital stay or within 90 days after Stage 2.

Grades	***Definition***
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Requiring surgical, endoscopic or radiological intervention.
- 3a	Intervention not under general anesthesia.
- 3b	Intervention under general anesthesia.
Grade 4	Life-threatening complication (including CNS complications)* requiring IC/ICU-management.
Grade 5	Death.

Table 9 - *Dindo-Clavien Classification (31). CNS: central nervous system; IC/ICU: intermediate care/intensive care unit.*

2.10 STAGING

TNM staging system, Grading, R-, Pn-, V- and L-Status are reported.

Tumor staging has been assessed according to staging system of the 7th American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) edition (245). A stage greater than 2 has been defined as advanced.

2.11 FOLLOW-UP

Follow-up (FUP) with clinical, laboratory and imaging evaluation was regularly conducted following the national standardized S3-guidelines. Patient survival, late complications and recurrence of the disease were recorded. Disease-free survival (DFS) and overall survival (OS) are reported after Stage 2.

2.12 STATISTICAL ANALISYS

Descriptive analyses were carried out for sociodemographic and clinical outcome parameters.

The categorical variables are described using absolute numbers and percentages. The continuous variables are expressed as median and range.

In order to assess the possible risk factors for mortality, a comparison was made between the two different outcome groups.

The P values were calculated using the $\chi 2$ test for the categorical variables and the Mann-Whitney U test for the continuous variables. P values below 0.05 were considered statistically significant.

All variables, which proved statistically significant in the comparison, were considered for univariate regression analysis. Due to limited mortality events

and according to 1-in-10 rule (1 covariate for every 10 observations), a multivariate analysis was not performed (180).

The Kaplan-Meier method has been used for the analysis of disease-free and overall survival evaluated from Stage 2.

The statistical analysis was performed using SPSS version 22 (Armonk, NY: IBM Corp.).

3 RESULTS

3.1 DEMOGRAPHICS

Between November 2010 and November 2019, we performed 53 ALPPS procedures, including 23 patients who were given ALPPS indication for suspected CCA (13 iCCA and 10 phCCA).

The final histology showed, however, only 21 true CCAs, of which 11 iCCA (2 were reclassified as phCCA) and 10 phCCA, which were included in the final cohort of this study.

Two other patients, originally considered as phCCA, had a Klatskin-mimicking tumors (1 intraductal papillary neoplasm (IPN) and 1 autoimmune cholangitis IgG4) and are discussed separately. The selection process is shown in Table 10.

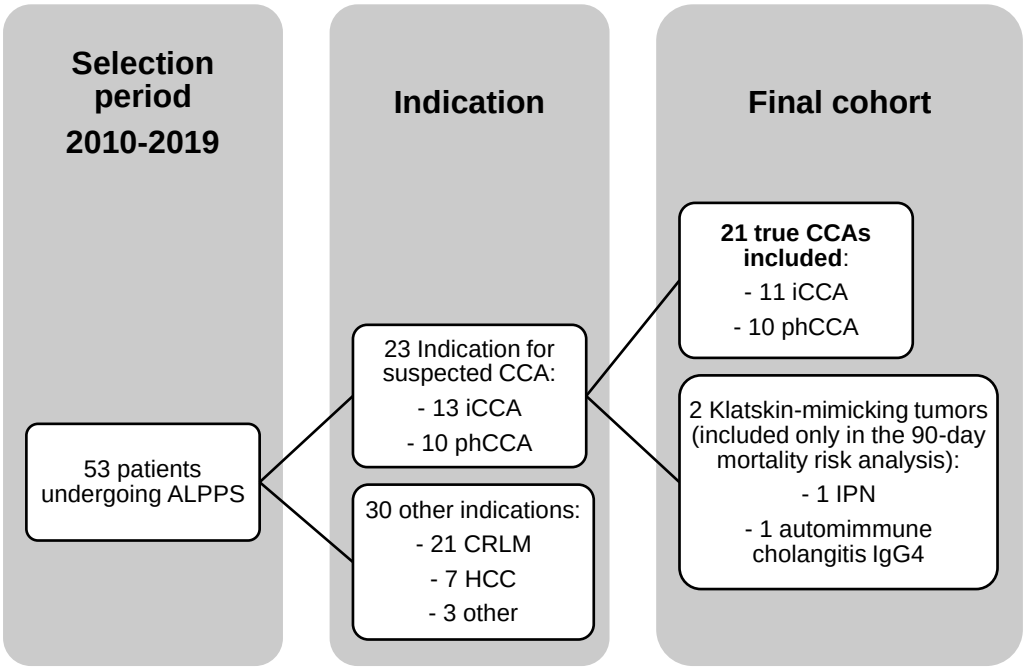


Table 10 - *Cohort selection process. CCA: Cholangiocarcinoma; CRLM: Colorectal Liver Metastasis; HCC: Hepatocellularcarcinoma; iCCA: intrahepatic Cholangiocarcinoma; IPN: intraductal papillary neoplasm; phCCA: perihilar Cholangiocarcinoma.*

The characteristics of the 21 patients included are summarized in Table 11.

A preoperative histology was available only in 10 (47%) cases (7 iCCA (63%) and 3 phCCA (30%)), but without distinguishing between the two subgroups, and in one phCCA without tumor detection.

Among the phCCA, three were preoperatively classified as Bismuth 3a, one as 3b and the others as type 4 (see Table 11).

Moreover, one patient had a recurrence after distal CCA (dCCA) five years after pancreatoduodenectomy at the confluence of the right and left bile ducts. Due to the localization of the recurrence it was classified as phCCA.

The overall median age was 69.3 years (range: 45.8-79.4), and for iCCA and phCCA it was 68.3 years (45.8-79.4) and 70.3 years (49.8-77.1) respectively. Most patients were over 60 years old (64% for iCCA and and 70% for phCCA) and 47% over 70 years old (45.5% for iCCA and and 50% for phCCA).

A multifocal tumor was found preoperatively in one patient with phCCA (10%) and one iCCA (9%). All other tumors were unifocal.

No patient has undergone preoperative systemic chemotherapy or any other treatment.

Three patients with phCCA (30%) and the patient with the Klatskin-mimicking IgG4-autoimmune cholangitis underwent ERCP and bile duct stenting (BD) before referral to our center. No patients received PTCD placement preoperatively.

Two patients with phCCA underwent Rescue-ALPPS after right PVE failure (see chapter 6.1.2.6 Rescue ALPPS)(246).

An ASA-score of 3 was observed in 10 patients (54.7%) (6 phCCA (60%), and 4 iCCA (36%)). The median age-adjusted Charlson Morbidity Score was 5 (0-6) (4.5 for phCCA (range: 0-6), and 5 for iCCA (2-6).

Median ALPPS-Risk Score at Stage 1 (ALPPS-RS 1) was the same for phCCA and iCCA, namely 5 (2-5). At Stage 2 the overall median ALPPS-RS 2 was 5.5 (3-7.6) (5.9 (3.8-7.3) for phCCA and 5.2 (3-7.6) for iCCA).

No patient was malnourished, defined as BMI <18.5 according to the World Health Organization classification. Overweighed patients (i.e. BMI:25-30) were 12 (57.1%) (7 (64%) iCCA and 5 (50%) phCCA), while obese patients (i.e. BMI≥30) were 3 (14.3%) (1 (9%) iCCA and 2 (20%) phCCA).

Patients characteristics	***phCCA (n=10)***	***iCCA (n=11)***
Age, median (range)	70.3 (49.8-77.1)	68.3 (45.8-79.4)
Sex male, n (%)	7 (70%)	3 (27.3 %)
BMI	28.9 (21.9-31.6)	27 (24-30)
ASA		
1, n(%)	0	1 (9%)
2, n(%)	4 (40%)	6 (54.4%)
3, n(%)	6 (60%)	4 (36.4%)
ACCI, median (range)	4,5 (0-6)	5 (2-6)
ALPPS-RS 1, median (range)	5 (2-5)	5 (2-5)
ALPPS-RS 2, median (range)	5,9 (3.8-73)	5.2 (3-7.6)
Preoperative biliary stent	3 (30%)	-
Rescue-ALPPS	2 (20%)	-
Bismuth Classification (preoperative)		
1	0	-
2	0	-
3a	2 (20%)	-
3b	3 (30%	-
4	4 (40%)	-

Table 11 – *Patients characteristics and preoperative Bismuth Classification for patients with phCCA (one patient was preoperatively assessed as iCCA). ACCI: age-adjusted Charlson Comorbidity Index; ASA: American Society of Anesthesiologists (ASA) physical status; ALPPS-RS 1 and 2: ALPPS Risk Score at Stage 1 and 2.*

3.2 OPERATIVE RESULTS

3.2.1 Stage 1

In all cases the extension of hepatectomy consisted of a right trisectionectomy according to the Brisbane's classification (30).

The overall median operation time was 246 minutes (134-515), while for phCCA and iCCA it was 258.5 (134-408) and 246 minutes (154-515) respectively. In most cases (19 out of 21) a classic ALPPS was performed. A partial ALPPS was performed in 2 (9,5%) cases (1 phCCA (10%) and 1 iCCA (9%)).

Vascular resection and reconstruction was performed at Stage 1 in one phCCA and one iCCA due to tumor invasion of the portal vein and right hepatic artery, respectively. MHV was dissected at this Stage in 5 cases (3 phCCA (30%) and 2 iCCA (18%)).

Three patients with phCCA (30%) underwent extrahepatic bile duct resection and biliodigestive anastomosis (BDA) already at Stage 1.

A T-tube was used intraoperatively to decompress the bile duct into two patients, one with phCCA and one with iCCA. The left lobe of two patients with phCCA (20%) had already been decompressed before surgery with a biliary stent (ERCD), while the other cases did not need decompression.

Systematic lymphadenectomy was performed at Stage 1 in 8 phCCA (80%) and 9 iCCA (82%). In the case with recurrence of dCCA, lymphadenectomy has already been performed during pancreatoduodenectomy.

In 1 case with iCCA a pancreatoduodenectomy was performed simultaneously due to enlarged retroperitoneal lymph nodes and a suspected extension of the tumor to the pancreas head. No additional resection was performed at Stage 1.

Only one patient with iCCA reported significant bleeding during Stage 1 due to a lesion in the right hepatic vein, which could be sutured immediately without further consequences.

3.2.2 Interstage

The overall median time interval (Interstage) between Stages 1 and 2 was 13 days (3-43), while specifically for iCCA and phCCA was 10 days (3-14) and 13.5 days (11-43), respectively.

Occurred complications and ICU-Stay in Interstage are reported in detail below (see chapter 3.6 Morbidity & Mortality). In one case the 2nd stage was performed already at POD 3 due to liver necrosis after right hepatic artery thrombosis (HAT).

3.2.3 Stage 2

All patients included in this cohort have completed the ALPPS procedure (100% feasibility rate).

The overall median operation length was 204.5 minutes (59-395), while for phCCA and iCCA were 226 minutes (59-395) and 204 minutes (91-290) respectively.

Only three patients with phCCA (30%) underwent portal resection and reconstruction at Stage 2: in two patients due to portal thrombosis of unknown origin and in the other due to tumor invasion. In the latter case, the reconstruction was performed with the interposition of a venous graft.

At this Stage, a BDA was performed in 15 cases: the remaining 7 cases with phCCA (70%) and 8 iCCA (73%) due to tumor involvement of the biliary bifurcation.

No other oncological resection was necessary at this Stage. Segment 1 was removed in 9 cases (42.9%) (5 phCCA (50%) and 4 iCCA (36.4%)).

Systematic lymphadenectomy was completed in the remaining 3 cases (1 phCCA and 2 iCCA).

3.3 LIVER QUALITY

Postoperative histological data on liver quality were available for 20 patients (10 phCCA (100%) and 10 iCCA (91%)) and are shown in Table 12.

Patients with phCCA (Median Ishak Score 2.5) revealed a more fibrotic liver than patients with iCCA (Median Ishak Score 0.5). 8 patients (40%) (7 phCCA (70%) and 1 iCCA (10%) revealed a Fibrosis-Ishak score of 1 or more. None of the patients had cirrhosis.

According to the Steatosis-Dixon scale, 3 (15%) patients were Grade II (5-25% of hepatocytes affected) and only one iCCA (10%) grade III (25-75% affected). 12 patients (60%), 6 iCCA (60%) and 6 phCCA (60%), showed no steatosis.

Two patients with phCCA (20%) showed severe intrahepatic cholestasis. Only one of them was stented. The patient with Klatskin-mimicking IgG4-autoimmune cholangitis also showed severe intrahepatic cholestasis and was stented.

One patient with iCCA (10%) and 4 with phCCA (40%) had moderate siderosis.

Histology	***Tumor Type***	
Fibrosis (Ishak Score)	**phCCA (n=10) n (%)**	**iCCA (n=10)***
0, n(%)	2 (20%)	5 (50%)
1, n(%)	1 (10%)	4 (40%)
2, n(%	2 (20%)	1 (9%)
3, n(%)	4 (40%)	-
4, n(%)	1 (10%)	-
Steatosis (Dixon Scale)	**phCCA (n=10) n (%)**	**iCCA (n=10)***
0, n(%)	6 (60%)	6 (60%)
1, n(%)	2 (20%)	1 (10%)
2, n(%)	2 (20%)	1 (10%)
3, n(%)	-	1 (10%)
4, n(%)	-	-
Cholestasis, n (%)	2 (20%)	-
Siderosis, n (%)	4 (40%)	1 (10%)

Table 12 – *Liver quality based on postoperative speciments.* In one patient with iCCA no data were available.*

3.4 LIVER LABORATORY VALUES AND FUNCTION

The course of laboratory values is subclassified in cholestasis, transaminases and functional parameters. These data are summarized below in Figure 8.

3.4.1 Cholestasis parameters

Severe cholestasis was present in 4 patients (19%) before Stage 1 or 2.

Before Stage 1, it was observed in three patients with phCCA (30%) (total bilirubin: 21, 5.4 and 4.4 mg/dl respectively), while before Stage 2 in two patients with phCCA (20%) (6.1 and 4.6 mg/dl) and one with iCCA (3.7 mg/dl). Two of them (one phCCA and one iCCA) died from PHLF after Stage 2.

3.4.2 Transaminase

Transaminase increased dramatically after Stage 1 (up to 100 fold normal values), probably due to parenchymal resection and deportalization or necrosis of Segment 4, but not after Stage 2.

3.4.3 Function parameters

Five patients (23.8%) had a MELD greater than 10 before either Stage 1 or 2. Before Stage 1, a MELD >10 was observed in three patients with phCCA (30%) (MELD 19, 16 and 13), and before Stage 2 in two patients with phCCA (20%) (MELD 17 and 12) and two with iCCA (18%) (both with MELD 22). Two of them (one phCCA and one iCCA) died due to PHLF after Stage 2.

Analysis of overall function using median MELD and Cholinesterase (CHE) showed preserved function after Stage 1 and decreased function after Stage 2. MELD was elevated mainly due to the increase in Bilirubin, while Creatinine and INR remained at normal levels.

MELD and Cholinesterase, once unbalanced, need almost one month after Stage 2 to normalize again, while the volumetry has already been recovered.

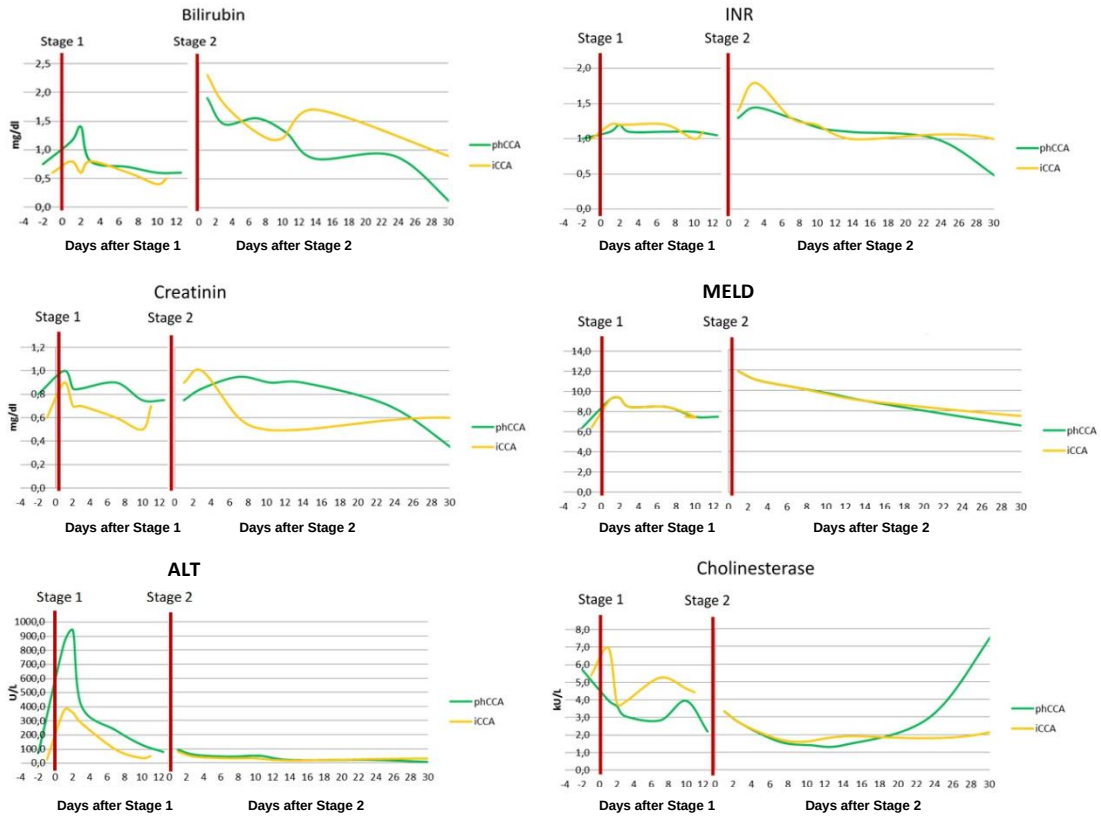


Figure 8 - *Course of laboratory values before and after Stage 1 and 2. INR: International Normalized Ration; ALT: Alanine Transaminase also known as serum Glutamic-Pyruvic Transaminase (GPT), MELD: Model for End-Stage Liver Disease.*

3.5 VOLUMETRY

The volumetric parameters are summarized in Table 13.

The overall preoperative median FLR volume before Stage 1 was 310 ml (105-440), while specifically for phCCA and iCCA it was 280 ml (155-440) and 319 (105-380) respectively

The overall FLR/TLV was before Stage 1 18.8% (11-31), and for phCCA and iCCA, 17.9% (12-25.3) and 18.8 (8.1-31.6) respectively

The overall median FLR/BW was before Stage 1 0.40 (0.2 - 0.7), while specifically for phCCA and iCCA it was 0.4 (0.25-0.6) and 0.4 (0.2-0.7), respectively.

After a median of 8 days after Stage 1 (range: 6 - 27d) sufficient hypertrophy was achieved. Only in one phCCA the second Stage was postponed at POD 43 due to primary insufficient FLR growth.

The overall median of FLR/TLV and FLR/BW increased from 18.8% (11-31.6) and 0.40 (0.2 - 0.7) to 32.5% (16.7-56.7) and 0.7 (0.4-1.2). Specifically by type of tumor, the median FLR/TLV and FLR/BW increased to 32.5% (27.2 - 43.5) and 0.7 (0.6 - 0.9) for phCCA, and 32.5% (16.7-56.7) and 0.7 (0.4-1.2) for iCCA, respectively (see Table 13).

The overall Median Volume Gain (MVG) was 76% (23.8-264.5), in particular 65.9% (23.8-264.5) for phCCA and 76% (26.5% - 142%) for iCCA.

The overall Kinetic Growth Ratio (KGR) as ml of FLR increase per day was 25.2 ml/d (8.7-71), specifically 21,6 ml/d (8,7-58,6) and 28,6 ml/d (12,7-71) for phCCA and iCCA, respectively.

The overall KGR as % of FLR increase per day was 8.4 %/d (2.4-37.8), while for phCCA and iCCA was 6,9 %/d (2,4-37,8) for phCCA and 10,9 %/d (3,8-20,7) for iCCA, respectively

The median KGR (as ml/day and %/day) in patients with different histological characteristics is given in Table 14.

Median volumetric parameter	***iCCA***	***phCCA***
Before Stage 1		
• *FLR volume, ml*	319 (105-380)	280 (155-440)
• *FLR/TLV before Stage 1, % (range)*	18.8 (8.1-31.6)	17.9 (12-25,3)
• *FLR/BW before Stage 1, range*	0.4 (0.2-0.7)	0.4 (0.25-0.6)
Before Stage 2		
• *FLR/TLV before Stage 2, % (range)*	32.5 (16.7-56.7)	32.5 (27.2 - 43.5)
• *FLR/BW before Stage 2, range*	0.7 (0.4-1.2)	0.7 (0.6 - 0.9)
• *KGR, ml/day (range)*	28.6 (12.7-71)	21.6 (8.7-58.6)
• *KGR, %/day (range)*	10.9 (3.8-20.7)	6.9 (2.4-37.8)

Table 13 - *Median volumetric parameters. KGR: Kinetic Growth Ratio; FLR: Future Liver Remnant; FLR/BW: FLR to Body Weight Ratio; FLR/TLV: FLR to standardized Total Liver Volume.*

Histological characteristic, n patients	***KGR, ml/day (range)***	***KGR, %/day (range)***
Fibrosis (Ishak Score ≥2), n=8	20.8 (10-58.6)	6.7 (2.4-37.8)
Steatosis (Dixon Scale ≥2), n=4	23.8 (8.7-43.6)	6.9 (4.3-13.7)
Cholestasis, n=2	16.3 (8.7-58.6)	7.4 (4.3-37.8)
Siderosis, n=5	19.1 (8.7-65)	6.7 (4.3-17.1)

Table 14 - *Median KGR (as ml/day and %/day) in patients with different histological characteristics. KGR: Kinetic Growth Ratio; Ishak Score and Dixon Scale are reported in Table 8.*

3.6 MORBIDITY & MORTALITY

The median ICU-stay after Stage 1 was 3 days for both phCCA (range 1-11) and iCCA (1-6). After Stage 2 the overall median ICU-stay was 5 days (1-40), while in particular 6 days (1-24) for phCCA and 4 days (1-40) for iCCA. The overall median hospital-stay was 34 days (22-78), specifically 36.5 days (22-78) for phCCA and 33 days (23-67) for iCCA.

3.6.1 Morbidity

Overall morbidity across the cohort was 85.7%, while for phCCA it was 80% with 27 complications in 8 patients and for iCCA 91% with 27 complications in 10 patients.

The majority of events occurred after the second Stage for both phCCA (56%) and iCCA (70%).

Overall severe complications (grade ≥IIIb) occurred in 6 phCCA (60%), 5 iCCA (45%) and in the patient with Klatskin-mimicking IgG4-autoimmune cholangitis.

3.6.1.1 *Biliary leakage*

Biliary leakage from the resected surface was observed in two patients with phCCA (20%) after Stage 2 and from the BDA in one iCCA (9%). All occurred after Stage 2 and where surgically treated. No mechanical cholestatic complications were observed.

3.6.1.2 *Vascular complications*

Vascular events occurred in 5 patients and are classified as follows.

3.6.1.2.1 Hepatic artery thrombosis (HAT)

A thrombosis of the right hepatic artery (HAT) in a patient with iCCA, in which a reconstruction of the right HA was performed, occurred after Stage 1 due to tumor invasion with consecutive necrosis of the right deportalized liver and sepsis. In this case, the second Stage was anticipated at POD 3.

One left HAT in phCCA and one in iCCA were observed after Stage 2 at POD 10 and 1, respectively, and were both successfully treated surgically with thrombectomy.

3.6.1.2.2 Portal vein thrombosis (PVT)

A partial portal vein thrombosis (PVT) was observed in a patient with iCCA on POD 7 after Stage 1 and was treated initially with a therapeutic dose of heparin and finally with thrombectomy and portal reconstruction at Stage 2.

A partial PVT in phCCA on POD 17 after Stage 2 was successfully treated with anticoagulants with no need of other intervention.

3.6.1.2.3 Venous outflow complications

Complication of left hepatic venous outflow with consecutive SFSS after Stage 2 was observed in a patient with iCCA on POD 25. Initially a radiologically percutaneous angioplasty was carried out and then, due to persistent kinking, the definitive radiological stenting was performed on POD 28.

3.6.1.2.4 Bleeding

A severe bleeding of unknown origin occurred in a patient with iCCA on POD 1 after Stage 2 and was successfully treated surgically with hematoma removal.

3.6.1.2.5 Pulmonary embolism (PE)

Two cases of pulmonary embolism (PE) were observed. One in a patient with iCCA occured on POD 5 after Stage 1 and was medically treated and subsequently had an uneventful course. Another PE in a patient with iCCA on POD 7 after Stage 2 required readmission to ICU due to cardiogenic shock. The patient died of septic shock on POD 32.

3.6.1.3 *Post-Hepatectomy Liver Failure (PHLF)*

Post-Hepatectomy Liver Failure (PHLF) after Stage 1 was observed in only one iCCA, due to right HAT and right liver necrosis.

After Stage 2, PHLF was observed in 5 phCCA (50%) and 4 iCCA (55%). PHLF Grade C was observed in 3 phCCA (30%) and 2 iCCA (18%).

3.6.2 Mortality

Four patients (19%) (2 phCCA and 2 iCCA) died within 90 days after Stage 2. Their characteristics are summarized in Table 15.

Overall in-hospital mortality was 20% for phCCA and 18% for iCCA.

Two patients with phCCA and one iCCA died after Stage 2 due to septic shock at POD 20, 37 and 32, respectively. Another patient with iCCA died from septic shock and liver failure at POD 19.

In addition, the patient with Klatskin-mimicking IgG4-autoimmune cholangitis died from severe acquired pneumonia at POD 36.

N	Diagnosis	Year of ALPPS	Tumor Stage	Age (year)	Sex	Interstage Time (days)	Grade Max Complicationn after Stage 1	Mortality (POD after Stage 2)	Cause of death
1	phCCA	2011	2	69	M	11	IV	20	Septic shock
2	phCCA	2012	3c	72	F	13	IIIa	37	Septic shock
3	iCCA	2013	2	68	M	3	IV	32	Septic shock
4	iCCA	2014	3a	78	M	13	II	19	Liver failure and Septic shock
5	IgG4-autoimm. Cholangitis	2011	-	77	M	14	IIIa	36	Severe acquired pneumonia

Table 15 - *Characteristics of patients that experienced postoperative mortality. iCCA: intrahepatic Cholangiocarcinoma; F: female; M: male; phCCA: perihilar Cholangiocarcinoma; Tumor stage according to 7th American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) edition (245).*

3.6.3 Learning Curve

The learning curve is shown in Table 16.

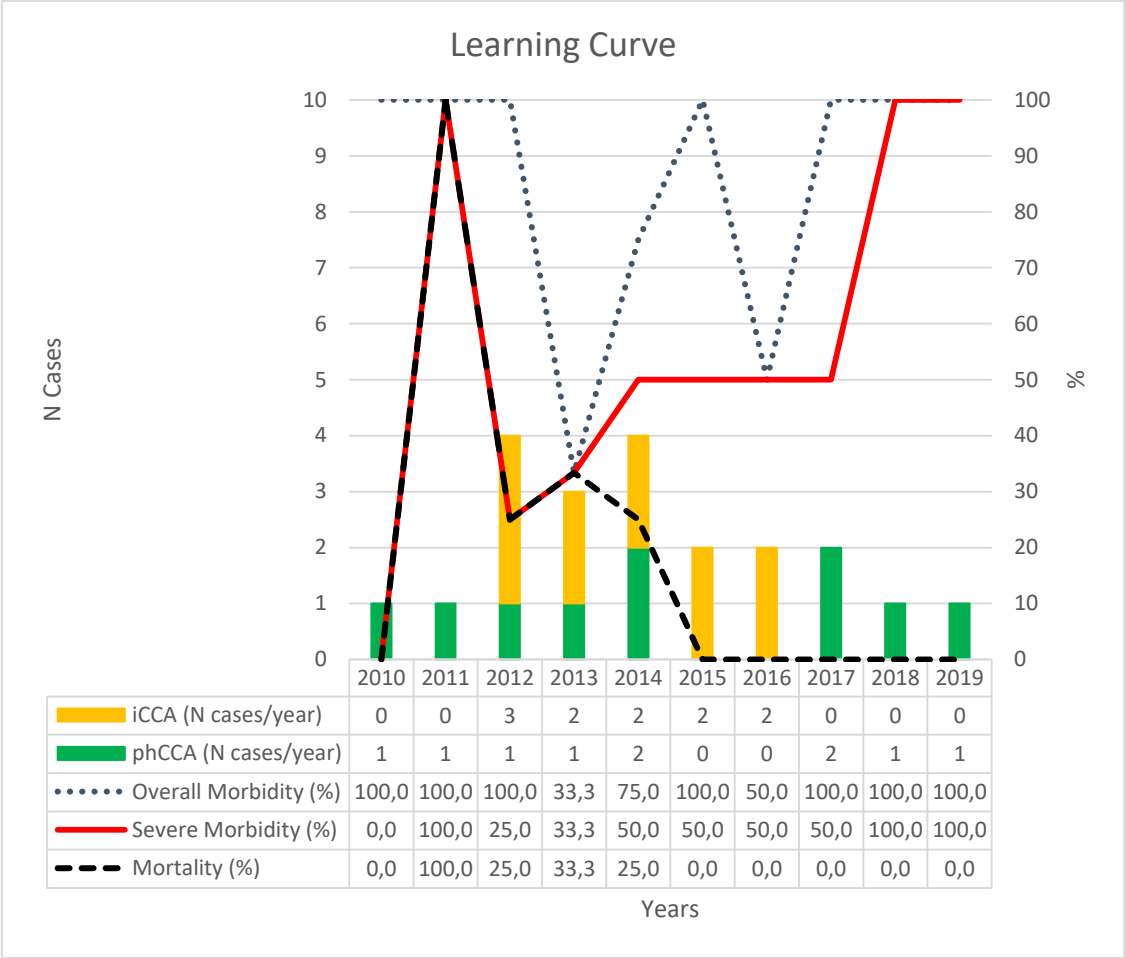
The ALPPS for phCCA, and CCA in general, has been performed regularly in the first 5 years after the introduction of the procedure itself at University Hospital Tübingen. The indication for CCA has been revised after our early single center experience (118), as well as the publications of the initial ALPPS Registry results (125, 240) and the first ALPPS Meeting (Hamburg 2015) (see chapter 1.4.1 History of ALPPS) (45).

A careful return to ALPPS for phCCA has been recorded in the last 3 years, with 4 cases since 2017. On the other hand, ALPPS for iCCA has been mostly performed between 2012 and 2016.

While overall morbidity remains consistently high throughout the observed period (only in 2013 it was < 50%), severe morbidity reaches peaks of 100% in 2011, as well as in 2018 and 2019.

Mortality is present only in the first 5 years of experience, while since 2015 no mortality has been recorded in patients undergoing ALPPS for CCA.

While in the first years severe morbidity is also related to mortality (red and black curves), in recent years no mortality has been observed even in the presence of severe morbidity.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
iCCA (N cases/year)	0	0	3	2	2	2	2	0	0	0
phCCA (N cases/year)	1	1	1	1	2	0	0	2	1	1
Overall Morbidity (%)	100,0	100,0	100,0	33,3	75,0	100,0	50,0	100,0	100,0	100,0
Severe Morbidity (%)	0,0	100,0	25,0	33,3	50,0	50,0	50,0	50,0	100,0	100,0
Mortality (%)	0,0	100,0	25,0	33,3	25,0	0,0	0,0	0,0	0,0	0,0

Table 16 - *Learning curve of 10 years of ALPPS experience at University Hospital Tübingen. iCCA: intrahepatic Cholangiocarcinoma; phCCA: perihilar Cholangiocarcinoma.*

3.6.4 Risk Analysis

The comparison of patients with and without death event and risk analysis are summarized in Tables 17 and 18.

Considering that the definitive diagnosis of CCA is made usually postoperatively and that the risk factors must be known preoperatively (regardless of whether the diagnosis of CCA will be confirmed later), we have considered here all patients with suspected preoperative cholangiocarcinoma to improve the statistical power of this analysis, i.e. also the two patients with Klatskin tumors mimicking tumors (one intraductal papillary neoplasia (IPN) and one autoimmune cholangitis IgG4).

Patients with postoperative mortality have significantly more comorbidity and fibrosis, a lower KGR in the Interstage, as well as a higher MELD and ALPPS-RS 2. They also experience more major complications (≥3a according to the Dindo-Clavien classification) during Interstage and more severe complications (≥3b according to the Dindo-Clavien classification) after Stage 2.

In the univariate risk analysis, however, no parameters available at Stage 1 have reached a significance, except histology, which in our case was collected after the completion of the procedure. Patients with an Ishak-Score of 3 or more have a 2.75 fold higher probability of postoperative mortality than patients with less or no liver fibrosis.

A MELD above 10 and a higher ALPPS-RS 2 should be risk-aware and possibly an indicator to postpone Stage 2. The presence of major complications after Stage 1 and severe complications after Stage 2 are associated with a significant risk of death.

The small number of cases results in a wide or non-measurable confidence interval at univariate analysis. For this reason, the results should be taken as indicative.

Risk Factor	***No mortality (n=18)***	***With mortality (n=5)***	***P***
Stage 1			
BMI, median (range)	27.2 (21.9-30.1)	25.5 (20.4-31.6)	0.655
Sex male, n (%)	7 (39%)	4 (80%)	0.131
Age, median (range)	69.25 (45.8-79.4)	72.2 (68.3-78.7)	0.264
ASA = 3, n(%)	7 (39%)	4 (80%)	0.131
ACCI, median (range)	4.5 (0-6)	6 (4-7)	***0.035****
Bilirubin before Stage 1, median (range)	0.6 (0.3-5.4)	0.8 (0.5-21)	0.114
MELD before Stage 1, median (range)	6 (6-16)	9 (6-19)	0.282
MELD ≥ 10 before Stage 1, n (%)	2 (11%)	2 (40%)	0.194
ALPPS-RS 1, median (range)	5 (2-5)	5 (5-5)	0.071
Biliary stent, n (%)	2 (11%)	2 (50%)	0.194
Stage 2			
Bilirubin before Stage 2, median (range)	0.5 (0.2-6.1)	0.8 (0.3-4.6)	0.133
MELD before Stage 2, median (range)	7 (6-22)	12 (7-22)	0.057
MELD ≥ 10 before Stage 2, n (%)	2 (11%)	3 (60%)	***0.048****
Major Complication before Stage 2, n (%)	3 (16.7%)	4 (80%)	***0.017****
Severe Complication before Stage 2, n (%)	2 (11.1%)	2 (40%)	0.194
ALPPS-RS 2, median (range)	5.3 (3-6.50)	6.4 (5.5-7.3)	***0.007****
Major Complication after Stage 2, n (%)	10 (55.6%)	5 (100%)	0.089
Severe Complication after Stage 2, n (%)	6 (33.3%)	5 (100%)	***0.014****
Overall Major Complication, n (%)	12 (66.7%)	5 (100%)	0.184
Overall Severe Complication, n (%)	7 (38.9%)	5 (100%)	***0.024****
Volumetry and Histology*			
KGR (ml/day), median (range)	27.1 (8.7-71)	15.5 (10-19)	***0.032****
Ishak Score (Fibrosis), median (range)	1 (0-3)	3 (1-4)	***0.027****
Ishak Score ≥ 3, n (%)	3 (17%)	3 (75%)	***0.046****
Dixon Scale (Steatosis) , median (range)	0 (0-3)	0 (0-1)	0.361
Dixon Scale ≥ 2	5 (27.8%)	-	0.535
Cholestasis, n (%)	2 (11.1%)	1 (20.0%)	0.470
Siderosis, n (%)	3 (16.7%)	2 (40.0%)	0.210

Table 17 – *Comparison of patients with and without death event. ACCI: Age adjusted Charlson Comorbidity Index; ALPPS-RS: ALPPS Risk Score; KGR: Kinetic Growth Ratio *for 1 patient with iCCA and postoperative mortality no histological data were available.*

Risk Factor	***Regression coefficient***	***Odds Ratio (95% CI)***	***P***
Stage 1			
ACCI	1.166	3.210 (0.875-11.775)	0.079
Stage 2			
MELD before Stage 2	0.165	1.180 (0.972-1.431)	0.094
MELD ≥ 10 before Stage 2, n (%)	2.485	12 (1.184-121.573)	***0.035****
Major Complication before Stage 2	2.996	20 (1.613-247.981)	***0.020****
ALPPS-RS 2	2.550	12.8 (1.059-154.880)	***0.045****
Severe Complication after Stage 2	21	high	-
Overall Severe Complication	20.8	high	-
Volumetry and Histology			
KGR (ml/day)	-0.178	0.837 (0.677-1.035)	0.100
Ishak Score	1.209	3.349 (0.984-11.403)	0.053
Ishak Score ≥ 3	2.708	15 (1.136-198.039)	***0.040****

Table 18 – *Univariate Analysis of the Risk Factors. ACCI: Age adjusted Charlson Comorbidity Index; ALPPS-RS: ALPPS Risk Score; KGR: Kinetic Growth Ratio*

3.7 ONCOLOGICAL SURGICAL RESULTS AND TUMOR STAGING

The oncological results are shown in Table 19.

An R0 resection was achieved in 15 patients (71.4%) (6 phCCA (60%) and 9 iCCA (82%)).

60% of patients with phCCA revealed a T-Stage of 2 and 20% greater than 2, while the majority of iCCA (55%) were in Stage 2b and 3 (64%).

Lymph node positivity (N) was found in 3 phCCA (30%) and 7 iCCA (64%).

Vascular invasion (V) was found in 1 phCCA (10%) and 1 iCCA (9%).

Perineural invasion (Pn) was found in 7 phCCA (70%) and 2 iCCA (18%).

Lymphatic-vascular invasion (L) was found in only 1 iCCA (9%).

40% of the phCCA had a grading of 2 and only 20% of 3. On the other hand, 70% of the iCCA had a grading of 3.

Histology of the pancreas in the patient with iCCA who underwent a concomitant pancreatoduodenectomy at Stage 1 revealed a benign cystic tumor.

According to the AJCC/UICC classification, 50% and 73% of patients with phCCA and iCCA, respectively, presented advanced stage (defined as Stage greater than 2).

Tumor multifocality was present in 2 iCCA (18%) and, unlike preoperative imaging, in none of the phCCA.

The median tumor size was 5.4 cm (1.5-11.7) (4.2 cm (1.5-6.6) for phCCA and 8.5 cm (2.8-11.7) for iCCA).

T	***phCCA (n=10)***	***iCCA (n=11)***
In situ	1 (10%)	0
1	1 (10%)	4 (45%)
2	-	1 (9%)
2 a	2 (20%)	1 (9%)
2 b	4 (40%)	3 (27%)
3	2 (20%)	3 (27%)
4	0	0
N		
0	6 (60%)	4 (36%)
1	3 (30%)	7 (64%)
X	1 (10%)	0
M		
0	10 (100%)	10 (90%)
1	0	1 (9%)
X	0	0
L		
0	10 (100%)	10 (90%)
1	0	1 (9%)
X	0	0

V	***phCCA (n=10)***	***iCCA (n=11)***
0	9 (90%)	10 (90%)
1	1 (10%)	1 (9%)
X	0	0
Pn		
0	3 (30%)	1 (9%)
1	7 (70%)	2 (18%)
X	0	8 (73%)
G		
0	1 (10%)	0
1	1 (10%)	0
2	4 (40%)	3 (27%)
3	2 (20%)	7 (50%)
X	0	1 (9%)
R		
0	6 (60%)	9 (82%)
1	4 (40%)	2 (20%)
X	0	0

Staging	***phCCA (n=10)***	***iCCA (n=11)***
0	1 (10%)	0
1	1 (10%)	
1 a		1 (9%)
1 b		0
2	3 (30%)	2 (18%)
3		
3 a	1 (10%)	1 (9%)
3 b	1 (10%)	1 (9%)
3 c	3 (30%)	
4a		6 (55%)

Table 19 - *Staging base on 7th American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) edition staging system (245). G: grading; L: Lymphatic-vascular invasion; M: distant metastasis; N: Lymph node positivity; Pn: Perineural invasion; R: Residual tumor; T: tumor size; V: Vascular invasion.*

3.8 FOLLOW-UP AND ONCOLOGICAL LONG-TERM RESULTS

A total of 17 patients, 8 with phCCA and 9 with iCCA, were included in the follow-up (FUP).

The median FUP time was 38.3 months (1.4-104.1) for phCCA and 36.4 months (2.5-63.4) for iCCA.

The Kaplan-Meier curves for Disease-Free Survival (DFS) and Overall Survival (OS) are shown in Fig. 9 and 10.

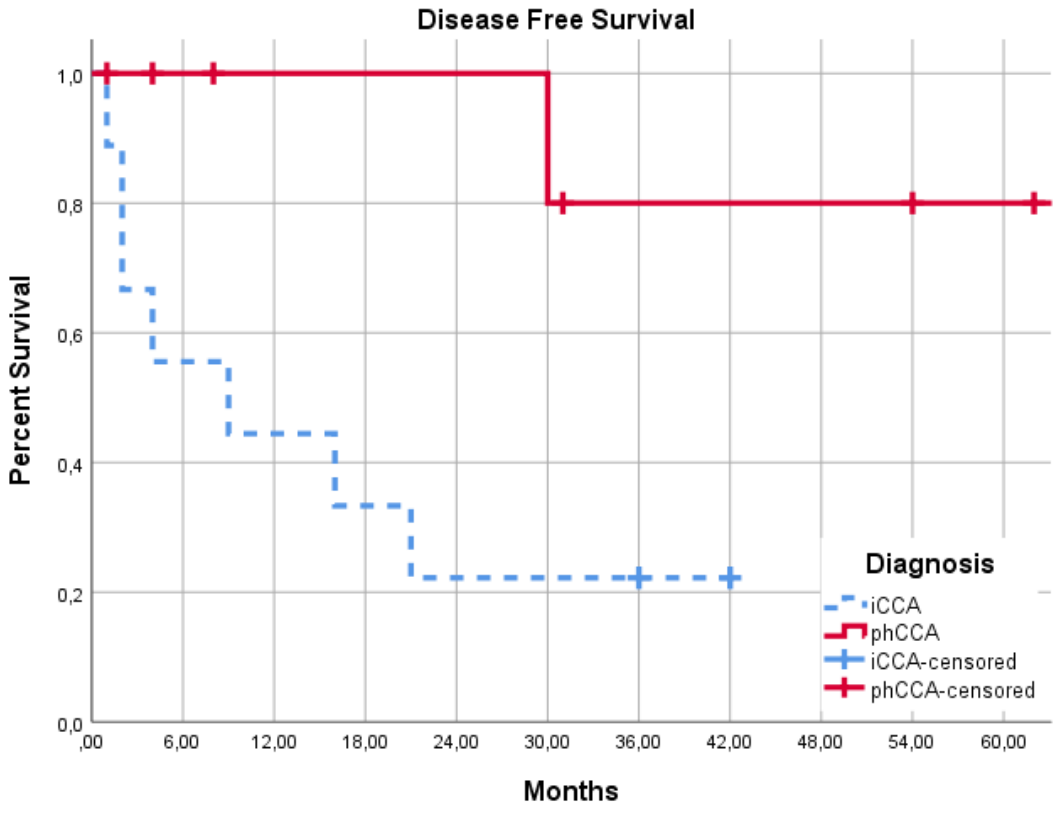


Figure 9 – *Kaplan-Meier Curve of the Overall Disease-Free Survival (DFS).*

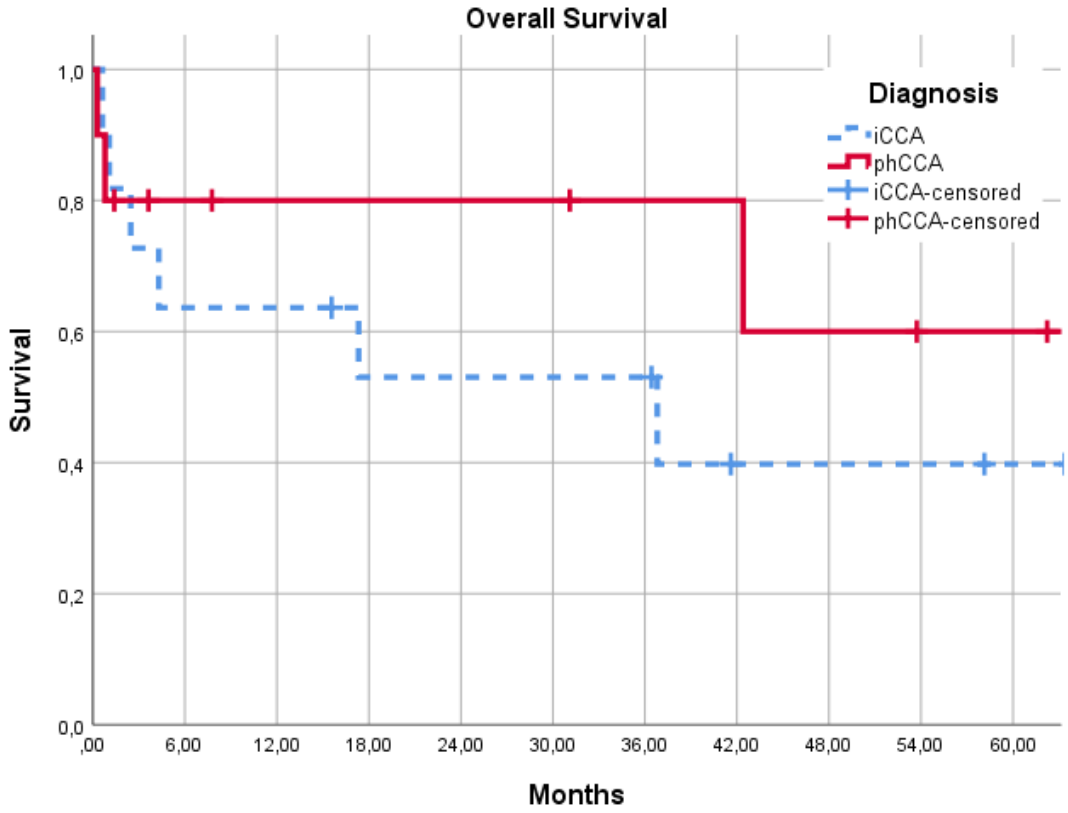


Figure 10 – *Kaplan-Meier Curve of the Overall Survival (OS).*

3.8.1 Tumor recurrence and DFS

A tumor recurrence was observed in only one patient with phCCA (12.5%) and in 7 patients with iCCA (77.8%) (see Table 20).

The median Disease-Free Survival (DFS) time was 29.5 months for the phCCA and 7.8 months (1-41.6) for iCCA.

The localization of tumor recurrence was intrahepatic for the phCCA and 5 (46%) iCCA.

Extrahepatic localization was detected in 5 iCCA patients (46%): in one case (9%) as lymph node metastasis, in two cases (18%) as bone metastasis and in

3 other cases (27%) as peritoneal carcinomatosis (one of these also with simultaneous bone metastasis).

The recurrence of phCCA was treated with chemotherapy.

iCCA recurrences were treated with chemotherapy in 5 cases (46%) and, one each, with radio frequency ablation (RFA), microwave ablation (MWA), selective internal radiotherapy (SIRT), surgery and Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC).

At last FUP, updated to December 2019, 7 patients with phCCA (88% of patients included in the FUP) and 3 with iCCA (33%) were tumor free. Among these, one iCCA was previously successfully treated with RFA after recurrence.

Among patients with recurrence, a R1 status was observed in 1 phCCA (25% of phCCA with R1) and 2 iCCA (100% of iCCA with R1), a N1 status in 1 phCCA (33% of phCCA with N1) and 6 iCCA (86% of iCCA with N1), a Pn1 status in 1 phCCA (14.3% of phCCA with Pn1) and 1 iCCA (50% of iCCA with Pn1).

The patient with iCCA and L1- and V1-status developed a recurrence (100% of iCCA with V1 and L1), while the phCCA with V1 did not. Only one patient with multifocal iCCA entered FUP and had a recurrence in the 21st postoperative month (POM) (see Table 20).

One patient with iCCA recurrence received another oncological resection (pancreaticoduodenectomy at Stage 1 due to enlarged retroperitoneal lymph nodes and suspected extension of the tumor to the pancreas head) and another iCCA a vascular reconstruction due to tumor invasion of the left hepatic vein.

The phCCA with recurrence was in Stage 3c while 6 of 7 patients (86%) with recurrence in iCCA groups were in Stage 3 (n = 1) and 4a (n = 5).

Median tumor size in patient with recurrence was 6.9 cm (3.9-11.7) (phCCA 4.2 cm and iCCA 9.2 cm (3.9-11.7)).

N	Diagnosis	FUP (months)	Tumor size max (cm)	Uni- or multifocal	Stage	TNM	Pn	V	L	R	G	Time of recur. (POM)	Localization of recur.	Recur. therapy	Death after Recur. (POM)	Tumor free after Therapy
1	*phCCA*	42,4	4.2	unifocal	3c	T2b, N1, M0	1	0	0	1	2	29,5	Liver	Chemo	42,4	no
2	*iCCA*	4,3	3,9	unifocal	4a	T2b, N1, M0	0	0	0	1	2	1	Peritoneum	Chemo	4,3	no
3	*iCCA*	36,8	10,5	unifocal	2	T2b, N0, M0	0	0	0	0	Nd	2,3	Liver	Chemo, MWA, SIRT	36,8	No
4	*iCCA*	63,4	10,2	unifocal	4a	T1 , N1 , M0	X	0	0	0	2/3	9,2	Liver	RFA	-	Yes
5	*iCCA*	58,1	10,5	multifocal	4a	T3, N1, M0	1	0	0	0	2/3	20,5	Liver, Peritoneum	Surgery, PIPAC	-	No
6	*iCCA*	17,3	10,3	unifocal	3b	T3, N1, M0	0	1	1	0	2	3,9	Liver, Bone	Chemo	17,3	no
7	*iCCA*	2,5	11,7	unifocal	4a	T2b, N1, M0	0	0	0	1	3	1,9	Liver, Peritoneu, Bone	Chemo	2,5	No
8	*iCCA*	16	7,5	unifocal	4a	T1, N1, M0	0	0	0	0	2	15,6	Lymph nodes	Chemo	-	no

Table 20 - *Characteristics of patients who have experienced recurrence in the FUP. Chemo: Chemotherapy; iCCA: intrahepatic Cholangiocarcinoma; MWA: microwave ablation; phCCA: perihilar Cholangiocarcinoma; PIPAC: Pressurized IntraPeritoneal Aerosol Chemotherapy; Recurr.: Recurrence; RFA: radio frequency ablation; SIRT: selective internal radiotherapy*

3.8.2 Overall Survival

Overall mortality after relapse was observed in one patient with phCCA (12.5%) and 4 patients with iCCA (44%).

The Overall Survival (OS) among patients who entered FUP was 88% for phCCA and 55% for iCCA.

The median OS was 36.8 months (1.4-104.1) and 36.4 months (2.5-63.4) for phCCA and iCCA respectively.

The 1-, 3- and 5-years cumulative survival was respectively 80%, 80% and 60% for phCCA, 64%, 55% and 40% for iCCA (see Fig. 10).

4 DISCUSSION

Late diagnosis, limited treatment options and poor prognosis make cholangiocarcinoma (CCA) a major challenge among liver tumors.

The introduction of the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) has encouraged the surgical community with a promising new surgical strategy to resect patients who would otherwise have no curative options (119, 125, 129, 130, 166).

However, early reports on deplorable morbidity and mortality (M&M), particularly in patients with CCA, cool the enthusiasm (47, 240).

Consequently, the indication to perform an ALPPS procedure in CCA remains hesitant, also because strong long-term oncological results are still lacking.

Our experience shows that ALPPS applied to CCA, in particular phCCA, could significantly extend the overall survival (OS) in selected patients otherwise condemned to a poor outcome. Here we will gradually discuss the different aspects of such a complex procedure, from patient selection to long-term outcomes.

4.1 PATIENT SELECTION

A great effort has been undertaken in ALPPS to identify the main risk factors, as well as to develop predictive scores in order to improve patient selection and reduce M&M (137, 158, 159).

4.1.1 Age and Comorbidities

A recent analysis by Linecker et al. showed that patient selection based, among other factors, on younger age and a shift in the indication towards colorectal

liver metastases (CRLM), has reduced mortality from about 17% to less than 5% in recent years (34, 159).

The demographic analysis of our study showed that patients with CCA, in particular with phCCA, were, as already known (247), older than reported in the general population undergoing ALPPS, including therefore mainly patients with CRLM (137, 240).

There is already evidence of an association between old age and increased rate of perioperative complications and postoperative mortality in ALPPS (45, 124, 137, 158, 240, 248).

Several cutoffs above the age of 60 have been arbitrarily proposed and analyzed (158, 240). Schadde et al. have shown that patients under 60 years of age have just 2% of mortality compared to 14% of patients over 60 years of age (158). The study supporting the ALPPS Risk Score, based on an accuracy analysis, reported the age of 67 as the optimal cutoff for predicting postoperative mortality (137).

De Santibañes et al. have shown that in elderly patients less hepatocytes enter the cell cycle and begin to replicate, suggesting a limited regenerative capacity in this subgroup (249). In addition, elderly patients present significantly more comorbidities and fibrosis (see chapter 4.2.2 Liver Quality).

In our study, 60% of patients with phCCA and 36% of patients with iCCA (and in particular 4 out of 5 patients with postoperative mortality!) had an ASA score of 3 and a higher comorbidity index before Stage 1, revealing that the comorbidity condition could play an important role in the final outcome.

Comorbidities, even if not manifest, are a well-known risk factor for a poor outcome in major liver surgery, as they can unbalance and complicate the postoperative course with PHLF and mortality (235, 250-257). Diabetes, obesity, malnutrition and frailty, hepatitis, renal dysfunction and age over 65 are associated with PHLF (235, 251-257). Severe comorbidities such as congestive

heart failure, severe kidney or lung disease are already considered a contraindication for a major liver resection (250).

However, comorbidities in ALPPS are still subject to debate and are not yet recognized as significant, either individually and globally (137, 158). Cardiovascular disease marginally failed statistical significance in some reports (137), while the global measure of comorbidities, usually evaluated with the age-adjusted Charlson Comorbidity Index (aCCI)(236, 258), has systematically failed any predictivity in ALPPS when used in mixed cohorts with primary and secondary liver tumors, probably due to an overestimation of secondary tumors, such as CRLM (137, 158, 161). For other scores, such as ECOG (Eastern Cooperative Oncology Group) and the Karnofski performance index, there is no consensus in the HPB-literature and they are not found in the ALPPS literature (255, 259-261).

Our risk analysis, however, despite based on just few events, showed that patients that experience postoperative mortality present significantly more comorbidities.

4.1.1.1 *Risk scores*

Currently two predictive scores are available: 1) the already validated ALPPS Risk Score (160) and 2) the proposed new Risk Score for the CRLM, which however can only be applied in this type of tumor (161). As mentioned above (see chapter 1.4.3.1 Patient selection and risk factors), both scores can be applied before both Stage 1 and Stage 2.

The ALPPS Risk Score (ALPPS-RS) was developed in 2016 (137), to help select patients before an ALPPS procedure (ALPPS-RS 1) or to decide the timing of the second Stage (ALPPS-RS 2). The ALPPS RS-1, which currently remains the only tool for skimming CCA patients preoperatively, will be discussed below, whereas the ALPPS-RS 2 in the chapter 4.5.2 Mortality.

The ALPPS-RS 1, based only on patient age and tumour type, can be applied to patients with CCA. However, it is not really suitable to differentiate between patients with this diagnosis, as these patients already receive the maximal points, if they are over 67 years of age.

The median preoperative 90-days risk in our population, evaluated with the ALPPS-RS-1 and based on the data of the original manuscript (137), was 37% in both phCCA and iCCA, and that would have contraindicated the operation in most patients.

For this reason, we still do not know how to clearly address the characteristics of patients, apart from their advanced age and tumor type. Once again it should be stressed that these two factors mainly exclude patients with primary tumors, such as HCC or CCA, from ALPPS.

A multicenter study has been planned by our institution to develop a score to better assess the risk of 90-day mortality. The data of 451 patients who underwent ALPPS from 13 high volume centers worldwide were analyzed and discussed with experts at the E-AHPBA Meeting 2019 in Amsterdam (*Personal communication of Capobianco, Nadalin et al.*). A risk score based on age, BSA, primary tumor, presence of renal disease, severe cardiovascular disease (defined as any of congestive heart disease, myocardial infarction and peripheral vascular disease), moderate or severe diabetes mellitus was developed and showed a better predictivity than ALPPS-RS-1 and -2. The new score now allows a much better selection of patients based, among other factors, on comorbidities, without excluding a priori patients with primary tumors.

4.1.2 Nutritional impairment and physical condition

Nutritional and physical conditions also play an important role in patients undergoing surgery, however there is little data in patients undergoing major liver resection. The improvement of the patient's condition at the time of surgery

is mandatory to optimize the outcome, and further studies on this aspect are to be expected in the future.

4.1.2.1 *Nutritional impairment*

Although there are no data on ALPPS, malnutrition is an important modifiable risk factor for a negative outcome after hepatectomy. It impaires the immune system and the capacity for liver synthesis and regeneration (188, 262).

It is known that 50-90% of patients with cirrhosis or cholestasis suffers from malnutrition (263-266). Similarly, patients with obesity often have liver steatosis (267) and sarcopenia. The latter, defined as depletion of lean muscle mass, was measured up to 43% of these patients (268), reflecting increased morbidity and mortality (186, 198, 269, 270).

4.1.2.2 *Physical condition*

A patient's physical condition includes all physiological parameters of body composition such as muscle strength, flexibility and exercise capacity (195, 271). Muscle strength is essential for recovery from major surgery. It depends on overall nutritional status and declines with age (195), while reduced exercise capacity has been associated with increased mortality after transplantation, regardless of liver function (195, 272-274).

4.2 LIVER ASSESSMENT

Liver volumetry, quality and function are the main factors influencing PHLF.

4.2.1 Volumetry

The median volume gain over the 13.5-day median Interstage time was 76% (26.5 - 142) and 65.9% (23.8 - 264.5) for iCCA and phCCA respectively, therefore comparable to the hypertrophic potential of ALPPS reported in the literature (see chapter 1.4 ALPPS and Table 3).

However, when analysing the liver hypertrophic potential rate by means of the KGR, the median KGR of the iCCA group was 28.6 ml/day (10.9 %/day) and thus further comparable with the literature (123, 275), whereas the KGR of the phCCA was only 21.6 ml/day (6.3 %/day). Kambakamba et al. have already demonstrated that a KGR <6 %/day was associated with a significantly higher risk of PHLF, showing an intrinsic property of the phCCA population (276). Furthermore, according to our experience, patients who experienced postoperative mortality showed a significantly lower KGR in the Interstage (15.5 ml/day (10-19) VS 27.1 ml/day (8.7-71)).

Li et al. found in an iCCA population that patients aged < 65 years have a higher KGR than patients aged > 65 years (123).

In addition, Huiskens et al., based on CRLM data alone, suggested that FLR/BW < 0.4 prior to Stage 1 could be predictive of 90-day mortality and proposed to perform PVE in these patients (161). It should not be forgotten that the common cutoff to perform a primary liver resection in healthy liver is 0.5 (146, 166, 172) and no information on liver quality, e.g. the presence of CASH, was provided in the study. Moreover, the cutoff of 0.4 would have excluded most patients, since 66% of the cohort and 64% of the patients who did not experience mortality reported a FLR/BW <0.4 (161). Furthermore, Linecker et al. found no predictive value for preoperative volumetry in the assessment of the ALPPS Risk Score (137).

Above all, an adequate FLR should be achieved before proceeding to the second Stage. Li has demonstrated that an insufficient FLR at Stage 2 (defined as FLR/BW <0.80) is a risk factor for severe complications and consequently for mortality (123).

Although, to the best of our knowledge, there are insufficient data or diagnostic possibilities to predict the exact regeneration potential of the liver, much more can be done to assess the quality and function of the liver preoperatively, as illustrated below.

4.2.2 Liver Quality

4.2.2.1 *Fibrosis and Cirrhosis*

Cirrhosis is a relative contraindication for ALPPS, as it limits the regeneration capacity of the liver. A comparison with published data is not always possible, as liver quality is often underreported and different scores are used.

Schadde et al. described, in one of the first reports from ALPPS Registry, a prevalence of fibrosis in patients undergoing ALPPS of 27% (158), while Li et al. reported a prevalence of fibrosis and cirrhosis in patients with iCCA of 26.2% and 2.4% respectively (123). Interestingly, Linecker et al. pointed out a decrease in the selection of patients with fibrosis from 21% before 2011 to 14% in 2015 (124).

However, the main data on this topic are based on HCC patients. In highly selected patients with HCC, ALPPS was already used in the presence of cirrhosis.

D'Haese et al. reported a significantly higher degree of fibrosis and a lower rate of hypertrophy (47 vs 76%) in patients with HCC compared to patients with CRLM (248). Chan et al. described similar results in patients with HCC in

cirrhosis compared to patients with chronic hepatitis (hypertrophy rate: 33% vs 53%, respectively) (277). Surprisingly, however, Vennarecci et al. found no difference at POD 7 between cirrhotic patients and normal liver (71.7% vs 64.8%)(278).

Histological analysis in our population showed that none of the patients presented cirrhosis. However, 90% of iCCA have low or non-fibrotic liver, while in phCCA 70% of patients presented a grade 2 or higher fibrosis, probably due to prolonged cholestasis. This point may also explain the reduced KGR in these patients, as already shown (see Table 14)(248).

In addition, in our cohort, patients with postoperative mortality presented significantly more fibrosis and, in the entire population, an Ishak-Score of 3 or more significantly increased the probability of postoperative mortality by 2.75 fold compared to patients with less or no liver fibrosis.

4.2.2.2 *Steatosis and Steatohepatitis*

The main steatohepatitis data are based on CRLM patients.

Schadde et al. reported a prevalence of 32% macrosteatosis and 9% microsteatosis in the ALPPS-Registry population (158), while Linecker et al. showed again a decrease in the selection of steatohepatitis patients from 22% before 2011 to 12% in 2015 (124). Interestingly the prevalence of macrosteatosis increased from 18% before 2012 to 25% in 2015 (124). Probably, this is mainly attributable to the switch of the indication to CRLM, namely patients who have mostly undergone preoperative chemotherapy. However, macrosteatosis alone does not seem to have a negative impact on the outcome. Li et al., considering steatosis as >30% of hepatocytes affected (approximately Grade 3 and 4 of the Dixon scale, see Table 8 in chapter 2.7 Liver Quality), reported a prevalence of 7.1% in patients with iCCA (123).

In our population, steatosis has been reported in about 40% of patients with either phCCA or iCCA, but has not been associated with increased mortality,

probably because only one iCCA had a Dixon ≥3. However, the four patients who presented a Dixon Scale ≥ 2 reported a lower median hypetrophy rate (KGR 23.8 ml/day and 6.9 %/day) than the general cohort.

This confirms the importance of assessing liver quality preoperatively, particularly in at-risk patients selected on the basis of age and comorbidity. This could be done by means of a biopsy, while other imaging approaches (e.g. US. Elastography, MRI and CT) have yet to be validated (see chapter 6.2 Assessment of Liver Quality). Promising results using elastography to predict PHLF were already published (279-281), while MRI allows segmental assessment of steatosis and can also be used to assess fibrosis, making it a potential one-stop-shop mode for both liver anatomy and quality and, ultimately, function (1, 216-224).

4.2.2.3 *Cholestasis*

The presence of histological cholestasis in ALPPS literature is not found or omitted. This is probably due to the fact that patients with cholestasis are usually patients with phCCA, and these are a minority in the ALPPS literature as well as patients with severe cholestasis are not indicated for ALPPS.

In our cohort, two patients with phCCA showed severe intrahepatic cholestasis and only one of them was stented. The patient with Klatskin-mimicking IgG4-autoimmune cholangitis also showed severe intrahepatic cholestasis and was stented.

The hypertrophy rate of these patients was lower than the general cohort (KGR 16.3 ml/day and 7.4 %/day).

4.2.2.4 *Siderosis*

Other types of pathological findings are also not analyzed in the literature. In our cohort, five patients presented with siderosis. Although this characteristic has

not been associated with increased mortality, these patients have a lower hypetrophy rate (KGR 19.1 ml/day and 6.7 %/day) than the general cohort.

4.2.3 Liver Function

In this retrospective study, liver function was considered only through laboratory findings, in particular by MELD-Score.

The first small series regarding ALPPS reported normalization of Bilirubin, INR or Prothrombin time (PT) and Creatinine within 12 days after completion of surgery in patients without complications (71, 119, 282) and, clinically, 20% of patients developed a new onset ascites, defined as more than 200 ml/g of abdominal fluid, and persisted for a median of 4 weeks (119).

In addition to this, our study reports that MELD and CHE, once unbalanced, need almost a month after Stage 2 to normalize again, while the volume has already been recovered.

A MELD-Score of more than 10 had already been recognized as a risk factor for 90-day mortality in the first analysis based on the ALPPS Registry (158).

Our findings confirm this statement, but only before Stage 2. Nevertheless, patients with in-hospital mortality had a higher MELD-Score at Stage 1 and 2 than the others.

However, a more recent analysis based on a larger data pool did not confirm these observations (137). This does not avoid that an unconserved liver function should be considered carefully before proceeding to the second Stage.

Several Interstage serological factors have been analyzed to understand the safety of proceeding to the second Stage or postponing it. The ALPPS-RS 2 focused on serum bilirubin and creatinine before Stage 2 as highly predictive of postoperative mortality, while the CRLM Risk Score focused only on creatinine

(see chapter 1.4.3.1 Patient selection and risk factors). In the presence of these serological risk factors the second Stage should be postponed until recovery.

One of the most exciting innovations is the ability to measure and visualize the precise function of the FLR by hepatobiliary scintigraphy (HBS) (see chapters 1.4.3.4 Liver Function and 6.3 Assessment of Liver Function).

Many authors have pointed out that the volume increase does not correspond to the function (68, 73, 180, 204, 212-214, 283). This may partly explain the high morbidity and mortality associated with ALPPS despite the unprecedented hypertrophy.

In addition, segmental function determination can help establish the correct interval in each two-stage procedure, such as PVE, TSH or ALPPS, before performing extensive resections and exposing patients to PHLF risk (213, 283-285). It is already known that the deportalized liver in the Interstage still contributes to total liver function (73), allowing the FLR to grow with low liver failure risk. Global function assessment techniques cannot differentiate between the deportalized hemiliver and the FLR (205), with the risk of overestimating the function of the latter. For this reason, knowing the exact functionality of the FLR should be mandatory (129).

One of the main advantages of HBS is that, in addition to showing segmental function, it is less affected by hyperbilirubinemia, and therefore it is applicable in cholestatic patients, as patients with CCA could be (286-288).

The use of HBS as 99mTc-Mebrophenine Hepatobiliary Scintigraphy (HIDA) had already been suggested in the first paper on ALPPS (see chapter 6.3 Assessment of Liver Function)(119).

However, there are only a few studies with small cohorts and even fewer mortality events (68, 213, 283, 289), so there is no consensus on the cutoff to be used in the different HBS techniques, limiting the interpretation of the data and their application.

HIDA was introduced at the University Hospital Tübingen at the end of 2016 and used only in two phCCA preoperatively and three phCCA in the Interstage.

We cannot therefore refer to any conclusions, as these evaluations are still ongoing.

Stockmann et al. suggested the use of LiMAx (see chapter 6.3.3 13C-Methacetin Breath Test (LiMAx)) considering the percentage of FLR to total liver volume as the percentage of FLR functionality (i.e. predicted Future Liver Remnant Function, pFLRF). The normal cutoff value is set to 311-575 µg/kg/h (207). Stockmann et al. have applied LiMAX to ALPPS and showed a drop in function after Stage 1 and, after Interstage recovery, after Stage 2. Furthermore, the authors showed an excellent correlation between pFLRF and measured postoperative liver function after Stage 2, insisting that pFLRF could be used to predict segmental function (73). Nevertheless, this ignores the lack of uniformity of hepatic function throughout the liver and in particular between the deportalized hemiliver and the FLR (205). In addition to the slight availability of the device, several factors such as smoking, nutrition and visceral hemodynamics can influence the results (290).

4.3 BILIARY DRAINAGE

Biliary drainage (BD) is usually indicated preoperatively in case of cholestasis in (1, 291-293):

1. patients with congestive cholangitis, severe malnutrition or liver or kidney failure induced by hyperbilirubinemia
2. patients undergoing preoperative augmentation procedure with long Interstage (i.e. PVE) or before neoadjuvant chemotherapy.

The aim of BD is to relieve jaundice and improve liver function and, secondly, to increase the regeneration capacity of the liver (1, 293). A preoperative total bilirubin level of <2–3 mg/dl is recommended (292, 294).

The BD can be placed by means of a retrograde cholangiopancreatography (ERCD or nasobiliary) or percutaneously by mean of transhepatic cholangiography (PTCD)(292, 295).

In our experience, three patients with phCCA (30%) and the patient with the Klatskin-mimicking IgG4-autoimmune cholangitis underwent ERCP and bile duct stenting (ERCD) before referral to our center, while no patients received PTCD placement preoperatively.

PTCD is superior to ERCD because it allows biliary sampling, does not need to be changed regularly and could also be used as a diagnostic tool to cholangiographically delineate the endobiliary tumor (296-298). On the other hand, PTCD can cause cholangitis and tumor seeding along the catheter tract (1). For this reason PTCD should be avoided in patients with an adequate nutritional status, slightly elevated bilirubin and without cholangitis (299). In case of bilateral cholestasis the drainage should be placed on the FLR site to improve recovery and regeneration of the liver (255). However, due to transhepatic insertion, the risk of implant metastasis and FLR lesions increases (1, 296-298).

Moreover, a recently published randomized controlled trial comparing phCCA patients who had undergone PTCD or ERCD prior to surgery showed that although the postinterventional complications rate was similar between the two groups, the mortality rate in the ERCD group was extremely higher (46% VS 11%) (300).

An additional benefit of the ERCD is that there is no risk of tumor seeding. However, in patients undergoing PVE or chemotherapy it should be changed regularly, it can trigger ascending cholangitis in the FLR and bile cannot be sampled for microbiological information.

An alternative could be a nasobiliary drainage, associated with a lower risk of cholangitis than ERCD and allowing sampling. Some eastern groups recommend it as the ideal method (301-303). However, patient discomfort is

higher (301, 304). In addition, over 50% of ERCD patients subsequently require a PTCD to achieve the required therapeutic effect (305).

For this reason the use of BD is still widely debated and there is a lack of studies demonstrating its unconditional effectiveness (294, 306, 307).

The use of BD in ALPPS has been criticized by Li et al. after the first experience in our center due to sepsis-related mortality in three patients after biliary drainage by ERCD (118, 308). The current cohort risk analysis, however, does not confirm this assumption.

In conclusion, a BD should only be used in case of strict indication and possibly after performed imaging to avoid artifacts.

4.4 SURGICAL TECHNIQUE

4.4.1 Stage 1

4.4.1.1 *Explorative Laparotomy and IOUS*

After laparotomy, abdominal exploration is of primary importance to determine the extent of the tumor and its resectability. Particularly in the case of CCA, CT and MRI are unable to detect a low volume of peritoneal metastases (1). Despite the improvement in imaging techniques in recent years (99, 306, 309, 310), 20 to 50% of patients still have liver or peritoneal metastases at the time of surgical exploration (27, 311-313). In addition, an intraoperative ultrasound (IOUS) of the liver can be performed to locate lesions and determine FLR inflow and outflow (118, 146).

In all cases, the procedure has remained in our experience, as planned, a right trisectionectomy. The first major reports based on the registry, showed that worldwide ALPPS was performed for right hemihepatectomy in most cases (52%)(158, 240), introducing BIAS and questions about the correctness of the indication in patients who may not have needed a two-stage hepatectomy. A study by Schnitzbauer et al. based on volumetric, liver quality and hypertrophy rate analysis compared patients undergoing ALPPS for right hemihepatectomy and extended right hemipatectomy (314). It was shown that in 15% of cases there was an overindication to ALPPS, especially in the group of patients with right hemihepatectomy (314).

4.4.1.2 *Mobilisation and approach to main structures*

Since in our CCA cohort there were no metastases in the left lateral segments, the left liver remained untouched at Stage 1. On the contrary, mobilization of the right liver was always performed before parenchymal transection to light out the posterior resection line (146, 237). Some groups, however, suggested that the right liver should not be mobilized at all at Stage 1 for oncological reasons and to reduce the surgical impact (see chapter 6.1.1.6 Anterior Approach) (126, 315).

4.4.1.2.1 Lymphadenectomy

In most cases, lymphadenectomy was performed at Stage 1 to better approach the liver hilum and to better expose the biliar, arterial and portal structures close to their bifurcations (118, 146, 237).

4.4.1.2.2 Approach to vasculobiliary structures

The invasion of vasculobiliary structures in CCA, particularly in phCCA, is common. In our series, while biliary structures were regularly resected due to

tumor involvement, two patients (one phCCA and one iCCA) required vascular reconstruction due to tumor invasion of the portal vein and right hepatic artery, respectively.

4.4.1.2.2.1 Bile duct

The right hepatic duct (RHD) is more often affected by the tumor up to its second-order branches because it is short and bifurcates early (1). In addition, possible anatomical variations (e.g. supra-portal right posterior sectorial duct, RPSD) may limit the extent of resection or require further resection of vascular structures (1). On the other hand, the left hepatic duct (LHD) is long and branches off in the second- order ducts far away from the hilum in the umbilical fissure (1). However, the bile ducts of the caudate lobe drain close to the biliary bifurcation and are invariably affected by the tumor in case of phCCA with a Bismuth-Corlette Stage of 3 or 4 (1, 295, 310, 316-320).

In this context, the improvement in R0 resection rates and overall survival associated with caudate lobectomy have been demonstrated in several retrospective series (1, 321-323). In addition, caudate lobe resection has also been proposed to reduce the potential bile leakage (324).

4.4.1.2.2.2 Portal vein

If the tumor adheres or infiltrates the right PV at its bifurcation, a resection of the bifurcation is necessary to obtain a negative margin (1, 310, 325, 326). For larger PV resections (approx. more than 5 cm) an interposition graft may be required (1).

At the University Hospital Tübingen the PV bifurcation was resected only if necessary and not, as proposed by the Neuhaus School, a priori (316, 317, 327-330).

4.4.1.2.2.3 Hepatic artery

Arterial perfusion of both hemiliver (FLR and deportalized liver) must be maintained until Stage 2. Infiltration of the hepatic artery requires its resection and reconstruction (particularly for left trisectionectomy as in case of phCCA Bismuth 3b) (1). Reconstruction with or without the use of several interposition grafts is technically demanding and requires a high degree of expertise (331).

If the arterial reconstructions can be performed correctly and safely, the oncological results are more than excellent. The results reported in the literature are very different in terms of patency, morbidity and mortality rates (332-336). However, in a study focused on patients with advanced phCCA undergoing simultaneous portal and hepatic artery resection after hepatectomy, the 1-, 3- and 5-year survival rates were 78.9, 36.3 and 30.3 % respectively (337).

4.4.1.3 *Parenchymal dissection*

Since all the cases were right trisectionectomies, the parenchymal dissection was performed along the falciform ligament anteriorly and the umbilical fissure posteriorly at the level of the inferior vena cava (118, 146, 237).

The dissection was always performed using cavitronic ultrasound surgical aspirator (CUSA), while other groups reported the use of harmonic scalpel, ultrasound dissector and bipolar forceps irrigated with saline solution (119, 126, 131, 237). Moreover, contrary to what proposed from some groups (71, 119, 146), the Pringle-maneuver was not used at this Stage in our series.

Despite a worldwide shift towards less invasive techniques (124) that minimize the Stage 1 procedure (139), the vast majority of our patients were performed with classic ALPPS technique, in particular to avoid a more challenging approach to the main structures at Stage 2 due to adhesions, and only two cases were performed with a partial parenchyma transection (partial ALPPS).

Similarly, no other minimally invasive technique or other variation (e.g. intraoperative PVE) has been applied in this series.

4.4.1.4 *Biliodigestive anastomosis and drainage of the right bile duct*

There is no agreement whether the bile digestive anastomosis, when necessary, should be performed during Stage 1 or Stage 2. Some authors suggest that it should be performed at Stage 1 for better access to the bile duct and to achieve better positioning and suturing of the BDA, together with drainage of the right bile duct (RHD) of the deportalized right liver (133). However, this may make the second Stage more challenging, as the BDA will rely on the hilar structures that should still be dissected, and the possible need for a longer Interstage would lead to adhesion formation.

In our series, only three patients received a BDA already at Stage 1, while 15 (71.4%) cases at stage 2.

In any case, the bile duct of both hemilivers must remain drained until the procedure is completed to avoid cholestasis, bile leaks and consequent contamination of the surgical site and infectious complications. In this regard, different strategies can be adopted depending on the biliary tree tumor involvement: 1) keep the BD bifurcation intact, 2) keep both lobes drained via PTCD or ERCD or 3) perform a BDA on the FLR and keep the right lobe drained or in continuity with the main BD.

RHD ligation to further increase FLR hypertrophy, as suggested by some authors (129, 134, 146, 237), showed no benefit and, on the contrary, increased bile leaks up to 88% (134, 143).

4.4.1.5 *Preparation of second Stage*

4.4.1.5.1 Vessel loops

The use of vessel loops can facilitate the identification of isolated structures during the second Stage, particularly in case of adhesions (126, 338, 339). It consists in encircling the different main structures (or its branches) using different color-coded silastic vessel loops (126, 150).

4.4.1.5.2 Anti-adhesion sheet

In addition, to avoid adhesions between the two hemilivers it was proposed to wrap the deportalized lobe with a plastic bag (118, 131, 237, 340). Alvarez et al. also proposed to place a drain into the bag to avoid the collection of fluids (146). However, it has been pointed out that this could increase the rate of infection and, in case of dropout, a laparotomy would be necessary for the removal of the foreign body (146, 341, 342). For this reason, Belghiti proposed the use of a type-I acellular collagen membrane on the transection surface, which does not increase morbidity (315). Other groups alternatively use a silicone sheet (118, 343) or an omentoplasty (344). At the University Hospital Tübingen we regularly used a bioresorbable membrane based on sodium hyaluronate. Whenever it is removed, the plastic bag or sheet should be submitted to microbiological examination (146).

4.4.1.5.3 Fibrin sealants

Finally, to prevent bleeding from resection plane, fibrin sealants or glue can be used on the transection surface (147, 154, 308, 345-347), which, unlike the plastic bag and sheet, must not be removed (237). However, they have no effect on biliary loss and it is not clear whether they reduce the adhesion rate, so these techniques can be combined (348).

4.4.2 Stage 2

All patients of our cohort have completed the ALPPS procedure (100% feasibility rate), confirming the lower dropout in the Interstage for ALPPS compared to other augmentation techniques (in particular PVE and TSH), where the dropout reaches 30% (see also Table 3 in chapter 1.3 Augmentation Techniques)(40, 95, 113, 114, 117).

It is interesting to note that the median lenght of the operation for both phCCA and iCCA in Stage 2 (226 minutes (59-395) and 204 minutes (91-290), respectively) was shorter than Stage 1 (258.5 (134-408) and 246 minutes (154-515), but still comparable. This is probably due to the making of the BDA in most cases (71.4%) at this Stage. In addition, a systematic lymphadenectomy was completed in three remaining cases (1 phCCA and 2 iCCA), while in three cases of phCCA (30%) a portal resection and reconstruction was performed at second Stage.

In one case, with tumor invasion of the PV, reconstruction with the interposition of a venous graft was postponed to Stage 2 to reduce the possible morbidity in the Interstage.

Despite the larger resection, radicality could be achieved in 60% of patients with phCCA and 82% of patients with iCCA, comparable to literature data on extended resections (15, 349). It should be borne in mind that without this procedure none of these patients would have had a radical resection option and a better chance of survival.

Finally, at the end of the second Stage it is crucial to secure the liver outflow. Therefore, an IOUS must be performed at the end of the procedure.

In addition, to avoid the twisting of the hepatic vein of the FLR (especially if it corresponds to the left lateral lobe) the falciform ligament can be used to fix the FLR to the abdominal wall (118, 119, 146, 147, 237).

4.5 MORBIDITY AND MORTALITY

4.5.1 Morbidity

The big debate on ALPPS is focused on morbidity and mortality with the detractors that stress the high prevalence of complications and mortality and the supporters that see it as a necessary (but still improvable!) sacrifice to break down the limits of the actual therapeutical possibilities.

Due to subclassification in two Stages, definition of morbidity (major or severe) and different indications, reports on morbidity in ALPPS is heterogeneous.

The overall major morbidity (defined as ≥ IIIa according to Dindo-Clavien classification) and overall severe morbidity (≥ IIIb according to Dindo-Clavien classification) are reported at about 40% and 27%, respectively (71, 119, 240).

The overall morbidity after Stage 1 and 2 is reported between 11-78% and 61-83%, respectively (71, 82, 124, 125, 350-352), while the severe morbidity after Stage 1 and 2 is reported between 3-15% and 25-31%, respectively (124, 125).

The high variability in the different studies also depends on the year of the report, the technique performed and the type of tumor.

Morbidity significantly decreased in the last years due to better patient selection from 77 to 61% (major 82 to 64% and severe morbidity 31 to 25%) (123, 124, 159).

Patients with CRLM have less morbidity (overall 29-66%, major 29-39% and severe 13-21%) compared to HCC (overall 21-63%, major 44% and severe 27%), iCCA (overall major 38%, with Stage 1 and Stage 2 overall morbidity, respectively, of 25% (severe 6%) and 76.8% (severe 41.4%)) and phCCA (overall major morbidity 64%, with 13% at Stage 1 and 22% at Stage 2) (47, 123, 125, 161, 240, 248, 277, 351).

In our cohort the overall morbidity remains higher than 80% for all the considered groups, and therefore higher as what reported in literature both for

ALPPS (34) as well as for major hepatectomies in CCA (19, 353, 354). However, severe morbidity in phCCA in our cohort resulted of 60%, inferior to the study of Olthof et al. based on phCCA and comparable with standard one stage extended right hepatectomy (59%) (47). Moreover, our reported severe morbidity in iCCA of 45.5% was comparable with the study of Li in ALPPS and a couple of studies about major hepatectomies that report a severe morbidity between 30 and 50% (123, 349, 353), depending on extent of resection, presence of comorbidities and liver quality at time of surgery (36, 355-358).

The most important observation in our cohort is the split-up between severe complications and mortality seen in the second half of the learning curve, where no mortality was observed despite persisting high and severe morbidity. It is interesting to note that this point in time corresponds to the introduction in 2016 of Standard Operating Procedures (SOPs) for major liver surgery and management of patients with liver failure (particularly prevention and treatment of PHLF).

This suggests that current success lies not only in the selection of the right patients and the evolution of surgical technique, but also in perioperative management.

Morbidity after Stage 1 is a known risk factor for postoperative mortality following complete resection (see chapter 1.4.3.1 Patient selection and risk factors).

PHLF on day 5 (158), complication ≥ IIIa (161) or ≥ IIIb (137) were all high significant risk factors in different analysis. Our study confirms these finding in our CCA cohort, since the presence of major complications in the Interstage as well as severe complications, after Stage 2 or overall, increases the risk of postoperative mortality.

Therefore, perioperative management is as important as the operating procedure to achieve a good result, particularly in avoiding or managing morbidity in the Interstage. This topic is still underrepresented in the ALPPS literature and no structured studies are available.

For example, the need for prophylactic antibiotics in the Interstage to prevent sepsis is unknown, while several groups use it regularly under conditions such as the presence of right ischemic hemiliver (and/or ischemic segment IV), the presence of a plastic bag/sheet in the abdominal cavity, and the presence of biliary stents (59, 146, 166, 282, 346, 359).

In addition, early enteral (or at least parenteral) nutrition and patient mobilization from the first POD to avoid weight and muscle loss is critical for FLR regeneration (293).

For all this reasons, ALPPS should only be offered in experienced centers to select patients accurately and for optimal perioperative management. It has already been pointed out that also this policy, among others, has significantly reduced morbidity in recent years (124, 159).

4.5.1.1 *Post-Hepatectomy Liver Failure (PHLF)*

Notwithstanding one of the main purposes of ALPPS is to reduce the incidence of PHLF by means of unparalleled hypertrophy in a short time, PHLF after Stage 1 is reported between 0-36% and after Stage 2 12.5%-36% (125, 137, 213, 248, 276, 350). Similarly to overall morbidity, PHLF is lower for CRLM (26%) than for HCC (34-40%), iCCA (35-38%) and phCCA (57%) (73, 123, 158, 162, 213, 248, 283, 360).

This persistent high incidence is often caused by an imbalance between the extremely high volumetric recovery and a slower functional recovery (68, 162, 170, 204, 212, 213, 276, 283). Histological analysis showed the immaturity of hepatocytes and bile canalicular network after rapid hypertrophy (360-362).

Overall PHLF in our cohort was observed in 5 phCCA (50%) and 6 iCCA (55%) after Stage 2, but a PHLF grade C was experienced in 3 phCCA (30%) and 2 iCCA (18%). These results are better than the overall incidence of PHLF seen in the ALPPS literature for phCCA (57%) but worse for iCCA (38%).

4.5.1.2 *Biliary leakage*

Biliary leakage is a known complication of extended liver resection, with an incidence up to 15% (119, 123, 357, 363-366).

In our experience it was observed in two patients with phCCA (20%) and in one iCCA (9%). All of them occurred after Stage 2. In the first two cases the leak was from the resected surface, while in the iCCA from the BDA.

In ALPPS, Schnitzbauer et al. have already reported a biliary leakage rate of 24% treated radiologically or endoscopically (119). This data have been recently confirm by Spetzler et al. with a bile leakage rate in ALPPS of 23%, comparable to that of a major liver resection (363).

Intraoperative identification of bile leaks can reduce postoperative morbidity. Different test have been used in the ALPPS Literature. These are mainly the “white test” (118, 166), the methylene blue test (341, 367, 368) and the hydraulic test (71, 146, 150, 369, 370), as well as intraoperative cholangiography (146, 150, 282).

The localization of the leakage, i.e. from parenchyma or from the BDA, is however underreported.

Also timing of the BDA is controversial, Schadde et al. reported the incidence of bile leak higher after Stage 2 (20.8%) than after Stage 1 (2.1%), as the parenchyma is resected, indirectly suggesting a higher prevalence of leakage from the BDA, that usually is created at Stage 2 (125). Similarly, Li et al., in a multicentric study based on only iCCA, reported a higher bile leak rate after Stage 2 than Stage 1 (12.6% after Stage 1 and quite 31% after Stage 2)(123).

On the other hand, Truant et al., in a franco-belgian experience with 62 patients undergoing ALPPS reported an exceptional cumulative rate of biliary leakage of 40%, equally distributed between Stage 1 and 2. Interestingly this cohort have a low prevalence of BDA (10%). More importantly, this work pointed out that a contamination of the biliary system can alter the regeneration capacity of the

liver and consequently the postoperative outcome, indifferently from the leak localization (151).

Finally, Nagino emphasizes that bile leaks should be avoided, in particular to prevent peritoneal spread, since bile in phCCA may contain floating cancer cells (46, 371).

4.5.1.3 *Vascular complications*

Vascular events can also have a relevant impact on the outcome. Fortunately, these events are rare and are not systematically reported in the ALPPS Literature (151).

4.5.1.3.1 Portal Vein Thrombosis (PVT)

Truant et al. reported a cumulative portal vein thrombosis (PVT) of 3.2% (2 patients out of 62)(151).

In our study we had two partial PVT, one in a patient with iCCA after Stage 1 and one in patient with phCCA after Stage 2. Both could be bridged or treated with anticoagulants and only the first, at the planed Stage 2, was further treated definitively by thrombectomy.

4.5.1.3.2 Hepatic Artery Thrombosis (HAT)

The role of a hepatic artery thrombosis (HAT) of the deportalized liver in the Interstage, although underreported, is controversially discussed.

In our experience, a patient with iCCA, that required a reconstruction of the right hepatic artery due to tumor invasion at Stage 1, experienced a HAT in the Interstage at POD 3, with acute liver failure and sepsis due to necrosis of the right deportalized liver. Despite the second Stage was preponed to remove the

necrotized liver, the patient died at POD 18 after Stage 2 due to liver insufficiency.

Sanjeevi et at., however, reported a case of a HAT at POD 3 after Stage 1 in a male patient with CRLM, who suffered a deterioration of liver function, but still with a volumetric increase in FLR of 138% already at POD 3 (372). In this patient, where it was possible to stabilize the reduced liver function in the Interstage, the second Stage took place at POD 7 with a further uneventful postoperative history.

A study on rats confirms this observations, showing that liver hypertrophy is more pronounced when, at the splitting of the liver, the portal vein and the hepatic artery are simultaneously ligated than the portal vein alone (373). However, this was also associated to higher injury of the hepatocytes of the deportalized and dearterialized liver, reducing the supporting function of the right hemiliver at the time of functional recovery of the FLR. For this reason, a HAT in the Interstage must be carefully considered and the patient's condition and liver function must be continuously monitored. In this case, the timing of the second Stage must be carefully balanced between deterioration of the devascularized hemiliver and recovery of the FLR. On the contrary, a left HAT should always be treated quickly to avoid FLR injury and liver failure.

4.5.1.3.3 Veno-Occlusive Disease

Two Veno-Occlusive Disease occurred after Stage 2 in our cohort.

One patient with phCCA and one patient with iCCA were successfully treated by means of radiological stenting on POD 28 and 25 respectively.

A Veno-Occlusive Disease as an Interstage complication is not reported in the ALPPS literature. It is possible that such an event in the Interstage on the right side, however, may lead to accelerated hypertrophy similar to extended liver venous deprivation (eLVD) (see chapter 1.3.4 Extended Liver Venous Deprivation (eLVD)). Again, intensive monitoring of liver function should be carried out.

4.5.2 Mortality

Postoperative mortality remains the Achilles heel of the ALPPS. 90-days mortality after completed ALPPS was initially reported up to 45%, depending on study cohort, with an average of 9-14.5% in the registry studies (82, 118, 125, 158, 159, 240, 352).

Furthermore, as already mentioned, Schadde et al. showed in patients younger than 60 years of age a mortality of 2% compared to 14% in patients older than 60 years of age (158). Similarly, the mortality was less in CRLM (5-8%), than in HCC (5.8-31.4%), iCCA (13-21%) and particularly phCCA (27-48%) (47, 123, 158, 161, 240, 248, 277, 351).

As for morbidity, a decrease in mortality from 17-45% to 3.8-16% has been observed in recent years, both in registries and single-centre studies (123, 124, 159).

Mortality following a major resection for CCA has been reported to range from 5 to 16% in larger series (12, 20, 36, 353, 374), compared to 5.6% in patients undergoing any liver resection (50, 375).

However, two recent studies on phCCA have found a mortality rate of 24-28% among patients who have undergone a major resection with an FLR of less than 30% (47, 255) and up to 25.5% if a BDA is required (36). Finally, the mortality among patients undergoing ALPPS for iCCA was about 13-21% and for phCCA up to 48% (47, 123, 158, 240).

In our study in-Hospital mortality was observed in two patients with phCCA (20%) and two with iCCA (18%). Moreover, another patient with Klatskin's IgG4-autoimmune cholangitis autoimmune, whose indication was given for suspected phCCA, died after surgery.

The main thing is to underline that all the futile events of our cohort are concentrated in the first years of our experience (see Table 16), namely at a time when the selection criteria were not clear and the results in the literature were still limited to small positive series. Once the learning curve has been

completed and the indication and selection has been redefined, no mortality event has been observed since 2015.

Once more, we should stress that patients who underwent an ALPPS procedure were untreatable with any other therapy and therefore condemned to a poor outcome.

The main cause of postoperative death, in the literature as in our study, is septic shock, usually after the development of PHLF (123, 158, 166, 360).

A major effort has been undertaken to identify main risk factors, as well as to develop predictive scores, in order to improve patient selection (124, 137, 157-159).

Age, volumetry, liver function, Interstage complications are already discussed above. In addition, patients with a secondary liver tumor, particularly CRLM, experience less postoperative mortality. For this reason, HCC and particularly biliary tumors are widely seen as a risk factor per se for ALPPS and often classified as a contraindication (47, 124, 137, 158).

There are currently two risk scores available which include the risk factors mentioned above and attempt to assess the risk for each patient before (see chapter 1.4.3.1 Patient selection and risk factors) (137, 161). However, their predictivity is barely acceptable, with a c-statistic of ALPPS Risk Score 1 and 2 after validation of 0.64 and 0.77 and a c-statistic of CRLM Risk Score 1 and 2 of 0.70 and 0.72, making the patient selection not always obvious (160).

In a CCA population, as the cohort of this study, just the ALPPS Risk Score (ALPPS-RS) is applicable (137), since the CRLM risk score was only developed for this type of cancer (161).

As already mentioned, the ALPPS-RS 1 (based on age ≥ 67 and type of tumor) does not seem to be really useful for screening patients preoperatively, since biliary tumor already receives the maximum points and age is the only variable. It should not be forgotten, however, that cholangiocarcinoma patients are older and the average age at diagnosis is ≥ 67 years for both phCCA and iCCA (247), as also confirmed by the population in our study.

The ALPPS Risk Score 2 is currently the best tool to decide the timing of Stage 2, since the score summarizes non-modifiable (ALPPS-RS 1 and presence of severe complications in Interstage) and modifiable (serum creatinine and bilirubin before Stage 2) variables. In our study the ALPPS-RS 2, differently from ALPPS-RS 1, applied to a CCA population was significantly higher in patients that experienced postoperative mortality and still highly predictive of 90-days mortality at univariate analysis.

As already mentioned above, in addition to identifying the risk factors, it is also useful to classify them in modifiable and non-modifiable (see Table 6 in chapter 1.4.3.1 Patient selection and risk factors). Non-modifiable variables such as age, tumor type and presence of comorbidities, as well as complications in Interstage, should be evaluated to decide whether or not to proceed to ALPPS Stage 1 or 2, respectively. On the other hand, modifiable variables such as MELD and other biochemical parameters, or partially liver volume, quality and function, could influence the timing of the procedure.

For this reason, if proper patient selection is made based on age, comorbidity, liver function and quality, and less invasive techniques are applied, we believe that post-operative mortality could be further reduced in patients with CCA.

4.6 ONCOLOGICAL OUTCOMES

The mortality reduction applied to ALPPS opens the discussion on oncological results. Solid long-term outcomes are still lacking, particularly if referred to patients with phCCA.

Olthof et al. reported a 3-year survival after ALPPS in patients with phCCA of about 45% (47).

Based on a few patients, 1y-DFS and -OS for iCCA were initially reported at 31-75% and 60-73% respectively (144, 240). Li et al. in a new multicentric study of

patients undergoing ALPPS for iCCA, report an overall 1- and 3-year recurrence rate of 55.1% and 92%, respectively, with a median recurrence time of 9 months (123). In the same study the median OS was 26 months, with a 1-, 3- and 5-year OS rate of 64.3%, 38.8% and 22.0%, respectively (123).

4.6.1 Disease-free Survival

Median overall DFS of patients undergoing any type of resection reported in the literature vary widely from 7 to 32 months for both phCCA and iCCA with a 5-year DFS ranging from 2 to 40% (11, 12, 16, 20, 376, 377). Our study confirms these observations with a median DFS for phCCA of 29.5 months, but a still limited DFS for iCCA of 7.8 months. The main site of recurrence was the liver and the majority of them were further treated with chemotherapy.

The known negative prognostic factors for phCCA are age, T stage, lymph node involvement, positive surgical margins, perineural and microvascular invasion and poor differentiation (378-380), while for iCCA they are age, the large size and multifocality of the tumor, tumor stage ≥ 3, lymph node involvement, positive surgical margin, perineural, macro- and microvascular invasion, presence of metastases and poor tumor differentiation (11, 28, 381).

According to the AJCC/UICC classification, 50% of patients in our cohort with phCCA and 73% of patients with iCCA were at an advanced stage.

Interestingly, the missed radicality does not seem to affect the result for the phCCA. Although R0 was achieved in 60% of phCCA, only one in four patients with R1 had a relapse after 30 months and died after 42 months. The same patient, however, had advanced stage 3c and had nodal and perineural invasion. According to literature data, such a patient should have a life expectancy of a few months if not resected (16, 17, 29).

The incidence of recurrence in iCCA is 66%. Most of them, however, presented an advanced stage 4a. All patients with R1, L1 and V1 status, as well as 86% of patients with nodal positivity, developed a recurrence.

4.6.2 Overall survival

Median OS for phCCA and iCCA in our study was 36.8 and 36.4 months, respectively, comparable with the literature (11, 13-17, 123).

However, the 3- and 5-year cumulative survival for phCCA at 80 and 60% is considerably better than in the literature, although only four patients have currently achieved a 3 year FUP.

On the other hand, patients with advanced iCCA, due to early recurrence, do not seem to have a significant advantage from the ALPPS procedure. However, it should be noted that most of them are patients with advanced stage cancer with R1 resection and lymph node positivity and therefore an expected 5-year survival < 20%, if resectable with traditional techniques (11, 17-25, 28).

In addition, Li et al. compared in a propensity score analysis patients with a locally advanced, initially non-resectable, iCCA undergoing ALPPS with chemotherapy patients (123). The study showed a greater 3-year OS in the ALPPS group. However, the authors also pointed out that this benefit is limited to single focal lesions, while multifocal lesions, due to high M&M and short OS, do not benefit from this procedure when compared to chemotherapy alone (123).

While the benefit for chemotherapy is unclear as primary therapy, the use of adjuvant systemic therapy in patients with high risk of recurrence (e.g. R1 resection) shows an improved 5-year OS (23), and this may partly clarify good OS in patients with iCCA despite poor DFS.

In addition, it should be stressed that the biggest drop in the survival curve is within the first 90 days. Avoiding postoperative mortality in CCA through better patient selection could lead to excellent oncological results.

4.6.3 Does ALPPS stimulate tumor growth?

It has already been hypothesized that ALPPS could stimulate tumor growth, since regenerative stimuli in the Interstage could also act on the remaining tumor in the diseased hemiliver (382). However, many studies on rodent models, as well as on humans, have not confirmed these results.

Although tumor progression was observed in the Interstage, this was not parallel to FLR hypertrophy and did not outgrow other augmentation techniques.

The group from Chiba, Japan, found no significant change in tumor volume when comparing ALPPS patients with TSH patients (383). In another cohort comparing ALPPS and TSH, the same group also observed a difference in Ki67 expression in liver cancer cells at Stage 1, but at Stage 2 it was greater in the TSH group than in ALPPS (352). Similar results have been described in mouse models, also in the comparison between ALPPS and PVL or standard liver resection (384-386).

A sub-study of the LIGRO-trial comparing 13 patients undergoing ALPPS with 11 patients undergoing radical resection after PVE for CRLM did not observe a higher rate of rapid recurrence in ALPPS (387). The authors, who also performed the genetic analysis of metastases, concluded that tumor recurrences are most likely caused by gene mutations, such as KRAS, NRAS, BRAF, PIC3CA and TP53, that from the procedure itself (387).

A better biological knowledge of tumors is also emerging with regard to CCA (388-391). This could be integrated into the patient selection flowchart in the future to determine which patient has the best chance of having a good prognosis and thus counterbalancing the perioperative risk.

4.7 ALPPS OR PVE FOR CCA?

ALPPS detractors for Cholangiocarcinoma suggest that PVE can achieve the same results with with significantly less M&M.

The longer time to move to Stage 2 in PVE is not seen as a problem in phCCA. as this tumor is usually a slow-growing cancer (46, 392). If a dropout caused by insufficient hypertrophy occurs, one might always consider a Rescue-ALPPS.

However, if this is not possible or if the dropout is caused by tumor growth, these patients are condemned to palliative treatment and a miserable outcome.

Moreover, it should be noted that PVE of the right portal vein alone is technically feasible with low complications, but would stimulate hypertrophy of the entire left liver. These patients, therefore, without Segment IV embolization, should be compared with patients undergoing a classic right hemipatectomy and probably do not need a right trisectomy with the ALPPS procedure, as usually required in a phCCA. For this reason they cannot be compared.

On the other hand, a further PVE of the branches of Segment IV, as proposed by Nagino (46, 393, 394), is a demanding technical procedure which requires experienced radiologists, as the possible accidental embolization of the Segment 2-3 branches would deportalize the entire liver without FLR hypertrophy (89).

Mise et al. reported that an additional embolization of Segment IV increases the degree of hypertrophy in the left lateral segments by only 2% (395). Moreover, Madoff still reported a dropout of 29%, mainly due to extrahepatic spread (90).

Morbidity after further embolization of segment IV is reported up to 10%, with complications as PVT, coil migration to the left PV and subcapsular hematoma. (396).

Mortality was reported about 3-7% after completion of resection considering the entire population that underwent PVE + segment IV embolization. However, the incidence of mortality increases to 7-10% excluding patients who did not

complete the surgery due to previous dropout (89, 90, 394, 396), compared to a current mortality in ALPPS of 3.8-16% (123, 124, 159)

Olthof et al. compared the mortality rate of 29 patients with phCCA from 23 centers included in the ALPPS Registry who underwent ALPPS with 29 patients from only two centers (the Amsterdam Medical Centre and the Memorial Sloan Kettering Cancer Center, New York) with a similar FLR that underwent standard primary resection (221). This study reported that mortality in patients undergoing ALPPS was twice as high (48% vs 24%). However, the matching of two different cohorts (Register VS two selected centers) has a huge BIAS. The median preoperative standard FLR/TLV was similar, but still greater, in the matched group (20 (16–26) VS 25 (19–29), p 0.079). Since the conventional cutoff for an augmentation technique with good liver quality is FLR/TLV > 25% (see chapter 1.4.3.2 Volumetry), and the data about liver quality are missing in this study, most patients in the paired group would probably not have needed ALPPS anyway. Still the morbidity rate in the matched group was 76% (47). For this reason, these results should be interpreted carefully.

Finally, Nagino reported a 5-year survival rate of almost 70% in phCCA patients undergoing PVE with R0 resection and N0 disease (46, 310). However, as soon as any type of positivity (nodal, perineural or surgical margins) is present, 5-year survival drops to 20% (310).

In summary, PVE involves a lower perioperative risk, however some preliminary data suggest a superiority of ALPPS in terms of procedure completion, radicality and therefore oncological results. Since clear guidelines are lacking, the decision between the different techniques requires a multidisciplinary approach including surgeons, hepatologists, radiologists and oncologists.

4.8 STRENGTH AND LIMITS

To the best of our knowledge, this series is the first to focus on ALPPS for right trisectionectomy in CCA patients and suggests promising long-term results, provided that postoperative mortality can be limited through careful patient selection.

However, the main limitations of this study are its retrospective nature and the small group of patients. Since the knowledge of ALPPS is still evolving, in parallel with the evolution of this cohort, many BIAS are present.

Many data concerning ALPPS, especially about liver regeneration, patient selection, perioperative patient management and long-term outcome, are scarce or mostly missing, and could be compared just with other liver augmentation and resection techniques.

5 SUMMARY AND CONCLUSION

Among liver tumors, cholangiocarcinoma (CCA) has still limited therapeutic possibilities, as surgery is the only option to achieve long-term survival, provided resection is possible.

In addition, because extended resection is required in most cases, the risk of Post-Hepatectomy Liver Failure (PHLF) and consequently mortality is high, sometimes subjecting the clinician to a difficult choice between giving the patient a risky chance or leaving him/her with a palliative situation and limited life expectancy.

Several two-step augmentation techniques have been developed to decrease the risk of PHLF and are currently available. However, while the PHLF problem may be limited by these techniques, morbidity and mortality after completion of the procedures are not to be ignored, and especially the problem of dropout due to tumor growth during Interstage remains high, with almost a quarter of patients unable to complete the procedure.

Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) was introduced in 2007 as a new two-stage augmentation technique with unprecedented hypertrophy in the shortest possible time, promising to reduce PHLF and dropout in one fell swoop.

It consists of ligation of the right portal vein and parenchymal transection during the first Stage, and finalization of the resection after Future Liver Remant (FLR) hypertrophy, usually within two weeks after Stage 1.

Although the ALPPS-related dropout is close to zero, allowing the resection of patients previously inoperable, the initially reported high morbidity and postoperative mortality quickly cooled down the initial enthusiasm. The morbidity is linked to the complexity of the procedure, but above all the risk of PHLF cannot be completely forgotten, as functional recovery is slower than hypertrophy, resulting in high mortality.

However, studies in recent years have shown that a careful selection of patients for ALPPS (mainly by age, tumor type and presence of comorbidity), the improvement of operating techniques and the introduction of less invasive alternatives have greatly reduced the mortality associated with this procedure from 17-45% to 3.8-16%, and therefore comparable to other major surgical procedures applied to the same type of tumor (12, 20, 36, 124, 353, 374).

Much can still be done with regard to preoperative liver assessment, especially with regard to quality and function.

This study includes 21 patients with CCA (10 phCCA and 11 iCCA) undergoing ALPPS between November 2010 and November 2019.

We have shown how any pathology of the liver parenchyma, particularly fibrosis, can slow down hypertrophy and the functional recovery, increasing the risk of PHLF. A preoperative assessment of histology by means of biopsy or imaging techniques should be mandatory in older and high risk patients.

In addition, the introduction of hepatobiliary scintigraphy (HBS) is a promising technique to study the exact segmental function of the liver, establish perioperative risk and identify the exact timing for the second Stage.

Our study has also shown how proper perioperative management can address morbidity and consequently reduce the mortality even in extended resection.

The long-term oncological results that can be obtained are very promising and game-changing for a type of patient, presenting CCA tumor in advanced-stage, who is currently otherwise sentenced to a very short life expectancy. Furthermore, increased knowledge about the biology of CCA can help to achieve even better results and balance perioperative risk with long-term benefit.

As a conclusion ALPPS in CCA is not a surgical Play-Doh but another card to play in patients with advanced cancer stages and without other treatment options. Excellent oncological results require a multidisciplinary approach including surgeons, hepatologists, radiologists and oncologists. For this reason the procedure should only be proposed in high volume centers.

5.1 ZUSAMMENFASSUNG (DE)

Unter den Lebertumoren weist das Cholangiokarzinom (CCA) nach wie vor nur begrenzte therapeutische Optionen auf. Sofern eine Resektion möglich ist, bietet eine Operation die einzige Möglichkeit, um ein langfristiges Überleben zu erreichen.

Da in den meisten Fällen eine erweiterte Resektion erforderlich ist, ist das Risiko eines Leberversagens nach Hepatektomie (Post-Hepatectomy Liver Failure, PHLF) und der damit verbundenen Mortalität hoch. Das stellt den Kliniker mitunter vor die schwierige Wahl, dem Patienten entweder eine riskante Chance zu geben oder ihn in einer palliativen Situation mit begrenzter Lebenserwartung zu belassen.

Um das Risiko von PHLF zu verringern, wurden mehrere zweizeitige Augmentationstechniken entwickelt und stehen derzeit zur Verfügung. Doch auch wenn das PHLF-Problem durch diese Techniken begrenzt werden kann, dürfen Morbidität und Mortalität nach Abschluss der Verfahren nicht ignoriert werden. Insbesondere das Problem des Abbruchs aufgrund von Tumorwachstum während der Interphase ist nach wie vor hoch, da fast ein Viertel der Patienten das Verfahren nicht abschließen kann.

Die Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) wurde 2007 als neue zweizeitige Augmentationstechnik mit beispielloser Hypertrophie in kürzester Zeit eingeführt. Sie verspricht die schlagartige Reduktion von PHLF und Dropout.

Sie besteht aus einer Ligatur der rechten Pfortader und einer Transektion des Parenchyms während der ersten Phase und dem Abschluss der Resektion nach einer Hypertrophie des zukünftigen Leberrests (Future Liver Remnant, FLR), normalerweise innerhalb von zwei Wochen nach der ersten Phase.

Obwohl der ALPPS-bedingte Abbruch beinahe bei Null liegt und damit die Resektion von zuvor inoperablen Patienten ermöglicht, dämpfte die zu Beginn berichtete hohe Morbidität und postoperative Mortalität zunächst die

anfängliche Begeisterung. Die Morbidität hängt mit der Komplexität des Eingriffs zusammen. Vor allem aber kann das Risiko von PHLF nicht völlig außer Acht gelassen werden, da die funktionelle Erholung langsamer ist als bei einer Hypertrophie, was wiederum zu einer hohen Mortalität führt.

Studien der letzten Jahre haben jedoch gezeigt, dass eine sorgfältige Auswahl der Patienten für ALPPS (hauptsächlich nach Alter, Tumorart und Vorhandensein einer Komorbidität), die Verbesserung der Operationstechniken und die Einführung weniger invasiver Alternativen die mit diesem Verfahren verbundene Sterblichkeit von 17-45% auf 3,8-16% stark reduziert haben. Somit sind sie mit anderen wichtigen chirurgischen Verfahren vergleichbar, die bei gleicher Tumorart angewandt werden (12, 20, 36, 124, 353, 374).

Hinsichtlich der präoperativen Beurteilung der Leber kann noch viel getan werden, insbesondere im Hinblick auf die Qualität und Funktion.

Diese Studie umfasst 21 Patienten mit CCA (10 phCCA und 11 iCCA), die zwischen November 2010 und November 2019 einer ALPPS unterzogen wurden.

Wir haben gezeigt, wie jede Pathologie des Leberparenchyms, insbesondere die Fibrose, die Hypertrophie und die funktionelle Erholung verlangsamen kann, wodurch sich das Risiko von PHLF erhöht. Eine präoperative Beurteilung der Histologie mittels Biopsie oder bildgebender Verfahren sollte daher bei älteren und Hochrisikopatienten obligatorisch sein.

Darüber hinaus ist die Einführung der hepatobiliären Szintigraphie (HBS) eine vielversprechende Technik, um die exakte Segmentfunktion der Leber zu untersuchen, das perioperative Risiko zu ermitteln und den genauen Zeitpunkt für den zweiten Schritt zu bestimmen.

Unsere Studie hat zudem gezeigt, wie durch ein geeignetes perioperatives Vorgehen die Morbidität angegangen und folglich die Mortalität auch bei einer ausgedehnten Resektion gesenkt werden kann.

Die langfristigen onkologischen Ergebnisse, die erzielt werden können, sind sehr vielversprechend und grundlegend für einen Patiententyp, der einen CCA-

Tumor im fortgeschrittenen Stadium aufweist und der ansonsten mit einer sehr kurzen Lebenserwartung zu rechnen hätte. Darüber hinaus kann ein erweitertes Wissen über die Biologie von CCA dazu beitragen, noch bessere Ergebnisse zu erzielen und ein Gleichgewicht zwischen perioperativem Risiko und langfristigem Gewinn herzustellen.

Zusammenfassend lässt sich sagen, dass ALPPS bei CCA kein chirurgisches Play-Doh ist, sondern eine weitere Karte, die bei Patienten mit fortgeschrittenen Krebsstadien und ohne andere Behandlungsmöglichkeiten ausgespielt werden kann. Ausgezeichnete onkologische Ergebnisse erfordern einen multidisziplinären Ansatz, der Chirurgen, Hepatologen, Radiologen und Onkologen mit einschließt. Aus diesem Grund sollte das Verfahren nur in hochvolumigen Zentren vorgeschlagen werden.

6 APPENDIX

6.1 TECHNICAL VARIANTS AND DETAILS

Several technical variants have been proposed. Lau and Lai divided the technical variants as follows (138):

1) Variants to decrease operative morbidity and mortality
2) Variants to extend resectability.

6.1.1 Variants to decrease operative morbidity and mortality

6.1.1.1 *Partial ALPPS (p-ALPPS)*

The partial ALPPS (p-ALPPS) was introduced in 2015 with the aim of reducing surgical invasiveness and thus reducing Interstage complication (139, 140).

It has been defined as an incomplete parenchymal transection up to the middle hepatic vein (MHV) or as a transection between 50 and 80% of the total parenchyma, preserving the liver veins, especially MHV.

No significant difference was reported regarding FLR hypertrophy between partial and classic ALPPS when applied in non-fibrotic livers, but a significant reduction in Interstage morbidity from 33-89% to 0-38%. It has been hypothesized that avoiding MHV transection reduced venous congestion within the FLR (59, 71, 140, 397). Some authors have pointed out that the complete devascularization of segment IV (portal + venous), as it happens in the classic ALPPS, causes ischemic necrosis of segment IV, complicating the Interstage and the postoperative course (136, 146, 308, 398).

However, other groups showed less hypertrophy in p-ALPPS than classic ALPPS in patients with chronic liver disease (238). Deal et al. showed in a pig

model that the growth rate is inversely proportional to the number of collaterals (399).

Currently p-ALPPS, alone or in combination with other techniques as described below, is the most widely used technical variant associated with a reduction in postoperative mortality (124, 400, 401).

6.1.1.2 *Radiofrequency-assisted ALPPS (RALPPS)*

Radio frequency ablation (RFA) is applied regularly for the treatment of hepatic tumors and leads to coagulative necrosis of the liver parenchyma by rapid alternating currents (59, 402).

Gall et al. reported for the first time the use of RFA during the first laparoscopic Stage to induce parenchymal necrosis along the planed transection line, ceasing blood flow between the FLR and the deportalized liver, associated with ligation of the right portal vein (141, 142). They reported a median hypertrophy of 62% in 22 days with 20% morbidity and no mortality (141).

The same group, in a case-controlled study comparing RALPPS with PVE and ALPPS, confirms a rate of hypertrophy comparable with ALPPS and less severe complications (in particular biliary leaks) in the RALPPS group (59).

This technique has already been successfully applied in open surgery in patients with HCC with cirrhotic liver (403, 404) and, in a modified technique with RFA and extracorporal PVE, in phCCA (*Alhikanov R, personal communication at E-AHPBA 2019, Amsterdam*).

The REBIRTH trial (Rapid Induction of Liver Regeneration for Major Hepatectomy (REBIRTH) trial), a registered, randomized controlled trial by the Imperial College of London comparing RALPPS vs PVE, showed a superiority of RALPPS in terms of hypertrophy and proceed to Stage 2, without any difference in morbidity (only three patients, 11.5%, in the RALPPS group experienced a complication ≥ IIIb) and one patient (3.8%) with 90-day mortality

after RALPPS (42). However, no patients with CCA and only one with HCC were included in the RALPPS group.

6.1.1.3 *Laparoscopic microwave ablation and portal vein ligation for staged hepatectomy (LAPS).*

Microwave ablation (MWA) also produces coagulative necrosis (59) and can be used as an alternative to RFA in RALPPS. Two Italian groups, respectively from Padua and Pisa, reported the use of LAPS in a first laparoscopic or robotic Stage (and in one case also at Stage 2) with results similar to RALPPS, i.e. hypertrophy comparable to ALPPS with a lower complication rate (405-407).

6.1.1.4 *Associating Liver Tourniquet and Portal ligation for Stage hepatectomy (ALTPS or Tourniquet ALPPS)*

In Tourniquet-ALPPS a 1 cm deep groove is made along the section line and a 3 mm Vicryl Tourniquet (V152; Ethicon, Somerville, New Jersey, USA) is placed and then narrowed over the transection line using an extraglissonian approach to prevent occlusion of the hepatic artery and bile duct. The main purpose of this technique is to reduce blood loss and surgical time during Stage 1.

The hypertrophy in this technique of 61-69% in 7 days was also comparable with classic ALPPS, and the overall morbidity of 0-27% and 22-36% after Stage 1 and 2, respectively, was lower than classic ALPPS (143-145).

The same principle was proposed in a laparoscopic variation by Cai et al (408). In this case a nasogastric tube was used as Tourniquet. However, the reported hypertrophy was only 37.9% (59, 408).

Finally, Tourniquet-ALPPS has also been successfully proposed associated with a delayed PVE (369).

6.1.1.5 *Mini-ALPPS or PVE-ALPPS*

Noting that the Interstage course and in particular the presence of comorbidities were a limiting factor for the success of ALPPS (see chapter 1.4.3.1 Patient selection and risk factors), De Santibañes proposed at the first ALPPS Meeting in Hamburg in 2015, and then published in 2016, a change in the whole ALPPS strategy: minimizing Stage 1, with the aim of reducing Interstage complications, and a longer and more aggressive Stage 2, with hylar preparation and completion of the parenchymal transection (139).

The Buenos Aires group has published a series with 4 patients who have undergone a p-ALPPS combined with intraoperative portal vein embolization (PVE) (139). Also in this case the median hypertrophy of 62.6% in 11 days was comparable to classic ALPPS. Moreover, a 100% feasibility with R0 margins was reported and any PHLF or major complications were observed (139).

6.1.1.6 *Anterior Approach*

In order to avoid liver mobilization (resulting in perihepatic and paracaval adhesions) and tumor dissemination (due to iatrogenic rupture of the tumor during right liver mobilization), the anterior approach for ALPPS for the first Stage was proposed (45, 315, 341, 368).

In the first Stage the parenchyma transection and portal occlusion are performed and the mobilization of the right liver is postponed to Stage 2 (341).

Li et al., strengthening the concept of minimizing Stage 1 (139), reported a "no-touch" approach in a patient with portal vein tumor infiltration due to advanced gallbladder cancer (45). In this case the parenchyma was transected with an anterior approach and the portal occlusion was postponed. A PVE was performed on POD 2, achieving 65% hypertrophy in 6 days (45).

6.1.1.7 *Laparoscopic and robotic procedure*

Laparoscopy has been repeatedly performed successfully in Stage 1 or both stages of ALPPS in many case reports and small series (59, 71, 126, 141, 142, 151, 156, 340, 348, 403, 405-414).

Although this technique was initially criticized because of its technical difficulties and limitations in detecting and palpating occult lesions (126, 146), its application is increasing due to its lower invasiveness and has reported fewer complications and adhesions after Stage 1 (406, 414). Two cases are reported using a robotic approach with similar results (415, 416). However, at the moment it is not possible to draw definitive conclusions on minimally invasive ALPPS (414).

6.1.1.8 *Resection of Segment IV*

As already mentioned above (see chapter 5.1.1.1 partial ALPPS) some authors have highlighted how the complete devascularization of Segment IV, as it happens in classic ALPPS, causes ischemic necrosis of Segment IV, complicating the Interstage and the postoperative course with the development of biliary leaks (136, 146, 308, 398). To avoid this, Andriani et al. proposed the simultaneous resection of Segment IV at Stage 1 (417).

6.1.2 Variants to extend resectability

6.1.2.1 *Left-ALPPS*

This procedure applies to left hepatectomy to preserve Segments 5-8. It may be necessary in case of small volume of the right hemiliver after removal of the tumor load (121, 131, 138). In Stage 1, after performing the wedge resection of the right hemiliver, the left portal vein is ligated and the transection is performed through the Cantlie's line (121, 131, 138).

6.1.2.2 *Right-ALPPS*

In this hemihepatectomy, Segments 2-4 are preserved. It is indicated in case of small FLR after removal of the tumor from the left hemiliver or in case of poor quality of the liver parenchyma. In Stage 1, after dissection of the right portal vein, the parenchyma is dissected along the main portal fissure (131, 138, 146).

6.1.2.3 *Segment 4, 5, 8-ALPPS*

The indication to Segment 4,5,8-ALPPS may be given in the case of pronounced tumor load, which requires resection of the lateral segments with possible preservation of the central liver sector after wedge resection in Segments 4, 5 and 8 (138).

In Stage 1 the sectionectomy of Segments 2-3 is performed, the right posterior portal vein is ligated to deportalize the right posterior segments and finally the multiple wedge resections in Segments 4, 5 and 8 are followed by the liver transection between the right anterior and posterior section (138).

6.1.2.4 *Double in situ split for stage mesohepatectomy*

This technique is used in patients with central tumor, limited FLR and low liver quality, who require resection of central segments and preservation of lateral segments 2-3 and 6-7 (138, 147).

6.1.2.5 *Monosegmental ALPPS*

Different types of monosegmental ALPPS have been proposed. It has been defined as any hepatectomy performed with the ALPPS procedure when the FLR consists of a single segment with or without the caudate lobe (149). This technique has been performed in patients with bilateral disease and high tumor load, where only one segment could be preserved.

In the literature are described (131, 138, 148-150):

- Segment 2 ALPPS
- Segment 2 with half Segment 4 ALPPS
- Segment 3 ALPPS
- Segment 3-1 ALPPS
- Segment 4 ALPPS
- Segment 4-1 ALPPS
- Segment 4 with half Segment 2 ALPPS
- Segment 6 ALPPS
- Segment 6-1 ALPPS

The intraoperative details have already been described by Schadde and de Santibañes (149, 150).

6.1.2.6 *Rescue ALPPS*

In case of failed or insufficient hypertrophy after PVE, or in case of insufficient intraoperative volume or quality after tumor removal by planned resection, ALPPS can be performed as a rescue technique. In this case the only thing necessary is the in-situ splitting along the preselected line, since the right portal vein is already obliterated.

In the literature there are many case studies or small series with reported clinical outcomes comparable to "planned" ALPPS (59, 86, 131, 151-156), underlining, once again, the innovative characteristics of ALPPS given by parenchymal transection.

6.2 ASSESSMENT OF LIVER QUALITY

The quality of the liver can be assessed preoperatively through the following procedures:

- Biopsy: liver biopsy is the gold standard and can provide exact information on liver quality (1, 184). However, it is an invasive procedure with possible complications, such as bleeding or infection, and may be associated with false negative results due to sampling errors or irregular distribution of intrahepatic disease (418-421).
- Ultrasonography (US): High frequency ultrasonography is a feasible and inexpensive tool that may suggest poor liver quality due to attenuation parameters (422). However, it shows a moderate sensitivity and need for clinical expertise (423).
- Elastography: Several ultrasound elastography techniques have been developed to detect liver fibrosis (Transient elastography, Real Time Elastography (RTE) or Acoustic Radiation Force Impulse Imaging (ARFI) and Shear Wave Elastography (SWE)). The European Federation of

Societies for Ultrasound in Medicine and Biology guidelines suggests that values above 6.8–7.6 kPa indicate the presence of significant fibrosis and that those ranging between 11.0–13.6 kPa may indicate cirrhosis (424).

- MRI: since conventional MRI can only evaluate indirect information in case of cirrhosis or portal hypertension, different techniques based on MR (MR Elastography, Diffusion-weighted MR (DWI), disodium glydoxetic acid (Gd-EOB-DTPA)) are now available to assess liver steatosis and fibrosis. The results are comparable to US-based elastography techniques.

  In addition, these MRI-based techniques are the most accurate to measure the fat content in the liver and, unlike US-based imaging, are also feasible in obese patients or individuals with ascites, and also allow for whole liver assessment (425-428). On the other side, this methods are expensive, associated to long examination time, patient compliance and could be limited by hepatic iron overload, vascular and biliary congestion (428-431).
- CT: the attenuation of the liver obtained by CT compared to that observed in the spleen may indicate liver steatosis (162, 432). However, CT has a low sensitivity in detecting fibrosis.

6.3 ASSESSMENT OF LIVER FUNCTION

Various methods can be used to assess global or segmental liver function. As already explained in the Introduction (see chapter 1.4.3.4 Liver Function), a global assessment can be obtained by blood analysis and imaging procedures (such as Indocyanine green clearance test (ICG) (205, 206) or 13C-Methacetin Breath Test (LiMAx)) (1, 207), while a segmental assessment can be determined by hepatobiliary scintigraphy (HBS) and MRI with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (gd-eob-dtpa) (216-224).

6.3.1 Biochemistry

Various laboratory parameters show the liver's capacity for synthesis or excretion. They include coagulation parameters (Prothrombin time (PT)/Quick/INR as well as coagulation factors), protein (albumin, total protein), cholinesterase (CHE) (203, 204) and cholestasis parameters (Bilirubin. gamma-Glutamyl Transferase (gGT), Alkaline Phosphatase (ALP)). Several series have shown inconsistent results when these parameters, individually or in combination, are taken as predictors of PHLF (433-437).

Indeed, these parameters can be influenced by several other factors (e.g. protein loss, deficiency state, substitution) as well as comorbidity such as systemic inflammation, nephrotic syndrome, malnutrition, or protein-losing enteropathy (1, 293).

6.3.2 Indocyanine green clearance test (ICG)

The ICG test is the most widely used test in liver surgery worldwide (205). It is based on the ability of ICG to be excreted, after intravenous administration, exclusively from the liver without biotransformation (ICG-15)(206, 438, 439).

The safety limit in predicting safe liver resection of ICG-15 varies between 15 and 20% in different studies (440-444). However, in approximately 20% of patients the severity of the liver disease is underestimated due to hyperbilirubinemia, since absorption is facilitated by common liver transporters, and impaired blood flow, as in the case of intrahepatic shunting (443).

Sparrelid et al. used ICG-15 in a cohort of 9 CRLM patients undergoing ALPPS (212). ICG-15 did not increase after Stage 1, suggesting that deportalized liver still contributes to overall liver function, but there was a significant increase in ICG-15 after Stage 2 and persisted for about 1 month, although no liver failure was reported.

The authors interpreted this result as a possible consequence of increased global blood flow (portal and arterial) to the FLR after completion of resection. However, due to the lack of Interstage increase, ICG-15 cannot yet be proposed to plan the second Stage.

6.3.3 13C-Methacetin Breath Test (LiMAx)

The LiMAx breath test is based on the metabolism of 13C-methacetin by the liver cytochrome CYP1A2. It evaluates the global liver function. However, it has been suggested to use the percentage of FLR to total liver volume as the percentage of function of the FLR (predicted future liver remnant function, pFLRF) (see chapter 4.2.3 Liver Function) (73, 207).

6.3.4 Hepatobiliary Scintigraphy (HBS)

Hepatobiliary Scintigraphy (HBS) can finally show the sectoriality of the liver function. The most discussed are ^{99m}Tc-Galactosyl Serum Albumin Scintigraphy (^{99m}Tc-GSA) and ^{99m}Tc-Mebrofenin Hepatobiliary Scintigraphy (HIDA), which show the absorption and excretion capacity of the liver respectively.

6.3.4.1 *99mTc-Galactosyl Serum Albumin Scintigraphy (99mTc-GSA)*

99mTc-GSA is uptaken only in the liver and is not affected by hyperbilirubinemia (208). In combination with dynamic single photon emission CT scan (SPECT-CT) it allows an accurate three-dimensional measurement of preoperative FLR even in cholestatic patients (286, 287).

Several studies have already shown that the FLR uptake ratio correlates well with the parameters of postoperative liver function and this method can be used to predict the postoperative outcome (287, 445-450).

The applicability of 99mTc-GSA SPECT-CT in monitoring the FLR after PVE has been assessed several time. The increase of the FLR function after PVE was more pronounced than the volumetric increase (284, 285). To the best of our knowledge, there is no report in the ALPPS literature.

6.3.4.2 *99mTc-Mebrofenin Hepatobiliary Scintigraphy (HIDA)*

Mebrophenin is a lidocaine analogue which, similar to ICG, is uptaken and excreted from the liver without undergoing any biotransformation (209-211). In addition, 99mTc-mebrophenin shows the lowest bilirubin displacement in case of hyperbilirubinemia. For this reason, it is particularly indicated in biliary diseases (288).

Since the results are similar to the ICG clearance test (451), HIDA correlates with the postoperative FLR function but allows a segmental view of it (211, 452-455). An uptake of 99mTc-mebrophenin in the FLR <2.69%/min/m2 is suggested to associate with high postoperative liver failure (454, 456).

HIDA has been applied a few times in case reports or small series in ALPPS, all with a disproportion between increasing the FLR function and volume (68, 212-215). Serenari et al. proposed a cutoff at 15%, however it should be noted that this analysis was done in only 20 patients of which only 4 developed PHLF (213). In addition, HIDA has so far been applied in the Interstage to determine the best time point to proceed to Stage 2, and not to select patients before Stage 1.

6.3.5 MRI with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (gd-eob-dtpa)

Gd-EOB-DTPA is a liver-specific contrast agent. About 50% is excreted by hepatocytes and the rest by the kidneys. The data on the evaluation of liver function with Gd-EOB-DTPA, proposed for the first time in 1993, confirmed the possibility of segmental liver function evaluation with MRI, however, again, there is no report in ALPPS (216-224).

7 REFERENCES

1. Capobianco I, Rolinger J, Nadalin S. Resection for Klatskin tumors: technical complexities and results. Transl Gastroenterol Hepatol. 2018;3:69.

2. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. Surg Gynecol Obstet. 1975;140(2):170-8.

3. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. Liver Int. 2019;39 Suppl 1:19-31.

4. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology. 2013;145(6):1215-29.

5. DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg. 2007;245(5):755-62.

6. Khan AS, Garcia-Aroz S, Ansari MA, Atiq SM, Senter-Zapata M, Fowler K, et al. Assessment and optimization of liver volume before major hepatic resection: Current guidelines and a narrative review. International journal of surgery. 2018;52:74-81.

7. Taylor-Robinson SD, Toledano MB, Arora S, Keegan TJ, Hargreaves S, Beck A, et al. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968-1998. Gut. 2001;48(6):816-20.

8. Khan SA, Taylor-Robinson SD, Toledano MB, Beck A, Elliott P, Thomas HC. Changing international trends in mortality rates for liver, biliary and pancreatic tumours. Journal of hepatology. 2002;37(6):806-13.

9. Bertuccio P, Bosetti C, Levi F, Decarli A, Negri E, La Vecchia C. A comparison of trends in mortality from primary liver cancer and intrahepatic cholangiocarcinoma in Europe. Ann Oncol. 2013;24(6):1667-74.

10. Squadroni M, Tondulli L, Gatta G, Mosconi S, Beretta G, Labianca R. Cholangiocarcinoma. Crit Rev Oncol Hematol. 2017;116:11-31.

11. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma: Systematic Review and Meta-analysis. JAMA Surg. 2014;149(6):565-74.

12. Blechacz B. Cholangiocarcinoma: Current Knowledge and New Developments. Gut Liver. 2017;11(1):13-26.

13. Roayaie S, Guarrera JV, Ye MQ, Thung SN, Emre S, Fishbein TM, et al. Aggressive surgical treatment of intrahepatic cholangiocarcinoma: predictors of outcomes. J Am Coll Surg. 1998;187(4):365-72.

14. Tamandl D, Herberger B, Gruenberger B, Puhalla H, Klinger M, Gruenberger T. Influence of hepatic resection margin on recurrence and survival in intrahepatic cholangiocarcinoma. Ann Surg Oncol. 2008;15(10):2787-94.

15. Unno M, Katayose Y, Rikiyama T, Yoshida H, Yamamoto K, Morikawa T, et al. Major hepatectomy for perihilar cholangiocarcinoma. J Hepatobiliary Pancreat Sci. 2010;17(4):463-9.

16. Groot Koerkamp B, Fong Y. Outcomes in biliary malignancy. J Surg Oncol. 2014;110(5):585-91.

17. Ruys AT, van Haelst S, Busch OR, Rauws EA, Gouma DJ, van Gulik TM. Long-term survival in hilar cholangiocarcinoma also possible in unresectable patients. World J Surg. 2012;36(9):2179-86.

18. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. Journal of hepatology. 2014;60(6):1268-89.

19. Chen XP, Lau WY, Huang ZY, Zhang ZW, Chen YF, Zhang WG, et al. Extent of liver resection for hilar cholangiocarcinoma. Br J Surg. 2009;96(10):1167-75.

20. Groot Koerkamp B, Wiggers JK, Allen PJ, Busch OR, D'Angelica MI, DeMatteo RP, et al. American Joint Committee on Cancer staging for resected perihilar cholangiocarcinoma: a comparison of the 6th and 7th editions. HPB (Oxford). 2014;16(12):1074-82.

21. Hyder O, Marques H, Pulitano C, Marsh JW, Alexandrescu S, Bauer TW, et al. A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience. JAMA Surg. 2014;149(5):432-8.

22. Lieser MJ, Barry MK, Rowland C, Ilstrup DM, Nagorney DM. Surgical management of intrahepatic cholangiocarcinoma: a 31-year experience. J Hepatobiliary Pancreat Surg. 1998;5(1):41-7.

23. Reames BN, Bagante F, Ejaz A, Spolverato G, Ruzzenente A, Weiss M, et al. Impact of adjuvant chemotherapy on survival in patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis. HPB (Oxford). 2017.

24. Ribero D, Pinna AD, Guglielmi A, Ponti A, Nuzzo G, Giulini SM, et al. Surgical Approach for Long-term Survival of Patients With Intrahepatic Cholangiocarcinoma: A Multi-institutional Analysis of 434 Patients. Arch Surg. 2012;147(12):1107-13.

25. Valverde A, Bonhomme N, Farges O, Sauvanet A, Flejou JF, Belghiti J. Resection of intrahepatic cholangiocarcinoma: a Western experience. J Hepatobiliary Pancreat Surg. 1999;6(2):122-7.

26. Farges O, Fuks D, Le Treut YP, Azoulay D, Laurent A, Bachellier P, et al. AJCC 7th edition of TNM staging accurately discriminates outcomes of patients with resectable intrahepatic cholangiocarcinoma: By the AFC-IHCC-2009 study group. Cancer. 2011;117(10):2170-7.

27. Matsuo K, Rocha FG, Ito K, D'Angelica MI, Allen PJ, Fong Y, et al. The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. J Am Coll Surg. 2012;215(3):343-55.

28. Dhanasekaran R, Hemming AW, Zendejas I, George T, Nelson DR, Soldevila-Pico C, et al. Treatment outcomes and prognostic factors of intrahepatic cholangiocarcinoma. Oncol Rep. 2013;29(4):1259-67.

29. Farley DR, Weaver AL, Nagorney DM. "Natural history" of unresected cholangiocarcinoma: patient outcome after noncurative intervention. Mayo Clin Proc. 1995;70(5):425-9.

30. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. HPB 2000; 2:333-39. HPB (Oxford). 2002;4(2):99; author reply -100.

31. 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(2):205-13.

32. Okamura Y, Ashida R, Ito T, Sugiura T, Mori K, Uesaka K. Preoperative neutrophil to lymphocyte ratio and prognostic nutritional index predict overall survival after hepatectomy for hepatocellular carcinoma. World J Surg. 2015;39(6):1501-9.

33. Dokmak S, Fteriche FS, Borscheid R, Cauchy F, Farges O, Belghiti J. 2012 Liver resections in the 21st century: we are far from zero mortality. HPB (Oxford). 2013;15(11):908-15.

34. Eshmuminov D, Raptis DA, Linecker M, Wirsching A, Lesurtel M, Clavien PA. Meta-analysis of associating liver partition with portal vein ligation and portal vein occlusion for two-stage hepatectomy. Br J Surg. 2016;103(13):1768-82.

35. Melloul E, Lesurtel M, Clavien PA. Modified associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure with right anterior liver sector congestion: Friend or foe? Surgery. 2016;160(3):820-1.

36. Filmann N, Walter D, Schadde E, Bruns C, Keck T, Lang H, et al. Mortality after liver surgery in Germany. Br J Surg. 2019.

37. Ray S, Mehta NN, Golhar A, Nundy S. Post hepatectomy liver failure - A comprehensive review of current concepts and controversies. Ann Med Surg (Lond). 2018;34:4-10.

38. Schreckenbach T, Liese J, Bechstein WO, Moench C. Posthepatectomy liver failure. Dig Surg. 2012;29(1):79-85.

39. Redaelli CA, Wagner M, Krahenbuhl L, Gloor B, Schilling MK, Dufour JF, et al. Liver surgery in the era of tissue-preserving resections: early and late outcome in patients with primary and secondary hepatic tumors. World J Surg. 2002;26(9):1126-32.

40. Yamashita S, Sakamoto Y, Yamamoto S, Takemura N, Omichi K, Shinkawa H, et al. Efficacy of Preoperative Portal Vein Embolization Among Patients with Hepatocellular Carcinoma, Biliary Tract Cancer, and Colorectal Liver Metastases: A Comparative Study Based on Single-Center Experience of 319 Cases. Ann Surg Oncol. 2017;24(6):1557-68.

41. Liu Y, Yang Y, Gu S, Tang K. A systematic review and meta-analysis of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus traditional staged hepatectomy. Medicine (Baltimore). 2019;98(15):e15229.

42. Jiao LR, Fajardo Puerta AB, Gall TMH, Sodergren MH, Frampton AE, Pencavel T, et al. Rapid Induction of Liver Regeneration for Major Hepatectomy (REBIRTH): A Randomized Controlled Trial of Portal Vein Embolisation versus ALPPS Assisted with Radiofrequency. Cancers (Basel). 2019;11(3).

43. Torzilli G, Adam R, Vigano L, Imai K, Goransky J, Fontana A, et al. Surgery of Colorectal Liver Metastases: Pushing the Limits. Liver Cancer. 2016;6(1):80-9.

44. Hasselgren K, Sandstrom P, Bjornsson B. Role of associating liver partition and portal vein ligation for staged hepatectomy in colorectal liver metastases: a review. World J Gastroenterol. 2015;21(15):4491-8.

45. Oldhafer KJ, Stavrou GA, van Gulik TM, Core G. ALPPS--Where Do We Stand, Where Do We Go?: Eight Recommendations From the First International Expert Meeting. Ann Surg. 2016;263(5):839-41.

46. Nagino M. Value of ALPPS in surgery for Klatskin tumours. Br J Surg. 2019;106(12):1574-5.

47. Olthof PB, Coelen RJS, Wiggers JK, Groot Koerkamp B, Malago M, Hernandez-Alejandro R, et al. High mortality after ALPPS for perihilar cholangiocarcinoma: case-control analysis including the first series from the international ALPPS registry. HPB (Oxford). 2017;19(5):381-7.

48. Rahbari NN, Reissfelder C, Koch M, Elbers H, Striebel F, Buchler MW, et al. The predictive value of postoperative clinical risk scores for outcome after hepatic resection: a validation analysis in 807 patients. Ann Surg Oncol. 2011;18(13):3640-9.

49. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg. 2005;242(6):824-8, discussion 8-9.

50. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg. 2007;204(5):854-62; discussion 62-4.

51. Miyaoka Y, Ebato K, Kato H, Arakawa S, Shimizu S, Miyajima A. Hypertrophy and unconventional cell division of hepatocytes underlie liver regeneration. Curr Biol. 2012;22(13):1166-75.

52. Moris D, Vernadakis S, Papalampros A, Vailas M, Dimitrokallis N, Petrou A, et al. Mechanistic insights of rapid liver regeneration after associating liver partition and portal vein ligation for stage hepatectomy. World J Gastroenterol. 2016;22(33):7613-24.

53. Schlegel A, Lesurtel M, Melloul E, Limani P, Tschuor C, Graf R, et al. ALPPS: from human to mice highlighting accelerated and novel mechanisms of liver regeneration. Ann Surg. 2014;260(5):839-46; discussion 46-7.

54. Shi H, Yang G, Zheng T, Wang J, Li L, Liang Y, et al. A preliminary study of ALPPS procedure in a rat model. Sci Rep. 2015;5:17567.

55. Taub R. Liver regeneration: from myth to mechanism. Nat Rev Mol Cell Biol. 2004;5(10):836-47.

56. Dhar DK, Mohammad GH, Vyas S, Broering DC, Malago M. A novel rat model of liver regeneration: possible role of cytokine induced neutrophil chemoattractant-1 in augmented liver regeneration. Ann Surg Innov Res. 2015;9:11.

57. Garcia-Perez R, Revilla-Nuin B, Martinez CM, Bernabe-Garcia A, Baroja Mazo A, Parrilla Paricio P. Associated Liver Partition and Portal Vein Ligation (ALPPS) vs Selective Portal Vein Ligation (PVL) for Staged Hepatectomy in a Rat Model. Similar Regenerative Response? PLoS One. 2015;10(12):e0144096.

58. Tashiro S. Mechanism of liver regeneration after liver resection and portal vein embolization (ligation) is different? J Hepatobiliary Pancreat Surg. 2009;16(3):292-9.

59. Edmondson MJ, Sodergren MH, Pucher PH, Darzi A, Li J, Petrowsky H, et al. Variations and adaptations of associated liver partition and portal vein ligation for staged hepatectomy (ALPPS): Many routes to the summit. Surgery. 2016;159(4):1058-72.

60. Tu Z, Bozorgzadeh A, Pierce RH, Kurtis J, Crispe IN, Orloff MS. TLR-dependent cross talk between human Kupffer cells and NK cells. J Exp Med. 2008;205(1):233-44.

61. Schoen JM, Wang HH, Minuk GY, Lautt WW. Shear stress-induced nitric oxide release triggers the liver regeneration cascade. Nitric Oxide. 2001;5(5):453-64.

62. Matsumoto K, Yoshitomi H, Rossant J, Zaret KS. Liver organogenesis promoted by endothelial cells prior to vascular function. Science. 2001;294(5542):559-63.

63. Troisi RI, Berardi G, Tomassini F, Sainz-Barriga M. Graft inflow modulation in adult-to-adult living donor liver transplantation: A systematic review. Transplant Rev (Orlando). 2017;31(2):127-35.

64. Demetris AJ, Kelly DM, Eghtesad B, Fontes P, Wallis Marsh J, Tom K, et al. Pathophysiologic observations and histopathologic recognition of the portal hyperperfusion or small-for-size syndrome. Am J Surg Pathol. 2006;30(8):986-93.

65. Bucur PO, Bekheit M, Audebert C, Othman A, Hammad S, Sebagh M, et al. Modulating Portal Hemodynamics With Vascular Ring Allows Efficient Regeneration After Partial Hepatectomy in a Porcine Model. Ann Surg. 2018;268(1):134-42.

66. Allard MA, Adam R, Bucur PO, Termos S, Cunha AS, Bismuth H, et al. Posthepatectomy portal vein pressure predicts liver failure and mortality after major liver resection on noncirrhotic liver. Ann Surg. 2013;258(5):822-9; discussion 9-30.

67. Schadde E, Tsatsaris C, Swiderska-Syn M, Breitenstein S, Urner M, Schimmer R, et al. Hypoxia of the growing liver accelerates regeneration. Surgery. 2017;161(3):666-79.

68. Tomassini F, D'Asseler Y, Giglio MC, Lecluyse C, Lambert B, Sainz-Barriga M, et al. Hemodynamic changes in ALPPS influence liver regeneration and function: results from a prospective study. HPB (Oxford). 2019;21(5):557-65.

69. Wilms C, Mueller L, Lenk C, Wittkugel O, Helmke K, Krupski-Berdien G, et al. Comparative study of portal vein embolization versus portal vein ligation for induction of hypertrophy of the future liver remnant using a mini-pig model. Ann Surg. 2008;247(5):825-34.

70. Dili A, Bertrand C, Lebrun V, Pirlot B, Leclercq IA. Hypoxia protects the liver from Small For Size Syndrome: A lesson learned from the associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure in rats. Am J Transplant. 2019.

71. Alvarez FA, Ardiles V, de Santibanes M, Pekolj J, de Santibanes E. Associating liver partition and portal vein ligation for staged hepatectomy offers high oncological feasibility with adequate patient safety: a prospective study at a single center. Ann Surg. 2015;261(4):723-32.

72. Ding BS, Nolan DJ, Butler JM, James D, Babazadeh AO, Rosenwaks Z, et al. Inductive angiocrine signals from sinusoidal endothelium are required for liver regeneration. Nature. 2010;468(7321):310-5.

73. Stockmann M, Bednarsch J, Malinowski M, Bluthner E, Pratschke J, Seehofer D, et al. Functional considerations in ALPPS - consequences for clinical management. HPB (Oxford). 2017;19(11):1016-25.

74. Terpstra OT, Schalm SW, Weimar W, Willemse PJ, Baumgartner D, Groenland TH, et al. Auxiliary partial liver transplantation for end-stage chronic liver disease. N Engl J Med. 1988;319(23):1507-11.

75. Line PD, Hagness M, Berstad AE, Foss A, Dueland S. A Novel Concept for Partial Liver Transplantation in Nonresectable Colorectal Liver Metastases: The RAPID Concept. Ann Surg. 2015;262(1):e5-9.

76. Konigsrainer A, Templin S, Capobianco I, Konigsrainer I, Bitzer M, Zender L, et al. Paradigm Shift in the Management of Irresectable Colorectal Liver Metastases: Living Donor

Auxiliary Partial Orthotopic Liver Transplantation in Combination With Two-stage Hepatectomy (LD-RAPID). Ann Surg. 2019;270(2):327-32.

77. Nadalin S, Konigsrainer A, Capobianco I, Settmacher U, Rauchfuss F. Auxiliary living donor liver transplantation combined with two-stage hepatectomy for unresectable colorectal liver metastases. Curr Opin Organ Transplant. 2019;24(5):651-8.

78. Nadalin S, Capobianco I. Comment on "The Contribution of the Deportalized Lobe to Liver Regeneration in Tourniquet-ALPPS". Ann Surg. 2020;271(3):e97.

79. Robles-Campos R, Navarro-Barrios A, Martinez-Caceres C, Revilla-Nuin B, Brusadin R, Lopez-Lopez V, et al. The Contribution of the Deportalized Lobe to Liver Regeneration in Tourniquet-ALPPS. Ann Surg. 2020;271(3):e94-e6.

80. Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunven P, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery. 1990;107(5):521-7.

81. Thakrar PD, Madoff DC. Preoperative portal vein embolization: an approach to improve the safety of major hepatic resection. Semin Roentgenol. 2011;46(2):142-53.

82. Shindoh J, Vauthey JN, Zimmitti G, Curley SA, Huang SY, Mahvash A, et al. Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. J Am Coll Surg. 2013;217(1):126-33; discussion 33-4.

83. Pamecha V, Levene A, Grillo F, Woodward N, Dhillon A, Davidson BR. Effect of portal vein embolisation on the growth rate of colorectal liver metastases. Br J Cancer. 2009;100(4):617-22.

84. Enne M, Schadde E, Bjornsson B, Hernandez Alejandro R, Steinbruck K, Viana E, et al. ALPPS as a salvage procedure after insufficient future liver remnant hypertrophy following portal vein occlusion. HPB (Oxford). 2017;19(12):1126-9.

85. Ulmer TF, de Jong C, Andert A, Bruners P, Heidenhain CM, Schoening W, et al. ALPPS Procedure in Insufficient Hypertrophy After Portal Vein Embolization (PVE). World J Surg. 2017;41(1):250-7.

86. Sparrelid E, Gilg S, Brismar TB, Lundell L, Isaksson B. Rescue ALPPS is efficient and safe after failed portal vein occlusion in patients with colorectal liver metastases. Langenbecks Arch Surg. 2017;402(1):69-75.

87. Liu H, Zhu S. Present status and future perspectives of preoperative portal vein embolization. Am J Surg. 2009;197(5):686-90.

88. Broering DC, Hillert C, Krupski G, Fischer L, Mueller L, Achilles EG, et al. Portal vein embolization vs. portal vein ligation for induction of hypertrophy of the future liver remnant. J Gastrointest Surg. 2002;6(6):905-13; discussion 13.

89. Capussotti L, Muratore A, Ferrero A, Anselmetti GC, Corgnier A, Regge D. Extension of right portal vein embolization to segment IV portal branches. Arch Surg. 2005;140(11):1100-3.

90. Madoff DC, Abdalla EK, Gupta S, Wu TT, Morris JS, Denys A, et al. Transhepatic ipsilateral right portal vein embolization extended to segment IV: improving hypertrophy and resection outcomes with spherical particles and coils. J Vasc Interv Radiol. 2005;16(2 Pt 1):215-25.

91. de Baere T, Robinson JM, Deschamps F, Rao P, Teriitheau C, Goere D, et al. Preoperative portal vein embolization tailored to prepare the liver for complex resections: initial experience. Cardiovasc Intervent Radiol. 2010;33(5):976-82.

92. Hwang S, Ha TY, Ko GY, Kwon DI, Song GW, Jung DH, et al. Preoperative Sequential Portal and Hepatic Vein Embolization in Patients with Hepatobiliary Malignancy. World J Surg. 2015;39(12):2990-8.

93. Munene G, Parker RD, Larrigan J, Wong J, Sutherland F, Dixon E. Sequential preoperative hepatic vein embolization after portal vein embolization for extended left hepatectomy in colorectal liver metastases. World J Surg Oncol. 2013;11:134.

94. May BJ, Madoff DC. Portal vein embolization: rationale, technique, and current application. Semin Intervent Radiol. 2012;29(2):81-9.

95. Sun Z, Tang W, Sakamoto Y, Hasegawa K, Kokudo N. A systematic review and meta-analysis of feasibility, safety and efficacy of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus two-stage hepatectomy (TSH). Biosci Trends. 2015;9(5):284-8.

96. Shindoh J, Tzeng CW, Aloia TA, Curley SA, Huang SY, Mahvash A, et al. Safety and efficacy of portal vein embolization before planned major or extended hepatectomy: an institutional experience of 358 patients. J Gastrointest Surg. 2014;18(1):45-51.

97. Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg. 2008;247(1):49-57.

98. van Lienden KP, van den Esschert JW, de Graaf W, Bipat S, Lameris JS, van Gulik TM, et al. Portal vein embolization before liver resection: a systematic review. Cardiovasc Intervent Radiol. 2013;36(1):25-34.

99. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. Ann Surg. 2006;243(3):364-72.

100. Capussotti L, Muratore A, Baracchi F, Lelong B, Ferrero A, Regge D, et al. Portal vein ligation as an efficient method of increasing the future liver remnant volume in the surgical treatment of colorectal metastases. Arch Surg. 2008;143(10):978-82; discussion 82.

101. Aussilhou B, Lesurtel M, Sauvanet A, Farges O, Dokmak S, Goasguen N, et al. Right portal vein ligation is as efficient as portal vein embolization to induce hypertrophy of the left liver remnant. J Gastrointest Surg. 2008;12(2):297-303.

102. Isfordink CJ, Samim M, Braat M, Almalki AM, Hagendoorn J, Borel Rinkes IHM, et al. Portal vein ligation versus portal vein embolization for induction of hypertrophy of the future liver remnant: A systematic review and meta-analysis. Surg Oncol. 2017;26(3):257-67.

103. Hwang S, Lee SG, Ko GY, Kim BS, Sung KB, Kim MH, et al. Sequential preoperative ipsilateral hepatic vein embolization after portal vein embolization to induce further liver regeneration in patients with hepatobiliary malignancy. Ann Surg. 2009;249(4):608-16.

104. Deshayes E, Schadde E, Piron L, Quenet F, Guiu B. Extended Liver Venous Deprivation Leads to a Higher Increase in Liver Function that ALPPS in Early Assessment : A comment to "Sparrelid, E. et al. Dynamic Evaluation of Liver Volume and Function in Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy. Journal of Gastrointestinal Surgery (2017)". J Gastrointest Surg. 2017;21(10):1754-5.

105. Guiu B, Quenet F, Escal L, Bibeau F, Piron L, Rouanet P, et al. Extended liver venous deprivation before major hepatectomy induces marked and very rapid increase in future liver remnant function. Eur Radiol. 2017;27(8):3343-52.

106. Guiu B, Chevallier P, Denys A, Delhom E, Pierredon-Foulongne MA, Rouanet P, et al. Simultaneous trans-hepatic portal and hepatic vein embolization before major hepatectomy: the liver venous deprivation technique. Eur Radiol. 2016;26(12):4259-67.

107. Hocquelet A, Sotiriadis C, Duran R, Guiu B, Yamaguchi T, Halkic N, et al. Preoperative Portal Vein Embolization Alone with Biliary Drainage Compared to a Combination of Simultaneous Portal Vein, Right Hepatic Vein Embolization and Biliary Drainage in Klatskin Tumor. Cardiovasc Intervent Radiol. 2018;41(12):1885-91.

108. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg. 2000;232(6):777-85.

109. Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg. 1996;224(4):509-20; discussion 20-2.

110. Jaeck D, Oussoultzoglou E, Rosso E, Greget M, Weber JC, Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg. 2004;240(6):1037-49; discussion 49-51.

111. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. N Engl J Med. 2007;356(15):1545-59.

112. Karoui M, Vigano L, Goyer P, Ferrero A, Luciani A, Aglietta M, et al. Combined first-stage hepatectomy and colorectal resection in a two-stage hepatectomy strategy for bilobar synchronous liver metastases. Br J Surg. 2010;97(9):1354-62.

113. Pamecha V, Nedjat-Shokouhi B, Gurusamy K, Glantzounis GK, Sharma D, Davidson BR. Prospective evaluation of two-stage hepatectomy combined with selective portal vein embolisation and systemic chemotherapy for patients with unresectable bilobar colorectal liver metastases. Dig Surg. 2008;25(5):387-93.

114. Wicherts DA, Miller R, de Haas RJ, Bitsakou G, Vibert E, Veilhan LA, et al. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. Ann Surg. 2008;248(6):994-1005.

115. Sandstrom P, Rosok BI, Sparrelid E, Larsen PN, Larsson AL, Lindell G, et al. ALPPS Improves Resectability Compared With Conventional Two-stage Hepatectomy in Patients With Advanced Colorectal Liver Metastasis: Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial). Ann Surg. 2018;267(5):833-40.

116. Narita M, Oussoultzoglou E, Jaeck D, Fuchschuber P, Rosso E, Pessaux P, et al. Two-stage hepatectomy for multiple bilobar colorectal liver metastases. Br J Surg. 2011;98(10):1463-75.

117. Muratore A, Ribero D, Zimmitti G, Mellano A, Langella S, Capussotti L. Resection margin and recurrence-free survival after liver resection of colorectal metastases. Ann Surg Oncol. 2010;17(5):1324-9.

118. Li J, Girotti P, Konigsrainer I, Ladurner R, Konigsrainer A, Nadalin S. ALPPS in right trisectionectomy: a safe procedure to avoid postoperative liver failure? J Gastrointest Surg. 2013;17(5):956-61.

119. Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;255(3):405-14.

120. Linecker M, Kron P, Lang H, de Santibanes E, Clavien PA. Too Many Languages in the ALPPS: Preventing Another Tower of Babel? Ann Surg. 2016;263(5):837-8.

121. Bertens KA, Hawel J, Lung K, Buac S, Pineda-Solis K, Hernandez-Alejandro R. ALPPS: challenging the concept of unresectability--a systematic review. Int J Surg. 2015;13:280-7.

122. Oldhafer KJ, Donati M, Jenner RM, Stang A, Stavrou GA. ALPPS for patients with colorectal liver metastases: effective liver hypertrophy, but early tumor recurrence. World J Surg. 2014;38(6):1504-9.

123. Li J, Moustafa M, Linecker M, Lurje G, Capobianco I, Baumgart J, et al. ALPPS for Locally Advanced Intrahepatic Cholangiocarcinoma: Did Aggressive Surgery Lead to the Oncological Benefit? An International Multi-center Study. Ann Surg Oncol. 2020.

124. Linecker M, Bjornsson B, Stavrou GA, Oldhafer KJ, Lurje G, Neumann U, et al. Risk Adjustment in ALPPS Is Associated With a Dramatic Decrease in Early Mortality and Morbidity. Ann Surg. 2017;266(5):779-86.

125. Schadde E, Ardiles V, Slankamenac K, Tschuor C, Sergeant G, Amacker N, et al. ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies: results of a multicenter analysis. World J Surg. 2014;38(6):1510-9.

126. Brustia R, Scatton O, Perdigao F, El-Mouhadi S, Cauchy F, Soubrane O. Vessel identifications tags for open or laparoscopic associating liver partition and portal vein ligation for staged hepatectomy. J Am Coll Surg. 2013;217(6):e51-5.

127. Schlitt HJ, Hackl C, Lang SA. 'In-Situ Split' Liver Resection/ALPPS - Historical Development and Current Practice. Visc Med. 2017;33(6):408-12.

128. Abstracts of the 9th Congress of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA). April 12-16, 2011. Cape Town, South Africa. HPB (Oxford). 2011;13 Suppl 2:1-145.

129. de Santibanes E, Alvarez FA, Ardiles V. How to avoid postoperative liver failure: a novel method. World J Surg. 2012;36(1):125-8.

130. de Santibanes E, Clavien PA. Playing Play-Doh to prevent postoperative liver failure: the "ALPPS" approach. Ann Surg. 2012;255(3):415-7.

131. Gauzolino R, Castagnet M, Blanleuil ML, Richer JP. The ALPPS technique for bilateral colorectal metastases: three "variations on a theme". Updates Surg. 2013;65(2):141-8.

132. Lang H, de Santibanes E, Schlitt HJ, Malago M, van Gulik T, Machado MA, et al. 10th Anniversary of ALPPS-Lessons Learned and quo Vadis. Ann Surg. 2019;269(1):114-9.

133. Aloia TA, Vauthey JN. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): what is gained and what is lost? Ann Surg. 2012;256(3):e9; author reply e16-9.

134. Dokmak S, Belghiti J. Which limits to the "ALPPS" approach? Ann Surg. 2012;256(3):e6; author reply e16-7.

135. Olthof PB, Schnitzbauer AA, Schadde E. The HPB controversy of the decade: 2007-2017 - Ten years of ALPPS. Eur J Surg Oncol. 2018;44(10):1624-7.

136. Hernandez-Alejandro R, Bertens KA, Pineda-Solis K, Croome KP. Can we improve the morbidity and mortality associated with the associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) procedure in the management of colorectal liver metastases? Surgery. 2015;157(2):194-201.

137. Linecker M, Stavrou GA, Oldhafer KJ, Jenner RM, Seifert B, Lurje G, et al. The ALPPS Risk Score: Avoiding Futile Use of ALPPS. Ann Surg. 2016;264(5):763-71.

138. Lau WY, Lai EC. Modifications of ALPPS - from complex to more complex or from complex to less complex operations. Hepatobiliary Pancreat Dis Int. 2017;16(4):346-52.

139. de Santibanes E, Alvarez FA, Ardiles V, Pekolj J, de Santibanes M. Inverting the ALPPS paradigm by minimizing first stage impact: the Mini-ALPPS technique. Langenbecks Arch Surg. 2016;401(4):557-63.

140. Petrowsky H, Gyori G, de Oliveira M, Lesurtel M, Clavien PA. Is partial-ALPPS safer than ALPPS? A single-center experience. Ann Surg. 2015;261(4):e90-2.

141. Gall TM, Sodergren MH, Frampton AE, Fan R, Spalding DR, Habib NA, et al. Radio-frequency-assisted Liver Partition with Portal vein ligation (RALPP) for liver regeneration. Ann Surg. 2015;261(2):e45-6.

142. Jiao LR, Hakim DN, Gall TM, Fajardo A, Pencavel TD, Fan R, et al. A totally laparoscopic associating liver partition and portal vein ligation for staged hepatectomy assisted with radiofrequency (radiofrequency assisted liver partition with portal vein ligation) for staged liver resection. Hepatobiliary Surg Nutr. 2016;5(4):382-7.

143. Robles R, Parrilla P, Lopez-Conesa A, Brusadin R, de la Pena J, Fuster M, et al. Tourniquet modification of the associating liver partition and portal ligation for staged hepatectomy procedure. Br J Surg. 2014;101(9):1129-34; discussion 34.

144. Lopez-Lopez V, Robles-Campos R, Brusadin R, Lopez-Conesa A, Navarro A, Arevalo-Perez J, et al. Tourniquet-ALPPS is a promising treatment for very large hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Oncotarget. 2018;9(46):28267-80.

145. Robles-Campos R, Brusadin R, Lopez-Conesa A, Lopez-Lopez V, Navarro-Barrios A, Lopez-Espin JJ, et al. Long-Term Outcome After Conventional Two-Stage Hepatectomy Versus Tourniquet-ALPPS in Colorectal Liver Metastases: A Propensity Score Matching Analysis. World J Surg. 2019;43(9):2281-9.

146. Alvarez FA, Ardiles V, Sanchez Claria R, Pekolj J, de Santibanes E. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): tips and tricks. J Gastrointest Surg. 2013;17(4):814-21.

147. Tsui TY, Heumann A, Vashist YK, Izbicki JR. How we do it: double in situ split for staged mesohepatectomy in patients with advanced gall bladder cancer and marginal future liver remnant. Langenbecks Arch Surg. 2016;401(4):565-71.

148. Montalva Oron EM, Maupoey Ibanez J, Banuelos Carrillo R, Bosca Robledo A, Orbis Castellanos JF, Moya Herraiz A, et al. Monosegment ALPPS: A new variant of the techniques for rapid hepatic regeneration. Critical review of the initial results of our series. Cir Esp. 2015;93(7):436-43.

149. Schadde E, Malago M, Hernandez-Alejandro R, Li J, Abdalla E, Ardiles V, et al. Monosegment ALPPS hepatectomy: extending resectability by rapid hypertrophy. Surgery. 2015;157(4):676-89.

150. de Santibanes M, Alvarez FA, Santos FR, Ardiles V, de Santibanes E. The associating liver partition and portal vein ligation for staged hepatectomy approach using only segments I and IV as future liver remnant. J Am Coll Surg. 2014;219(2):e5-9.

151. Truant S, Scatton O, Dokmak S, Regimbeau JM, Lucidi V, Laurent A, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): impact of the inter-stages course on morbi-mortality and implications for management. Eur J Surg Oncol. 2015;41(5):674-82.

152. Maulat C, Suc B, Muscari F. Rescue ALPPS after portal embolization for colorectal metastases (with video). J Visc Surg. 2018;155(1):77-8.

153. Maulat C, Philis A, Charriere B, Mokrane FZ, Guimbaud R, Otal P, et al. Rescue associating liver partition and portal vein ligation for staged hepatectomy after portal embolization: Our experience and literature review. World J Clin Oncol. 2017;8(4):351-9.

154. Jackson T, Siegel KA, Siegel CT. Rescue ALPPS: Intraoperative Conversion to ALPPS during Synchronous Resection of Rectal Cancer and Liver Metastasis. Case reports in surgery. 2014;2014:487852.

155. Bjornsson B, Gasslander T, Sandstrom P. In situ split of the liver when portal venous embolization fails to induce hypertrophy: a report of two cases. Case reports in surgery. 2013;2013:238675.

156. Conrad C, Shivathirthan N, Camerlo A, Strauss C, Gayet B. Laparoscopic portal vein ligation with in situ liver split for failed portal vein embolization. Ann Surg. 2012;256(3):e14-5; author reply e6-7.

157. Olthof PB, van Dam R, Jovine E, Campos RR, de Santibanes E, Oldhafer K, et al. Accuracy of estimated total liver volume formulas before liver resection. Surgery. 2019.

158. Schadde E, Raptis DA, Schnitzbauer AA, Ardiles V, Tschuor C, Lesurtel M, et al. Prediction of Mortality After ALPPS Stage-1: An Analysis of 320 Patients From the International ALPPS Registry. Ann Surg. 2015;262(5):780-5; discussion 5-6.

159. Stavrou GA, Donati M, Fard-Aghaie MH, Zeile M, Huber TM, Stang A, et al. Did the International ALPPS Meeting 2015 Have an Impact on Daily Practice? The Hamburg Barmbek Experience of 58 Cases. Visc Med. 2017;33(6):456-61.

160. Linecker M, Kuemmerli C, Kambakamba P, Schlegel A, Muiesan P, Capobianco I, et al. Performance validation of the ALPPS risk model. HPB (Oxford). 2019;21(6):711-21.

161. Huiskens J, Schadde E, Lang H, Malago M, Petrowsky H, de Santibanes E, et al. Avoiding postoperative mortality after ALPPS-development of a tumor-specific risk score for colorectal liver metastases. HPB (Oxford). 2019;21(7):898-905.

162. Shoup M, Gonen M, D'Angelica M, Jarnagin WR, DeMatteo RP, Schwartz LH, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointest Surg. 2003;7(3):325-30.

163. Truant S, Oberlin O, Sergent G, Lebuffe G, Gambiez L, Ernst O, et al. Remnant liver volume to body weight ratio > or =0.5%: A new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. J Am Coll Surg. 2007;204(1):22-33.

164. Lo CM, Fan ST, Chan JK, Wei W, Lo RJ, Lai CL. Minimum graft volume for successful adult-to-adult living donor liver transplantation for fulminant hepatic failure. Transplantation. 1996;62(5):696-8.

165. Ribero D, Chun YS, Vauthey JN. Standardized liver volumetry for portal vein embolization. Semin Intervent Radiol. 2008;25(2):104-9.

166. Nadalin S, Capobianco I, Li J, Girotti P, Konigsrainer I, Konigsrainer A. Indications and limits for associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Lessons Learned from 15 cases at a single centre. Z Gastroenterol. 2014;52(1):35-42.

167. Helling TS. Liver failure following partial hepatectomy. HPB (Oxford). 2006;8(3):165-74.

168. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13(10):1271-80.

169. Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg. 2007;94(3):274-86.

170. Alizai PH, Haelsig A, Bruners P, Ulmer F, Klink CD, Dejong CHC, et al. Impact of liver volume and liver function on posthepatectomy liver failure after portal vein embolization- A multivariable cohort analysis. Ann Med Surg (Lond). 2018;25:6-11.

171. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist. 2008;13(1):51-64.

172. Tucker ON, Heaton N. The 'small for size' liver syndrome. Curr Opin Crit Care. 2005;11(2):150-5.

173. D'Onofrio M, De Robertis R, Demozzi E, Crosara S, Canestrini S, Pozzi Mucelli R. Liver volumetry: Is imaging reliable? Personal experience and review of the literature. World J Radiol. 2014;6(4):62-71.

174. Tu R, Xia LP, Yu AL, Wu L. Assessment of hepatic functional reserve by cirrhosis grading and liver volume measurement using CT. World J Gastroenterol. 2007;13(29):3956-61.

175. Torzilli G, Montorsi M, Del Fabbro D, Palmisano A, Donadon M, Makuuchi M. Ultrasonographically guided surgical approach to liver tumours involving the hepatic veins close to the caval confluence. Br J Surg. 2006;93(10):1238-46.

176. Ulla M, Ardiles V, Levy-Yeyati E, Alvarez FA, Spina JC, Garcia-Monaco RD, et al. New surgical strategy to induce liver hypertrophy: role of MDCT-volumetry to monitor and predict liver growth. Hepatogastroenterology. 2013;60(122):337-42.

177. Pomposelli JJ, Tongyoo A, Wald C, Pomfret EA. Variability of standard liver volume estimation versus software-assisted total liver volume measurement. Liver Transpl. 2012;18(9):1083-92.

178. Soyer P, Roche A, Elias D, Levesque M. Hepatic metastases from colorectal cancer: influence of hepatic volumetric analysis on surgical decision making. Radiology. 1992;184(3):695-7.

179. Suzuki K, Epstein ML, Kohlbrenner R, Garg S, Hori M, Oto A, et al. Quantitative radiology: automated CT liver volumetry compared with interactive volumetry and manual volumetry. AJR Am J Roentgenol. 2011;197(4):W706-12.

180. Vauthey JN, Abdalla EK, Doherty DA, Gertsch P, Fenstermacher MJ, Loyer EM, et al. Body surface area and body weight predict total liver volume in Western adults. Liver Transpl. 2002;8(3):233-40.

181. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987;317(17):1098.

182. Strohaker J, Konigsrainer A, Nadalin S. [Role of the radiologist in surgery of colorectal liver metastases : What should be removed and what must remain]. Radiologe. 2019;59(9):791-8.

183. Ercolani G, Zanello M, Grazi GL, Cescon M, Ravaioli M, Del Gaudio M, et al. Changes in the surgical approach to hilar cholangiocarcinoma during an 18-year period in a Western single center. J Hepatobiliary Pancreat Sci. 2010;17(3):329-37.

184. Sotiropoulos GC, Saner FH, Molmenti EP, Radtke A, Timm S, Baba HA, et al. Unexpected liver failure after right hemihepatectomy for colorectal liver metastasis due to chemotherapy-associated steato-hepatitis: time for routine preoperative liver biopsy? Int J Colorectal Dis. 2009;24(2):241.

185. Cucchetti A, Cescon M, Ercolani G, Di Gioia P, Peri E, Pinna AD. Safety of hepatic resection in overweight and obese patients with cirrhosis. Br J Surg. 2011;98(8):1147-54.

186. Vetelainen R, van Vliet A, Gouma DJ, van Gulik TM. Steatosis as a risk factor in liver surgery. Ann Surg. 2007;245(1):20-30.

187. Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C. How much remnant is enough in liver resection? Dig Surg. 2012;29(1):6-17.

188. van den Broek MA, Olde Damink SW, Dejong CH, Lang H, Malago M, Jalan R, et al. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. Liver Int. 2008;28(6):767-80.

189. Tanabe G, Sakamoto M, Akazawa K, Kurita K, Hamanoue M, Ueno S, et al. Intraoperative risk factors associated with hepatic resection. Br J Surg. 1995;82(9):1262-5.

190. Farges O, Malassagne B, Flejou JF, Balzan S, Sauvanet A, Belghiti J. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. Ann Surg. 1999;229(2):210-5.

191. Politano N, Jaskolka M, Blakey G, Turvey T, White R, Phillips C. The effect of preoperative recombinant erythropoietin on postoperative hematocrit level after orthognathic surgery. J Oral Maxillofac Surg. 2012;70(11):e625-30.

192. Reeves JG, Suriawinata AA, Ng DP, Holubar SD, Mills JB, Barth RJ, Jr. Short-term preoperative diet modification reduces steatosis and blood loss in patients undergoing liver resection. Surgery. 2013;154(5):1031-7.

193. Sullivan S. Implications of diet on nonalcoholic fatty liver disease. Curr Opin Gastroenterol. 2010;26(2):160-4.

194. Behrns KE, Tsiotos GG, DeSouza NF, Krishna MK, Ludwig J, Nagorney DM. Hepatic steatosis as a potential risk factor for major hepatic resection. J Gastrointest Surg. 1998;2(3):292-8.

195. Walcott-Sapp S, Billingsley KG. Preoperative optimization for major hepatic resection. Langenbecks Arch Surg. 2018;403(1):23-35.

196. Sahajpal A, Vollmer CM, Jr., Dixon E, Chan EK, Wei A, Cattral MS, et al. Chemotherapy for colorectal cancer prior to liver resection for colorectal cancer hepatic metastases does not adversely affect peri-operative outcomes. J Surg Oncol. 2007;95(1):22-7.

197. Scoggins CR, Campbell ML, Landry CS, Slomiany BA, Woodall CE, McMasters KM, et al. Preoperative chemotherapy does not increase morbidity or mortality of hepatic resection for colorectal cancer metastases. Ann Surg Oncol. 2009;16(1):35-41.

198. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg. 2006;243(1):1-7.

199. Kishi Y, Zorzi D, Contreras CM, Maru DM, Kopetz S, Ribero D, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol. 2010;17(11):2870-6.

200. Ribeiro HS, Costa WL, Jr., Diniz AL, Godoy AL, Herman P, Coudry RA, et al. Extended preoperative chemotherapy, extent of liver resection and blood transfusion are predictive factors of liver failure following resection of colorectal liver metastasis. Eur J Surg Oncol. 2013;39(4):380-5.

201. Cherqui D, Benoist S, Malassagne B, Humeres R, Rodriguez V, Fagniez PL. Major liver resection for carcinoma in jaundiced patients without preoperative biliary drainage. Arch Surg. 2000;135(3):302-8.

202. Yokoyama Y, Nagino M, Nimura Y. Mechanism of impaired hepatic regeneration in cholestatic liver. J Hepatobiliary Pancreat Surg. 2007;14(2):159-66.

203. Donadon M, Cimino M, Procopio F, Morenghi E, Montorsi M, Torzilli G. Potential role of cholinesterases to predict short-term outcome after hepatic resection for hepatocellular carcinoma. Updates in surgery. 2013;65(1):11-8.

204. Nadalin S, Testa G, Malago M, Beste M, Frilling A, Schroeder T, et al. Volumetric and functional recovery of the liver after right hepatectomy for living donation. Liver Transpl. 2004;10(8):1024-9.

205. Cieslak KP, Runge JH, Heger M, Stoker J, Bennink RJ, van Gulik TM. New perspectives in the assessment of future remnant liver. Dig Surg. 2014;31(4-5):255-68.

206. de Liguori Carino N, O'Reilly DA, Dajani K, Ghaneh P, Poston GJ, Wu AV. Perioperative use of the LiMON method of indocyanine green elimination measurement for the prediction and early detection of post-hepatectomy liver failure. Eur J Surg Oncol. 2009;35(9):957-62.

207. Stockmann M, Lock JF, Riecke B, Heyne K, Martus P, Fricke M, et al. Prediction of postoperative outcome after hepatectomy with a new bedside test for maximal liver function capacity. Ann Surg. 2009;250(1):119-25.

208. Hoekstra LT, de Graaf W, Nibourg GA, Heger M, Bennink RJ, Stieger B, et al. Physiological and biochemical basis of clinical liver function tests: a review. Ann Surg. 2013;257(1):27-36.

209. de Graaf W, Hausler S, Heger M, van Ginhoven TM, van Cappellen G, Bennink RJ, et al. Transporters involved in the hepatic uptake of (99m)Tc-mebrofenin and indocyanine green. J Hepatol. 2011;54(4):738-45.

210. Krishnamurthy GT, Krishnamurthy S. Cholescintigraphic measurement of liver function: how is it different from other methods? Eur J Nucl Med Mol Imaging. 2006;33(10):1103-6.

211. Krishnamurthy S, Krishnamurthy GT. Technetium-99m-iminodiacetic acid organic anions: review of biokinetics and clinical application in hepatology. Hepatology. 1989;9(1):139-53.

212. Sparrelid E, Jonas E, Tzortzakakis A, Dahlen U, Murquist G, Brismar T, et al. Dynamic Evaluation of Liver Volume and Function in Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy. J Gastrointest Surg. 2017;21(6):967-74.

213. Serenari M, Collaud C, Alvarez FA, de Santibanes M, Giunta D, Pekolj J, et al. Interstage Assessment of Remnant Liver Function in ALPPS Using Hepatobiliary Scintigraphy: Prediction of Posthepatectomy Liver Failure and Introduction of the HIBA Index. Ann Surg. 2018;267(6):1141-7.

214. Lam HD, van der Pas SL, Baranski A, van Hoek B, Burgmans MC, Bennink RJ, et al. The role of proportionate kinetic growth rate fraction in future remnant liver function over volume determined by (99m)Tc-Mebrofenin hepatobiliary scintigraphy including SPECT and computed tomography in the risk prediction of postoperative mortality in ALPPS. Surgery. 2019;165(6):1244-5.

215. Truant S, El Amrani M, Baillet C, Ploquin A, Lecolle K, Ernst O, et al. Laparoscopic Partial ALPPS: Much Better Than ALPPS! Ann Hepatol. 2019;18(1):269-73.

216. Schuhmann-Giampieri G. Liver contrast media for magnetic resonance imaging. Interrelations between pharmacokinetics and imaging. Invest Radiol. 1993;28(8):753-61.

217. Nilsson H, Blomqvist L, Douglas L, Nordell A, Janczewska I, Naslund E, et al. Gd-EOB-DTPA-enhanced MRI for the assessment of liver function and volume in liver cirrhosis. Br J Radiol. 2013;86(1026):20120653.

218. Tschirch FT, Struwe A, Petrowsky H, Kakales I, Marincek B, Weishaupt D. Contrast-enhanced MR cholangiography with Gd-EOB-DTPA in patients with liver cirrhosis: visualization of the biliary ducts in comparison with patients with normal liver parenchyma. Eur Radiol. 2008;18(8):1577-86.

219. Motosugi U, Ichikawa T, Sou H, Sano K, Tominaga L, Kitamura T, et al. Liver parenchymal enhancement of hepatocyte-phase images in Gd-EOB-DTPA-enhanced MR imaging: which biological markers of the liver function affect the enhancement? J Magn Reson Imaging. 2009;30(5):1042-6.

220. Takao H, Akai H, Tajima T, Kiryu S, Watanabe Y, Imamura H, et al. MR imaging of the biliary tract with Gd-EOB-DTPA: effect of liver function on signal intensity. Eur J Radiol. 2011;77(2):325-9.

221. Tajima T. [The relationship between self-concept variability and psychological well-being: a survey of female undergraduate students]. Shinrigaku Kenkyu. 2010;81(5):523-8.

222. Katsube T, Okada M, Kumano S, Hori M, Imaoka I, Ishii K, et al. Estimation of liver function using T1 mapping on Gd-EOB-DTPA-enhanced magnetic resonance imaging. Invest Radiol. 2011;46(4):277-83.

223. Nishie A, Ushijima Y, Tajima T, Asayama Y, Ishigami K, Kakihara D, et al. Quantitative analysis of liver function using superparamagnetic iron oxide- and Gd-EOB-DTPA-enhanced MRI: comparison with Technetium-99m galactosyl serum albumin scintigraphy. Eur J Radiol. 2012;81(6):1100-4.

224. Nilsson H, Blomqvist L, Douglas L, Nordell A, Jonas E. Assessment of liver function in primary biliary cirrhosis using Gd-EOB-DTPA-enhanced liver MRI. HPB (Oxford). 2010;12(8):567-76.

225. Lhuaire M, Piardi T, Bruno O, Sibert A, Kianmanesh R, Sommacale D. Post-hepatectomy liver failure: Should we consider venous outflow? Int J Surg Case Rep. 2015;16:154-6.

226. Dirsch O, Madrahimov N, Chaudri N, Deng M, Madrahimova F, Schenk A, et al. Recovery of liver perfusion after focal outflow obstruction and liver resection. Transplantation. 2008;85(5):748-56.

227. Radtke A, Nadalin S, Sotiropoulos GC, Molmenti EP, Schroeder T, Valentin-Gamazo C, et al. Computer-assisted operative planning in adult living donor liver transplantation: a new way to resolve the dilemma of the middle hepatic vein. World J Surg. 2007;31(1):175-85.

228. Radtke A, Sgourakis G, Molmenti EP, Beckebaum S, Cicinnati V, Broelsch CE, et al. Computer-assisted surgical planning in adult-to-adult live donor liver transplantation: how much does it help? A single center experience. Transplantation. 2012;94(11):1138-44.

229. Radtke A, Sotiropoulos GC, Molmenti EP, Schroeder T, Peitgen HO, Frilling A, et al. Computer-assisted surgery planning for complex liver resections: when is it helpful? A single-center experience over an 8-year period. Ann Surg. 2010;252(5):876-83.

230. Radtke A, Sgourakis G, Sotiropoulos GC, Molmenti EP, Nadalin S, Fouzas I, et al. Hepatic hilar and sectorial vascular and biliary anatomy in right graft adult live liver donor transplantation. Transplant Proc. 2008;40(9):3147-50.

231. Tomassini F, D'Asseler Y, Giglio MC, Lecluyse C, Lambert B, Sainz-Barriga M, et al. Hemodynamic changes in ALPPS influence liver regeneration and function: results from a prospective study. HPB (Oxford). 2018.

232. Ito T, Kiuchi T, Yamamoto H, Oike F, Ogura Y, Fujimoto Y, et al. Changes in portal venous pressure in the early phase after living donor liver transplantation: pathogenesis and clinical implications. Transplantation. 2003;75(8):1313-7.

233. Troisi RI, Vanlander A, Giglio MC, Van Limmen J, Scudeller L, Heyse B, et al. Somatostatin as Inflow Modulator in Liver-transplant Recipients With Severe Portal Hypertension: A Randomized Trial. Ann Surg. 2019;269(6):1025-33.

234. Rhaiem R, Piardi T, Chetboun M, Pessaux P, Lestra T, Memeo R, et al. Portal Inflow Modulation by Somatostatin After Major Liver Resection: A Pilot Study. Ann Surg. 2018;267(6):e101-e3.

235. Aloia TA, Fahy BN, Fischer CP, Jones SL, Duchini A, Galati J, et al. Predicting poor outcome following hepatectomy: analysis of 2313 hepatectomies in the NSQIP database. HPB (Oxford). 2009;11(6):510-5.

236. 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(5):373-83.

237. Torres OJ, Moraes-Junior JM, Lima e Lima NC, Moraes AM. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): a new approach in liver resections. Arquivos brasileiros de cirurgia digestiva : ABCD = Brazilian archives of digestive surgery. 2012;25(4):290-2.

238. Chan AC, Chok K, Dai JW, Lo CM. Impact of split completeness on future liver remnant hypertrophy in associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) in hepatocellular carcinoma: Complete-ALPPS versus partial-ALPPS. Surgery. 2017;161(2):357-64.

239. Radtke A, Sotiropoulos GC, Nadalin S, Molmenti EP, Schroeder T, Lang H, et al. Preoperative volume prediction in adult living donor liver transplantation: how much can we rely on it? Am J Transplant. 2007;7(3):672-9.

240. Schadde E, Ardiles V, Robles-Campos R, Malago M, Machado M, Hernandez-Alejandro R, et al. Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg. 2014;260(5):829-36; discussion 36-8.

241. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995;22(6):696-9.

242. Dixon JB, Bhathal PS, Hughes NR, O'Brien PE. Nonalcoholic fatty liver disease: Improvement in liver histological analysis with weight loss. Hepatology. 2004;39(6):1647-54.

243. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-96.

244. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011;149(5):713-24.

245. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-4.

246. Tschuor C, Croome KP, Sergeant G, Cano V, Schadde E, Ardiles V, et al. Salvage parenchymal liver transection for patients with insufficient volume increase after portal vein occlusion - An extension of the ALPPS approach. Eur J Surg Oncol. 2013;39(11):1230-5.

247. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. Oncologist. 2016;21(5):594-9.

248. D'Haese JG, Neumann J, Weniger M, Pratschke S, Bjornsson B, Ardiles V, et al. Should ALPPS be Used for Liver Resection in Intermediate-Stage HCC? Ann Surg Oncol. 2016;23(4):1335-43.

249. de Santibanes M, Dietrich A, Alvarez FA, Ardiles V, Loresi M, D'Adamo M, et al. Biological Substrate of the Rapid Volumetric Changes Observed in the Human Liver During the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy Approach. J Gastrointest Surg. 2016;20(3):546-53.

250. Kotewall CN, Cheung TT. Optimizing hepatectomy for hepatocellular carcinoma in Asia-patient selection and special considerations. Transl Gastroenterol Hepatol. 2018;3:75.

251. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg. 2002;236(4):397-406; discussion -7.

252. Eguchi H, Umeshita K, Sakon M, Nagano H, Ito Y, Kishimoto SI, et al. Presence of active hepatitis associated with liver cirrhosis is a risk factor for mortality caused by posthepatectomy liver failure. Dig Dis Sci. 2000;45(7):1383-8.

253. Tzeng CW, Cooper AB, Vauthey JN, Curley SA, Aloia TA. Predictors of morbidity and mortality after hepatectomy in elderly patients: analysis of 7621 NSQIP patients. HPB (Oxford). 2014;16(5):459-68.

254. Golse N, Bucur PO, Adam R, Castaing D, Sa Cunha A, Vibert E. New paradigms in post-hepatectomy liver failure. J Gastrointest Surg. 2013;17(3):593-605.

255. Wiggers JK, Groot Koerkamp B, Cieslak KP, Doussot A, van Klaveren D, Allen PJ, et al. Postoperative Mortality after Liver Resection for Perihilar Cholangiocarcinoma: Development of a Risk Score and Importance of Biliary Drainage of the Future Liver Remnant. J Am Coll Surg. 2016;223(2):321-31 e1.

256. Rahnemai-Azar AA, Cloyd JM, Weber SM, Dillhoff M, Schmidt C, Winslow ER, et al. Update on Liver Failure Following Hepatic Resection: Strategies for Prediction and Avoidance of Post-operative Liver Insufficiency. J Clin Transl Hepatol. 2018;6(1):97-104.

257. Valero V, 3rd, Amini N, Spolverato G, Weiss MJ, Hirose K, Dagher NN, et al. Sarcopenia adversely impacts postoperative complications following resection or transplantation in patients with primary liver tumors. J Gastrointest Surg. 2015;19(2):272-81.

258. Mehta HB, Dimou F, Adhikari D, Tamirisa NP, Sieloff E, Williams TP, et al. Comparison of Comorbidity Scores in Predicting Surgical Outcomes. Med Care. 2016;54(2):180-7.

259. Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Pedersen R, Kremers W, et al. Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. Transplantation. 2006;82(12):1703-7.

260. Park J, Kim MH, Kim KP, Park DH, Moon SH, Song TJ, et al. Natural History and Prognostic Factors of Advanced Cholangiocarcinoma without Surgery, Chemotherapy, or Radiotherapy: A Large-Scale Observational Study. Gut Liver. 2009;3(4):298-305.

261. Olthof PB, Wiggers JK, Groot Koerkamp B, Coelen RJ, Allen PJ, Besselink MG, et al. Postoperative Liver Failure Risk Score: Identifying Patients with Resectable Perihilar Cholangiocarcinoma Who Can Benefit from Portal Vein Embolization. J Am Coll Surg. 2017;225(3):387-94.

262. Bozzetti F. Rationale and indications for preoperative feeding of malnourished surgical cancer patients. Nutrition. 2002;18(11-12):953-9.

263. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. Clin Gastroenterol Hepatol. 2012;10(2):117-25.

264. Huisman EJ, Trip EJ, Siersema PD, van Hoek B, van Erpecum KJ. Protein energy malnutrition predicts complications in liver cirrhosis. Eur J Gastroenterol Hepatol. 2011;23(11):982-9.

265. Kalaitzakis E, Simren M, Olsson R, Henfridsson P, Hugosson I, Bengtsson M, et al. Gastrointestinal symptoms in patients with liver cirrhosis: associations with nutritional status and health-related quality of life. Scand J Gastroenterol. 2006;41(12):1464-72.

266. O'Brien A, Williams R. Nutrition in end-stage liver disease: principles and practice. Gastroenterology. 2008;134(6):1729-40.

267. Prado CM, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. Proc Nutr Soc. 2016;75(2):188-98.

268. Batsis JA, Mackenzie TA, Barre LK, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and mortality in older adults: results from the National Health and Nutrition Examination Survey III. Eur J Clin Nutr. 2014;68(9):1001-7.

269. Tsai S. Importance of lean body mass in the oncologic patient. Nutr Clin Pract. 2012;27(5):593-8.

270. de Meijer VE, Kalish BT, Puder M, Ijzermans JN. Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. Br J Surg. 2010;97(9):1331-9.

271. Jones JC, Coombes JS, Macdonald GA. Exercise capacity and muscle strength in patients with cirrhosis. Liver Transpl. 2012;18(2):146-51.

272. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, et al. Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol. 2012;10(2):166-73, 73 e1.

273. Bernal W, Martin-Mateos R, Lipcsey M, Tallis C, Woodsford K, McPhail MJ, et al. Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease. Liver Transpl. 2014;20(1):54-62.

274. Dharancy S, Lemyze M, Boleslawski E, Neviere R, Declerck N, Canva V, et al. Impact of impaired aerobic capacity on liver transplant candidates. Transplantation. 2008;86(8):1077-83.

275. Croome KP, Hernandez-Alejandro R, Parker M, Heimbach J, Rosen C, Nagorney DM. Is the liver kinetic growth rate in ALPPS unprecedented when compared with PVE and living donor liver transplant? A multicentre analysis. HPB (Oxford). 2015;17(6):477-84.

276. Kambakamba P, Stocker D, Reiner CS, Nguyen-Kim TD, Linecker M, Eshmuminov D, et al. Liver kinetic growth rate predicts postoperative liver failure after ALPPS. HPB (Oxford). 2016;18(10):800-5.

277. Chan A, Zhang WY, Chok K, Dai J, Ji R, Kwan C, et al. ALPPS Versus Portal Vein Embolization for Hepatitis-related Hepatocellular Carcinoma: A Changing Paradigm in Modulation of Future Liver Remnant Before Major Hepatectomy. Ann Surg. 2019.

278. Vennarecci G, Grazi GL, Sperduti I, Busi Rizzi E, Felli E, Antonini M, et al. ALPPS for primary and secondary liver tumors. International journal of surgery. 2016;30:38-44.

279. Han H, Hu H, Xu YD, Wang WP, Ding H, Lu Q. Liver failure after hepatectomy: A risk assessment using the pre-hepatectomy shear wave elastography technique. Eur J Radiol. 2017;86:234-40.

280. Lei JW, Ji XY, Hong JF, Li WB, Chen Y, Pan Y, et al. Prediction of posthepatectomy liver failure using transient elastography in patients with hepatitis B related hepatocellular carcinoma. BMC Gastroenterol. 2017;17(1):171.

281. Nishio T, Taura K, Koyama Y, Tanabe K, Yamamoto G, Okuda Y, et al. Prediction of posthepatectomy liver failure based on liver stiffness measurement in patients with hepatocellular carcinoma. Surgery. 2016;159(2):399-408.

282. Sala S, Ardiles V, Ulla M, Alvarez F, Pekolj J, de Santibanes E. Our initial experience with ALPPS technique: encouraging results. Updates Surg. 2012;64(3):167-72.

283. Olthof PB, Tomassini F, Huespe PE, Truant S, Pruvot FR, Troisi RI, et al. Hepatobiliary scintigraphy to evaluate liver function in associating liver partition and portal vein ligation for staged hepatectomy: Liver volume overestimates liver function. Surgery. 2017;162(4):775-83.

284. Hirai I, Kimura W, Fuse A, Suto K, Urayama M. Evaluation of preoperative portal embolization for safe hepatectomy, with special reference to assessment of nonembolized lobe function with 99mTc-GSA SPECT scintigraphy. Surgery. 2003;133(5):495-506.

285. Nishiyama Y, Yamamoto Y, Hino I, Satoh K, Wakabayashi H, Ohkawa M. 99mTc galactosyl human serum albumin liver dynamic SPET for pre-operative assessment of hepatectomy in relation to percutaneous transhepatic portal embolization. Nucl Med Commun. 2003;24(7):809-17.

286. Mimura T, Hamazaki K, Sakai H, Tanaka N, Mimura H. Evaluation of hepatic functional reserve in rats with obstructive jaundice by asyaloglycoprotein receptor. Hepatogastroenterology. 2001;48(39):777-82.

287. Satoh K, Yamamoto Y, Nishiyama Y, Wakabayashi H, Ohkawa M. 99mTc-GSA liver dynamic SPECT for the preoperative assessment of hepatectomy. Ann Nucl Med. 2003;17(1):61-7.

288. Loberg MD, Cooper M, Harvey E, Callery P, Faith W. Development of new radiopharmaceuticals based on N-substitution of iminodiacetic acid. J Nucl Med. 1976;17(7):633-8.

289. Cieslak KP, Olthof PB, van Lienden KP, Besselink MG, Busch OR, van Gulik TM, et al. Assessment of Liver Function Using (99m)Tc-Mebrofenin Hepatobiliary Scintigraphy in ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy). Case Rep Gastroenterol. 2015;9(3):353-60.

290. Stockmann M, Lock JF, Malinowski M, Niehues SM, Seehofer D, Neuhaus P. The LiMAx test: a new liver function test for predicting postoperative outcome in liver surgery. HPB (Oxford). 2010;12(2):139-46.

291. Anderson CD, Pinson CW, Berlin J, Chari RS. Diagnosis and treatment of cholangiocarcinoma. Oncologist. 2004;9(1):43-57.

292. Mansour JC, Aloia TA, Crane CH, Heimbach JK, Nagino M, Vauthey JN. Hilar cholangiocarcinoma: expert consensus statement. HPB (Oxford). 2015;17(8):691-9.

293. Capobianco I, Strohaker J, Della Penna A, Nadalin S, Konigsrainer A. [Preconditioning of the liver]. Chirurg. 2019;90(7):542-7.

294. Nimura Y. Preoperative biliary drainage before resection for cholangiocarcinoma (Pro). HPB (Oxford). 2008;10(2):130-3.

295. Nimura Y, Kamiya J, Kondo S, Nagino M, Uesaka K, Oda K, et al. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. J Hepatobiliary Pancreat Surg. 2000;7(2):155-62.

296. van Delden OM, Lameris JS. Percutaneous drainage and stenting for palliation of malignant bile duct obstruction. Eur Radiol. 2008;18(3):448-56.

297. George C, Byass OR, Cast JE. Interventional radiology in the management of malignant biliary obstruction. World J Gastrointest Oncol. 2010;2(3):146-50.

298. Paik WH, Park YS, Hwang JH, Lee SH, Yoon CJ, Kang SG, et al. Palliative treatment with self-expandable metallic stents in patients with advanced type III or IV hilar cholangiocarcinoma: a percutaneous versus endoscopic approach. Gastrointest Endosc. 2009;69(1):55-62.

299. Liu F, Li Y, Wei Y, Li B. Preoperative biliary drainage before resection for hilar cholangiocarcinoma: whether or not? A systematic review. Dig Dis Sci. 2011;56(3):663-72.

300. Coelen RJS, Roos E, Wiggers JK, Besselink MG, Buis CI, Busch ORC, et al. Endoscopic versus percutaneous biliary drainage in patients with resectable perihilar cholangiocarcinoma: a multicentre, randomised controlled trial. Lancet Gastroenterol Hepatol. 2018;3(10):681-90.

301. Kawashima H, Itoh A, Ohno E, Itoh Y, Ebata T, Nagino M, et al. Preoperative endoscopic nasobiliary drainage in 164 consecutive patients with suspected perihilar cholangiocarcinoma: a retrospective study of efficacy and risk factors related to complications. Ann Surg. 2013;257(1):121-7.

302. Komaya K, Ebata T, Yokoyama Y, Igami T, Sugawara G, Mizuno T, et al. Verification of the oncologic inferiority of percutaneous biliary drainage to endoscopic drainage: A propensity score matching analysis of resectable perihilar cholangiocarcinoma. Surgery. 2017;161(2):394-404.

303. Komaya K, Ebata T, Fukami Y, Sakamoto E, Miyake H, Takara D, et al. Percutaneous biliary drainage is oncologically inferior to endoscopic drainage: a propensity score matching analysis in resectable distal cholangiocarcinoma. J Gastroenterol. 2016;51(6):608-19.

304. Kawakami H, Kuwatani M, Onodera M, Haba S, Eto K, Ehira N, et al. Endoscopic nasobiliary drainage is the most suitable preoperative biliary drainage method in the management of patients with hilar cholangiocarcinoma. J Gastroenterol. 2011;46(2):242-8.

305. Walter T, Ho CS, Horgan AM, Warkentin A, Gallinger S, Greig PD, et al. Endoscopic or percutaneous biliary drainage for Klatskin tumors? J Vasc Interv Radiol. 2013;24(1):113-21.

306. Rocha FG, Matsuo K, Blumgart LH, Jarnagin WR. Hilar cholangiocarcinoma: the Memorial Sloan-Kettering Cancer Center experience. J Hepatobiliary Pancreat Sci. 2010;17(4):490-6.

307. 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(2):191-204.

308. Ratti F, Cipriani F, Gagliano A, Catena M, Paganelli M, Aldrighetti L. Defining indications to ALPPS procedure: technical aspects and open issues. Updates Surg. 2014;66(1):41-9.

309. Song SC, Choi DW, Kow AW, Choi SH, Heo JS, Kim WS, et al. Surgical outcomes of 230 resected hilar cholangiocarcinoma in a single centre. ANZ J Surg. 2013;83(4):268-74.

310. Nagino M, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. Ann Surg. 2013;258(1):129-40.

311. Bird N, Elmasry M, Jones R, Elniel M, Kelly M, Palmer D, et al. Role of staging laparoscopy in the stratification of patients with perihilar cholangiocarcinoma. Br J Surg. 2017;104(4):418-25.

312. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BJ, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg. 2001;234(4):507-17; discussion 17-9.

313. Groot Koerkamp B, Wiggers JK, Gonen M, Doussot A, Allen PJ, Besselink MG, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. Ann Oncol. 2016;27(4):753.

314. Schnitzbauer AA, Schadde E, Linecker M, Machado MA, Adam R, Malago M, et al. Indicating ALPPS for Colorectal Liver Metastases: A Critical Analysis of Patients in the International ALPPS Registry. Surgery. 2018;164(3):387-94.

315. Belghiti J, Guevara OA, Noun R, Saldinger PF, Kianmanesh R. Liver hanging maneuver: a safe approach to right hepatectomy without liver mobilization. J Am Coll Surg. 2001;193(1):109-11.

316. Govil S, Reddy MS, Rela M. Surgical resection techniques for locally advanced hilar cholangiocarcinoma. Langenbecks Arch Surg. 2014;399(6):707-16.

317. Nagino M. Perihilar cholangiocarcinoma: a surgeon's viewpoint on current topics. J Gastroenterol. 2012;47(11):1165-76.

318. Nimura Y, Hayakawa N, Kamiya J, Kondo S, Shionoya S. Hepatic segmentectomy with caudate lobe resection for bile duct carcinoma of the hepatic hilus. World J Surg. 1990;14(4):535-43; discussion 44.

319. Wang SF, Huang ZY, Chen XP. Biliary complications after living donor liver transplantation. Liver Transpl. 2011;17(10):1127-36.

320. Reichert PR, Renz JF, D'Albuquerque LA, Rosenthal P, Lim RC, Roberts JP, et al. Surgical anatomy of the left lateral segment as applied to living-donor and split-liver transplantation: a clinicopathologic study. Ann Surg. 2000;232(5):658-64.

321. Cheng QB, Yi B, Wang JH, Jiang XQ, Luo XJ, Liu C, et al. Resection with total caudate lobectomy confers survival benefit in hilar cholangiocarcinoma of Bismuth type III and IV. Eur J Surg Oncol. 2012;38(12):1197-203.

322. Kow AW, Wook CD, Song SC, Kim WS, Kim MJ, Park HJ, et al. Role of caudate lobectomy in type III A and III B hilar cholangiocarcinoma: a 15-year experience in a tertiary institution. World J Surg. 2012;36(5):1112-21.

323. Wahab MA, Sultan AM, Salah T, Fathy O, Elebidy G, Elshobary M, et al. Caudate lobe resection with major hepatectomy for central cholangiocarcinoma: is it of value? Hepatogastroenterology. 2012;59(114):321-4.

324. Knoefel WT, Gabor I, Rehders A, Alexander A, Krausch M, Schulte am Esch J, et al. In situ liver transection with portal vein ligation for rapid growth of the future liver remnant in two-stage liver resection. Br J Surg. 2013;100(3):388-94.

325. de Jong MC, Marques H, Clary BM, Bauer TW, Marsh JW, Ribero D, et al. The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases. Cancer. 2012;118(19):4737-47.

326. Ramos E. Principles of surgical resection in hilar cholangiocarcinoma. World J Gastrointest Oncol. 2013;5(7):139-46.

327. Hirano S, Kondo S, Tanaka E, Shichinohe T, Tsuchikawa T, Kato K. No-touch resection of hilar malignancies with right hepatectomy and routine portal reconstruction. J Hepatobiliary Pancreat Surg. 2009;16(4):502-7.

328. Neuhaus P, Thelen A, Jonas S, Puhl G, Denecke T, Veltzke-Schlieker W, et al. Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. Ann Surg Oncol. 2012;19(5):1602-8.

329. Tamoto E, Hirano S, Tsuchikawa T, Tanaka E, Miyamoto M, Matsumoto J, et al. Portal vein resection using the no-touch technique with a hepatectomy for hilar cholangiocarcinoma. HPB (Oxford). 2014;16(1):56-61.

330. Rela M, Rajalingam R, Shanmugam V, A OS, Reddy MS, Heaton N. Novel en-bloc resection of locally advanced hilar cholangiocarcinoma: the Rex recess approach. Hepatobiliary Pancreat Dis Int. 2014;13(1):93-7.

331. Uchiyama H, Shirabe K, Araki K, Sugimachi K, Morita K, Takenaka K, et al. Left hepatectomy with simultaneous hepatic artery and portal vein reconstructions in the operation for cholangiocarcinoma: the surgical techniques comprised of step-by-step established procedures. Transl Gastroenterol Hepatol. 2017;2:34.

332. Miyazaki M, Kato A, Ito H, Kimura F, Shimizu H, Ohtsuka M, et al. Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not? Surgery. 2007;141(5):581-8.

333. Sakamoto Y, Sano T, Shimada K, Kosuge T, Kimata Y, Sakuraba M, et al. Clinical significance of reconstruction of the right hepatic artery for biliary malignancy. Langenbecks Arch Surg. 2006;391(3):203-8.

334. Shimada H, Endo I, Sugita M, Masunari H, Fujii Y, Tanaka K, et al. Hepatic resection combined with portal vein or hepatic artery reconstruction for advanced carcinoma of the hilar bile duct and gallbladder. World J Surg. 2003;27(10):1137-42.

335. Yamanaka N, Yasui C, Yamanaka J, Ando T, Kuroda N, Maeda S, et al. Left hemihepatectomy with microsurgical reconstruction of the right-sided hepatic vasculature. A strategy for preserving hepatic function in patients with proximal bile duct cancer. Langenbecks Arch Surg. 2001;386(5):364-8.

336. Yokoyama Y, Nagino M, Nishio H, Ebata T, Igami T, Nimura Y. Recent advances in the treatment of hilar cholangiocarcinoma: portal vein embolization. J Hepatobiliary Pancreat Surg. 2007;14(5):447-54.

337. Nagino M, Nimura Y, Nishio H, Ebata T, Igami T, Matsushita M, et al. Hepatectomy with simultaneous resection of the portal vein and hepatic artery for advanced perihilar cholangiocarcinoma: an audit of 50 consecutive cases. Ann Surg. 2010;252(1):115-23.

338. Scatton O, Katsanos G, Soubrane O. Two-stage hepatectomy: tape it and hang it, while you can. World J Surg. 2012;36(7):1647-50.

339. Donati M, Stavrou GA, Oldhafer KJ. Current position of ALPPS in the surgical landscape of CRLM treatment proposals. World J Gastroenterol. 2013;19(39):6548-54.

340. Machado MA, Makdissi FF, Surjan RC. Totally laparoscopic ALPPS is feasible and may be worthwhile. Ann Surg. 2012;256(3):e13; author reply e6-9.

341. Chan AC, Pang R, Poon RT. Simplifying the ALPPS procedure by the anterior approach. Ann Surg. 2014;260(2):e3.

342. Narita M, Oussoultzoglou E, Ikai I, Bachellier P, Jaeck D. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-

staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;256(3):e7-8; author reply e16-7.

343. Lau WY, Lai EC, Lau SH. Associating liver partition and portal vein ligation for staged hepatectomy: the current role and development. Hepatobiliary Pancreat Dis Int. 2017;16(1):17-26.

344. Troja A, Khatib-Chahidi K, El-Sourani N, Antolovic D, Raab HR. ALPPS and similar resection procedures in treating extensive hepatic metastases: our own experiences and critical discussion. International journal of surgery. 2014;12(9):1020-2.

345. Machado MA, Makdissi FF, Surjan RC. ALPPS procedure with the use of pneumoperitoneum. Ann Surg Oncol. 2013;20(5):1491-3.

346. Ielpo B, Caruso R, Ferri V, Quijano Y, Duran H, Diaz E, et al. ALPPS procedure: our experience and state of the art. Hepatogastroenterology. 2013;60(128):2069-75.

347. Olthof PB, Rassam F, van Gulik TM. The use of a NHS-PEG coated, collagen-based sealant in a patient undergoing Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS). Int J Surg Case Rep. 2018;47:7-10.

348. Torres OJ, Fernandes Ede S, Oliveira CV, Lima CX, Waechter FL, Moraes-Junior JM, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): the Brazilian experience. Arquivos brasileiros de cirurgia digestiva : ABCD = Brazilian archives of digestive surgery. 2013;26(1):40-3.

349. Doussot A, Lim C, Gomez Gavara C, Fuks D, Farges O, Regimbeau JM, et al. Multicentre study of the impact of morbidity on long-term survival following hepatectomy for intrahepatic cholangiocarcinoma. Br J Surg. 2016;103(13):1887-94.

350. Ratti F, Schadde E, Masetti M, Massani M, Zanello M, Serenari M, et al. Strategies to Increase the Resectability of Patients with Colorectal Liver Metastases: A Multi-center Case-Match Analysis of ALPPS and Conventional Two-Stage Hepatectomy. Ann Surg Oncol. 2015;22(6):1933-42.

351. Vennarecci G, Ferraro D, Tudisco A, Levi Sandri GB, Guglielmo N, Berardi G, et al. The ALPPS procedure: hepatocellular carcinoma as a main indication. An Italian single-center experience. Updates in surgery. 2019;71(1):67-75.

352. Tanaka K, Matsuo K, Murakami T, Kawaguchi D, Hiroshima Y, Koda K, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): short-term outcome, functional changes in the future liver remnant, and tumor growth activity. Eur J Surg Oncol. 2015;41(4):506-12.

353. Zhang XF, Bagante F, Chakedis J, Moris D, Beal EW, Weiss M, et al. Perioperative and Long-Term Outcome for Intrahepatic Cholangiocarcinoma: Impact of Major Versus Minor Hepatectomy. J Gastrointest Surg. 2017.

354. Wang K, Zhang H, Xia Y, Liu J, Shen F. Surgical options for intrahepatic cholangiocarcinoma. Hepatobiliary Surg Nutr. 2017;6(2):79-90.

355. Sgourakis G, Sotiropoulos GC, Bockhorn M, Fouzas I, Radtke A, Molmenti EP, et al. Major liver resections for primary liver malignancies in the elderly. Acta Chir Belg. 2009;109(3):340-4.

356. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg. 2000;191(1):38-46.

357. Breitenstein S, DeOliveira ML, Raptis DA, Slankamenac K, Kambakamba P, Nerl J, et al. Novel and simple preoperative score predicting complications after liver resection in noncirrhotic patients. Ann Surg. 2010;252(5):726-34.

358. Lang H, Sotiropoulos GC, Fruhauf NR, Domland M, Paul A, Kind EM, et al. Extended hepatectomy for intrahepatic cholangiocellular carcinoma (ICC): when is it worthwhile? Single center experience with 27 resections in 50 patients over a 5-year period. Ann Surg. 2005;241(1):134-43.

359. Herman P, Kruger JA, Perini MV, Coelho FF, Cecconello I. High Mortality Rates After ALPPS: the Devil Is the Indication. J Gastrointest Cancer. 2015;46(2):190-4.

360. Kang D, Schadde E. Hypertrophy and Liver Function in ALPPS: Correlation with Morbidity and Mortality. Visc Med. 2017;33(6):426-33.

361. Matsuo K, Murakami T, Kawaguchi D, Hiroshima Y, Koda K, Yamazaki K, et al. Histologic features after surgery associating liver partition and portal vein ligation for staged hepatectomy versus those after hepatectomy with portal vein embolization. Surgery. 2016;159(5):1289-98.

362. Tanaka K, Kikuchi Y, Kawaguchi D, Murakami T, Hiroshima Y, Matsuo K. Modified ALPPS Procedures Avoiding Division of Portal Pedicles. Ann Surg. 2017;265(2):e14-e20.

363. Spetzler VN, Schepers M, Pinnschmidt HO, Fischer L, Nashan B, Li J. The incidence and severity of post-hepatectomy bile leaks is affected by surgical indications, preoperative chemotherapy, and surgical procedures. Hepatobiliary Surg Nutr. 2019;8(2):101-10.

364. Capussotti L, Ferrero A, Vigano L, Sgotto E, Muratore A, Polastri R. Bile leakage and liver resection: Where is the risk? Arch Surg. 2006;141(7):690-4; discussion 5.

365. Yamashita Y, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, Shimada M, et al. Bile leakage after hepatic resection. Ann Surg. 2001;233(1):45-50.

366. Nagano Y, Togo S, Tanaka K, Masui H, Endo I, Sekido H, et al. Risk factors and management of bile leakage after hepatic resection. World J Surg. 2003;27(6):695-8.

367. Chan A, Chung PH, Poon RT. Little girl who conquered the "ALPPS". World J Gastroenterol. 2014;20(29):10208-11.

368. Chan AC, Poon RT, Chan C, Lo CM. Safety of ALPPS Procedure by the Anterior Approach for Hepatocellular Carcinoma. Ann Surg. 2016;263(2):e14-6.

369. Robles Campos R, Brusadin R, Lopez Conesa A, Parrilla Paricio P. Staged liver resection for perihilar liver tumors using a tourniquet in the umbilical fissure and sequential portal vein embolization on the fourth postoperative day (a modified ALTPS). Cir Esp. 2014;92(10):682-6.

370. Vennarecci G, Laurenzi A, Levi Sandri GB, Busi Rizzi E, Cristofaro M, Montalbano M, et al. The ALPPS procedure for hepatocellular carcinoma. Eur J Surg Oncol. 2014;40(8):982-8.

371. Hattori M, Nagino M, Ebata T, Kato K, Okada K, Shimoyama Y. Prospective study of biliary cytology in suspected perihilar cholangiocarcinoma. Br J Surg. 2011;98(5):704-9.

372. Sanjeevi S, Sparrelid E, Gilg S, Jonas E, Isaksson B. Arterial ischemia in the deportalized liver following associating liver partition and portal vein ligation for staged hepatectomy. World J Hepatol. 2015;7(23):2492-6.

373. Yao LB, Li CH, Wu XJ, Wang XD, Ge XL, Zhang AQ, et al. In situ splitting after selective partial portal vein ligation or simultaneous hepatic artery ligation promotes liver regeneration. Sci Rep. 2018;8(1):8699.

374. Kimura N, Young AL, Toyoki Y, Wyatt JI, Toogood GJ, Hidalgo E, et al. Radical operation for hilar cholangiocarcinoma in comparable Eastern and Western centers: Outcome analysis and prognostic factors. Surgery. 2017.

375. Asiyanbola B, Chang D, Gleisner AL, Nathan H, Choti MA, Schulick RD, et al. Operative mortality after hepatic resection: are literature-based rates broadly applicable? J Gastrointest Surg. 2008;12(5):842-51.

376. Saxena A, Chua TC, Chu FC, Morris DL. Improved outcomes after aggressive surgical resection of hilar cholangiocarcinoma: a critical analysis of recurrence and survival. Am J Surg. 2011;202(3):310-20.

377. Groot Koerkamp B, Wiggers JK, Allen PJ, Besselink MG, Blumgart LH, Busch OR, et al. Recurrence Rate and Pattern of Perihilar Cholangiocarcinoma after Curative Intent Resection. J Am Coll Surg. 2015;221(6):1041-9.

378. Wirasorn K, Ngamprasertchai T, Chindaprasirt J, Sookprasert A, Khantikaew N, Pakkhem A, et al. Prognostic factors in resectable cholangiocarcinoma patients: Carcinoembryonic antigen, lymph node, surgical margin and chemotherapy. World J Gastrointest Oncol. 2013;5(4):81-7.

379. Groot Koerkamp B, Wiggers JK, Gonen M, Doussot A, Allen PJ, Besselink MG, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. Ann Oncol. 2015;26(9):1930-5.

380. 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;105(11):1408-16.

381. Hu LS, Weiss M, Popescu I, Marques HP, Aldrighetti L, Maithel SK, et al. Impact of microvascular invasion on clinical outcomes after curative-intent resection for intrahepatic cholangiocarcinoma. J Surg Oncol. 2019;119(1):21-9.

382. Garcia-Perez R, Ferrer Fabrega J, Varona-Bosque A, Martinez CM, Revilla-Nuin B, Cabellos L, et al. Role of Kupffer cells in the progression of CRC liver metastases after the first stage of ALPPS. Sci Rep. 2018;8(1):8089.

383. Kikuchi Y, Hiroshima Y, Matsuo K, Murakami T, Kawaguchi D, Endo I, et al. Remnant Liver Tumor Growth Activity During Treatment Associating Liver Partition and Portal Vein Occlusion for Staged Hepatectomy (ALPPS). J Gastrointest Surg. 2017;21(11):1851-8.

384. Kikuchi Y, Hiroshima Y, Matsuo K, Murakami T, Kawaguchi D, Kasahara K, et al. Impact of associating liver partition and portal vein occlusion for staged hepatectomy on tumor growth in a mouse model of liver metastasis. Eur J Surg Oncol. 2018;44(1):130-8.

385. Joechle K, Moser C, Ruemmele P, Schmidt KM, Werner JM, Geissler EK, et al. ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) does not affect proliferation, apoptosis, or angiogenesis as compared to standard liver resection for colorectal liver metastases. World J Surg Oncol. 2017;15(1):57.

386. Kambakamba P, Linecker M, Schneider M, Reiner CS, Nguyen-Kim TDL, Limani P, et al. Impact of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) on growth of colorectal liver metastases. Surgery. 2018;163(2):311-7.

387. Rosok BI, Host-Brunsell T, Brudvik KW, Carling U, Dorenberg E, Bjornsson B, et al. Characterization of early recurrences following liver resection by ALPPS and two stage hepatectomy in patients with colorectal liver-metastases and small future liver remnants; a translational substudy of the LIGRO-RCT. HPB (Oxford). 2019;21(8):1017-23.

388. Labib PL, Goodchild G, Pereira SP. Molecular Pathogenesis of Cholangiocarcinoma. BMC Cancer. 2019;19(1):185.

389. Li Z, Shen J, Chan MT, Wu WK. The role of microRNAs in intrahepatic cholangiocarcinoma. J Cell Mol Med. 2017;21(1):177-84.

390. Sanada Y, Kawashita Y, Okada S, Azuma T, Matsuo S. Review to better understand the macroscopic subtypes and histogenesis of intrahepatic cholangiocarcinoma. World J Gastrointest Pathophysiol. 2014;5(3):188-99.

391. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018;15(2):95-111.

392. Klatskin G. Adenocarcinoma of the Hepatic Duct at Its Bifurcation within the Porta Hepatis. An Unusual Tumor with Distinctive Clinical and Pathological Features. Am J Med. 1965;38:241-56.

393. Nagino M, Nimura Y, Kamiya J, Kondo S, Uesaka K, Kin Y, et al. Right or left trisegment portal vein embolization before hepatic trisegmentectomy for hilar bile duct carcinoma. Surgery. 1995;117(6):677-81.

394. Nagino M, Kamiya J, Kanai M, Uesaka K, Sano T, Yamamoto H, et al. Right trisegment portal vein embolization for biliary tract carcinoma: technique and clinical utility. Surgery. 2000;127(2):155-60.

395. Mise Y, Passot G, Wang X, Chen HC, Wei S, Brudvik KW, et al. A Nomogram to Predict Hypertrophy of Liver Segments 2 and 3 After Right Portal Vein Embolization. J Gastrointest Surg. 2016;20(7):1317-23.

396. Kishi Y, Madoff DC, Abdalla EK, Palavecino M, Ribero D, Chun YS, et al. Is embolization of segment 4 portal veins before extended right hepatectomy justified? Surgery. 2008;144(5):744-51.

397. Linecker M, Kambakamba P, Reiner CS, Linh Nguyen-Kim TD, Stavrou GA, Jenner RM, et al. How much liver needs to be transected in ALPPS? A translational study investigating the concept of less invasiveness. Surgery. 2017;161(2):453-64.

398. Tanaka K, Endo I. ALPPS: Short-term Outcome and Functional Changes in the Future Liver Remnant. Ann Surg. 2015;262(2):e88-9.

399. Deal R, Frederiks C, Williams L, Olthof PB, Dirscherl K, Keutgen X, et al. Rapid Liver Hypertrophy After Portal Vein Occlusion Correlates with the Degree of Collateralization Between Lobes-a Study in Pigs. J Gastrointest Surg. 2018;22(2):203-13.

400. Huang HC, Bian J, Bai Y, Lu X, Xu YY, Sang XT, et al. Complete or partial split in associating liver partition and portal vein ligation for staged hepatectomy: A systematic review and meta-analysis. World J Gastroenterol. 2019;25(39):6016-24.

401. Wu X, Rao J, Zhou X, Deng R, Ma Y. Partial ALPPS versus complete ALPPS for staged hepatectomy. BMC Gastroenterol. 2019;19(1):170.

402. Goldberg SN. Radiofrequency tumor ablation: principles and techniques. Eur J Ultrasound. 2001;13(2):129-47.

403. Rong Z, Lu Q, Yan J. Totally laparoscopic radiofrequency-assisted liver partition with portal vein ligation for hepatocellular carcinoma in cirrhotic liver. Medicine (Baltimore). 2017;96(51):e9432.

404. Wang Q, Yan J, Feng X, Chen G, Xia F, Li X, et al. Safety and efficacy of radiofrequency-assisted ALPPS (RALPPS) in patients with cirrhosis-related hepatocellular carcinoma. Int J Hyperthermia. 2017;33(7):846-52.

405. Gringeri E, Boetto R, D'Amico FE, Bassi D, Cillo U. Laparoscopic microwave ablation and portal vein ligation for staged hepatectomy (LAPS): a minimally invasive first-step approach. Ann Surg. 2015;261(2):e42-3.

406. Cillo U, Gringeri E, Feltracco P, Bassi D, D'Amico FE, Polacco M, et al. Totally Laparoscopic Microwave Ablation and Portal Vein Ligation for Staged Hepatectomy : A New Minimally Invasive Two-Stage Hepatectomy. Ann Surg Oncol. 2015;22(8):2787-8.

407. Boggi U, Napoli N, Kauffmann EF, Presti GL, Moglia A. Laparoscopic Microwave Liver Ablation and Portal Vein Ligation: An Alternative Approach to the Conventional ALPPS Procedure in Hilar Cholangiocarcinoma. Ann Surg Oncol. 2016;23(Suppl 5):884.

408. Cai X, Peng S, Duan L, Wang Y, Yu H, Li Z. Completely Laparoscopic ALPPS Using Round-the-Liver Ligation to Replace Parenchymal Transection for a Patient with Multiple Right Liver Cancers Complicated with Liver Cirrhosis. Journal of laparoendoscopic & advanced surgical techniques Part A. 2014;24(12):883-6.

409. Xiao L, Li JW, Zheng SG. Totally laparoscopic ALPPS in the treatment of cirrhotic hepatocellular carcinoma. Surg Endosc. 2015;29(9):2800-1.

410. Surjan RC, Makdissi FF, Basseres T, Leite D, Charles LF, Bezerra RO, et al. First totally laparoscopic ALPPS procedure with selective hepatic artery clamping: Case report of a new technique. Medicine (Baltimore). 2016;95(29):e4236.

411. Ha HT, Han YS, Chun JM. Totally laparoscopic associating liver partition and portal vein ligation for staged hepatectomy using anterior approach in HCC patient with Type II portal vein anomaly: a case report. Ann Hepatobiliary Pancreat Surg. 2017;21(4):217-22.

412. Machado MA, Makdissi FF, Surjan RC, Basseres T, Schadde E. Transition from open to laparoscopic ALPPS for patients with very small FLR: the initial experience. HPB (Oxford). 2017;19(1):59-66.

413. Pekolj J, Alvarez FA, Biagiola D, Villegas L, Ardiles V, de Santibanes E. Totally Laparoscopic Mini-ALPPS Using a Novel Approach of Laparoscopic-Assisted Transmesenteric Portal Vein Embolization. Journal of laparoendoscopic & advanced surgical techniques Part A. 2018;28(10):1229-33.

414. Melandro F, Giovanardi F, Hassan R, Larghi Laureiro Z, Ferri F, Rossi M, et al. Minimally Invasive Approach in the Setting of ALPPS Procedure: a Systematic Review of the Literature. J Gastrointest Surg. 2019;23(9):1917-24.

415. Vicente E, Quijano Y, Ielpo B, Fabra I. First ALPPS procedure using a total robotic approach. Surg Oncol. 2016;25(4):457.

416. Krishnamurthy J, Naragund AV, Mahadevappa B. First Ever Robotic Stage One ALPPS Procedure in India: for Colorectal Liver Metastases. Indian J Surg. 2018;80(3):269-71.

417. Andriani OC. Long-term results with associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Ann Surg. 2012;256(3):e5; author reply e16-9.

418. Heimbach JK, Sanchez W, Rosen CB, Gores GJ. Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. HPB (Oxford). 2011;13(5):356-60.

419. Lindor KD, Bru C, Jorgensen RA, Rakela J, Bordas JM, Gross JB, et al. The role of ultrasonography and automatic-needle biopsy in outpatient percutaneous liver biopsy. Hepatology. 1996;23(5):1079-83.

420. McGill DB, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. Gastroenterology. 1990;99(5):1396-400.

421. Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology. 2005;128(7):1898-906.

422. Fujiwara Y, Kuroda H, Abe T, Ishida K, Oguri T, Noguchi S, et al. The B-Mode Image-Guided Ultrasound Attenuation Parameter Accurately Detects Hepatic Steatosis in Chronic Liver Disease. Ultrasound Med Biol. 2018.

423. Allan R, Thoirs K, Phillips M. Accuracy of ultrasound to identify chronic liver disease. World J Gastroenterol. 2010;16(28):3510-20.

424. Cosgrove D, Piscaglia F, Bamber J, Bojunga J, Correas JM, Gilja OH, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. Ultraschall Med. 2013;34(3):238-53.

425. Lee SS, Park SH, Kim HJ, Kim SY, Kim MY, Kim DY, et al. Non-invasive assessment of hepatic steatosis: prospective comparison of the accuracy of imaging examinations. J Hepatol. 2010;52(4):579-85.

426. McDonald N, Eddowes PJ, Hodson J, Semple SIK, Davies NP, Kelly CJ, et al. Multiparametric magnetic resonance imaging for quantitation of liver disease: a two-centre cross-sectional observational study. Sci Rep. 2018;8(1):9189.

427. Imajo K, Kessoku T, Honda Y, Tomeno W, Ogawa Y, Mawatari H, et al. Magnetic Resonance Imaging More Accurately Classifies Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease Than Transient Elastography. Gastroenterology. 2016;150(3):626-37 e7.

428. Lv S, Jiang S, Liu S, Dong Q, Xin Y, Xuan S. Noninvasive Quantitative Detection Methods of Liver Fat Content in Nonalcoholic Fatty Liver Disease. J Clin Transl Hepatol. 2018;6(2):217-21.

429. van Werven JR, Marsman HA, Nederveen AJ, Smits NJ, ten Kate FJ, van Gulik TM, et al. Assessment of hepatic steatosis in patients undergoing liver resection: comparison of US, CT, T1-weighted dual-echo MR imaging, and point-resolved 1H MR spectroscopy. Radiology. 2010;256(1):159-68.

430. Bohte AE, Garteiser P, De Niet A, Groot PF, Sinkus R, Stoker J, et al. MR elastography of the liver: defining thresholds for detecting viscoelastic changes. Radiology. 2013;269(3):768-76.

431. Venkatesh SK, Yin M, Ehman RL. Magnetic resonance elastography of liver: technique, analysis, and clinical applications. J Magn Reson Imaging. 2013;37(3):544-55.

432. Panicek DM, Giess CS, Schwartz LH. Qualitative assessment of liver for fatty infiltration on contrast-enhanced CT: is muscle a better standard of reference than spleen? J Comput Assist Tomogr. 1997;21(5):699-705.

433. Nagashima I, Takada T, Okinaga K, Nagawa H. A scoring system for the assessment of the risk of mortality after partial hepatectomy in patients with chronic liver dysfunction. J Hepatobiliary Pancreat Surg. 2005;12(1):44-8.

434. Garcea G, Ong SL, Maddern GJ. Predicting liver failure following major hepatectomy. Dig Liver Dis. 2009;41(11):798-806.

435. Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. Ann Surg. 2006;243(3):373-9.

436. Kamath PS, Kim WR, Advanced Liver Disease Study G. The model for end-stage liver disease (MELD). Hepatology. 2007;45(3):797-805.

437. Zheng Y, Yang H, He L, Mao Y, Zhang H, Zhao H, et al. Reassessment of different criteria for diagnosing post-hepatectomy liver failure: a single-center study of 1683 hepatectomy. Oncotarget. 2017;8(51):89269-77.

438. Caesar J, Shaldon S, Chiandussi L, Guevara L, Sherlock S. The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. Clin Sci. 1961;21:43-57.

439. Paumgartner G. The handling of indocyanine green by the liver. Schweiz Med Wochenschr. 1975;105(17 Suppl):1-30.

440. Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. Br J Surg. 1997;84(9):1255-9.

441. Fan ST, Lai EC, Lo CM, Ng IO, Wong J. Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. Arch Surg. 1995;130(2):198-203.

442. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg. 2004;240(4):698-708; discussion -10.

443. Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M. Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg. 2005;12(1):16-22.

444. Fazakas J, Mandli T, Ther G, Arkossy M, Pap S, Fule B, et al. Evaluation of liver function for hepatic resection. Transplant Proc. 2006;38(3):798-800.

445. Beppu T, Hayashi H, Okabe H, Masuda T, Mima K, Otao R, et al. Liver functional volumetry for portal vein embolization using a newly developed 99mTc-galactosyl human serum albumin scintigraphy SPECT-computed tomography fusion system. J Gastroenterol. 2011;46(7):938-43.

446. Iimuro Y, Kashiwagi T, Yamanaka J, Hirano T, Saito S, Sugimoto T, et al. Preoperative estimation of asialoglycoprotein receptor expression in the remnant liver from CT/99mTc-GSA

SPECT fusion images correlates well with postoperative liver function parameters. J Hepatobiliary Pancreat Sci. 2010;17(5):673-81.

447. Kim YK, Nakano H, Yamaguchi M, Kumada K, Takeuchi S, Kitamura N, et al. Prediction of postoperative decompensated liver function by technetium-99m galactosyl-human serum albumin liver scintigraphy in patients with hepatocellular carcinoma complicating chronic liver disease. Br J Surg. 1997;84(6):793-6.

448. Kokudo N, Vera DR, Tada K, Koizumi M, Seki M, Matsubara T, et al. Predictors of successful hepatic resection: prognostic usefulness of hepatic asialoglycoprotein receptor analysis. World J Surg. 2002;26(11):1342-7.

449. Nanashima A, Yamaguchi H, Shibasaki S, Morino S, Ide N, Takeshita H, et al. Relationship between indocyanine green test and technetium-99m galactosyl serum albumin scintigraphy in patients scheduled for hepatectomy: Clinical evaluation and patient outcome. Hepatol Res. 2004;28(4):184-90.

450. Takeuchi S, Nakano H, Kim YK, Kumada K, Nagasaki H, Sasaki J, et al. Predicting survival and post-operative complications with Tc-GSA liver scintigraphy in hepatocellular carcinoma. Hepatogastroenterology. 1999;46(27):1855-61.

451. Erdogan D, Heijnen BH, Bennink RJ, Kok M, Dinant S, Straatsburg IH, et al. Preoperative assessment of liver function: a comparison of 99mTc-Mebrofenin scintigraphy with indocyanine green clearance test. Liver Int. 2004;24(2):117-23.

452. Bennink RJ, Dinant S, Erdogan D, Heijnen BH, Straatsburg IH, van Vliet AK, et al. Preoperative assessment of postoperative remnant liver function using hepatobiliary scintigraphy. J Nucl Med. 2004;45(6):965-71.

453. de Graaf W, Bennink RJ, Vetelainen R, van Gulik TM. Nuclear imaging techniques for the assessment of hepatic function in liver surgery and transplantation. J Nucl Med. 2010;51(5):742-52.

454. Dinant S, de Graaf W, Verwer BJ, Bennink RJ, van Lienden KP, Gouma DJ, et al. Risk assessment of posthepatectomy liver failure using hepatobiliary scintigraphy and CT volumetry. J Nucl Med. 2007;48(5):685-92.

455. Trauner M, Meier PJ, Boyer JL. Molecular pathogenesis of cholestasis. N Engl J Med. 1998;339(17):1217-27.

456. de Graaf W, van Lienden KP, Dinant S, Roelofs JJ, Busch OR, Gouma DJ, et al. Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. J Gastrointest Surg. 2010;14(2):369-78.

AKNOWLEDGEMENTS:

I have a lot of people to thank for this work. First and foremost I have to thank my supervisor and mentor Prof. Silvio Nadalin. By giving me the opportunity to work with him and trusting me, he opened up the fascinating world of HPB surgery to me. He continually encouraged and pushed me, not only to become a better clinician and surgeon, but also a researcher. He has constantly reviewed this work to make the most of this small but unique experience. ALPPS is not only a new surgical technique, working on these data has allowed me to expand my knowledge on liver regeneration, surgical oncology and its technical development, reaching and overcoming surgical limits, patient selection, perioperative management, statistics and risk analysis.

Prof. Alfred Königsrainer gave me the opportunity to work in his team and to have a home for my career. His daily example is an inspiration to face the joy and challenge of being a surgeon. His review of this work has provided useful insights and led to important improvements.

I am also indebted to many colleagues. Each of them has contributed with their experience to my personal growth. In particular, I have to thank Paolo Girotti and Jun Li who first followed the experience with ALPPS at the University Hospital Tübingen and supported me in my first steps on this topic. Other colleagues also provided essential assistance: Jens Rolinger, David Tumiati and Kai Jansen helped me with data collection and checking numerous details.

A huge thank you goes to Beate Harder, for the support and friendship expressed from day one. Every help, even on this work, has always come with a smile!

Finally, this work would never have been possible without my family and Sofia. They pulled for me every step of the way, sacrificing a lot of time that we could have spent together, silently accepting every delay. For your generosity, patience and support, my biggest thanks go to you!

AUTHOR CONTRIBUTION STATEMENT:

Ivan Capobianco and Silvio Nadalin have conceived and designed this study. Ivan Capobianco acquired the data and conducted the analysis and interpretation of the data. Jens Rolinger, David Tumiati and Kai Jansen made minor contribution to data collection. All the tables and images have been made by Ivan Capobianco. Ivan Capobianco drafted the current work. Silvio Nadalin critically reviewed it for important intellectual content and gave the final approval to the current version to be presented.

_____

Ivan Capobianco