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ORIGINAL ARTICLE

The role of ALPPS in intrahepatic cholangiocarcinoma

Jan Bednarsch[1] · Zoltan Czigany[1] · Isabella Lurje[1] · Pavel Strnad[2] · Philipp Bruners[3] · Tom Florian Ulmer[1] · Marcel den Dulk[1,4] · Georg Lurje[1] · Ulf Peter Neumann[1,4]

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Abstract

Purpose Surgical resection constitutes the mainstay of curative treatment for intrahepatic cholangiocarcinoma (iCCA). Complete tumor clearance can only be achieved with extended liver resections and as such, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) may facilitate surgical resectability. The present study aims to evaluate the technical feasibility and oncologic outcome of ALPPS in iCCA.

Methods A set of 14 patients who underwent ALPPS in a single center between 2011 and 2017 were statistically analyzed for perioperative and oncologic outcome.

Results Of all patients undergoing stage 1 of ALPPS, 12 (86%) patients were subsequently completed in stage 2 surgery. Patients who completed the ALPPS procedure showed a median overall survival (OS) of 4.2 years and a 3-year survival of 64%. Individuals without lymphatic metastases ($n = 7$) were all alive 1 year after surgery and if deceased, they died more than 4 years after surgery, while no patient with lymphatic metastases ($n = 5$) was alive 1 year after surgery.

Conclusion This is the largest single-center experience of ALPPS in iCCA currently available in the literature showing excellent technical feasibility and encouraging overall survival in these patients.

Keywords Intrahepatic cholangiocarcinoma (iCCA) · ALPPS · Oncological outcome

Abbreviations

AJCC	American Joint Committee on Cancer
ALPPS	Associating liver partition and portal vein ligation for staged hepatectomy
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
BMI	Body mass index
BSA	Body surface area
BSC	Best supportive care
BW	Body weight
Cap	Capecitabine
cFLR	Calculated future liver remnant
CI	Confidence interval
Cis	Cisplatin
CRLM	Colorectal liver metastases
CRP	C-reactive protein
CT	Computed tomography
CUSA	Cavitron Ultrasonic Surgical Aspirator
DFS	Disease-free survival
EASL	European Association for Studies of the Liver
ECOG	Eastern Cooperative Oncology Group
FLR	Future liver remnant
GD-EOB-DPTA	Gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid
Gem	Gemcitabine
GGT	Gamma glutamyltransferase

Georg Lurje and Ulf Peter Neumann contributed equally to this work.

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✉ Georg Lurje
glurje@ukaachen.de

[1] Department of Surgery and Transplantation, University Hospital RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany

[2] Department of Medicine III, University Hospital RWTH Aachen, Aachen, Germany

[3] Department of Radiology, University Hospital RWTH Aachen, Aachen, Germany

[4] Department of Surgery, Maastricht University Medical Centre (MUMC), Maastricht, Netherlands

HCC	Hepatocellular carcinoma
INR	International normalized ratio
LiMAx	Maximum liver function capacity
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
OS	Overall survival
Ox	Oxaliplatin
PET	Positron emission tomography
PVE	Portal vein embolization
RWTH	Rheinisch-Westfälische Technische Hochschule
SIRT	Selective internal radio therapy
SRT	Stereotactic radio therapy
TLV	Total liver volume
TR	Tumor recurrence
TSH/PVE	Two-stage hepatectomy with inter-stage portal vein embolization
UICC	Union for international cancer control

Introduction

Cholangiocellular carcinoma (CCA) is the second most common primary liver cancer and is presumed to originate from the biliary tract epithelium. Typically, CCAs are diagnosed at advanced disease stages; their pathogenesis is poorly understood and their dismal prognosis has resulted in an overall nihilistic approach to their management [1, 2]. The classification of CCA is based on the anatomic location within the biliary tree, distinguishing intrahepatic CCA (iCCA), perihilar CCA, and distal CCA [3]. Chronic inflammation with the release of inflammatory cytokines as well as structural changes of the liver parenchyma (fibrosis or cirrhosis) promote CCA tumorigenesis with clonorchiasis, primary sclerosing cholangitis, hepatolithiasis, choledochal cysts, and Caroli syndrome being major risk factors [4, 5]. Interestingly, other risk factors as liver cirrhosis, chronic hepatitis, and alcoholic liver disease which are usually associated with hepatocellular carcinoma are nowadays also considered to be risk factors for the development of CCA [5].

Patients with iCCA frequently present with advanced disease stages, oftentimes comprising large tumor masses with involvement of the liver hilum or the infrahepatic vena cava [6, 7]. In this context, radical surgical resection in combination with extended lymphadenectomy is typically necessary to achieve complete tumor clearance. Increasing surgical resectability in iCCA has been in the spotlight of interest in the last decade, since outcome in palliative systemic therapy is extremely poor, with a median overall survival (OS) of less than 1 year despite the utilization of potent chemotherapy [8]. To further increase resectability rates in patients requiring extended liver resections in general, the novel surgical technique called associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been introduced in the recent years [9, 10]. While both the safety profile as well as the oncological outcome of ALPPS for colorectal liver metastases (CRLMs) have shown encouraging results, the role of ALPPS in non-colorectal liver tumors still needs to be systematically analyzed. Early reports emphasized a significant rate of postoperative liver failure and perioperative morbidity as well as mortality in ALPPS for CCA [11]. While ALPPS in CCA is associated with significantly higher perioperative mortality than in CRLMs, these results might be due to the generally very poor outcome of pCCA or gallbladder carcinoma. Compared to the dismal survival results of best supportive care, ALPPS may therefore still be a viable option for patients with otherwise irresectable iCCA [11, 12].

To explore the role of ALPPS in iCCA, we retrospectively evaluated survival, volumetric data, surgical data, and postoperative complications as well as clinicopathological parameters of 14 patients operated at our center. In this currently largest single-center cohort of ALPPS patients, we evaluated the technical feasibility and oncologic outcome of this technique.

Material and methods

Patients

Between 2011 and 2017, 14 (n = 14) patients with extended iCCA who were scheduled to undergo ALPPS at the University Hospital RWTH Aachen (UH-RWTH) were included in this study. All of these patients had localized tumors without signs of systemic disease. Clinical staging was performed according to the International Union Against Cancer (UICC) classification. The study was conducted at the UH-RWTH in accordance with the requirements of the Institutional Review Board of the RWTH-Aachen University (EK 252/15), the current version of the Declaration of Helsinki, and the good clinical practice guidelines (ICH-GCP).

Staging and clinical management

All patients who were referred for surgical treatment of iCCA to our institution underwent a detailed clinical work-up. It included at least one preoperative cross-sectional imaging such as contrast-material-enhanced multiphase computed tomography (CT) to rule out the presence of distant metastases and CT or dynamic magnetic resonance imaging (MRI) of the liver to visualize the invasion of major vessels in the liver hilum. In iCCAs extending to the liver hilum, an endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) was performed

to assess the tumor anatomy. The evaluation of the patients' perioperative risk was based on the American Society of Anesthesiologists (ASA) and the Eastern Cooperative Oncology Group (ECOG) performance status, the analysis of the quantitative and functional parenchymal liver function as assessed by laboratory parameters, the LiMAx (maximum liver function capacity) test and CT or MRI-based 3D calculation of the future liver remnant (FLR) [13]. The decision for surgery as primary treatment and the specific surgical procedure was made by an experienced hepatobiliary surgeon in conjunction with the interdisciplinary institutional tumor board in all cases.

Surgical technique and timing of the procedure

ALPPS was considered in cases requiring extended liver resections with a preoperatively estimated FLR of less than 30%. In a subset of patients (4/14, 29%), the decision for ALPPS was made intraoperatively without a preoperative volumetric analysis due to an intraoperatively larger appearing tumor as preoperatively assessed. A volumetric analysis was subsequently carried out retrospectively for these particular individuals and showed FLRs marginally larger than 30% (31.2%, 31.4%, 32.1%, 39.7%). Surgical resection was conducted in accordance with common clinical standards. After each laparotomy, an intraoperative ultrasound was performed to evaluate the tumor size as well as other suspicious lesions.

ALPPS was uniformly performed in every patient as classic ALPPS [9]. Briefly, during stage I, the liver parenchyma was fully transected in the planned resection line. Parenchymal transection was carried out using the Cavitron Ultrasonic Surgical Aspirator (CUSA) with low central venous pressure and intermittent Pringle maneuvers if necessary. The portal branches supplying the parts of the liver that would be subsequently removed were resected while arterial inflow and bile ducts were preserved. Liver veins were also preserved to avoid congestion. An omental flap was placed in the resection line and on hilar structures to avoid adhesions. Before stage II, all patients received an abdominal CT scan to confirm volume growth. Stage II was subsequently carried out if both liver hypertrophy in the inter-stage CT scan and liver function monitored by LiMAx and standard liver function tests were deemed sufficient. In stage II, the hepatectomy was completed by removal of the pre-defined liver specimen.

Lymphadenectomy was usually carried out during stage 2 of the procedure and comprised the pericholedochal, the periportal, the common hepatic lymph nodes, the posterior pancreaticoduodenal, and the celiac lymph nodes. All surgical specimens underwent routine histopathological work-up according to current national guidelines and WHO and UICC classifications. Tumor staging was reported according to the seventh edition of the AJCC staging for intrahepatic cholangiocarcinoma [14].

Surgical procedures were classified in accordance to the Brisbane 2000 terminology of liver anatomy and resections [15]. In brief, our cohort comprised right hepatectomies (resection of segment V-VIII ± segment I), extended right hepatectomies (resection of segment V-VIII ± segment I and partially segment IV) and right trisectionectomies (resection of segment IV-VIII ± segment I).

Volumetric analysis

Digital volumetric analysis was carried out with volumetric analysis module of the IntelliSpace Portal 8.0 (Philips healthcare, Amsterdam, The Netherlands). Preoperative volumetric analysis was based on a contrast-enhanced CT scan or MRI with gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (GD-EOB-DPTA, EOB·Primovist®). Volume measurements were done manually by delineation of margins in every CT or MRI slide by a senior HPB fellow. Total liver volume (TLV) and FLR were subsequently calculated by IntelliSpace Portal 8.0 (Philipps, Amsterdam, The Netherlands). Tumor volume (TV) was considered as non-functional liver parenchyma and thus subtracted from the TLV in every assessment of the calculated FLR (cFLR). The cFLR was determined as the ratio of the FLR to the functional liver volume (cFLR [%] = FLR [ml] / (TLV [ml] − TV [ml]) × 100). Volume hypertrophy between the stages was defined as the percental increase of the cFLR (Hypertrophy [%] = (cFLR-stage2 / cFLR-stage1) × 100).

Follow-up

Each patient was assessed regularly by the referring oncologist or the local outpatient clinic. The follow-up included clinical examinations, standard blood tests with follow-up tumor markers (CA 19-9), and radiologic cross-sectional imaging. If a tumor recurrence was suspected, an additional imaging and/or biopsy was performed to confirm the diagnosis. The referring oncologists and the local outpatient clinic provided all analyzed follow-up data.

Statistical analysis

The primary endpoint in this study was OS, measured from the date of resection to the date of death from any cause or the last contact if the patient was still alive. Categorical data are presented in the form of numbers and percentages. Data derived from continuous variables are presented as median and interquartile range. Survival curves were generated by the Kaplan-Meier method. Median follow up was accessed with the reverse Kaplan-Meier method. Analyses were performed using SPSS Statistics 24 (IBM Corp., Armonk, NY, USA)).

Results

Preoperative, operative, and postoperative data

A total of 14 patients with a median age of 66 years and median BMI of 25 kg/m^2 were scheduled to undergo ALPPS for iCCA at our institution from 2011 to 2017. Of all patients undergoing stage 1 of ALPPS, 12 (86%) patients were subsequently completed in stage 2 surgery, while two patients were not completed due to insufficient hypertrophy. A detailed overview of the cohort and drop-out rate due to ALPPS failure is given in Fig. 1.

In all cases, right-sided hepatectomies were performed with two right hepatectomies (11%), two extended right hepatectomies (11%), and 10 right trisectionectomies (78%). The median degree of hypertrophy was 65% with an increase in the median cFLR from 24% to 31%. While significant complications defined as ≥ 3a according to the Clavien-Dindo scale were occasionally observed after stage 1 (4/14, 29%), major complications occurred in the majority of patients undergoing stage 2 (10/12, 83%) with one case of in-house mortality in the overall cohort (1/12, 8%). A detailed synopsis regarding patients' characteristics as well as volumetric data and postoperative complications after each stage is presented in Table 1.

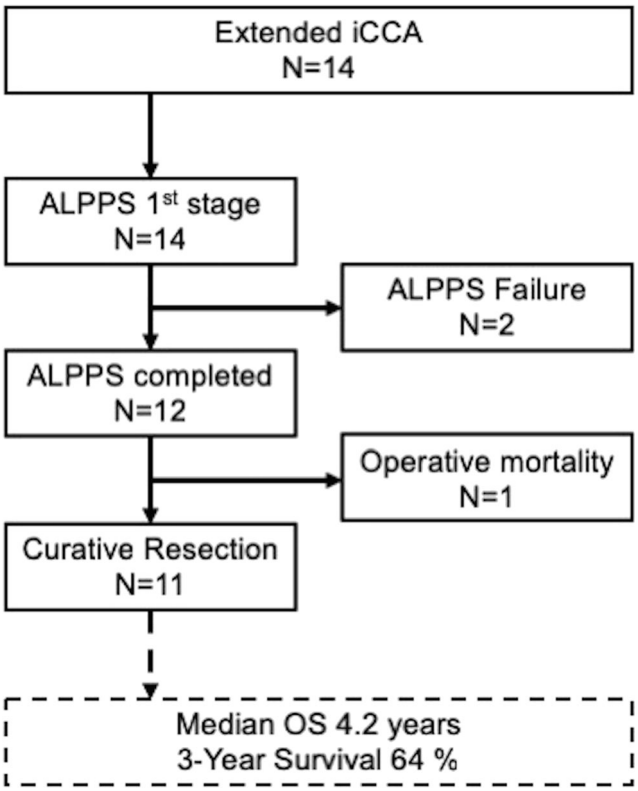

Fig. 1 Patient cohort with extended intrahepatic cholangiocarcinoma

Table 1 Clinicopathological characteristics

Variable	ALPPS cohort $N = 14$
Demographics	Median (IQR)
Gender, m/f, *n* (%)	8 (57)/6 (43)
Age (years)	66 (63–71)
BMI (kg/m^2)	25 (22–28)
ASA, *n* (%)	
I	
II	6 (43)
III	8 (57)
IV	
V	
Preoperative chemotherapy, *n* (%)	1 (7)
Number of tumors	2 (1–3)
Max tumor diameter (mm)	80 (46–103)
Preoperative liver function	
Albumin (g/dl)	39 (36–45)
AST (U/l)	49 (34–62)
ALT (U/l)	38 (29–91)
GGT (U/l)	298 (108–521)
Total bilirubin (mg/dl)	.58 (.34–1.53)
Platelet count (/nl)	275 (201–322)
Alkaline phosphatase (U/l)	215 (120–368)
Prothrombin time (%)	91 (80–102)
INR	1.06 (0.96–1.16)
Hemoglobin (g/dl)	13.1 (11.8–13.9)
CRP (mg/dl)	17 (11–32)
Volumetric data	
Stage 1	
TLV (ml)	1453 (1373–1956)
TV (ml)	138 (91–218)
FLR (ml)	336 (231–519)
cFLR (%)	24 (20–31)
Stage 2	
TLV (ml)	1882 (1670–1979)
TV (ml)	139 (81–218)
FLR (ml)	524 (454–669)
cFLR (%)	31 (26–36)
Degree of hypertrophy	65 (22–84)
Operative data	
Operative time (min) stage 1	290 (230–361)
Operative procedure stage 1, *n* (%)	
Right hepatectomy split	2 (14)
Ext. right hepatectomy split	2 (14)
Right trisectionectomy split	10 (71)
Interval between stages (days)	10 (7–12)
Operative time (min) stage 2	130 (103–171)
Operative procedure stage 2, *n* (%)	
ALPPS completion	12 (86)
Non-completion	2 (14)

Table 1 (continued)

Variable	ALPPS cohort $N = 14$
Reason for ALPPS failure, *n* (%)	
Insufficient hypertrophy	2 (100)
Tumor progression	0
Postoperative data	
Clavien-Dindo stage 1 ≥ IIIa, *n* (%)	4 (29)
Clavien-Dindo stage 1 = V, *n* (%)	0
Clavien-Dindo stage 2 ≥ IIIa, *n* (%)	10 (83)
Clavien-Dindo stage 2 = V, *n* (%)	1 (8)
Pathological data	
R category, *n* (%)	
R0	11 (79)
R1	1 (7)
n.a.	2 (14)
T category, *n* (%)	
T1/T2	11 (79)
T3/T4	3 (21)
N category, *n* (%)	
NX	2 (14)
N0	7 (50)
N1	5 (36)
G category	
G1/G2	9 (64)
G3/G4	2 (14)
n.a.	3 (21)
Tumor stage UICC, *n* (%)	
I/II	6 (43)
III/IV	6 (43)
n.a.	2 (14)

Data presented as median and interquartile range if not noted otherwise

ALPPS Associating liver partition with portal vein ligation for staged hepatectomy, *ALT* alanine aminotransferase, *ASA* American society of anesthesiologists classification, *AST* aspartate aminotransferase, *BMI* body mass index, *cFLR* calculated future liver remnant, *CRP* c-reactive protein, *FLR* future liver remnant, *GGT* gamma glutamyltransferase, *INR* international normalized ratio, *n.a.* not applicable, *TLV* total liver volume, *TV* tumor volume, *UICC* Union for international cancer control

Survival analysis

After exclusion of patients who were not completed ($n = 2$) and perioperative mortality ($n = 1$), a total of 11 patients who underwent ALPPS were eligible for follow-up after curative surgery. This subset of patients showed a median OS of 4.2 years and a 3-year survival of 64%. Individuals without lymphatic metastases ($n = 7$) were all alive 1 year after surgery and if deceased, they died more than 4 years after surgery, while no patient with lymph node metastases ($n = 5$) was alive 1 year after surgery. The majority of patients (9/11) experienced tumor recurrence during the period of follow-up. More details regarding survival, duration of follow-up, and the incidence of tumor recurrence as well as recurrence treatment of patients are given in Tables 2, 3 and Fig. 2.

Discussion

At time of patient presentation, iCCAs are oftentimes large and involve major vessels and/or the liver hilum. As such, only a fraction (18% to 70%) of patients is eligible for curative resection [13, 16]. The introduction of ALPPS has significantly shaped the clinical practice of hepatobiliary surgery, since the liver hypertrophy induced by this technique enables curative resection in patients formerly ineligible for surgery due to an insufficient FLR.

Surgical resection is the mainstay of treatment for iCCA, since it offers a superior oncologic outcome compared to local or systemic therapy options. While 5-year survival of 20 to 40% has been reported in surgical series, chemotherapy, e.g., gemcitabine/cisplatin, in case of irresectable disease showed dismal outcome with a median survival of less than 1 year [8, 17–19]. Local therapies have been investigated in irresectable iCCAs, but the currently limited evidence does not allow a clear recommendation [20].

The bulk of oncologic outcome data after ALPPS is derived from CRLM surgery, where 3-year overall survival (OS) of 50% has been reported, an encouraging number considering the metastatic nature of the disease [21]. Colorectal metastases also constitute the best-established indication for ALPPS, while ALPPS in primary liver tumors is less well studied. Hepatocellular carcinoma (HCC) often originates from compromised liver tissue which preludes extensive surgery such as ALPPS. CCAs usually arise in normal liver tissue and therefore may be more suitable for such a radical surgical treatment. At the same time, a significant rate of postoperative liver failure and perioperative morbidity and mortality in ALPPS for CCA was observed in earlier reports [11]. In this study, ALPPS showed an acceptable perioperative mortality of 8.3% (1/12). Moreover, the resected patients presented with an excellent median OS of 4.2 years. This is in particular appealing if compared with the median OS of 11.7 months described in the ABC trial evaluating the efficiency of the currently administered first-line chemotherapy gemcitabine/cisplatin in irresectable disease [8].

Our small sample size limited the feasibility of a detailed statistical analysis. However, when stratified for nodal status, individuals without lymphatic metastases ($n = 7$) were all alive 1 year after surgery and if deceased, they died more than 4 years after surgery, while no patient with lymphatic metastases ($n = 5$) was alive 1 year after surgery (Table 2). Several studies have reported the presence of lymphatic metastases as the most powerful independent predictor of inferior survival [22–24]. Our clinical routine includes lymphadenectomy in

Table 2 Survival data of patients undergoing ALPPS for intrahepatic cholangiocarcinoma

Patient number	Completed (yes/no)	Perioperative mortality (yes/no)	Alive (yes/no)	Follow-up/OS (months)	TR (yes/no)	RFS (months)	T—category	N-category (N0/N1/NX)
1	Yes	No	Yes	66	Yes	13	T2	N0 (0/12)
2	Yes	No	No	65	Yes	30	T3	N0 (0/15)
3	Yes	No	No	51	Yes	8	T2	N0 (0/14)
4	Yes	No	No	50	Yes	7	T2	N0 (0/5)
5	Yes	No	Yes	21	Yes	6	T2	N0 (0/6)
6	Yes	No	Yes	19	No	19	T2	N0 (0/6)
7	Yes	No	Yes	16	No	16	T2	N0 (0/5)
8	Yes	No	No	10	Yes	2	T2	N1 (1/5)
9	Yes	No	No	5	Yes	5	T2	N1 (1/14)
10	Yes	No	No	4	Yes	3	T2	N1 (7/8)
11	Yes Yes	No	No	2	Yes	2	T2	N1 (8/9)
12	Yes	Yes	n.a.	n.a.	n.a.	n.a.	T2	N1 (1/9)
13	No	No	No	4	n.a.	n.a.	T3	NX
14	No	No	Yes	2	n.a.	n.a.	T3	NX

Survival data of each patient of the cohort is shown

ALPPS associating liver partition with portal vein ligation for staged hepatectomy, *n.a.* not applicable, *OS* overall survival, *RFS* recurrence-free survival, *TR* tumor recurrence

Table 3 Patterns of tumor recurrence and recurrence treatment

Patient number	Adjuvant therapy	1st recurrence site	1st recurrence treatment	2nd recurrence Site	2nd recurrence treatment	3rd recurrence Site	3rd recurrence treatment
1	No	Liver	CTx (Gem/Cis) SRT	–	–	–	–
2	No	Extrahepatic Lymph node	CTx (Gem/Cis)	–	–	–	–
3	No	Liver Lung	CTx (Gem/Cis)	–	–	–	–
4	No	Liver	Surgery	Liver	Surgery CTx (Gem/Cis)	Liver	CTx (FOLFIRI) SIRT
5	Cap	Liver	Surgery CTx (Gem/Cis)	Liver	CTx (Gem/Cis)	–	–
6	No	–	–	–	–	–	–
7	Cap	–	–	–	–	–	–
8	No	Liver Bone	CTx (Gem/Ox) SRT	–	–	–	–
9	No	Liver	BSC	–	–	–	–
10	No	Liver Lung Peritoneum	BSC	–	–	–	–
11	No	Liver	BSC	–	–	–	–
12	n.a.	–	–	–	–	–	–
13	SIRT[a]	–	–	–	–	–	–
14	BSC[a]	–	–	–	–	–	–

Patterns of tumor recurrence and recurrence treatment is shown for each patient

BSC best supportive care, *Cap* capecitabine, *Cis* cisplatin, *Gem* gemcitabine, *n.a.* not applicable, *Ox* oxaliplatin, *SIRT* selective internal radio embolization, *SRT* stereotactic radio therapy

[a] Not adjuvant, but palliative therapy

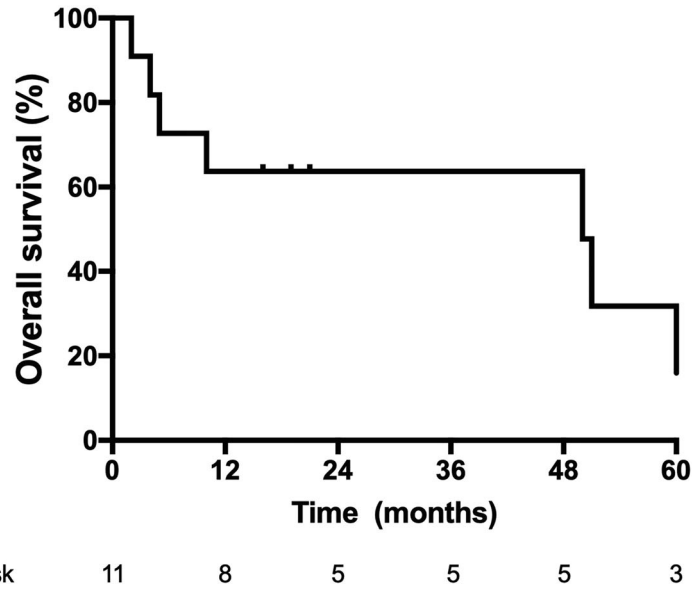

Fig. 2 Overall survival after ALPPS for intrahepatic cholangiocarcinoma

every patient undergoing surgery in CCA. Interestingly, the number of harvested lymph nodes during surgery appears also to be of prognostic relevance. A recent paper of Guglielmi et al. evaluated the prognostic value of harvested lymph nodes in iCCA patients without lymph node metastases who underwent curative surgery. Here, patients with one to three retrieved lymph nodes survived for 38 months, while those with more than three retrieved lymph nodes survived for 69 months [25]. We carried out systemic lymph node harvesting during surgery with a minimum of five harvested lymph nodes in our cohort (Table 2). Unfortunately, we are not able to conduct a similar statistical analysis due to our small sample size. However, despite being speculative, it appears that the patients with the best survival have more than 10 lymph nodes harvested during surgery, supporting the findings of Guglielmi et al. Of note, preoperative diagnosis of lymph node metastases is challenging and no available imaging modality has shown sufficient diagnostic accuracy to exclude a patient with suspected lymph node metastases from surgery. This includes positron emission tomography (PET) which is frequently used in other malignancies [26, 27].

Despite our good overall survival, tumor recurrence (TR) appeared as a major problem in our ALPPS cohort with nine out of 11 patients experiencing TR. Recurrence after surgical resection has been reported to occur in up to 60% of patients with a median disease-free survival of slightly more than 2 years [28, 29]. Due to limited sample size, we are not able to conduct a specific analysis for recurrence sites and prognostic markers for TR. Interestingly, the OS after recurrence in our ALPPS patients was still good in a subset of patients, while other individuals showed accelerated tumor progression and did decease shortly after diagnosis of TR. We applied a multimodal treatment including repeated surgical resection, interventional therapies, and chemotherapy in case of TR [30]. Especially our patients with good survival after TR underwent repeated surgery or interventional treatment and showed significant response to systemic therapy whereas patients with poor outcome after TR usually presented with large tumor burden and were often referred to best supportive care due to impaired physical performance. Of note, adjuvant therapy was seldom applied in our patients which we do attribute to the study period with most of the patients undergoing therapy prior to the results of the BILCAP trial [31].

The specific role of ALPPS in iCCA is currently poorly explored and its superiority over conventional portal vein embolization (PVE) or two-stage hepatectomy with inter-stage PVE (TSH/PVE) a matter of debate. In our considerably smaller experience with TSH/PVE, we observed a lower rate of completion due to inter-stage tumor progression (data not shown, supplementary table 1). Also, PVE with subsequent liver resection was less frequently applied than ALPPS during the study period in our department, since we assume that a shorter inter-stage interval might be beneficial in case of an aggressive primary tumor such as iCCA (supplementary table 2). However, a comparative analysis between ALPPS and other treatment modalities is not the aim of this study because the relatively small sample sizes would not allow a statically meaningful comparison.

Currently, there are no sufficient perioperative and long-term oncologic data available on iCCA patients undergoing ALPPS procedure and the current literature consists of case reports and small single-center series including up to three patients [32–38]. Notably, some of these reports display significant perioperative mortality. Troya et al. reported one single patient who died in postoperative course as well as Vennarecci et al. who reported on two postoperatively deceased patients [32, 37].

The international ALPPS registry provides the largest multicentric ALPPS dataset, but the currently available reports comprise only small groups of iCCA patients. The first registry report by Schadde et al. included eight patients with iCCA, but outcome data were limited to 1-year DFS and 1-year OS [39]. A subsequent report from the registry included 13 iCCA patients but focused on perioperative outcomes and therefore did not provide an oncologic follow up [11]. Interestingly, the reported perioperative mortality of 15% exceeded our death rate (8.3%) but these numbers have to be interpreted with caution due to low sample sizes in both studies.

As with all clinical outcome studies, our analysis has limitations. We are not able to report on technical variations of ALPPS and the corresponding potential benefits, since all our patients underwent classic ALPPS. Also, our study is retrospective in nature and the analysis based on single-center data. The limited size of our patient cohort can be attributed to, firstly, the low incidence of iCCA and secondly, to the fact that ALPPS is an infrequently used procedure. Thus, the implications of our paper have to be interpreted with respect to the limited sample size and its retrospective nature. However, no multicentric analysis addressing this particular topic in iCCA are currently available in literature.

Conclusions

Despite the aforementioned limitations, our analysis represents the largest available single-center cohort of ALPPS in iCCA. We conclude that ALPPS is technically feasible in iCCA and shows an encouraging overall survival. Multicentric, prospective clinical trials in larger patient cohorts are warranted to confirm and validate our preliminary findings.

Authors' contributions All the authors contributed significantly to this manuscript and are in agreement with the content. The authors contributed as follows: Study conception and design: JB, GL, UPN. Acquisition of data: JB, ZC, IL, MD. Analysis and interpretation of data: PS, TFU, GL. Drafting of manuscript: JB, GL, UPN. Critical revision of manuscript: PS, PB.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was conducted at the UH-RWTH in accordance with the requirements of the Institutional Review Board of the RWTH-Aachen University. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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