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The Therapeutic Benefit of ALPPS Technique for Classically Described Marginal Irresectable Intrahepatic Cholangiocarcinoma Tumors: A Propensity Score Analysis

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Coordinator: Prof. Paolo Angeli
Supervisor: Prof. Umberto Cillo
Co-Supervisor: Ch.mo Associate. Prof. Jun Li

Ph.D. student: Mohamed Ezeldin Moustafa

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Introduction:

- (1.1) Definition and Epidemiology*:*

Cholangiocarcinoma (CC) refers to all tumors originating from bile duct epithelial cells. Adenocarcinoma represents more than 90% of Cholangiocarcinoma. Distinguished by its anatomical location, CCs are classified into intrahepatic, perihilar, or distal. Intrahepatic cholangiocarcinoma (IC) is located within the liver parenchyma and subdivided according to its growth pattern into: mass forming; peri-ductal and intra-ductal growing.[1-3] Mass forming subtype is the most common and presents as a solid nodule within the liver parenchyma. The intraductal subtype is the least common and least aggressive. Periductal infiltrating IC invade the liver parenchyma along portal structures and metastasize to hilar lymph nodes. In a Japanese series, a combined mass-forming–periductal-infiltrating tumor is an aggressive subtype. In western populations, this observation has not been reported.[4-8]

In a population-based data from United States; the incidence of IC is 1.5 times in men as in women with an average age of diagnosis of 50 years.[9] Despite its rarity, IC accounts for 20% to 25% of all CC and represents the second most frequent primary liver tumor after Hepatocellular carcinoma (HCC). The incidence of IC is increasing in western population with a reported incidence 2.1 per 100,000.[10-12]

Reports of annual increase of mortality rates have been published from Italian, German, Korean databases and globally reported by World Health Organization's database. [13-17] It is not yet well understood whether this increase due to recent increase in Hepatitis C incidence, due to increased tumor detection or attributable to recent changes in its staging system. However, no significant increase is reported in the proportion of smaller detected tumors. Therefore, there's no strong evidence to prove the correlation between the rise in incidence and early tumor detection.[18,19]

- (1.2) Predisposing Factors

Unfortunately, studies examining potential risk factors often do not differentiate between CC subtypes.[20,21] Although in most of diagnosed IC patients have not reported associated risk factors. Nevertheless, some case-controlled studies have reported Hepatitis B, C viral infection and liver cirrhosis as a significant risk factors for IC. Indeed, the impact and incidence of these risk factors is higher in HCC than for IC.[22-24] Less well-established local risk factors for IC include chronic biliary inflammation as in hepatobiliary flukes, primary sclerosing cholangitis, biliary tract cysts. Other general risk factors include diabetes, obesity, alcohol, tobacco smoking. Further studies are needed to verify the risk factors are potentially associated with IC. [25]

- (1.3) Staging and Prognostic Factors

In the 6th edition of American Joint committee on Cancer (AJCC), the staging system for IC was identical to Hepatocellular Carcinoma (HCC). This staging system did not include any clinical or pathological predictive factors which are related to IC exclusively. [26]

The first independent staging system for IC was published on 2010 by the AJCC in its revised 7th edition. Tumor number, vascular invasion, periductal invasion and lymph node metastasis status were identified as the main prognostic factors which influence survival after liver resection. Nathan et al have identified these factors as independent predictors of survival and proposed the new staging system in their retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER) database. As reported in his study, tumor size per se has no impact on survival. [27-28] Authors have reported that AJCC 7th edition can accurately discriminate outcome of patients with resectable IC and can predict the survival according to TNM staging system. [29]

Recently, the AJCC has released the 8th edition in which tumor size and number, vascular invasion, lymph node involvement and invasion of visceral peritoneum were major prognostic factors for IC. Periductal invasion has not been recognized a as a prognostic factor in the 8th edition. Tumor size was independent prognostic factor in absence of Lymph-vascular involvement. [30]

The 8th edition did not show any significant advantage over 7th edition in overall prognostic discrimination except for stage III and T3 lesions.[31]

- (1.4) Clinical presentation and diagnosis

Most of IC are asymptomatic in their early stages. Patients with IC are more likely to present with non-specific symptoms such as vague abdominal pain or discomfort. In advanced stages, IC is accompanied by weight loss, hepatomegaly and may present with a palpable abdominal mass. Biliary obstruction related symptoms are less frequent to occur in IC as in extrahepatic cholangiocarcinoma.[32]

IC may be incidentally diagnosed by cross-sectional imaging performed for other reason e.g. ultrasonography (US) or computed tomography (CT). On US, IC appears as a hypoechoic mass and possibly peripheral ductal dilatation. Dynamic CT scanning describes the location and extension of the lesion, lymph-vascular involvement and can help to distinguish between IC and HCC. Magnetic Resonant Cholangio-Pancreatography (MRCP) has higher sensitivity, specifity and better diagnostic accuracy than any imaging modality.[33-35] Invasive cholangiography such as Endoscopic Retrograde Cholangio-Pancreatography (ERCP) or Percutaneous Cholangiography (PTC) are recommended when palliative biliary decompensation is required.[36] Positron emission tomography (PET) is of limited role in diagnosis when CT or MRI imaging has been performed for diagnosis of IC. [37]

Liver core biopsy is recommended for definitive diagnosis of IC patients undergoing systemic chemotherapy, radiation therapy or for enrollment in a therapeutic clinical trial. For patients undergoing resection, liver biopsy is not recommended due to risk of tumor seedings. [38]

Tumor markers as Carbohydrate Antigen (CA) 19.9 and carcinoembryonic antigen (CEA) are of limited use in the clinical practice due to low sensitivity and specifity. They may be of diagnostic value as some studies have shown that CA 19-9 values greater than 100 U/ml were associated with worse recurrence-free survival after surgical resection.[39]

- (1.5) Treatment

Complete surgical resection (SR) is the gold standard treatment with potential curative intent for patients with IC. The National Comprehensive Cancer network (NCCN) guidelines has stratified non-metastatic IC patients into potential resectable and non-resectable cases.

For accurate staging, it highly recommends staging laparoscopy and regional lymphadenectomy.[41] Curative resection referred to achieving negative margin (R0) with adequate function future remnant liver volume (FLR). Ribero et al from the Italian Intrahepatic Cholangiocarcinoma Study group reported that margin status is a significant predictor of survival and recurrence. [42,43] R0 resection should be the goal of the surgical procedure regardless the local extension of the disease as it provides a better chance for prolonged survival, particularly in lymph node negative patients (N0). [44-46]

However, curative surgical resection remains challenging not only in terms of achieving negative margin but also to keep a sufficient FLR to avoid post-hepatectomy liver failure (PHLF). Plenty high volume Hepatobiliary centers have reported that, extended hepatectomy with/ without biliary reconstruction were performed in majority of IC cases due to extension, location or multifocality of the disease.[45,47-50]

In order to avoid PHLF due to small FLR after resection, different vascular manipulations have been performed in order to induce residual liver parenchyma hypertrophy. The first attempt attributed to Makuuchi in 1980, who invented the portal vein embolization (PVE) of the right portal vein branch to induce left lobe hypertrophy. [51] PVE could induce up to 70% increase in the standardized FLR within 6 weeks duration as reported by Kianmanesh et al.[52] The second attempt was developed by surgeons at Hospital Paul Brousse in Paris, France who have introduced the 1st "two-stage hepatectomy" concept in which sequential operations performed to stepwise resect multiple tumors allowing the liver to regenerate between procedures.[53] Daniel Jaeck from Strasbourg, France has utilized these techniques and routinely performed PVE after initial excision of left liver lobe tumors to achieve clean left lobe and afterwards performed a safe right or extended right hemihepatectomy. [54] This technique has been rapidly adopted by many surgeons but instead to PVE, portal vein ligation was performed alternatively in the first stage operation along with excision of left lobe tumors. Few weeks later, an extended right hepatectomy was performed.

Data have showed that PVL induce similar or better left lobe hypertrophy response. [55-57] However, the need for long intervals between interventions (6–12 weeks) allows progression of the disease that might postpone stage-2 hepatectomy. About 19 –33% of patients who undergo conventional 2 stage hepatectomy fail to undergo the second stage operation due to insufficient hypertrophy and/or tumor progression.[58-60]

In 2012, Schnitzbauer et al has introduced the initial novel experience of a 2-stage hepatectomy technique which was performed in 25 patients from 5 hepatobiliary German Centers. The novelty of this technique attributed to the in-situ split in the stage-1 hepatectomy. This approach combines liver partition (in-situ spilt) in the first operation with PVL followed by a second operation to remove the diseased part of the liver. The preliminary results, in terms of accelerated (6-20 days) FLR hypertrophy and R0 resection for classically described marginal non-resectable disease, were surprisingly promising.[61] Later on, this technique was widely practiced among hepatobiliary surgeons' community and known as *"Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy."* with the acronym ALPPS.[62-64]

Despite of its encouraging primary results, ALPPS procedure remains highly controversial. Some understandable concerns were raised due to high rates of morbidity and in-hospital mortality compared to conventional major hepatectomies. Authors recommended that ALPPS procedure should be performed strictly in trials and registries, namely in primary liver tumors. Others

reported that low morbidity and negligible mortality could be achieved with more strict risk adjustments and in colorectal liver metastasis patients. [65-67]

At present, the mid and long-term outcome of ALPPS procedures performed for IC patients remain unverified. No studies yet have been performed to investigate its long-term survival and oncological outcomes in comparison to the palliative chemotherapy. Therefore, we sought to retrospectively evaluate the therapeutic benefit of ALPPS procedure performed for Intrahepatic Cholangiocarcinoma patients with special emphasis on post-operative morbidity and early mortality.

2. Aim of Work

To evaluate the long-term therapeutic benefit of ALPPS procedure for Intrahepatic cholangiocarcinoma in terms of oncological outcome and overall survival, in comparison to palliative chemotherapy with special emphasis on morbidity and early mortality.

3. Patients and Methods

- (3.1) Study Design:

This is a longitudinal cohort multicenter study with prospective evaluation of long-term outcome of ALPPS procedure for IC patients in comparison to palliative chemotherapy (CTH).

- (3.2) Study population and Data collection:

a) ALPPS patients:

All adult patients with primary diagnosis of IC underwent ALLPS procedure during the period from July/2011 till January/2018, with either data recorded in ALPPS registry or from some other hepatobiliary centers not recorded in the registry, were included in the study. Patients with unknown survival or did not complete the 2nd stage hepatectomy were excluded from the survival analysis.

The International ALPPS Registry was set up in 2012 and is coordinately maintained by the Department of Surgery, University of Zurich, Switzerland, approved by the Cantonal Ethics Committee of Zurich (KEK 2013-0326) and is registered at ClinicalTrials.gov (NCT01924741). The registry serves as a data platform to prospectively collect the worldwide experience of this procedure using a web-based data capture system secuTrial (Interactive System, Berlin, Germany). Registry data were exported for the current analysis starting from November, 2017 till July, 2018.

About 25 hepatopancreatobiliary centers have participated in this study. Clinical investigators or directors of these units were invited to participate via e-mails or personal contacts. The participant centers are:

- Germany: University Hospital-Aachen, University Hospital-Tübingen; University Medical Center-Hamburg, University Hospital-Jena; University Hospital-Cologne; University medical center-Frankfurt; Neuperlach clinic-Munch; medical center-Barmbek; medical center-Karlsruhe.
- Italy: Padua University Hospital, San Raffaele Hospital-Milano, Polytechnic University of Marche-Ancona.
- Switzerland: University Hospital-Zurich
- China: Sun Yat-sen Memorial University Hospital
- Argentina: Hospital Italiano de Buenos Aires
- Turkey: Ankara University Hospital
- Czech Republic: Institute for Clinical and Experimental Medicine-Prague.
- Spain: Virgen de la Arrixaca University Hospital, Madrid Sanchinarro University Hospital.
- Sweden: Linköping University Hospital
- Canada: Western University Hospital in London-Ontario
- Belgium: Gent University Hospital.
- France: Hospital Paul Brousse-Villejuif
- Japan: Matsuyama Red Cross Hospital
- Russia: Scientific Center of FMBA-Moscow.

b) CTH patients:

All adult patients in the Surveillance, Epidemiology, and End Results (SEER) database diagnosed with primary IC who received CTH as a palliative treatment and didn't undergo surgical resection but between January.2010 till December.2013 were included. Patients with unknown survival or non-pathology evidence were excluded from the study.

The SEER database is issued by the National Cancer Institute (NCI) (www.seer.cancer.gov) in the United States and collects data from 18 population-based cancer registries covering approximately 28% of the US cancer population. The SEER*Stat statistical software, version 8.3.2 was used in this study. We would like to underline that SEER database administration does not provide chemotherapy data automatically. A special request was submitted to retrieve these data independently. The chemotherapy data represented as (Yes, No/unknown). The chemotherapy regimens are not described in detail as regard CTH regime, response rate, recurrence rate or associate complications

- <u>(3.3) Variable definitions:</u>

a) ALPPS Patients:

Data on patient demographics, comorbidities, liver parenchyma (normal vs. diseased: histology evidence of liver steatosis, fibrosis or cirrhosis), volumetric data, procedure details, tumor pathology, complications, follow up, survival, and recurrence were provided by ALPPS registry and participating centers and were exported into a Microsoft Excel table.

b) CTH Patients:

Patients with a primary IC were identified according to the International Classification of Diseases for Oncology, 3rd Edition, ICD-O-3/WHO 2008. TNM staging was derived from the 7th editions of the AJCC Staging System. The SEER Program Coding and Staging Manual (2015) was used to select the study population, i.e. the primary site code "C22.1" for the intrahepatic bile duct, ICD-O-3 histology/behavior code "8160/3" for cholangiocarcinoma. The codes for tumor size, extension, multifocality, and vascular invasion, the data on lymph node metastases, were interpreted using the Collaborative Stage data set. (http://web2.facs.org/cstage0205/liver/Liverschema.html)

- (3.4) Outcome assessment

The main outcome was mortality which is subclassified into early mortality (90-day mortality), and disease related or non-related mortality. Overall survival (OS) was defined from the date of the 2nd stage hepatectomy until death or August 2018. Complications were identified according to liver surgery specific clinical endpoints (CEP). The five elements of CEP beside mortality are post hepatectomy liver failure (PHLF), ascites, biliary complications, infection and post hepatectomy haemorrhage (PHH).[68] Complications were presented according to the definitions of the International Study Group of Liver Surgery (ISGLS) and the Dindo-Clavien classification.[69-72] We defined severe complications as a Dindo-Clavien grade IIIb or greater with in-hospital mortality included.

Oncological results, which are sub-classified short term represented by free tumor resection margin (R0) and mid, long-term which represented by recurrence rate, risk of recurrence and time to recurrence. Time to recurrence was determined from the hepatectomy until recurrence at any site (hepatic or extra-hepatic). Long-term outcomes of all patients were retrospectively analyzed. Further outcome parameters included volumetry study which is represented by FLR and FLR over body weight (FLR/BW). The median values of FLR/BW after stage-1 and stage-2 hepatectomies were utilized as a cut-off values for logistic regression analyses. We would like to underline that, the represented percentages in the result section exclude the missing values.

- (3.5) Statistical analysis

Continuous variables are expressed as median (minimum-maximum) and were analyzed by the Mann-Whitney U test. Categorical-nominal variables are presented as a number (percentage) and were analyzed by the C2 or Fisher's exact tests, as appropriate. For the ALPPS group, Uni- and multivariate logistic regression analyses were performed to verify risk factors for severe complications and univariate logistic regression for 90-day mortality cases.

The Kaplan Meier method was utilized to calculate overall survival and recurrence, and the Log-rank test was used to assess difference between curves. Cox proportional hazard regression was performed to evaluate risk factors associated with prognosis. Variables with $p<0.1$ in the univariate analysis were further included in the multivariate Cox proportional hazards regression analysis

with a stepwise forward conditional selection. Based on the propensity score (PS), one-to-one nearest neighbor matching with replacement was adopted to overcome selection bias and minimized difference between CTH group and ALPPS group. The propensity score calculated by a logistic regression model represent the probability of each patients being assigned to each treatment. The variables included in this model were: Age, Gender, Stage, N status. The use of PS analysis along with multivariate cox proportional hazard modeling have proved to be beneficial to adjust for confounders in small datasets in terms of be less biased, more robust, and more precise than standard multivariable methods. The number of enrolled patients in the propensity score analysis might be minimized according to missing values and to achieve patients' matching. Two-tailed $p<0.05$ values were considered statistically significance and all statistical calculations were performed using SPSS version 21.0 (Chicago, IL).

4. Results:

- 4.1 Demographics and Patients' Characteristics:

a) ALPPS group

Out of 86 patients undergoing ALPPS procedure between July/2011 till January/2018, 84 patients have completed the 2nd stage hepatectomy. Two patients didn't undergo 2nd stage hepatectomy due to insufficient FLR. The median age was 65 years old ranging from 35 to 80 and around 47.6% above 65 years (n=40). Female patients represented 59 % (n = 50). (Table.1)

The median value of body mass index (BMI) was 25.3 ranging from 16.3 to 38.3. Diabetes mellitus presented in 12% of the patients, other comorbidities e.g. hypertension or obstructive lung disease was diagnosed in 14 %. Neoadjuvant CTH was given in 7 patients. Radiological interventions were performed in 5% of the patients prior to ALPPS. Only one patient underwent major abdominal surgery prior to ALPPS procedure. (Table.2)

By preoperative radiological evaluation, 73.2% of the patients had a single lesion centrally located (n=60); 19.5% of the patients had multiple tumors located in right liver lobe required extended right hepatectomy (n=16) and 7% of the patients had bilobar tumors required clearance of FLR and right or extended right hepatectomy (n=6). According to surgeons' assessment, 97% of the cases had insufficient FLR (n=81). (Table.2)

b) CTH group

In SEER database, 484 patients were diagnosed with primary IC. 453 with pathological diagnostic confirmation of IC. Around 46% above 65 years (n=208). Female patients represented 55.4 % (n = 251). Based on the AJCC 7th edition, Stage I represents 21.2% (n=96), stage II represents 27.4% (n=124). Stage III and IV a represent 35.4% (n= 160). Unknown staging was reported in 16% of the patients (n=73). Majority of CTH group patients (44.6%) presented with T2 lesions (n=202). Regional lymph node metastasis was reported in 25.2% (n=114). 90-day mortality after CTH treatment was reported in 13.9% (n=63). Overall mortality was reported in 64.9% (n= 294). Other demographics and clinico-pathological characteristics are presented in table 1.

Table no.1: Patients' characteristics and demographic data			
Variable	**Categorization**	**CTH Group (453)**	**ALPPS Group (84)**
Age	continuous	64 (26-85)	65 (35-80)
	<65	244 - 53,9%	44 - 52,4%
	>65	208 - 46,1%	40 - 47,6
Gender	F	251- 55,4%	50 - 59,2%
	M	202 - 44,6%	34 - 40,8%
Grade	G1	16 - 3,5%	6 - 7,1%
	G2	63 - 13,9%	43 - 51,2%
	G3	84 - 18,5%	28 - 33,3%
	Missing value	290 - 64,1%	7 - 8,4%
Stage	I	96 - 21,2%	6 - 7,1%
	II	124 - 27,4%	33 - 39,3%
	III	27 - 6%	7 - 8,4%
	IVa	133 - 29,4%	34 - 40,5%
	Missing value	73 - 16%	4 - 4,7%
T	T1	129 - 25,8%	9 - 10,4%
	T2	202 - 44,6%	55 - 65,5%
	T3	46 - 10,1%	15 - 17,9%
	T4	32 - 9,8%	1 - 1,5%
	TX	44 - 9,7%	4 - 4,7%
N	N0	272 - 60%	48 - 57,1%
	N1	114 - 25,2%	33 - 39,3%
	NX	67 - 14,8%	3 - 3,6%
M	M0	453 - 100%	81 - 100%
	M1	0 - 0%	0 - 0%
	MX	67 - 14,8%	3 - 3,6%
Size	continuous	70 (5-200)	85 (6-260)
90-day Mortality	N	390 - 86,1%	66 - 78,6%
	Y	63 - 13,9%	16 - 19%
Mortality	N	159 - 35,1%	47 - 55,9%
	Y	294 - 64,9%	35 - 41,7%
	Missing value	0 - 0%	2 - 2,4%

- Missing data were excluded from percentage

Table 2: Co-morbidities and Diagnostics for ALPPS patients		
Variable	**Categorization**	**All patients = 86**
• **BMI**		25,3 (16,3-38,3)
• **DM**	Yes	10/84 – 11,9%
• **Other Comorbidities**	Yes	12/86 – 13,9%
• **Previous Major Surgery**	Yes	1/86 – 1,2%
• **Neoadjuvant CTH**	Yes	7/85 – 8,1%
• **Previous radiology intervention**	Yes	4/82 – 4,9%
• **Tumor Location**	single lesion centrally located	60/82 – 73,2%
	multiple tumors located in right liver lobe requiring extended right hepatectomy	16/82 – 19,5%
	Bilobar tumors requiring clearance of FLR and right or extended right hepatectomy	6/82 – 7,3%
• **Surgeon Decision**	neither volume nor function of FLR is sufficient	81/83 – 98,6%
	volume enough but functional FLR is not sufficient	2/83 – 2,4%

- Missing data were excluded from percentage

- (4.2) procedure details:

a. Stage-1 Hepatectomy

About 18.8% of the patients (n=16) received blood transfusion during the operation. Lymphadenectomy was performed in 64.2% of the patients (n=52/81) The duration between the 2 stages was ranging from 3 to 49 days (median value = 11 days) and the average post-operative intensive care unit (ICU) admission ranged from 0 to 13 days (mean = 1 day).

b. Stage-2 Hepatectomy

About 30.3% of the patients (n=20) received blood transfusion during the second operation. Lymphadenectomy was performed in 23.4% of the patients (n=18). The average post-operative ICU admission ranged from 0 to 40 days (median value = 1 day).

Table. 3: Procedure Details	
1st stage Hepatectomy	
Variable	All patients = 86
Days between 1st and 2nd stage	11 (3-49)
RBC transfusion	16/85 – 18,8%
Lymphadenectomy performed	52/81 – 64,2%
PO ICU days	1 (0-13)
2nd stage Hepatectomy	
Variable	All patients = 84
Days between 1st and 2nd stage	11 (3-49)
RBC transfusion	20/66 – 30,3%
Lymphadenectomy performed	18/77 – 23,4%
PO ICU days	1 (0-40)

- Missing data were excluded from percentage

- (4.3) Volumetry Study Results

The median FLR volume before stage one operation was 328 ml (128-664). The median FLR/ body weight (BW) ratio of stage one operation was 0.46 (0.19-0.84). The median FLR volume before stage two was 547 ml (270-933 ml). The FLR/ body weight (BW) ratio ranged from 0.35 to 1.51 (median = 0.84). The Delta FLR between the first and second operations ranged from 13 ml to 504 ml (median= 234 ml). Delta FLR/BW ratio ranged from 0.02 to 0.94 (median=0.32). (Table 4)

Table. 4: Volumetry study	
Variabile	**Values**
FLR stage 1	328 (128-664). ml
FLR/BW stage 1	0.46 (0.19-0.84).
FLR stage 2	574 (270 – 933). ml
FLR/BW stage 2	0,84 (0.35-1.51)
Delta FLR stage 1-2	234 (13-504). ml
Delta FLR/BW ratio stage 1-2	0.32 (0.02-0.94)

- (4.4) Histopathology Assessment.

Among studied population, adenocarcinoma was reported in 91.5% (n=75). Negative margin was achieved in 86.4% (n=70). Based on the 7th edition of AJCC staging system, stage I was reported in 7.8% (n=6), stage II in 41% (n=33), stage III in 8.7% (n=7) and stage IVa reported in 42.5% (n=34). Lymph node was positive in 40.7% (n=33). Multifocality was reported in 39,8% (n=33). According to degree of differentiation; well differentiated tumor (Grade I) was reported in about 8% of the patients (n= 6) while moderate differentiated (Grade II) was seen in 56% (n=43). Poor differentiation was reported in 36% (n=34). Normal liver parenchyma was documented in 62.5% (n=45). A Detailed list of histo-pathological features is shown in Table no. 5.

Table. 5: Histopathology assessment		
Variable	**Definition**	**Number and Percentage All patients = 84**
Histology	Adenocarcinoma	75/82 – 91,5%
	Other	7/82 – 8,5%
Margin	negative of tumor	70/81 – 86,4%
	positive of tumor	11/81 – 13,6%
Grading	I	6/77 – 7,8%
	II	43/77 – 55,8%
	III	28/77 – 36,4%
Stage 7th edition AJCC	I	6/80 – 7,8%
	II	33/80 – 41,2%
	III	7/80 – 8,7%
	IVa	34/80 – 42,5%
T 7th edition AJCC	T1	9/80 – 11,2%
	T2	35/80 – 43,7%
	T2a	6/80 – 7,8%
	T2b	14/80 – 17,5%
	T3	15/80 – 18,7%
	T4	1/80 – 1,1%
N	N0	48/81 – 59,3%
	N1	33/81 – 40,7%
Metastasis	M0	83/83 – 97,6%
	M1	0/83 – 2,4%
Multifocal lesion	N	50/83 – 60,2%
	Y	33/83 – 39,8%
Largest tumor size (mm)		85 (6-260)
Liver Parenchyma status	Normal	45/72 – 62,5%
	Fibrosis	17/72 – 23,1%
	Steatosis more than 30%	6/72 – 8,3%
	CASH	3/72 – 4,2%
	Cirrhosis	1/72 – 1,9%

- Missing data were excluded from percentage

- (4.5) Survival analysis and Recurrence:

a) Before propensity score analysis:

For ALPPS group (n= 82), the median follow-up was 10.7 months (0-36). The median overall survival (OS) was 27.6 months. The 1,2,3-year survival rates were 67,8%, 60.3% and 41%. For CTH group (n=453), the median follow-up was 8 months (0-36). The median OS was 10 months. The 1,2,3-year survival rates were 43,8%, 18.3% and 5.6%. (p value < 0.001- table 6 and fig. 1). After exclusion the 90-day mortality from the analysis, survival rates were superior in ALPPS group in comparison to CTH group. (table 7 and fig. 2).

b) After propensity score analysis:

For ALPPS group (n=79), the median OS was 27.6 months. The 1,2,3-year survival rates were 68,1%, 60.1% and 40.8%. For matched group of CTH patients (n=79), the median OS was 12 months. The 1,2,3-year survival rates were 49,7%, 18.4% and 9.2%. (p value < 0.004- table 8 and fig. 3). After exclusion the 90-day mortality from the analysis, survival rates and OS were superior in ALPPS group in comparison to CTH group. (table 9 and fig. 4).

During study period recurrence rate was 57.5% (n=46/80). Hepatic recurrence rate was reported in 48.7% (n=37) while extrahepatic recurrence was detected in 32.4% (n=23). The risk of local or extrahepatic recurrence after liver resection was 61%, 75% and 86% for the 1st, 2nd and 3rd year respectively. The median time to recurrence was 8.2 months ranging from 6.4 to 10 months as documented in tables 10a-c and figures 5a-c.

Figure 1: OS in all patients before PS

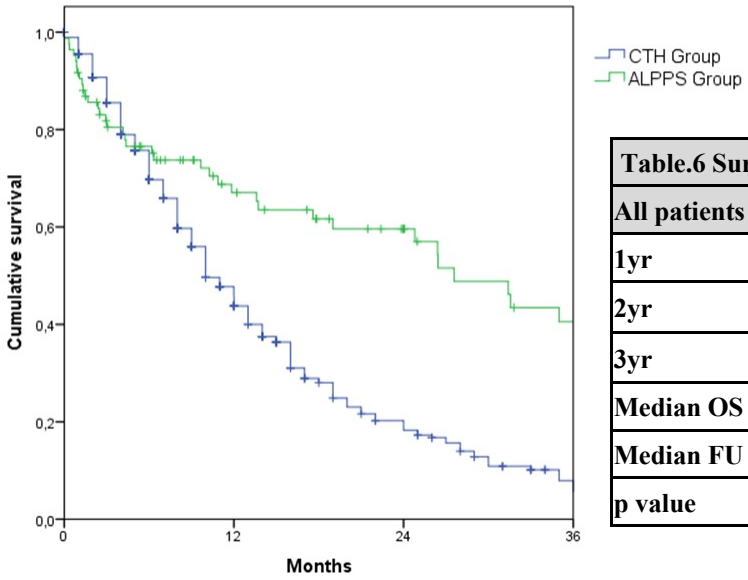


Table.6 Survival Rates before propensity analysis		
All patients	**CTH Group (453)**	**ALPPS Group (82)**
1yr	43,80%	67,80%
2yr	18,30%	60,30%
3yr	5,60%	41,00%
Median OS	10,00	27,60
Median FU	8 (0-36)	10,7 (0-36)
p value	<0,001	

Figure 2: OS before PS after exclusion 90-Day mortality patients.

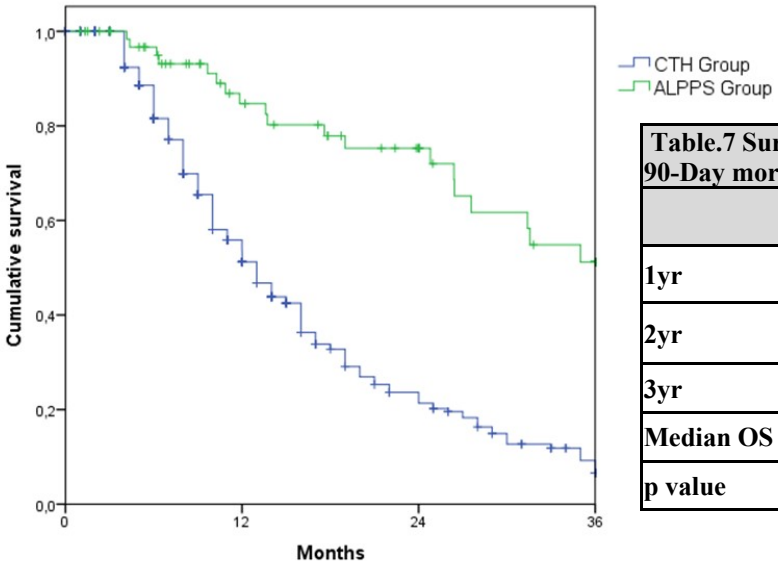


Table.7 Survival Rates before propensity analysis 90-Day mortality nor included		
	CTH Group (390)	**ALPPS Group (66)**
1yr	51,20%	84,70%
2yr	21,40%	75,30%
3yr	6,60%	51,20%
Median OS	13,00	-
p value	<0,001	

Figure 3: OS in all patients after PS

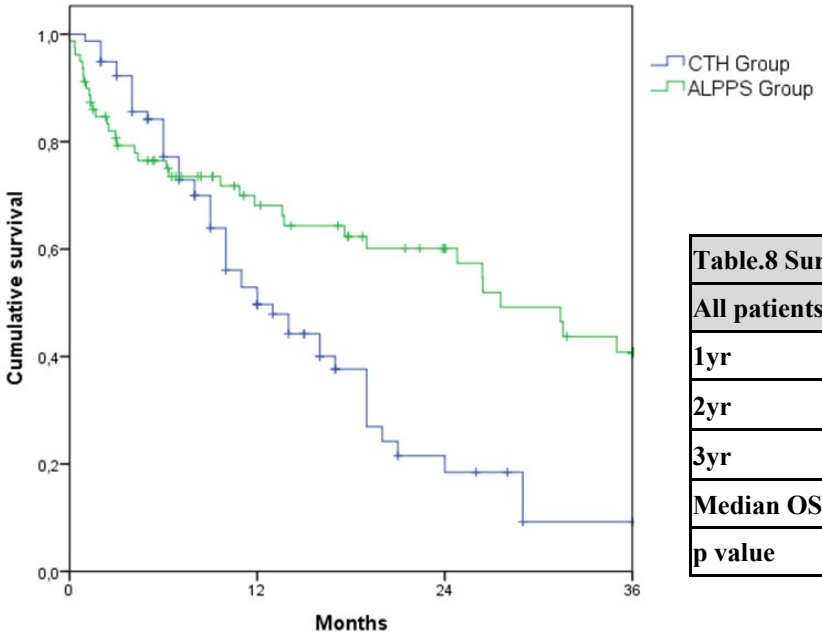


Table.8 Survival Rates after propensity analysis		
All patients	**CTH Group (79)**	**ALPPS Group (79)**
1yr	49,70%	68,10%
2yr	18,40%	60,10%
3yr	9,20%	40,80%
Median OS	12,00	27,60
p value	0,004	

Figure 4: OS in after PS after exclusion 90-Day mortality patients

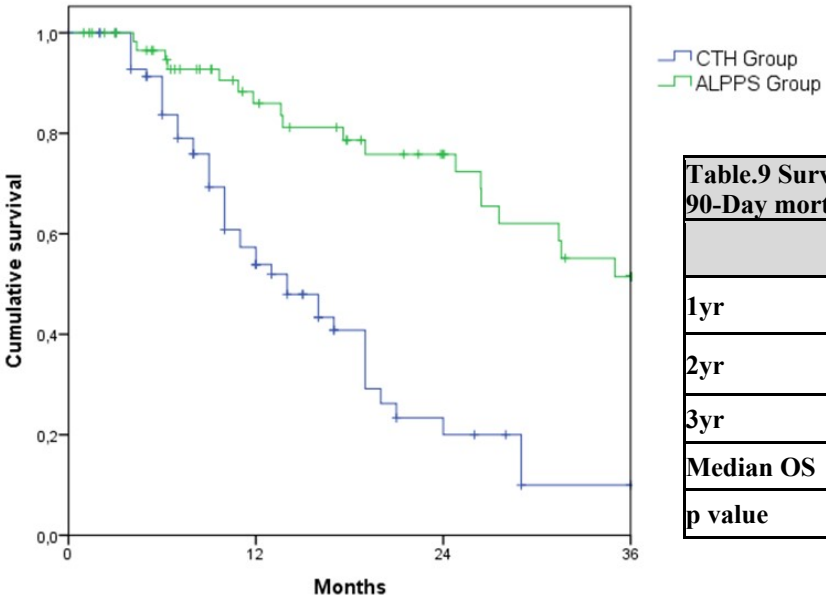


Table.9 Survival Rates after propensity analysis 90-Day mortality nor included		
	CTH Group (73)	**ALPPS Group (63)**
1yr	53.90%	85.90%
2yr	20.00%	75.80%
3yr	10.00%	51.50%
Median OS	14.00	-
p value	<0,001	

Figure 5a: Risk of recurrence Intrahepatic

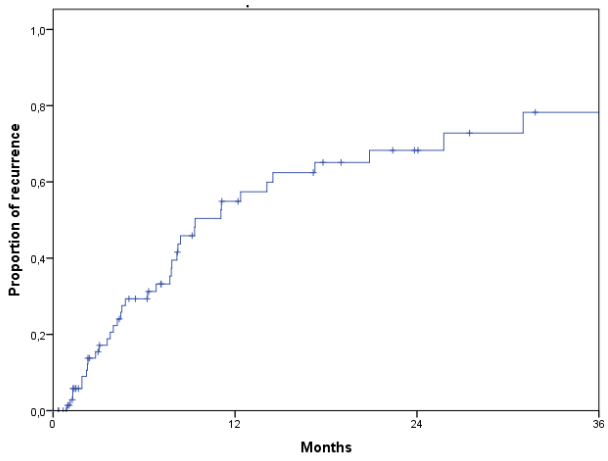


Table 10a: Risk of recurrence Intrahepatic	
year	ALPPS Group (76)
1yr	54.9%
2yr	68.3%
3yr	78.2%
Time to Recurrence	9,4 (5,2-13,5)

Figure 5b: Risk of recurrence Extrahepatic

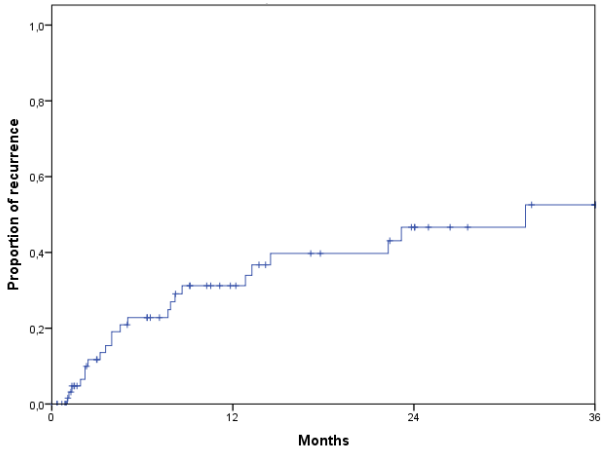


Table 10b: Risk of recurrence Extrahepatic	
year	ALPPS Group (71)
1yr	31.2%
2yr	46.6%
3yr	52.6%
Time to Recurrence	31.4 (13,3-36)

Figure 5c: Risk of recurrence Intrahepatic

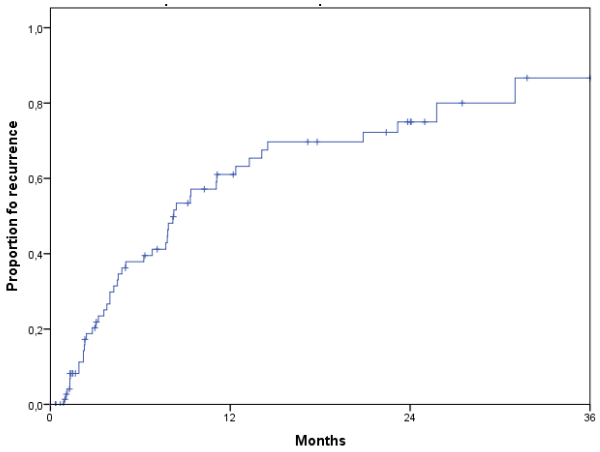


Table 10c: Risk of recurrence any where	
year	ALPPS Group (71)
1yr	61%
2yr	75%
3yr	86.7%
Time to Recurrence	8.2 (6.4-10)

- (4.6) Overall survival prognostic factors:

In order to identify prognostic factors, those independently affect survival, univariate then multivariate COX regression survival analyses were performed.

a) Univariate COX regression analysis (table.11A):

Poor prognosis has been reported in male patients (p=0.02, HR=2.2, 95% CI), above 60 (p=0.04, HR=2.3, CI 95%), with ICU admission > one day post-operative stage-1 (p=0.05, HR=1.9, CI 95%). Factors related to post stage-2 operation with poorer prognosis were; post-operative ascites (p=0.065, HR= 2.2, CI 95%), infection (p=0.04, HR= 2.0, CI 95%) and / or complications classified as Dindo-Clavien ≥ 3b (p=0.03, HR= 2.0, CI 95%). Lymph node metastasis was the only reported pathological feature with a poor prognosis (p=0.01, HR=2.4, CI 95%).

b) Multivariate COX regression analysis (table.11B):

In multivariate module, poor prognosis has been reported for cases developing infection post 2nd stage hepatectomy (p=0.03, HR=2.1, CI= 95%) and/or positive lymph node metastasis (p=0.007, HR=2.7, CI95%). All other considered covariables were statistically not significant.

Table. 11: Univariate and Multivariate COX regression for overall survival				
A. Univariate analysis				
Demogarphics pre-operative and Variables	**P value**	**HR**	**95% CI**	
Age	,005	1,061	1,018	1,105
AGE > 60	,041	2,371	1,036	5,428
AGE > 65	,129	1,678	,860	3,273
Gender: Male	,023	2,200	1,116	4,336
BMI	,651	,982	,910	1,061
BMI>25	,575	1,212	,620	2,370
BMI>30	,198	,459	,140	1,502
*ASA>3	,123	1,813	,850	3,865
Co-morbidity (Y)	,666	1,190	,541	2,615
DM (Y)	,967	1,022	,361	2,893
Neoadjuvant_Chemotherapy (Y)	,580	,668	,160	2,786
Preoperative radiological intervention (Y)	,340	,380	,052	2,779
Tumor distribution single centrally located lesion (Baseline)	,427			
Tumor distribution: Multifcoal in Rt lobe	,202	1,652	,764	3,574
Tumor distribution: Biloblar, Multifocal	,597	1,333	,458	3,878
Stage-1 Variabels	**P value**	**HR**	**CI 95%**	
Stage_1_RBC_transfusion(Y)	,874	1,066	,485	2,343
lymphadenectomy_Stage_1(Y)	,414	1,360	,650	2,845
**Post_stage1_Intensice Care Unit/days	,004	1,208	1,063	1,373
Post_stage1_Intensice Care Unit/days >1	,051	1,923	,996	3,714
Liver Failure Stage 1 (Y)	,969	1,021	,355	2,935
Ascites Stage-1 (Y)	,707	1,228	0,421	3,588
Haemorrhage Stage 1 (Y)	,361	,661	,273	1,604
Infection Stage 1 (Y)	,204	1,777	,732	4,316
Biliary complications Stage-1 (Y)	,138	,407	,124	1,336
Dindo-Clavien Stage 1≥3a	,477	1,377	,570	3,325
Dindo-Clavien 1≥3b	,990	,987	,134	7,257
Days_between_1st_and_2nd_stage_operation	,544	1,013	,971	1,058
Days_between_1st_and_2nd_stage_operation>11	,414	1,320	,678	2,570
Stage-2 Variabels	**P value**	**HR**	**CI 95%**	
Post_stage_2_Intensice Care Unit_days	,000	1,075	1,033	1,119
Post_stage_2_Intensice Care Unit_days>1	,259	1,483	,748	2,938
Stage_2_op_RBCs_Transfusion(Y)	,268	1,567	,708	3,469
Stage_2_lymphadenectomy(Y)	,545	,744	,285	1,943
Liver Failure Stage 2 (Y)	,613	1,212	,576	2,550
Ascites Stage-2 (Y)	,065	2,257	,950	5,364

Haemorrhage Stage 2 (Y)	,364	1,387	,684	2,814
Infection Stage 2 (Y)	,040	2,029	1,031	3,992
Biliary complications Stage 2 (Y)	,600	,825	,403	1,689
Dindo-Clavien Stage 2≥3a	,110	1,739	,882	3,429
Dindo-Clavien Stage 2≥3b	,038	2,035	1,039	3,986
Volumetry study Variabels	**P value**	**HR**	**CI 95%**	
FLR_clean_stage_1	,882	1,000	,997	1,003
FLR/BW_stage_1	,735	,658	,058	7,429
FLR/BW_stage_1>0,46	,857	1,070	0,514	2,225
FLR_stage_2	,390	,999	,997	1,001
FLR/BW_stage_2	,265	,427	,096	1,905
FLR/BW_stage_2>0,84,	,417	0,755	0,383	1,488
Pathological features Variabels	**P value**	**HR**	**CI 95%**	
Margin positive of tumor	,496	,718	,276	1,866
Grading G1 (Baseline)	,351			
Grading G2	,244	,521	,174	1,562
Grading G3	,699	,800	,259	2,475
AJCC 7th Stage I (Baseline)	,063			
AJCC 7th Stage II	,362	,550	,152	1,988
AJCC 7th Stage III	,394	,457	,075	2,769
AJCC 7th Stage IVA	,540	1,467	,430	5,003
T1 (Baseline)	,951			
T2	,580	1,405	,421	4,684
T3	,597	1,441	,372	5,584
T4	,703	1,558	,160	15,163
N1	,011	2,453	1,228	4,900
Multifocal lesion (Y)	,700	1,142	,583	2,237
Largest_tumor_size_mm	,337	1,004	,996	1,012
Largest_tumor_size>85	,170	1,606	,816	3,162
liver parenchyma histology result - Not normal	,608	1,213	0,58	2,538
B. Multivariate Analysis				
Variabels	**P value**	**HR**	**95% CI**	
Infection Stage 2 (Y)	0,039	2,134	1,038	4,388
Dindo-Clavien Stage 2≥3b	0,173	1,636	0,806	3,319
N1	0,007	2,724	1,312	5,652

*ASA: American Society of Anesthesiologists score,

- (4.7) Post-operative Complications (table.12-Fig.6)

a) Post Stage-1 Hepatectomy

According Dindo-Clavien classification; 8.5% of the patients had score =3a (n= 7/82), while only 4.9% (n=4/81) had Dindo-Clavien score ≥ 3b. No mortality was reported after stage 1. More details are shown in table 12.

b) Post Stage-2 Hepatectomy

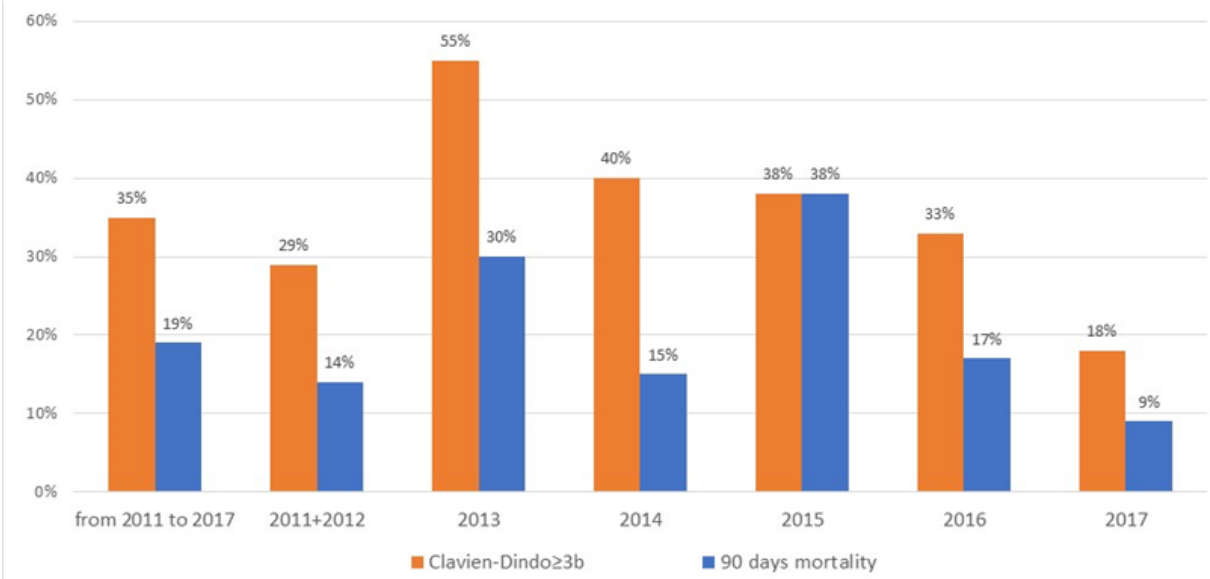
According Dindo-Clavien classification; 18.5% of the patients had Dindo-Clavien score = 3a (n=15/81), score while 34.5% had Dindo-Clavien score ≥ 3b (n=28/81). According to ISLGS grading system 13.4 % of the patients (n=9/67) have developed PHLF classified as grade C. 27.3% of the patients (n=15) has developed ascites > 1000ml/ day after day-7 which required medical treatment. Sever infection classified as Dindo-Clavien grade IIIb was reported in 9% (n=7/77). 13% of the patients has a reported infection with no further details revealed (n=10). Biliary leakage reported in 9 % of the patients which is classified as grade C according to ISLGS grading system (n=7). 12.8% of the patients developed biliary complications with no further details revealed. PHH that require re-operation has been reported in 3 patients only.

During the study period, mortality rate was reported in 43% of the studied population. 90-day mortality rate was reported in 19% of the cases (n= 16). 90-D mortality rates / year were 30%, 38% and 9% in 2013, 2015 and 2017 respectively. (Fig. 6)

Table. 12: Post-operative Complications (stage1-2)			
Complications	**Grade Definition (ISGLS or Dindo-Clavien)**	**Post stage-1 patients = 86**	**Post stage-2 patients =84**
Liver Failure (ISLGS grade)	No Reported PHLF	59/67 – 88,1%	43/67 – 64,2%
	Grade A (Elevated bilirubin and INR, no treatment)	06/67 – 8,9%	08/67– 11,9%
	Grade B (infusion of albumin, FFP)	02/67 – 3%	09/67 – 13,4%
	Grade C (ICU treatment or surgery)	00/67 – 0%	07/67 – 10,5%
Ascites	Not reported or less than 500 ml	51/60 – 85%	28/55 – 50,9%
	over 500 ml without medical treatment	06/60 – 10%	06/55 – 10,9%
	less than1000 ml after day 7 with medical treatment	01/60 – 1,7%	06/55 – 10,9%
	more than 1000 ml after day 7 with medical treatment	02/60 – 3,3%	15/55 – 27,3%
	reported as ascites with no further detail	0/60 – 0%	0/55 – 0%
Haemorrhage (ISGLS grade)	No transfusion required	59/78 – 75,6%	52/77 – 67,5%
	Grade A: transfusion up to 2 Units of RBC	04/78 – 5,1%	06/77 – 7,8%
	Grade B: transfusion more than 2 Units of RBC	02/78 – 2,6%	04/77 – 5,2%
	Grade C: intervention or reoperation	01/78 – 1,3%	03/77 – 3,9%
	reported as haemorrhage with no further detail	12/78 – 15,4%	12/77 – 15,6%
Infection (Dindo-Clavien)	No Reported infection	68/77 – 88,3%	49/77 – 63,6%
	Grade II Dindo-Clavien (medications)	08/77 – 10,4%	07/77 – 9,1%
	Grade IIIa (interventional)	01/77 – 1,3%	04/77 – 5,2%
	Grade IIIb and more (re-OP or ICU)	00-/77– 0%	07/77 – 9,1%
	reported as infection with no further detail	00/77 – 0%	10/77 – 13%
Biliary Leakage (ISGLS grade)	No reported leakage	69/79 – 87,4%	50/78 – 64,1%
	grade A (observation till day 7 with existing drainage	07/79 – 8,9%	04/78 – 5,1%
	grade B (leak more than 7 days or needs intervention)	03/79 – 37%	07/78 – 9%
	grade C (re-operation, or ICU)	00/79 – 0%	07/78 – 9%
	reported as biliary complication with no further detail	00/79 – 0%	10/78 – 12,8%

- Missing data were excluded from percentage
- Some complications were reported as Dindo-Clavien ≥ 3b without further details.

Figure 6: Morbidity and 90-day mortality rates / year



- (4.8) Risk Factors for Severe Complications (Clavien-Dindo ≥3B)

To verify risk factors for complications graded as Clavien-Dindo ≥3b, univariate and multivariate logistic regression analyses has been conducted to the parameters demonstrated in table 13.

a) Univariate logistic regression: (Table 13)

Statistically significant risk factors were; age > 65 years (p=0.005, ODDS =3.9, CI95%), blood transfusion during 1st stage operation (p=0.09, ODDS=2.6, CI 95%), PHH stage-1(p= 0.09, ODDS=2.5, CI 95%) and/ or prolonged ICU admission >1day post stage-1 (p=0.08, ODDS=2.2, CI 95%).

Risk factors related to 2nd stage hepatectomy were; prolonged ICU admission >1day (p=0.01, ODDS=2.5, CI 95%), PHH (p=0.001, ODDS=5.9, CI 95%), PHLF (p=0.04, ODDS=2.9, CI 95%), post stage-2 infection (p=0.0031, ODDS=4.5, CI 95%).

Patients with; FLR/BW>0,46 post stage-1(p=0.05, ODDS=0.3, CI 95%) and/or FLR/BW>0,84 post stage-2 (p=0.01, ODDS=0.2, CI 95%) are less likely to develop sever complications.

b) multivariate logistic regression analysis: (table. 13B)

A patient age > 65 years old (p=0.03, ODDS =3.9) and post stage-2 infection (p=0.049, ODDS=3.1) were statistically significant risk factors.

Patients with FLR/BW>0,46 post stage-1 (p=0.09, ODDS=.03) are less likely to develop sever complications by multivariate logistic.

Table 13: Univariate and Multivariate Logistic Regression for Dindo-Clavien ≥3b				
A- UNIVARIAT ANALYSIS for Dindo-Clavien ≥3b				
Demogarphics and co-morbidity Variabels	**p value**	**ODDS**	**95% CI**	
Age	,009	1,073	1,018	1,131
AGE>65	**,005**	**3,977**	**1,513**	**10,453**
Male	,119	2,083	,827	5,248
BMI	,540	1,035	,926	1,157
BMI>25	,542	1,333	,529	3,363
BMI>30	,361	1,753	,526	5,843
*ASA score>3	,391	1,571	,559	4,414
Comorbidity (Y)	,878	1,087	,374	3,158
DM (Y)	,792	1,200	,309	4,658
Neoadjuvant CTH(Y)	,728	,738	,134	4,074
Pre-operative radiology intervention(Y)	,562	1,815	,242	13,619
Stage-1 Variabels	**P value**	**ODDS**	**95% CI**	
Stage_1_RBC_transfusion(Y)	,097	2,629	,839	8,237
lymphadenectomy_Stage_1(Y)	,402	,667	,258	1,721
Post_stage1_Intensive Care Unit admission_ days	,017	1,293	1,046	1,599
Post_stage1_Intensive Care Unit admission_ days>1	**,086**	**2,256**	**,890**	**5,720**
PHLF Stage 1 (Y)	,841	1,170	,253	5,401
Ascites Stage 1 (Y)	1,000	1,000	,222	4,496
Post hepatectomy haemorrhage Stage 1 (Y)	**,094**	**2,562**	**,851**	**7,713**
Infection Stage 1 (Y)	,501	1,558	,429	5,662
Biliary complications Stage 1 (Y)	,262	,394	,078	2,003
Days_between_1st_and_2nd_stage_operation	,428	1,022	,968	1,079
Days_between_1st_and_2nd_stage_operation>11days	,387	1,498	,599	3,746
Stage-2 Variabels	**P value**	**ODDS**	**95% CI**	
Post_stage_2_ Intensive Care Unit admission _days	,016	1,192	1,033	1,376

Post_stage_2_ Intensive Care Unit admission _days>1	**,055**	**2,595**	**,982**	**6,858**
Stage_2_op_RBCs_Transfusion(Y)	,257	1,870	,634	5,517
Stage_2_lymphadenectomy(Y)	,417	1,560	,533	4,569
PHLF Stage 2 (Y)	**,047**	**2,909**	**1,015**	**8,341**
Ascites Stage 2 (Y)	,337	1,765	,554	5,620
PHH Stage 2 (Y)	**,001**	**5,926**	**2,093**	**16,778**
Infection Stage 2 (Y)	**,003**	**4,500**	**1,671**	**12,120**
Biliary complications Stage 2 (Y)	,150	2,022	,776	5,270
Other Variabels	**P value**	**ODDS**	**95% CI**	
FLRBW_stage_1>0,46	**,055**	0,362	0,128	1,021
FLRBW_stage_2>0,84	**,015**	0,287	0,105	0,783
liver parenchyma histology result – diseased parenchyma	,513	1,403	0,509	3,869
B- MULTIVARIAT ANALYSIS for Dindo-Clavien ≥3b				
Variabels	**p value**	**ODDS**	**95% CI**	
AGE>65	,030	3,900	1,145	13,286
Infection Stage 2 (Y)	,049	3,182	1,005	10,079
FLRBW_stage_1>0,46	,094	,352	,104	1,194

*ASA: American Society of Anesthesiologists

- (4.9) Risk factors for 90-day mortality (table.14):

To verify significant risk factors for 90-day mortality, univariate logistic regression has been performed considering the parameters demonstrated in table 14. Statistical significant factors were; male gender (p=0.05, ODDS=3.0, CI=95%), age above 65 (p=0.1, ODDS=4.5, CI=95%) and/or prolonged ICU admission> one day post stage-1 (p=0.01, ODDS= 4.4, CI 95%).

Other significant risk factors related to 2nd stage hepatectomy were; prolonged ICU admission >1day (p=0.01, ODDS=6, CI 95%), PHH (p=0.06, ODDS=3.0, CI 95%), PHLF (p=0.03, ODDS=3.8, CI 95%), post-operative ascites (p=0.07, ODDS=4.5, CI 95%) and/or complications classified as Dindo-Clavien ≥3b (p=0.01, ODDS=4.3, CI 95%) or as Dindo-Clavien ≥3a (p=0.01, ODDS=5.0, CI 95%). All other considered covariables were not statistically significant.

Table 14: UNIVARIATE LOGISTIC REGRESSION 90-Day Mortality				
Demogarphics and co-morbidities Variabels	**p value**	**ODDS**	**95% CI**	
AGE>65	0,016	4,556	1,330	15,608
M	0,052	3,056	0,989	9,437
BMI>25	0,983	1,012	0,329	3,114
*ASA>3	0,513	1,474	0,461	4,712
Comorbidity (Y)	0,800	1,178	0,331	4,188
DM (Y)	0,967	1,036	0,198	5,424
Neoadjuvant CTH(Y)	0,728	,678	0,076	6,063
Stage-1 Variabels	**p value**	**ODDS**	**95% CI**	
Stage_1_RBC_transfusion(Y)	0,464	,551	0,112	2,713
lymphadenectomy_Stage_1(Y)	0,738	,821	0,260	2,598
PO_stage1_ICU_days	0,010	1,349	1,073	1,696
PO_stage1_ICU_days>1	0,013	4,400	1,359	14,241
Liver Failure Stage 1 (Y)	0,603	,560	0,063	4,995
Ascites Stage 1 (Y)	0,744	1,333	0,237	7,510
Haemorrhage Stage 1 (Y)	0,316	,442	0,090	2,177
Infection Stage 1 (Y)	0,947	1,058	0,200	5,581
Biliary complications Stage 1 (Y)	0,999	,000	0,000	
C-D Stage 1≥3a	0,469	,452	0,053	3,872
C-D Stage 1≥3b	0,512	2,286	0,194	26,999
Days_between_1st_and_2nd_stage_operation	0,838	,993	0,926	1,065
Days_between_1st_and_2nd_stage_operation>11days	0,577	1,369	0,454	4,123
Stage-2 Variabels	**p value**	**ODDS**	**95% CI**	
Post_stage_2_ICU_days	0,003	1,280	1,087	1,508
Post_stage_2_ICU_days>1	0,010	6,000	1,530	23,530
Stage_2_op_RBCs_Transfusion(Y)	0,348	1,857	0,510	6,766
Stage_2_lymphadenectomy(Y)	0,731	,783	0,195	3,152
Liver Failure Stage 2 (Y)	0,038	3,800	1,077	13,408
Ascites Stage 2 (Y)	0,076	4,550	0,851	24,318
Haemorrhage Stage 2 (Y)	0,061	3,025	0,951	9,628
Infection Stage 2 (Y)	0,113	2,543	0,802	8,068
Biliary complications Stage 2 (Y)	0,881	1,091	0,350	3,404
Dindo-Clavien Stage 2≥3a	0,018	5,056	1,315	19,439
Dindo-Clavien Stage 2≥3b	0,012	4,352	1,380	13,726

Volumetry Variabels	**p value**	**ODDS**	**95% CI**	
FLR/BW_stage_1>0,46	0,631	,729	0,201	2,651
FLR/BW_stage_2>0,84	0,205	,460	0,139	1,527
Pathological features	**p value**	**ODDS**	**95% CI**	
Multifoca lesion (Y)	0,978	,984	0,319	3,039
Largest_tumor_size>85 mm	0,500	1,463	0,484	4,424
Margin positive of tumor	0,348	,360	0,043	3,041
liver parenchyma histology result- diseased parenchyma	0,506	1,510	0,448	5,089
Grading G1 (Baseline)	0,344			
Grading G2	0,877	,833	0,082	8,433
Grading G3	0,554	2,000	0,201	19,914
AJCC 7th Stage I (Baseline)	0,460			
AJCC 7th Stage II	0,760	,690	0,063	7,512
AJCC 7th Stage III	0,615	2,000	0,134	29,808
AJCC 7th Stage IVA	0,589	1,875	0,192	18,324
T1 (Baseline)	0,743			
T2	0,456	2,286	0,260	20,131
T3T4	0,621	1,846	0,163	20,939
N1	0,144	2,292	0,754	6,968

Discussion:

The majority of patients with intrahepatic cholangiocarcinoma present in an advanced unresectable stage with limited treatment options. These patients who do not qualify for surgery usually undergo palliative systemic chemotherapy.[7,49] Currently, the gold standard for advanced biliary tumors consists of a combination of gemcitabine plus cisplatin, which offers a modest survival over gemcitabine monotherapy (11.7 vs 8.1 months, respectively). Other gemcitabine-based regimens, notably gemcitabine plus oxaliplatin, have shown similar efficacy.[73,74]

Other published data showed that combined systemic and hepatic arterial infusion chemotherapy treatment is associated with better prognosis, superior response and overall survival than systemic chemotherapy alone. The median overall survival for the study cohort for patients with locally advance or nodal disease was 17.1 months (range: 1.4–58.9 months).[75]

Other alternative approaches are loco-regional treatment such as radiofrequency (RFA) and microwave ablation (MWA). These approaches are frequently applied with small localized unresectable tumors, recurrence or residual tumor after surgery. However, few studies suggested that RFA may have survival benefits when compared with other palliative treatment methods in patients with small, single unresectable IC lesions with no distant metastasis.[76-79]

Despite of the availability of modern treatments for IC, curative resection remains the treatment of choice which offers a chance for long term survival; resulting in a median survival ranging from 27 to 36 months. However, the safe

removal of large amount of liver parenchyma is still a challenge in HPB surgery. The majority of IC cases presented in advanced stages at time of diagnosis which require extensive liver resection and so high risk to develop PHLF due to low FLR. [45-50]

Recently, Schnitzbauer et al. has introduced ALPPS approach to enable curative resection for advanced liver tumors. It was literally described as “one of the most promising advances in modern oncological liver surgery” not only by making marginal irresectable lesions resectable, but also its exceptional results of surgically induced, fast liver hypertrophy .[61,62]

A definitive evidence for long term benefit in terms of survival and oncological outcome of ALPPS procedure for IC is still lacking. Currently, there is no large comparative study available to evaluate the cost-benefit ratio of ALPPS procedure in comparison to routinely offered palliative chemotherapy. Another vital criticism has been conducted to ALPPS procedure due to relatively high morbidity and mortality. Particularly in primary liver tumors, authors recommended not perform this approach outside studies and registries.[80]

Herby, we sought to investigate the long-term outcome of ALPPS procedure for Intrahepatic cholangiocarcinoma patients as regard the overall survival, oncological outcome highlighting morbidities and 90-day mortality.
The message we wanted to verify by this study is, whether surgeons could keep performing ALPPS for IC, due to its long-term survival benefits, with strict risk adjustments to avoid unfavorable outcome or shall this procedure be restricted due to its inevitable overwhelming morbidities and mortalities.

The results of our comparative survival analysis provide a strong evidence for superior long-term outcome of ALPPS procedure over palliative chemotherapy. Despite of its relatively high 90-day mortality, ALPPS has shown a better 3 years survival rates which has been reconfirmed by propensity score analysis as well (Fig.1-4). Therefore, we believe that extensive liver resection by ALPPS procedure could provide a better chance of cure for this high-risk population with locally advanced IC lesions, who usually offered palliative chemotherapy.

Indeed, the 90-day mortality of 19% in our study is undoubtedly high in comparison with mortality rate for conventional hepatectomies or ALPPS performed for colorectal liver metastasis.[65] We would like to underline that, the reported results of early mortality in our cohort represent both the initial and the recent experiences. The 90-day mortality for ALPPS procedure performed for IC in 2106 and 2017 was 9% (n=1/11). While the 90-day mortality rates were 14% (n=2/14) in 2012, 30% (n=3/10) in 2013, 15% (n=3/20) in 2014 and 38% (n=5/13) in 2015 (2/12) in 2016 (Fig6). We claim that; the inherited learning curve would inversely proportionate to morbidity and mortality rates and a better outcome will be achieved by time.

Obviously, achieving complete tumor resection (R0 in 86.4%) in this study was on the cost of post-operative morbidity and mortality. In our cohort study, 34.6% of the patients suffered from severe complication which demanded intervention under general Anesthesia (Dindo-Clavien >3b).

Similar to conventional liver surgery results, [81] the main causes for severe complications in ALPPS group were, abdominal sepsis, biliary leakage and PHLF. (table. 12)

There is no doubt that, achieving R0 would result in better long term oncological outcome. [44,45] However, the risk to develop post-operative morbidity and mortality in ALPPS procedure with R0 resection should be weighed against the hazard of incomplete resection (R1) using conventional approach. Decision making remains in some cases a major challenge as the post-operative course and the procedure outcome are -to some extent- unpredictable and ambiguous even in highly specialized centers. In addition, it is not yet well understood how to objectively define the acceptable morbidity mortality rates for such advanced malignancies in correlation to the curative potentiality of this surgical approach.

The cumulative experiences of this procedure have led to risk adjustments' maneuvers which resulted in significant improvements in the surgical technique and better decisions as regard patients' selection and management.[82] For example, some authors have considered cholestatic liver underwent ERCP or PTC as a contraindication for ALPPS due to unacceptable rates of biliary and septic complications.[83]

Additional to that, a new concept of incomplete liver resection in stage-1 hepatectomy known as partial ALPPS was proposed to reduce the risk of inter-stage complications as biliary leakage and liver ischemia.[84,85] These refinements will eventually lead to acceptable rates of morbidities, mortalities and will result in more convincing short and long-term surgical outcomes.

To reach the standard outcome for conventional major hepatectomies, some authors have hypothetically proposed the following recommendations:[80]

1. Patients should be clearly informed about the higher risk to develop perioperative morbidity and early mortality through an informed consent.
2. The procedure should be performed in highly specialized centers by the expertise in complex liver surgery.
3. ALPPS approach is preferentially performed in the setting of large tumor load with marginal FLR with curative intent.
4. Should be used with caution in patients older than 70 years and/or with primary liver tumors (HCC, CCC).
5. Concomitant major abdominal surgery should be avoided.
6. Sharing experiences and knowledge through registration of patients in the international registry (www.alpps.net)

The main limitation of this study attributed to its retrospective methodology nature which leads to selection bias in both groups. A randomized control trial to investigate short and long-term outcomes would provide a more reliable results. Another limitation of the study conducted to the missing values and unshared informations of the procedure e.g. some operative details regarding technical variations, perioperative laboratory findings… etc. Completeness of the data will result in better stratification of the patients which will help to accurately define the significant risk factors and to identify the sub-group of patients who are vulnerable to develop sever post-operative complications or in-hospital mortality.

We have utilized the AJCC staging system, 7th edition in our analysis which is the same edition utilized in both ALPPS and SEER database. Recently, the AJCC has released a new staging system for IC in its 8th edition. Nevertheless, Pawlik et al. reported that 8th edition staging system for IC has not shown a significant privilege over 7th edition in the overall prognostic discrimination except for stage III which represent only 8.7% of our patients. [31]

From another aspect, a major advantage of this study is utilizing ALPPS registry-database as a baseline to create an international ALPPS prospective cohort with a longitudinal study design by retrieving new data on ALPPS approach not reported by the registry web site. This advantage will facilitate establishment further studies to investigate more detailed long-term oncological outcome of ALPPS procedure and risk adjustments analyses as well. However, further work is needed to achieve a significant improvement in the completeness and the quality of the data. Therefore, we urge all expertise to share their experiences and data through registration to ALPPS registry. (www.alpps.net)

Conclusion:

Despite of its relatively high morbidity and early mortality; ALPPS approach shows remarkable superior results in overall survival analysis compared to palliative chemotherapy for Intrahepatic cholangiocarcinoma patients. More strict risk adjustments are mandatory to avoid post-operative morbidity and mortality. Further studies are needed to identify the subgroup of IC patients who would potentially benefit from the procedure with acceptable morbidities and negligible early postoperative mortality.

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