Annals of Medicine and Surgery 25 (2018) 6–11

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Impact of liver volume and liver function on posthepatectomy liver failure after portal vein embolization– A multivariable cohort analysis

Patrick H. Alizai[a,*], Annabel Haelsig[a], Philipp Bruners[b], Florian Ulmer[a], Christian D. Klink[a], Cornelis H.C. Dejong[c], Ulf P. Neumann[a,c], Maximilian Schmeding[a,d]

[a] Department of General, Visceral and Transplantation Surgery, RWTH Aachen University Hospital, Pauwelsstr. 30, 52074 Aachen, Germany
[b] Department for Diagnostic and Interventional Radiology, RWTH Aachen University Hospital, Pauwelsstr. 30, 52074 Aachen, Germany
[c] Department of Surgery, Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands
[d] Department of Surgery, Klinikum Dortmund, Beurhausstraße 40, 44137 Dortmund, Germany

ARTICLE INFO

Keywords:
Portal vein embolization
Posthepatectomy liver failure
Liver function
Future liver remnant
LiMAx test
Liver resection

ABSTRACT

Background: Liver failure remains a life-threatening complication after liver resection, and is difficult to predict preoperatively. This retrospective cohort study evaluated different preoperative factors in regard to their impact on posthepatectomy liver failure (PHLF) after extended liver resection and previous portal vein embolization (PVE).

Methods: Patient characteristics, liver function and liver volumes of patients undergoing PVE and subsequent liver resection were analyzed. Liver function was determined by the LiMAx test (enzymatic capacity of cytochrome P450 1A2). Factors associated with the primary end point PHLF (according to ISGLS definition) were identified through multivariable analysis. Secondary end points were 30-day mortality and morbidity.

Results: 95 patients received PVE, of which 64 patients underwent major liver resection. PHLF occurred in 7 patients (11%). Calculated postoperative liver function was significantly lower in patients with PHLF than in patients without PHLF (67 vs. 109 μg/kg/h; p = 0.01). Other factors associated with PHLF by univariable analysis were age, future liver remnant, MELD score, ASA score, renal insufficiency and heart insufficiency. By multivariable analysis, future liver remnant was the only factor significantly associated with PHLF (p = 0.03). Mortality and morbidity rates were 4.7% and 29.7% respectively.

Conclusion: Future liver remnant is the only preoperative factor with a significant impact on PHLF. Assessment of preoperative liver function may additionally help identify patients at risk for PHLF.

1. Introduction

Surgical resection is the mainstay of curative treatment for most primary and secondary liver tumors. Progresses in surgical techniques, anesthesiology and postoperative treatment have considerably reduced perioperative complications. The morbidity and mortality rates in modern series are lower than 30% and 3% respectively [1]. However, posthepatectomy liver failure (PHLF) remains a life-threatening complication, and is reported in up to 15% of patients [2,3]. It is known that patients with a smaller future liver remnant develop more complications after liver resections [4]. Therefore, a remnant liver volume of 25% of total liver volume has been proposed in healthy patients and a volume of 40% in patients with underlying parenchymal disease. Portal vein embolization (PVE) is a preoperative intervention aimed to increase the future liver remnant (FLR) and reduce the risk of hepatic failure after extended hepatectomy. Following PVE, surgery is usually carried out 3–6 weeks later with a resectability rate of approximately 70–80% [5,6]. Despite this preoperative treatment, 6–10% of patients develop posthepatectomy liver failure [5,7]. However, it is still not clear if liver volume, liver function or patient characteristics play the key role in determining postoperative outcome. We therefore analyzed patients who underwent PVE with regard to liver failure after resection. Liver function was assessed by the new LiMAx test, which is based on hepatic ^{13}C-methacetin metabolism by the cytochrome P450 1A2 system [8–10]. The aim of this study was to identify preoperative factors, including patient characteristics, liver volume and liver function, that predict posthepatectomy liver failure after PVE.

* Corresponding author. Department of General, Visceral- and Transplantation Surgery, University Hospital of the RWTH Aachen, Pauwelsstr. 30, 52074 Aachen, Germany.
E-mail addresses: palizai@ukaachen.de (P.H. Alizai), ahaelsig@ukaachen.de (A. Haelsig), pbruners@ukaachen.de (P. Bruners), fulmer@ukaachen.de (F. Ulmer), cklink@ukaachen.de (C.D. Klink), chc.dejong@mumc.nl (C.H.C. Dejong), uneumann@ukaachen.de (U.P. Neumann), mschmeding@ukaachen.de (M. Schmeding).

https://doi.org/10.1016/j.amsu.2017.12.003
Received 15 September 2017; Received in revised form 25 November 2017; Accepted 4 December 2017

2. Methods

This retrospective cohort analysis included patients who underwent a portal vein embolization with subsequent liver resection at the Department of General, Visceral- and Transplantation Surgery of the RWTH Aachen University Hospital, Germany, between August 2011 and December 2014. Data on all liver resections and portal vein embolizations were prospectively collected, pseudonymised and saved in a secured database. Inclusion criteria were portal vein embolization, major liver resection (right hemihepatectomy, right trisectorectomy), availability of preoperative computed tomography and preoperative liver function. Exclusion criteria were heavy smoking (> 15 cigarettes per day), resections other than right hemihepatectomy and trisectorectomy (e.g. ALPPS procedures [11], segmental resections, concomitant bowel or pancreas resection). Data regarding patient demographics, tumor entity, comorbidities, ASA score, pre- and postoperative laboratory tests, MELD score, Child-Pugh score, postoperative complications, length of hospital stay and mortality were gathered from the hospital's medical reports.

The primary end point was posthepatectomy liver failure (PHLF). Taking into account the definition of the International Study Group of Liver Surgery (ISGLS), we defined grade 0 and grade A (no change in patients' clinical management) as 'no liver failure' and grade B (deviation from the regular course) and grade C (need for invasive therapy) as 'liver failure' [12]. Additional outcome parameters were 30-day mortality, morbidity and length of hospital stay. Postoperative complications were assessed using the Clavien-Dindo classification; morbidity rate was defined as grade III-V complications [13].

The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments and had received previous approval by the Local Ethics Committee (EK 270/15). Written informed consent was obtained from the patients. The study has been reported in line with the STROCSS criteria [14] and is registered in the Research Registry (UIN 3005).

2.1. Portal vein embolization

All patients underwent percutaneous transhepatic embolization of the right portal system (segments V – VIII). PVE was performed in a standardized manner by one of two experienced interventional radiologists. Combined fluoroscopic/ultrasound guided access to a peripheral right portal venous branch was gained using a 21 gauge chiba needle. After puncture of the portal system, the chiba needle was replaced by a 19 gauge coaxial needle (Cook Medical Europe ltd., Limerick, Ireland) using Seldinger technique. Subsequently a stiff guidewire (Amplatz, Cook Medical Europe ltd., Limerick, Ireland) was inserted into the superior mesenteric vein and the coaxial needle was removed, followed by placement of a 5 F sheath (Progreat, Terumo Medical, Somerset, USA) to gain interventional access to the portal vein. Direct portography was performed to visualize portal vein anatomy. A reverse catheter (SOS Omni, AngioDynamics, Amsterdam, Netherlands) was inserted to gain anterograde access to the right portal vein system. Branches of the right portal vein were selectively catheterized with a 2.7 F microcatheter (Progreat, Terumo Medical, Somerset, USA) followed by embolization with a mixture (1:2–1:3) of *n*-butyl-cyanoacrylate (Braun, Tuttlingen, Germany) and lipiodol (Guerbet, Roissy, France). The stasis in all right portal branches of liver segments V-VIII and unrestricted flow to the left liver segments was confirmed by ultimate portography. No additional embolization of segment I or IV branches was performed. Patients were usually discharged 1 day after PVE and readmitted 3–4 weeks later for surgery.

2.2. CT volumetry

Prior to PVE and prior to surgery, patients underwent a multiphase contrast-enhanced CT scan. Volumetric assay was performed using OsiriX MD version 5.8.2 software (Pixmeo SARL, Bernex, Switzerland). The total liver volume, tumor volume, liver volume to be resected and future remnant liver volume were measured. This was done manually by delineation of margins in CT slides (slice thickness: 5 mm) using the 'closed polygram' feature. Afterwards, the volumes were calculated automatically with the ROI function 'compute volume', according to the delineations and slice thickness.

Future liver remnant (FLR) was calculated as follows: for right trisectorectomy volume of liver segments 2 and 3 was measured and for right hemihepatectomy liver segments 2, 3, 4 and 1 (according to extent of the resection). Functional remnant liver volume (FRLV) in % was calculated according to Jara et al. [10]: 100x ((total liver volume – resected volume)/(total liver volume – tumor volume)).

2.3. Liver function capacity

Liver function capacity was measured routinely by the LiMAx test prior to surgery. The LiMAx test is based on hepatic ^{13}C-methacetin (Euriso-top, Saint-Aubin Cedex, France) metabolism by the cytochrome P450 1A2 system (CYP1A2). ^{13}C-Methacetin was applied as a 2 mg/kg body-weight adjusted intravenous bolus injection. Following injection, ^{13}C-methacetin is metabolized into acetaminophen and $^{13}CO_2$, of which the latter is then exhaled. The analysis of emerging $^{13}CO_2$ was performed by online breath sampling with real-time bedside analysis by a modified nondispersive isotope-selective infrared spectroscope (FLIP, Humedics, Berlin, Germany). The normal range of liver function capacity is considered as > 315 µg/kg/h [9]. The assumed postoperative LiMAx value was calculated as follows: $LiMAx_{postop} = LiMAx_{preop}$ x FRLV (%) [10].

2.4. Laboratory tests

Biochemical parameters (AST, ALT, γ-GT, bilirubin, albumin, creatinine, INR) were recorded before and after surgery. All parameters were determined at the Institute of Clinical Chemistry of the RWTH Aachen University Hospital. The normal range of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was 10–50 U/l. For γ-glutamyl transferase (γ-GT) 10–71 U/l and bilirubin < 1.2 mg/dl was considered normal. The normal value of albumin was 3.5–5.2 g/dl, for creatinine 0.5–0.9 mg/dl for women and 0.7–1.2 mg/dl for men.

2.5. Liver resection

Laparotomy was performed by median epigastric incision and transverse upper abdominal incision. After mobilization of the liver by dissecting the falciform and triangular ligaments, the hepatic veins were exposed. Hilar structures were then prepared and the lymph nodes dissected. Routine cholecystectomy was performed, and extrahepatic bile ducts were resected if Klatskin tumors were present. The right hepatic artery and right portal vein were then ligated. After ligation of the right hepatic vein (and, if necessary, middle vein and additional veins to segment 1), parenchymal transection began according to Couinaud's liver segments. For right hemihepatectomy liver segments 5–8 were resected, for right trisectorectomy segments 1 and 4–8. In right trisectorectomy for hilar cholangiocarcinoma, biliary reconstruction with hepatojejunostomy was routinely performed. We used the Cavitron Ultrasonic Surgical Aspirator (CUSA, Tyco Healthcare, MA, USA) for parenchymal transection. Small vessels were closed with non-absorbable clips, while larger vessels were ligated. Hemostasis at the resection surface was achieved using bipolar forceps and infrared coagulation. A drain was placed at the resection surface and the abdomen closed. All procedures were performed by two experienced hepatobiliary surgeons.

2.6. Statistical analysis

Statistical evaluation was carried out using the SAS/STAT® software (Version 9.3 for Windows, SAS Institute Inc., Cary, NC, USA.). Values are presented as mean and standard deviation or median and interquartile range (IQR) if not otherwise specified. Univariable analysis was performed with logistic regression for binary variables. For categorical and continuous variables ANOVA/ANCOVA was applied. The unpaired *t*-test was used for analysis of mean values. Variables with a p value less than 0.2 by univariable analysis were enrolled into multivariable analysis. Multivariable analysis was performed analogous to univariable analysis: logistic regression for binary variables, ANOVA/ANCOVA for categorical und continuous variables. A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Between August 2011 and December 2014, a cohort of 95 patients underwent portal vein embolization. Of these, 4 patients underwent resection in other hospitals, and in 3 patients portal vein embolization failed due to bleeding (n = 1), or due to the portal vein not being accessible (n = 2). Of the remaining patients, 3 were found to be inoperable due to general poor health (n = 2) or newly emerged metastases (n = 1). After laparotomy, planned resection was not carried out in 10 patients due to peritoneal carcinomatosis (n = 4), expanded tumor manifestation (n = 3) or previously unknown liver cirrhosis (n = 3). Nine patients underwent ALPPS procedure (Associating Liver Partition and Portal vein ligation for Staged hepatectomy) due to lack of hypertrophy. Thus, of the initial 95 patients, 66 patients underwent the planned resection: right hemihepatectomy (n = 31) or right trisectorectomy (n = 35). Preoperative liver function capacity and computed tomography were available for 64 patients, who then were finally included in this study. Detailed clinical and demographic data are summarized in Table 1.

23 patients of the 64 patients (35.9%) were female. The average age of the patients was 63.5 ± 9.6 years. Tumor entities were: colorectal metastases 27 (42.2%), hepatocellular cancer 3 (4.7%), intrahepatic cholangiocarcinoma 4 (6.3%), Klatskin tumor 26 (40.6%) and other 4 (6.3%). Mean BMI was 25.8 (± 4.4) kg/m^2. Co-morbidities were: coronary heart disease 7 (10.9%), type 2 diabetes mellitus 16 (25%), renal insufficiency 5 (7.8%), hypertension 34 (53.1%) and chronic pulmonary disease 9 (14%) (Table 1). Liver resection was performed after a median of 27 (IQR = 20) days following PVE.

Table 1
Patient characteristics.

Female	23	36%
Male	41	64%
Age (years)	63.5	± 9.6
BMI (kg/m^2)	25.8	± 4.4
Entities		
Colorectal metastases	27	42%
Hepatocellular cancer	3	5%
Intrahepatic Cholangiocarcinoma	4	6%
Klatskin tumor	26	41%
Other	4	6%
Comorbidities		
Coronary heart disease	7	11%
Diabetes mellitus	16	25%
Arrhythmia	8	13%
Renal insufficiency	5	8%
Hypertension	34	53%
Chronic obstructive pulmonary disease	9	14%
Liver parameters		
$LiMAx_{preop}$ (µg/kg/h)	372	± 138
$LiMAx_{postop}$ (µg/kg/h)	104	± 68
Total liver volume (ml)	1847	± 528
Future liver remnant (ml)	461	± 215
Functional remnant liver volume (%)	28	± 12
ASA	3	± 1
MELD	7	± 2
Child-Pugh	5	± 0

Mean preoperative liver function capacity ($LiMAx_{preop}$) was 372 (± 138) µg/kg/h. Mean preoperative liver volume was 1847 (± 528) ml. Mean volume of future liver remnant (FLR) was 461 (± 215) ml and mean functional liver remnant volume (FRLV) was 28 (± 12) %. Mean calculated postoperative liver function capacity ($LiMAx_{postop}$) was 104 (± 68) µg/kg/h.

3.2. Postoperative outcome

The primary end point posthepatectomy liver failure (PHLF) occurred in 7 patients (10.9%) (Table 2). By univariable analysis, factors associated with PHLF ($p < 0.2$) were age, future liver remnant (FLR), functional remnant liver volume (FRLV), calculated postoperative liver function ($LiMAx_{postop}$), MELD score, ASA score, renal insufficiency and heart insufficiency (NYHA). In patients with PHLF, mean calculated postoperative liver function ($LiMAx_{postop}$) was 67 µg/kg/h, which was significantly lower than in patients without PHLF (109 µg/kg/h; p = 0.01). By multivariable analysis, volume of future liver remnant (FLR) was the only significant predictor of PHLF (p = 0.03).

30-day mortality rate was 4.7% (n = 3). The causes of death were: peritonitis after small bowel perforation (n = 1), pneumonic sepsis (n = 1) and bile leakage with multiorgan dysfunction (n = 1). Heart insufficiency according to NYHA classification was the only significant predictor for mortality in univariable analysis, but not in multivariable analysis.

Postoperative complications as assessed by the Clavien-Dindo classification were 4 grade I (6.3%), 9 grade II (14.1%), 12 grade III (18.8%), 4 grade IV (6.3%) and 3 grade V (4.7%) complications. Grade III-V complications were summed up as morbidity rate (29.7%). Median length of stay in hospital was 14 (IQR = 17) days, median ICU stay was 1 day (IQR = 2).

4. Discussion

Liver resection remains the best treatment for primary and secondary liver tumors, if they can be resected completely with negative margins. The major limitation for extended hepatectomy is the lack of adequate and functioning future remnant liver. Different techniques and strategies have therefore been introduced in order to resect liver tumors despite small size of the liver remnant, e.g. portal vein ligation, portal vein embolization and ALPPS [5,11]. The amount of remnant liver after resection is known to be an important prognostic factor determining recovery following an extended hepatectomy. Preoperative evaluation of liver function is also essential, but difficult to determine accurately due to the wide variety of complex functions, including protein synthesis as well as metabolic, immune and storage functions. So far, liver function after portal vein embolization was assessed by conventional laboratory tests (albumin, ALT, AST, AP, bilirubin, γGT, serum glucose), Child-Pugh score, indocyanine green test (ICG) [15], 99mTc-galactosyl human serum albumin scintigraphy SPECT [16] or Gd-EOB-MRI [17]. Malinowski and co-workers measured liver function in patients after PVE with the LiMAx test [18]. This liver function test is based on hepatic ^{13}C-methacetin metabolism and has already been used to determine liver function in liver resection [9], liver transplantation [19], sepsis [20], liver cirrhosis [21] and non-alcoholic steatohepatitis [22]. For our patients with PHLF, mean calculated postoperative liver function capacity was 67 µg/kg/h, which was significantly lower than in patients without PHLF (109 µg/kg/h). This is in line with an

Table 2
Posthepatectomy liver failure.

	Liver failure	No liver failure	p univariate	p multivariate
Number of patients	7 (11%)	57 (89%)		
Age (years)	68.1 ± 7.4	62.9 ± 9.7	0.18	0.19
Gender			0.69	
Male	3 (43%)	37 (65%)		
Female	4 (57%)	20 (35%)		
BMI (kg/m^2)	27.7 ± 3.5	25.6 ± 4.5	0.24	
Smoker	1 (14.3%)	14 (24.6%)	0.55	
Liver parameters				
Total liver volume (ml)	1699.6 ± 383	1865.3 ± 543	0.44	
Tumor volume (ml)	241 ± 518	112 ± 330	0.36	
Resected liver volume (ml)	1293.9 ± 412	1384 ± 449	0.61	
Future liver remnant (ml)	291.4 ± 68	481.3 ± 218	< 0.001	0.03
$LiMAx_{preop}$ (μg/kg/h)	323.6 ± 116	378.3 ± 140	0.33	
$LiMAx_{postop}$ (μg/kg/h)	66.9 ± 28	108.5 ± 70.6	0.01	0.09
FRLV (%)	21.9 ± 10	28.3 ± 12.5	0.20	0.16
MELD	8 ± 5	7 ± 1	0.20	0.26
Child-Pugh	5 ± 1	5 ± 0	0.25	
Interval PVE to OP (days)	25 ± 13	27 ± 20	0.60	
Comorbidities				
ASA	3 ± 0	3 ± 1	0.10	0.17
NYHA	2 ± 1	1 ± 1	0.02	0.06
Chemotherapy before surgery	1 (14%)	21 (37%)	0.26	
Coronary heart disease	1 (14%)	6 (11%)	0.76	
Arrhythmia	1 (14%)	7 (12%)	0.88	
Diabetes mellitus II	2 (29%)	14 (25%)	0.82	
Renal insufficiency	2 (29%)	3 (5%)	0.05	0.07
Hypertension	5 (71%)	29 (51%)	0.32	
Chronic pulmonary disease	0 (0%)	9 (16%)	0.96	
Laboratory tests				
Bilirubin (mg/dl)	0.9 ± 0.7	0.8 ± 0.7	0.71	
Albumin (g/l)	36.4 ± 3.1	37.8 ± 4.9	0.49	
Creatinine (mg/dl)	1.1 ± 0.6	0.9 ± 0.3	0.36	
INR	1.1 ± 0.1	1 ± 0.1	0.33	
ALT (U/l)	72.2 ± 81.9	60.2 ± 50.8	0.61	
AST (U/l)	117.3 ± 175.6	55.1 ± 52.2	0.39	

algorithm by Stockmann et al., who reported that liver resections are feasible in patients with a calculated postoperative LiMAx value > 100 μg/kg/h, but should be reconsidered in patients with planned residual LiMAx < 80 μg/kg/h [8].

The Child-Pugh score is widely used for estimating liver function, but the score is a poor indicator in patients with mild to moderate liver dysfunction [23]. The MELD score, originally designed to predict short-term outcomes after transjugular intrahepatic portosystemic shunt (TIPSS) procedures and now used for the allocation of donor livers, has also been applied to predict the postoperative risk of patients undergoing liver resection [24,25]. In the present study, Child-Pugh score, MELD score and preoperative laboratory parameters were not able to predict postoperative outcome. Previous studies showed that the MELD- and Child-Pugh scores are not useful for predicting postoperative outcome in patients without cirrhosis [26,27].

We additionally analyzed patient characteristics including age, sex and co-morbidities. None of these factors significantly predicted PHLF in the multivariable analysis. Interestingly, 34% of our patients received chemotherapy within the last two years before resection, which caused us to expect an inferior outcome due to additionally acquired liver damage [28,29]. However, chemotherapy in this study had no influence on PHLF. It is likely that chemotherapy regimens were too heterogeneous to have any effect.

Future remnant liver volume was the sole factor which significantly influenced PHLF. This is in line with previous studies, which demonstrated the crucial importance of future liver remnant (FLR) with regard to postoperative outcome [30–32]. An inadequate volume of FLR correlates with poor surgical outcome and remains a contraindication for liver resection. In order to minimize the risk of PHLF, preoperative analysis of FLR must be included in the surgical planning of every major liver resection. If FLR is still inadequate after PVE, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is an option [33]. Another method to increase resectability in case of bilateral disease is classical 2-stage resection [34].

In the present study, resectability rate was 73%, corresponding to the literature [5,35,36]. Postoperative mortality and morbidity rates were 5% and 30%, respectively. These results are in line with previous studies, which report mortality rates between 3 and 9% and morbidity rates between 15 and 45% in similar series [35–37].

The primary end point of this study was posthepatectomy liver failure, which occurred in 11% of patients. Other studies report a posthepatectomy liver failure in 2–20% of patients [35–37]. A systematic review by Vyas et al. analyzed 20 studies with a total of more than 1500 patients and found post-resection liver failure in 6.3% patients [5]. However, these studies defined posthepatectomy liver failure differently, and currently no standardized definition or terminology for PHLF is established [2,12]. The International Study Group of Liver Surgery (ISGLS) defined PHLF as an increased international normalized ratio and concomitant hyperbilirubinemia on or after the fifth postoperative [12]. The severity of PHLF is differentiated in 3 grades from A to C. In grade A, laboratory parameters are abnormal but no change in the clinical management is required [12]. Bilirubin or INR are often slightly increased after extended hepatectomy without any impairment of the patient. Therefore, we decided to define grade B and C as 'liver failure', as these result in a deviation from regular clinical management. Other authors only regard grade C PHLF as 'liver insufficiency' [38]. Skrzypczyk et al. assessed the ISGLS definition of PHLF compared to the well-established 50-50 criteria and the $_{Peak}$Bili > 7 [3]. In 680 hepatectomies, they found that the ISGLS definition was less discriminatory than the other 2 criteria in identifying patients at risk of posthepatectomy major complications or death. Though data is inconsistent, the ISGLS definition of PHLF is currently the most widely used and was therefore applied in this study.

There are some limitations of the present study that need to be addressed. The first limitation concerns the retrospective nature of the study. Secondly, the number of patients included in the study is relatively small, and some patients underwent surgery in external hospital. Additionally, it would be interesting to have postoperative computed tomography and liver function capacity in every patient. However, this is the first study evaluating PVE patients with LiMAx and CT volumetry with regard to posthepatectomy liver failure after resection.

5. Conclusion

The future liver remnant is the only preoperative factor with a significant impact on posthepatectomy liver failure after previous portal vein embolization. Assessment of preoperative liver function may additionally help identify patients at risk for PHLF.

Declaration of interest

The authors report no conflicts of interest.

Ethical approval

The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments and had received approval by the Local Ethics Committee Aachen, Germany (EK 270/15).

Funding

Funding played no role in this study.

Author contribution

Alizai: data collection, data analysis, drafted the manuscript.
Haelsig: data collection, data analysis.
Bruners: performed portal vein embolization, wrote parts of the manuscript.
Ulmer: performed surgery, data collection.
Klink: data analysis, revised manuscript.
Dejong: study conception, revised manuscript.
Neumann: study conception, revised manuscript, performed surgery.
Schmeding: performed surgery, study conception, wrote parts of the manuscript.

Conflicts of interest

The authors report no conflicts of interest.

References

[1] M.E. Clark, R.R. Smith, Liver-directed therapies in metastatic colorectal cancer, J. Gastrointest. Oncol. 5 (5) (2014 Oct) 374–387.
[2] T. Schreckenbach, J. Liese, W.O. Bechstein, C. Moench, Posthepatectomy liver failure, Dig. Surg. 29 (1) (2012) 79–85.
[3] C. Skrzypczyk, S. Truant, A. Duhamel, C. Langlois, E. Boleslawski, D. Koriche, et al., Relevance of the ISGLS definition of posthepatectomy liver failure in early prediction of poor outcome after liver resection study on 680 hepatectomies, Ann. Surg. 260 (5) (2014 Nov) 865–870.
[4] C. Yigitler, O. Farges, R. Kianmanesh, J.M. Regimbeau, E.K. Abdalla, A. Belghiti, The small remnant liver after major liver resection: how common and how relevant? Liver Transplant. 9 (9) (2003 Sep) S18–S25.
[5] S. Vyas, S. Markar, S. Partelli, T. Fotheringham, D. Low, C. Imber, et al., Portal vein embolization and ligation for extended hepatectomy, Ind. J. Surg. Oncol. 5 (1) (2014 Mar) 30–42.
[6] J. Shindoh, C.W.D. Tzeng, T.A. Aloia, S.A. Curley, G. Zimmitti, S.H. Wei, et al., Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival, Br. J. Surg. 100 (13) (2013 Dec) 1777–1783.
[7] J. Shindoh, C.W.D. Tzeng, T.A. Aloia, S.A. Curley, S.Y. Huang, A. Mahvash, et al., Safety and efficacy of portal vein embolization before planned major or extended hepatectomy: an institutional experience of 358 patients, J. Gastrointest. Surg. 18 (1) (2014 Jan) 45–51.
[8] M. Stockmann, J.F. Lock, M. Malinowski, S.M. Niehues, D. Seehofer, P. Neuhaus, The LiMAx test: a new liver function test for predicting postoperative outcome in liver surgery, Hpb 12 (2) (2010 Mar) 139–146.
[9] J.F. Lock, M. Malinowski, D. Seehofer, S. Hoppe, R.I. Rohl, S.M. Niehues, et al., Function and volume recovery after partial hepatectomy: influence of preoperative liver function, residual liver volume, and obesity, Langenbeck's Arch. Surg. 397 (8) (2012 Dec) 1297–1304.
[10] M. Jara, J. Bednarsch, J.F. Lock, M. Malinowski, A. Schulz, D. Seehofer, et al., Enhancing safety in liver surgery using a new diagnostic tool for evaluation of actual liver function capacity - the LiMAx test, Dtsch. Med. Wochenschr. 139 (8) (2014 Feb) 387–391.
[11] E. Schadde, V. Ardiles, R. Robles-Campos, M. Malago, M. Machado, R. Hernandez-Alejandro, et al., Early survival and safety of ALPPS first report of the international ALPPS registry, Ann. Surg. 260 (5) (2014 Nov) 829–838.
[12] N.N. Rahbari, O.J. Garden, R. Padbury, M. Brooke-Smith, M. Crawford, R. Adam, et al., Posthepatectomy liver failure: a definition and grading by the international study Group of liver surgery (ISGLS), Surgery 149 (5) (2011 May) 713–724.
[13] D. Dindo, N. Demartines, P.A. Clavien, Classification of surgical complications - a new proposal with evaluation in a cohort of 6336 patients and results of a survey, Ann. Surg. 240 (2) (2004 Aug) 205–213.
[14] R.A. Agha, M.R. Borrelli, M. Vella-Baldacchino, R. Thavayogan, D.P. Orgill, The STROCSS statement: strengthening the reporting of cohort studies in surgery, Int. J. Surg. (2017 Sep 7).
[15] R. Higuchi, M. Yamamoto, Indications for portal vein embolization in perihilar cholangiocarcinoma, J. Hepato-Biliary-Pancreatic Sci. 21 (8) (2014 Aug) 542–549.
[16] T. Beppu, H. Hayashi, H. Okabe, T. Masuda, K. Mima, R. Otao, et al., Liver functional volumetry for portal vein embolization using a newly developed Tc-99m-galactosyl human serum albumin scintigraphy SPECT-computed tomography fusion system, J. Gastroenterol. 46 (7) (2011 Jul) 938–943.
[17] D. Geisel, L. Ludemann, V. Froling, M. Malinowski, M. Stockmann, A. Baron, et al., Imaging-based evaluation of liver function: comparison of Tc-99m-mebrofenin hepatobiliary scintigraphy and Gd-EOB-DTPA-enhanced MRI, Eur. Radiol. 25 (5) (2015 Mar) 1384–1391.
[18] M. Malinowski, D. Geisel, V. Stary, T. Denecke, D. Seehofer, M. Jara, et al., Portal vein embolization with plug/coils improves hepatectomy outcome, J. Surg. Res. 194 (1) (2015 Mar) 202–211.
[19] M. Stockmann, J.F. Lock, M. Malinowski, D. Seehofer, G. Puhl, J. Pratschke, et al., How to define initial poor graft function after liver transplantation? - a new functional definition by the LiMAx test, Transpl. Int. 23 (10) (2010 Oct) 1023–1032.
[20] M.F. Kaffarnik, J.F. Lock, H. Vetter, N. Ahmadi, C. Lojewski, M. Malinowski, et al., Early diagnosis of sepsis-related hepatic dysfunction and its prognostic impact on survival: a prospective study with the LiMAx test, Crit. Care 17 (5) (2013).
[21] M. Malinowski, M. Jara, K. Luttgert, J. Orr, J.F. Lock, E. Schott, et al., Enzymatic liver function capacity correlates with disease severity of patients with liver cirrhosis: a study with the LiMAx test, Dig. Dis. Sci. 59 (12) (2014 Dec) 2983–2991.
[22] P.H. Alizai, J. Wendl, A.A. Roeth, C.D. Klink, T. Luedde, I. Steinhoff, et al., Functional liver recovery after bariatric surgery-a prospective cohort study with the LiMAx test, Obes. Surg. (2015 Apr 14).
[23] T.I. Huo, H.C. Lin, J.C. Wu, F.Y. Lee, M.C. Hou, P.C. Lee, et al., Proposal of a modified Child-Turcotte-Pugh scoring system and comparison with the model for end-stage liver disease for outcome prediction in patients with cirrhosis, Liver Transplant. 12 (1) (2006 Jan) 65–71.
[24] S.H. Teh, J. Christein, J. Donohue, F. Que, M. Kendrick, M. Farnell, et al., Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: model of end-stage liver disease (MELD) score predicts perioperative mortality, J. Gastrointest. Surg. 9 (9) (2005 Dec) 1207–1215.
[25] A. Cucchetti, G. Ercolani, M. Cescon, M. Ravaioli, M. Zanello, M. Del Gaudio, et al., Recovery from liver failure after hepatectomy for hepatocellular carcinoma in cirrhosis: meaning of the model for end-stage liver disease, J. Am. Coll. Surg. 203 (5) (2006 Nov) 670–676.
[26] S.H. Teh, B.C. Sheppard, J. Schwartz, S.L. Orloff, Model for End-stage Liver Disease score fails to predict perioperative outcome after hepatic resection for hepatocellular carcinoma in patients without cirrhosis, Am. J. Surg. 195 (5) (2008 May) 697–701.
[27] P.L. Ge, S.D. Du, Y.L. Mao, Advances in preoperative assessment of liver function, Hepatobiliary Pancreat. Dis. Int. 13 (4) (2014 Aug 15) 361–370.
[28] J.N. Vauthey, T.M. Pawlik, D. Ribero, T.T. Wu, D. Zorzi, P.M. Hoff, et al., Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases, J. Clin. Oncol. 24 (13) (2006 May 1) 2065–2072.
[29] L. Rubbia-Brandt, V. Audard, P. Sartoretti, A.D. Roth, C. Brezault, M. Le Charpentier, et al., Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer, Ann. Oncol. 15 (3) (2004 Mar) 460–466.
[30] X.J. Lin, J. Yang, X.B. Chen, M. Zhang, M.Q. Xu, The critical value of remnant liver volume-to-body weight ratio to estimate posthepatectomy liver failure in cirrhotic patients, J. Surg. Res. 188 (2) (2014 May) 489–495.
[31] M. Narita, E. Oussoultzoglou, P. Fuchshuber, P. Pessaux, M.P. Chenard, E. Rosso,

et al., What is a safe future liver remnant size in patients undergoing major hepatectomy for colorectal liver metastases and treated by intensive preoperative chemotherapy? Ann. Surg Oncol. 19 (8) (2012 Aug) 2526–2538.
[32] U. Leung, A.L. Simpson, R.L.C. Araujo, M. Gonen, C. McAuliffe, M.I. Miga, et al., Remnant growth rate after portal vein embolization is a good early predictor of post-hepatectomy liver failure, J. Am. Coll. Surg. 219 (4) (2014 Oct) 620–630.
[33] A.A. Schnitzbauer, S.A. Lang, H. Goessmann, S. Nadalin, J. Baumgart, S.A. Farkas, 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. 255 (3) (2012 Mar) 405–414.
[34] K. Tanaka, H. Shimada, K. Matsuo, M. Ueda, I. Endo, S. Togo, Regeneration after two-stage hepatectomy vs repeat resection for colorectal metastasis recurrence, J. Gastrointest. Surg. 11 (9) (2007 Sep) 1154–1161.
[35] M. Nagino, J. Kamiya, H. Nishio, T. Ebata, T. Arai, Y. Nimura, Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer - surgical outcome and long-term follow-up, Ann. Surg. 243 (3) (2006 Mar) 364–372.
[36] D. Ribero, E.K. Abdalla, D.C. Madoff, M. Donadon, E.M. Loyer, J.N. Vauthey, Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome, Br. J. Surg. 94 (11) (2007 Nov) 1386–1394.
[37] D.A. Wicherts, R.J. de Haas, P. Andreani, D. Sotirov, C. Salloum, D. Castaing, et al., Impact of portal vein embolization on long-term survival of patients with primarily unresectable colorectal liver metastases, Br. J. Surg. 97 (2) (2010 Feb) 240–250.
[38] J. Dong, X.F. Zhang, Y. Zhu, F. Ma, C. Liu, W.L. Wang, et al., The value of the combination of fibrosis index based on the four factors and future liver remnant volume ratios as a predictor on posthepatectomy outcomes, J. Gastrointest. Surg. 19 (4) (2015 Apr) 682–691.