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

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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.

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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 hepato-biliary surgeons.