10th anniversary of ALPPS - lessons learned and quo Vadis

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Abstract: OBJECTIVE: Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) has been tested in various indications and clinical scenarios, leading to steady improvements in safety. This report presents the current status of ALPPS. SUMMARY BACKGROUND DATA: ALPPS offers improved resectability, but drawbacks are regularly pointed out regarding safety and oncologic benefits. METHODS: During the 12th biennial congress of the European African-Hepato-Pancreato-Biliary Association (Mainz, Germany, May 23-26, 2017) an expert meeting "10th anniversary of ALPP" was held to discuss indications, management, mechanisms of regeneration, as well as pitfalls of this novel technique. The aim of the meeting was to make an inventory of what has been achieved and what remains unclear in ALPPS. RESULTS: Precise knowledge of liver anatomy and its variations is paramount for success in ALPPS. Technical modifications, mainly less invasive approaches like partial, mini- or laparoscopic ALPPS, mostly aiming at minimizing the extensiveness of the first-stage procedure, are associated with improved safety. In fibrotic/cirrhotic livers the degree of future liver remnant hypertrophy after ALPPS appears some less than that in noncirrhotic. Recent data from the only prospective randomized controlled trial confirmed significant higher resection rates in ALPPS with similar peri-operative morbidity and mortality rates compared with conventional 2-stage hepatectomy including portal vein embolization. ALPPS is effective reliably even after failure of portal vein embolization. CONCLUSIONS: Although ALPPS is now an established 2-stage hepatectomy additional data are warranted to further refine indication and technical aspects. Long-term oncological outcome results are needed to establish the place of ALPPS in patients with initially nonresectable liver tumors.

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10th Anniversary of ALPPS—Lessons Learned and quo Vadis

Hauke Lang, MA, MD, FACS,[*] Eduardo de Santibañes, MD,[†] Hans J. Schlitt, MD,[‡] Massimo Malagó, MD,[§] Thomas van Gulik, MD, PhD,[¶] Marcel A. Machado, MD,[||] Elio Jovine, MD,[**] Stefan Heinrich, MD,[*] Giuseppe Maria Ettorre, MD,[††] Albert Chan, MD,[‡‡] Roberto Hernandez-Alejandro, MD,[§§] Ricardo Robles Campos, MD,[¶¶] Per Sandström, MD,[||||] Michael Linecker, MD,[***] and Pierre-Alain Clavien, MD, PhD[***]

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Results: Precise knowledge of liver anatomy and its variations is paramount for success in ALPPS. Technical modifications, mainly less invasive approaches like partial, mini- or laparoscopic ALPPS, mostly aiming at minimizing the extensiveness of the first-stage procedure, are associated with improved safety. In fibrotic/cirrhotic livers the degree of future liver remnant hypertrophy after ALPPS appears some less than that in noncirrhotic. Recent data from the only prospective randomized controlled trial confirmed significant higher resection rates in ALPPS with similar peri-operative morbidity and mortality rates compared with conventional 2-stage hepatectomy including portal vein embolization. ALPPS is effective reliably even after failure of portal vein embolization.

Conclusions: Although ALPPS is now an established 2-stage hepatectomy additional data are warranted to further refine indication and technical aspects. Long-term oncological outcome results are needed to establish the place of ALPPS in patients with initially nonresectable liver tumors.

From the [*]Department of General, Visceral and Transplantation Surgery, Universitätsmedizin Mainz, Mainz, Germany; [†]Department of Surgery, Division of HPB Surgery, Liver Transplant Unit, Italian Hospital Buenos Aires, Buenos Aires, Argentina; [‡]Department of Surgery, University of Regensburg, Regensburg, Germany; [§]Department of HPB- and Liver Transplantation Surgery, University College London, Royal Free Hospitals, London, UK; [¶]Department of Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [||]Department of Surgery, University of São Paulo, São Paulo, Brazil; [**]Department of Surgery, Maggiore Hospital, Bologna, Italy; [††]Department of Surgery, Camillo Hospital, Rome, Lazio, Italy; [‡‡]Division of Hepatobiliary and Pancreatic Surgery and Liver Transplantation, Department of Surgery, The University of Hong Kong, Hong Kong; [§§]Division of Transplantation, Hepatobiliary Surgery, University of Rochester, Rochester, NY; [¶¶]Department of Surgery and Liver and Pancreas Transplantation, Virgen de la Arrixaca Clinic and University Hospital, Murcia, Spain; [||||]Department of Surgery and Clinical and Experimental Medicine, University of Linkoping, Linkoping, Sweden; and [***]Swiss HPB and Transplantation Center, Department of Surgery, University Hospital Zurich, Zurich, Switzerland.

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Reprints: Prof. Hauke Lang, MA, MD, FACS, Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Universitätsmedizin Mainz, Langenbeckstraße 1, 55131 Mainz, Germany; E-mail: hauke.lang@unimedizin-mainz.de.

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In autumn 2007, about 10 years ago, Prof. HJ Schlitt from Regensburg, Germany, performed, somewhat incidentally, the first ''*in-situ-split*'' procedure.[1] This innovative concept rapidly spread throughout Germany. It was introduced in the surgical world in 2011 at the congress of the European African-Hepato-Pancreato-Biliary Association, held in Capetown, South Africa, where it triggered tremendous curiosity. One year later, the initial experience with 25 cases operated in 5 German centers was reported as the inaugural study in this journal.[1] In an accompanying editorial, this procedure was quoted as ''a novel concept representing one of the most promising advances in oncological liver surgery so far.''[2] This provocative statement subsequently triggered a vivid discussion among the HPB community. To ease communication for future reports the acronym ALPPS (''Associating Liver Partition and Portal vein ligation for Staged hepatectomy'') was introduced, and subsequently rapidly adopted.[2] Soon after, an international registry was created to collect data on a voluntary basis from many centers around the world[3], which currently counts more than 1000 cases.

ALPPS was tested by many groups in various indications and clinical scenarios leading on one hand to improved resectability, but also to the identification of significant drawbacks. Nevertheless, ALPPS is currently considered by many as a true innovative procedure, since it enables extensive liver resections well beyond the safe resection of 70% of liver volume.[4]

Originally, the ALPPS procedure was designed for a right trisectionectomy. Interestingly, a first report from the International ALPPS Registry indicated that this approach was also applied for standard right hepatectomy in about half of the cases; mainly in livers with steatosis or underlying parenchymal injuries, typically related to the use of excessive chemotherapy or, with the need for tumorectomy or ablative surgery in the remnant liver.

From a survey sent in 2014 to surgeons participating in the International ALPPS Registry, a high variability in indications, patient selection, and surgical technique was documented, highlighting the need for standardization. The first International Expert meeting, held in Hamburg in 2015, produced 8 recommendations regarding technique and indication for ALPPS[5], as well as suggestions for standardization for the terminology.[6]

The 10th anniversary of ALPPS was ''celebrated'' during the 12th biennial congress of the European African-Hepato-Pancreato-Biliary Association (Mainz, Germany, May 23–26, 2017) at an expert meeting to discuss indications, management, mechanisms of regeneration, as well as pitfalls of this novel technique. The aim of the meeting was to make an inventory of what has been achieved and what remains unclear in ALPPS. Each expert contributed to this manuscript by providing the key features of his topic.

How It Began? The First ''In-Situ Split Liver Resection''

Liver resection with potential for cure is technically possible in many cases, but often cannot be done because of a too small future liver remnant (FLR). This scenario occurred in a 49-year-old patient with perihilar cholangiocarcinoma (PHC) operated at Regensburg University, Germany, in September 2007. Right trisectionectomy was required, but the predicted FLR seemed to be critically small. Despite this concern, the decision for exploration was made. Intraoperatively, the first step was to divide the left hepatic duct at the base of the round ligament. A frozen section showed a tumor-free resection margin. After minimal preparation in the hilum, the right portal vein was divided followed by transection of the liver parenchyma along the falciform ligament down to the inferior vena cava, and to the confluence of the left and middle hepatic veins. The right hemi-liver was then mobilized from the retroperitoneum and the right hepatic vein encircled with a vessel-loop. At this point of the operation, reassessment of volume and parenchymal quality of the FLR (segment II and III) re-emerged the concern of a too small volume. The surgeon decided to stop the procedure omitting the completion of the resection leaving the right hemiliver in situ with preserved arterial perfusion and preserved venous and biliary drainage. Finally, the central stump of the left duct was suture-closed and a Roux-en-Y hepatico-jejunostomy was performed to the left hepatic duct.

Since the patient tolerated this aborted procedure well, a computed tomography (CT) scan was performed after 1 week disclosing an almost doubling in volume of FLR. This led the surgeon to proceed with a second step surgery to complete, only 8 days after the initial surgery, the hepatectomy. While the patient had an uneventful recovery, she developed peritoneal carcinomatosis within 6 months of surgery.

The same approach was planned and carried out with minor modifications in 2 subsequent patients, one with colorectal liver metastases and the other with intrahepatic cholangiocarcinoma. This new approach originally termed ''in-situ-split liver resection'' was adopted by a few German centers, and their inaugural experience was published in 2012.[1]

Is Knowledge of the Anatomy Central for Successful ALPPS?

The ALPPS concept is based on a complete portal venous devascularization of the tumor carrying liver with preservation of the arterial blood flow triggering tremendous hypertrophy of the contralateral part of the liver. Injury to branches of the hepatic artery on the tumor carrying liver (the future specimen) may cause necrosis and failure of the procedure. Also, injury to biliary structures and bile leak during the interstage phase must be avoided. Consequently, precise anatomical knowledge is crucial. Due to the high proportion of vasculo-bilary variants, preoperative imaging is mandatory to assess not only the FLR, but all individual anatomical details.[7]

Hepatic Artery (HA)

Attention must be paid to the hilar/intrahepatic branching of the HA. Replaced right and left HA are the most propitious arterial variants. The HA is seldom dissected in ALPPS and the arteries are divided into supra-glissonian intrahepatic technique at the second stage. However, the ''middle hepatic artery'' and the branches supplying segment IV are important in right trisectionectomy, and their preservation at stage 1 is imperative for proper perfusion of segment IV.[8]

Portal Vein (PV)

PV anatomical variants are well known[9,10] with most variations on the right side. Single PV branching (Types I or A according to Cheng and Nakamura, respectively) or trifurcation (Types II or B) versus truly abnormal configurations of the origin of the right (Type 3-4/C-D) must be recognized. Missing a PV is more likely to happen at stage 1, when a medial right sectorial PV is overlooked. Failure of regeneration may occur due to lack of obliteration of a PV branch either because of large tumors on the right hilum, or an aberrant anatomy.

Bile Duct (BD)

The bile duct should not be transected during stage 1, and the approach to the bile ducts is extra-glissonian at stage 2, thus usually unproblematic following correct lines of resection. However, the risk of bile leak is more prominent at right trisectionectomy with intrahepatic biliary obstruction (eg, in PHC), when inappropriate umbilical groove dissection can cause bile duct injury.[11] A single left hepatic duct is present in 98% of cases, but a standard left BD anatomy, with a single segment IV BD distant from the SII-III bifurcation is present in only 55% of cases.[12] Thus, a segment IV BD entering the BD to segment III might be injured during parenchymal transection resulting in bile leak. Special consideration is needed regarding right ducts draining into the left biliary system, particularly right posterior ducts described as Choi type 3 A, *Huang A3*/Nakamura C or Couinaud D1/D2.[10,13–15] In both, partial and full ALPPS, a Glissonian pedicle will be expected and preserved in the deeper extent of the parenchymal dissection.

Hepatic Vein (HV)

The general principle of preserving the venous outflow to the remnant liver is respected also for ALPPS at stage 1. In right hepatectomy, the preservation of the left main HV only, despite all variants, is sufficient and well tolerated. In ALPPS for right trisectionectomy, preservation of the middle HV outflow is advised at stage 1.[12] The venous drainage of the left lateral segments is quite constant with a common stem of the left HV.[12] The rare case of a Segment III HV draining into the middle HV needs to be considered. This potentially risky constellation requires the preservation of the proximal middle HV in continuity with the aberrant HV at stage 2.

Particular Surgical Consideration Regarding Segment IV

Segment IV ischemia and bile leaks can be observed in right trisectionectomy following injuries of segment IV HA and bile duct at stage 1. To prevent such complications, an anatomical intraglissonian dissection at the umbilical groove is required, preserving segment IV HA and respecting segment IV biliary anatomy. This approach is preferred to a direct nonanatomical parenchymal division into segment IV at the level of the umbilical line.

What Are the Essential Diagnostic Tools Prior to Engage in ALPPS?

The 2 main diagnostic issues in ALPPS are the volumetric assessment of the FLR (preferably using the standardized future liver remnant volume (FLRV) or the ratio of FLRV and body weight (FLRV-BWR)) and the timing of stage 2 (sufficient volume gain or better sufficient gain of functional volume). Correlations of CT-volumetry with liver function and postoperative outcomes are, however, not consistent, since FLRV does not necessarily reflect function, which might be impaired by an underlying parenchymal damage. Of note, liver failure after ALPPS occurred in 14 and 30% after stage 1 and 2, respectively, and 75% of the deaths after ALPPS are related to liver failure.[16] This discrepancy between volume increase (up to 200%) and the high rate of liver failure may be

attributed to a lack of maturity of the regenerating hepatocytes, and suggests the necessity to assess liver function in addition to volume.[17]

Liver Function Tests

The indocyanine green (ICG) clearance test is a quantitative liver function test, which depends on overall liver blood flow. The test is therefore less applicable during ALPPS because of unilateral division of the portal vein and redistribution of portal and hepatic arterial flow. Furthermore, the ICG clearance test is a global liver function test, which does not provide information on segmental function.

Assessment of Volume and Function in ALPPS

Scintigraphic liver function tests, such as hepatobiliary scintigraphy (HBS) using ^{99m}Tc-labeled iminodiacetic acid derivates, have the advantage of providing quantitative and visual information on regional hepatic function. The combination of HBS with single-photon emission computed tomography delivers quantitative information regarding segmental liver function, and therefore provides a regional measure of the function of the FLR. In surgical populations with and without compromised liver parenchyma, the FLR uptake rate for safer liver resection was calculated to be 2.7/min/m^2 or higher, and this cut-off value has been used regardless of the quality of the liver.[18] This technique is now routinely used in several centers in the work-up of patients eligible for major liver resection. When the FLR uptake rate is found to be less than 1.7/min/m^2, patients are unlikely to reach sufficient FLR function after portal vein embolization (PVE) rendering these patients upfront candidates for ALPPS.[19]

Sequential measurements of HBS appear also attractive to assess the functional response to ALPPS: it was shown that as soon as the FLR uptake rate has reached 2.7/min/m^2, the second stage can be undertaken. The use of HBS for timing of stage 2 in ALPPS was compared with CT volumetry in 60 patients completing ALPPS in 6 centers. The results showed that often volumetry overestimated liver function.[20]

What Are the Underlying Mechanisms of Liver Growth in ALPPS?

The key feature of the ALPPS approach is the rapid volume increase in response to stage 1. The presumed molecular pathways behind this unprecedented liver regeneration remain unclear, although some interesting observations are emerging. Despite the exponentially growing number of technical and clinical studies on ALPPS, the number of laboratory studies has remained modest (Fig. 1). Various animal models, in mouse, rat, and swine, have been developed mimicking ALPPS in human. Although there is no consensus which lobe of the liver to choose as the FLR, the common finding is that these ALPPS models exhibit accelerated regeneration compared with conventional portal vein occlusion. The first ALPPS model, developed in mice, revealed accelerated liver regeneration of a very small FLR after stage 1, allowing the successful completion of stage 2 within 48 hours of surgery.[21] This model induced liver hypertrophy superior to portal vein ligation (PVL) already 24 hours after stage 1 (Fig. 2). The injection of ALPPS mouse plasma in mice subjected only to PVL, that is, omitting the transection in stage 1, led to a comparable degree of regeneration as the complete ALPPS procedure. This simple approach suggested that circulating inflammatory and growth factors mediate liver regeneration in ALPPS. Specifically, IL-6 and TNFα appeared upregulated after stage 1, with similar observation in humans.[21] Other ALPPS models in rats disclosed analogous results with additionally upregulation of pSTAT3, nuclear NFkBp65, and YAP.[22,23]

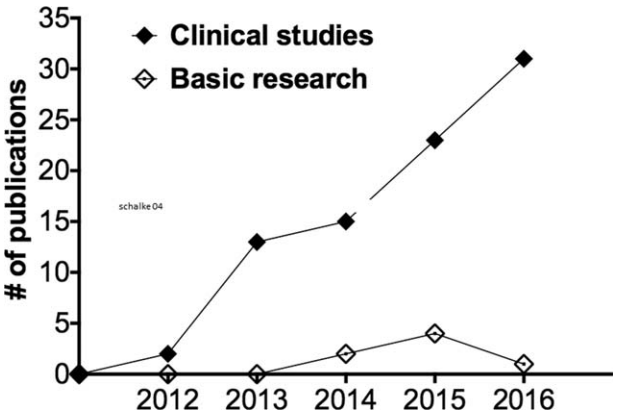

FIGURE 1. Discrepancy of clinical and basic science studies on ALPPS. While the number of clinical studies is steadily increasing, experimental studies looking on the mechanism of this accelerated regeneration process remain rare.

Interesting laboratory works further showed that the cell cycle entry and progression were found to be accelerated in ALPPS compared with PVL controls. Transcriptomic data identified Indian hedgehog (Ihh) to be upregulated in ALPPS, as early as 4 hours after stage 1. Functional experiments by injection of recombinant Ihh combined with PVL mimicked the quick regeneration seen in complete ALPPS stage 1, and neutralization of Ihh abrogated the regeneration normally seen in ALPPS.[24] These results cemented the importance of the hedgehog pathway. Furthermore, Ihh was present early after stage 1 in human plasma, confirming there is a clinical relevance to this molecular pathway.[24]

In patients, studies aimed to elucidate many technical aspects, mostly with the aim of reducing morbidity. For example, the search for the minimum amount of transection necessary to induce ALPPS showed that full versus partial transection induced comparable increase in liver growth. Using the ALPPS mouse model, it was found that a minimum of 50% transection was necessary to induce the accelerated regeneration process.[25]

Another study was designed to determine, which components cause the large volume increase in ALPPS—hepatocyte

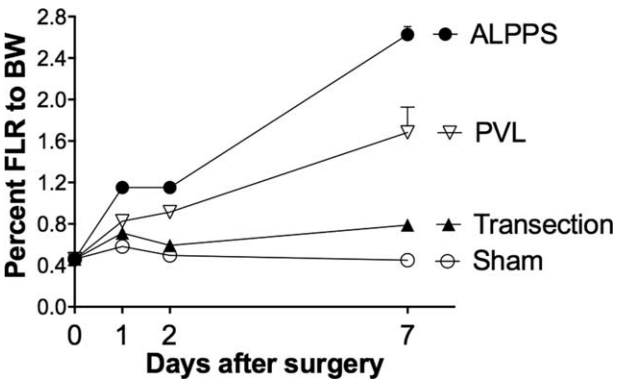

FIGURE 2. ALPPS-induced liver regeneration appears markedly increased compared with PVL. Experimental data in mice show a significantly increased FLR to BW compared with PVL and the respective controls, transection alone and sham laparotomy already 24 hours after stage 1.[21] BW indicates body weight.

proliferation, steatosis, or edema.[26] Analyzing biopsies from patients including Ki67 and pH3 staining, steatosis, as well as water fraction, it was found that the volume increase in ALPPS patients results from efficient hepatocyte proliferation, rather than steatosis or edema. The observation, however, that volume does not match full liver function suggests that apparently cell proliferation does not lead immediately to full maturity.[17]

There is still much to be investigated regarding the optimization of the ALPPS procedure and the molecular mechanisms that drive the unprecedented liver regeneration. Accepting 1 animal model would create a consistent platform to investigate the regeneration of the FLR after ALPPS, thereby creating the opportunity for solid links to be made between basic research and clinical data. Many questions remain open and further investigations of pathways essential to liver regeneration will lead the way to better understanding this complex procedure, and improving clinical care.

Can Technical Modifications Improve Safety?

The current paradigm of ALPPS is represented by an invasive and prolonged first surgical procedure (stage 1) followed by a somehow shorter and less aggressive second stage.[1,2] This strategy with complete transection has been adopted by most centers as the *classical* ALPPS technique. Partial transection offers comparable FLR hypertrophy, but significantly lower morbidity, when compared with total transection (38.1 vs. 88.9%; $P = 0.049$) and near zero mortality.[27,28] Recent clinical and experimental evidence from a multicentric study suggests that parenchymal transection in *partial ALPPS* should be at least 50% to achieve equivalent hypertrophy compared with complete transection.[25] Total transection should therefore only be performed, when a tumor is too close to the FLR boundaries to isolate the tumor and prevent margin invasion.

When completing stage 1 procedure, it is advisable to perform a *transcystic hydraulic, air-bubble or "white" test (eg, use of propofol)* and sometimes cholangiography to prevent interstage bile leaks. Bile duct ligation should never be performed, as it might cause cholestasis, infection, and bile leaks. The identification of the vasculo-biliary structures with vessel loops is recommended to facilitate their identification at stage 2.[29]

Some authors have initially proposed to place a plastic sheet at the liver partition site with the aim of minimizing adhesions, today most surgeons prefer a hemostatic sheet. The resection of the tumor-carrying liver is facilitated using vascular staplers for vascular structures and the remaining liver parenchyma, if present. Finally, it is also recommended to repeat a bile leak test after stage 2.

Given the existence of many technical variants described with inconsistent and confusing names, a ''consensus'' terminology has been recently reported.[6] Some authors have replaced transection during the 1st stage by applying a tourniquet around a parenchymal groove of 1 cm in the future transection line (*Tourniquet ALPPS*). However, the 64% morbidity and 9% mortality in their series did not reflect a real improvement in terms of patient safety [30]. Others have proposed to replace parenchymal transection by using radiofrequency or microwave ablation (*Radiofrequency and Microwave ALPPS*) to create a functional liver partition through a ''necrotic groove.'' These approaches provided a similar hypertrophic profile than the standard ALPPS, but with putatively with less complications and mortality.[31] Following the trend to less invasiveness, the ligation of the portal venous branches to the tumor-carrying liver may also be replaced by PVE during the interval period.[32]

In line with this concept, the so-called ''mini-ALPPS,'' combining partial parenchymal transection and intraoperative PVE, that is, obviating the need for the dissection of the porta hepatis, minimize the surgical impact of first stage promoting better patient recovery prior to the 2nd stage.[33]

Is Laparoscopic ALPPS Feasible and Safe?

As for open surgery, the first stage includes the exploration of the abdominal cavity and ultrasound through a 4-trocar approach. If necessary, nonanatomical resections can be performed in the FLR using laparoscopic ultrasound as guidance. The portal vein is ligated with a nonabsorbable suture followed by transection, and parenchymal transection is carried from caudal to cephalad.

Stage 2 procedure can also be performed laparoscopically: the right liver is fully mobilized off the retroperitoneum, diaphragm, and inferior vena cava. The right Glissonian pedicle is divided with an endostapler. Staplers are also used to transect the right and—and in some patients—the middle hepatic veins followed by the removal of the specimen inside a large plastic bag through a suprapubic incision.

At the University of São Paulo, between 2011 and 2016, first stage of ALPPS was performed in 30 patients with noncirrhotic liver, and 28 underwent the second stage. The procedure was performed laparoscopically without conversion in 10 patients, of whom 2 underwent ALPPS with a right-sided FLR and 1 patient had a monosegment ALPPS. In laparoscopic ALPPS, no mortality and no complication $\geq$ grade 3 occurred, and no liver failure was observed.[34] Moreover, the hospital stay was shorter in the laparoscopic, when compared with open ALPPS groups (11 vs. 14 days; $P = 0.01$).[35,36] These results indicate that laparoscopic ALPPS is feasible, and it is not inferior to the open approach.

Is the Interstage Course Central for Optimal Outcome?

Recent results from the ALPPS registry showed that the vast majority (93%) of deaths occur after stage 2 with posthepatectomy liver failure being the first cause of poor outcome.[16] Poststage 1 morbidity appears as a strong predictor for poststage 2 mortality. Thus, complications during the interstage phase are determinant for the outcome after ALPPS.

The prestage 1 risk score depicts patient age (>67 yrs) and tumor type as independent risk factors for futile outcome. Importantly, biliary tumors with associated cholestasis represent a high-risk entity in this score.[16,37] Interstage morbidity $\geq$ grade 3b complications[34] and prestage 2 bilirubin and creatinine levels are associated with higher 90-day mortality after stage 2.[37]

A recent analysis demonstrated that results of ALPPS have significantly improved over the years due to patient selection, reduced invasiveness of the ALPPS procedure due to technical refinements, mostly aiming at a reduction of stage 1 trauma. Both developments decrease the interstage complication rates and consequently morbidity and mortality after stage 2.[38]

Is ALPPS in Fibrotic/Cirrhotic Livers Safely Feasible?

Surgery for hepatocellular carcinoma (HCC) in cirrhosis represents a particular challenge. While the functional and regenerative capacity of a cirrhotic liver is difficult to assess preoperatively, the use of PVE or ALPPS stage 1 is a valuable test for the regenerative ability and presumed outcome after the completion of the hepatectomy. Patients with liver cirrhosis additionally poorly tolerate complications, even during a limited stage 1 procedure.

At San Camillo Forlanini in Rome, 16 ALPPS have been performed for HCC and in 1 for HCC-ICC, including 3 ALPPS as rescue therapy after failure of PVE or PVL. All but 1 patient were Child A with a median MELD score of 9. In 9 cases a vascular thrombus was removed during stage-1 to secure vascularization of the FLR. One patient died within 90 days postoperatively.

At The University of Hong Kong, patients with HCC are eligible for ALPPS when the FLR volume is $\leq 30\%$ of the estimated standard liver volume in the presence of Child A cirrhosis, the ICG clearance rate is $< 20\%$ at 15 minutes, the platelet count $> 100\times10^9$/L, and in absence of complete right PV thrombosis (partial right PV thrombosis is regarded as a good indication for ALPPS). Forty-two patients underwent an ALPPS procedure, of whom 38 patients (90%) had HCC (hepatitis B = 36, hepatitis C = 1, fatty liver = 1) and all of them underwent both stage I and II operation. In the initial report there was a volume gain of the FLR of 48.7% inducing an increment of FLR/estimated standard liver volume ratio from 24.2 to 38.5% over a median of 6 days.[39] The 90-day mortality rate was 7.1% (n = 3) consistently related to liver failure. In addition to the benefit of shorter waiting time to hepatectomy there are 2 main advantages of ALPPS compared with PVE in fibrotic/cirrhotic livers, both related to stage 1: first, the visual assessment of liver parenchyma quality plus a possibility for liver biopsies to stage the degree of cirrhosis before proceeding to hepatectomy. Second, intraoperative measurement of portal hemodynamics enables better assessment of the postoperative liver failure risk and the opportunity to apply flow modulation, for example, splenic artery ligation if needed.

Although the degree of FLR hypertrophy in fibrotic/cirrhotic livers appears somewhat less substantial than that in noncirrhotic, noncholestatic livers[3], the Rome and Hong Kong experience shows that the ALPPS procedure remained an effective approach for FLR augmentation in patients with hepatitis-related HCC.

Is Colorectal Liver Metastases the Best Indication for ALPPS?

In Western countries, colorectal liver metastases represent the main indications for liver surgery. Due to the pattern of metastasis with frequent multifocal and bilateral liver involvement, various 2-stage procedures have been developed, including ALPPS.[2] The first report of the International ALPPS Registry in 2014 revealed that colorectal liver metastases (CRLM) was the indication in 70% of the 212 initial patients. Compared with other indications, the morbidity and mortality after ALPPS was the lowest.[3]

A subsequent publication from the ALPPS registry disclosed a mortality rate of 5% for CRLM after stage 2,[16] a figure in the range of the reported mortality after major hepatectomy.

The most recent publication of the ALPPS registry in 2016 noted a continuous drop in risk-adjusted early mortality and morbidity. Centers with the most experience performing ALPPS showed a shift in indication toward CRLM after neoadjuvant chemotherapy. The results confirm that patients with CRLM have the lowest complication and mortality rates, even after chemotherapy.[38]

ALPPS has expanded the treatment options for patients with CLRM once deemed unresectable due to high tumor load and a small FLR volume. Though recurrence rates appear higher, when compared with patients with conventional liver resections, ALPPS is offering a chance for cure for those patients, who otherwise would have no surgical option. Robust long-term clinical and oncological outcome studies of ALPPS for CRLM are, however, still lacking, but 3-year overall survival of 50% and a disease-free survival rate of 13% at 3 years with quality of life similar to the general population have been reported.[40]

Is ALPPS a Viable Option for Perihilar Cholangiocarcinoma?

While the very first ALPPS procedure was performed in a patient with PHC[1], the international ALPPS registry counts only 11 patients with PHC with a 90 day-mortality rate of 27%. This figure is consistent with an Italian multicenter study demonstrating a high mortality rate in biliary tumors (10% after stage 1 and 30% after stage 2).[41] Most recently, biliary tumors and elevated serum bilirubin (pre stage 2) were identified as predictors of futile outcome after ALPPS.[37] A comparison between ALPPS versus PVE and right trisectionectomy for PHC using a matched case-control 1:1 from the international ALPPS registry with data from the Amsterdam Medical Center and the Memorial Sloan Kettering Cancer Center suggested that mortality was twice higher in the ALPPS group (48 vs. 24%). Moreover, median survival was only 6 months after ALPPS and 29 months in the matched controls ($P = 0.05$). In the ALPPS group, 4 patients died after stage 1, and another 10 patients after stage 2.[42] There are, however, some shortcomings with the study in terms of patient selection. Additionally, these results were obtained by conventional ALPPS procedures (ie, complete transection) representing the initial experience, (ie, learning curve with ALPPS in all centers). With the recent modifications it is expected that morbidity and mortality would be much lower. The most attractive new variant for PHC appears to be partial parenchymal transection in combination with PVE instead of portal vein ligation/transection, thus reducing post stage 1 morbidity by avoiding hilar dissection. PVE can be perfomed either during stage-1 (*Mini-ALPPS*) or in the interstage course.[32,33] These techniques trigger a suitable FLR in a shortest possible time, thus avoiding the high drop-out of the PVE alone. However, these variations have not been convincingly tested in PHC, yet.

What Does ALPPS Offer Compared With Conventional Two-stage Hepatectomy and to Portal Vein Embolization?

So far, there is only 1 randomized controlled trial available comparing ALPPS with TSH in patients with a standardized FLR less than 30% (LIGRO Trial).[43] This trial confirmed a significant higher resection rate in ALPPS (main endpoint of the study) and comparable surgical margins, peri-operative complications and mortality rates. While the study offers a level 1 evidence for the previous observations in the ALPPS registry, that is, higher rates of R0 resection, faster regeneration with comparable perioperative mortality and morbidity, we still need data regarding long-term outcome.[43] Noteworthy, 35 of 49 patients in the conventional 2-stage hepatectomy group were treated with PVE. The study, therefore, clearly indicated that ALPPS offers higher resection rates than PVE, importantly without higher rates of complications. Also, ALPPS is effective after failure of PVE or PVL (in 12 of 13 cases), known as rescue ALPPS.[43]

DISCUSSION

ALPPS is a recently developed procedure, first performed by HJ Schlitt in Regensburg, Germany, with the inaugural small series published by a few German surgeons 5 years later.[1] Despite increased morbidity and mortality in the early phase, this novel procedure has triggered major interest, and has rapidly climbed the IDEAL concept of new surgical procedures or devices.[44] Early after the inaugural publication [1] accompanied by an editorial,[2] an international registry[3] was initiated with currently more than 1000 patients included. With this tool, a collaborative effort from many centers all around the world enabled us to improve patient selection, timing of stage 2, and refinements of operative techniques, which allowed ALPPS morbidity and mortality rates to match standard major liver resections. New technical modifications, mostly minimizing the extensiveness of the first-stage procedure, were associated with significant improvements in safety, while preserving a high rate of curative resection.[38] Stage 2 should be delayed or even abandoned in case of compromised clinical status, complications, or abnormal liver function tests to prevent postoperative mortality. Recent data from the only available prospective RCT confirmed significant higher resection rates in ALPPS and similar peri-operative complications and mortality

figures compared with conventional 2-stage hepatectomy including PVE.[43] While the ALPPS technique is now becoming an established concept, for example, for failure of PVE, several questions remain unanswered, mostly in the L (long-term results) of the IDEAL concept.[44] The single RCT showed that ALPPS does not replace other techniques, such as PVE for later hepatectomy, but it is central in the toolkit of liver resection in the hands of experienced liver surgeons. Attention should be put on important features to optimize the ALPPS concept for specific situations in selecting not only proper indications, but also regarding the adequate timing in the course of the disease, for example, use of proper chemotherapy prior to any surgery. Evidently, ALPPS is only 1 aspect of the overall oncologic therapeutic concept of the patients.

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