

Parenchyma Sparing ALPPS – Ultrasound Guided Partition Through Segment 4 to Maximize Resectability (with video)

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Abbreviations:

ALAT: Alanine transaminase;
ALPPS: Associating Liver Partition
and Portal vein ligation for Staged
hepatectomy;
ASAT: Aspartate transaminase;
CRLM: Colorectal liver metastases;
FLR: Future liver remnant;
HBV: Hepatitis B virus;
HCC: Hepatocellular carcinoma;
HV: Hepatic vein;
ICU: Intensive care unit;
IHCC: Intrahepatic cholangiocarcinoma;
IOUS: Intraoperative ultrasound;
IRB: Institutional review board;
ISGLS: International study group of
liver surgery;
IVC: inferior vena cava;
LT: Liver transplantation;
MELD: Model of end-stage liver
disease;

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Rezumat

Parenchyma sparing ALPPS - maximizarea rezecabilității prin partiționarea ecoghidată a segmentului 4

Introducere: Asocierea partiției hepatice și a ligaturii venei porte (ALPPS) a evoluat ca strategie de tratament pentru pacienții cu tumori hepatice care nu sunt eligibili pentru hepatectomie din cauza unui volum hepatic restant (VHR) cu volum insuficient. Scopul acestui studiu a fost acela de a testa aplicabilitatea unei proceduri chirurgicale care combină conceptul chirurgiei rezectiv conservatorii cu cel al ALPPS, prin deplasarea planului de transecție prin segmentul 4, în favoarea VHR, rezultând o nouă variantă tehnică a ALPPS, intitulată parenchyma sparing ALPPS (psALPPS).

Material și metodă: Pacienții care nu au fost eligibili pentru ALPPS cu trisectionectomie dreaptă, din cauza VHR insuficient, au fost considerați eligibili pentru psALPPS, constând cu partiție hepatică prin segmentul 4 folosind ghidaj ecografic.

Rezultate: Între aprilie 2017 și aprilie 2021, cinci pacienți cu vârsta medie de 68 de ani (interval: 66-78), patru bărbați și o femeie, au beneficiat de psALPPS pentru metastaze hepatice colo-rectale (N=2), colangiocarcinom intrahepatic (N=2) și carcinom hepatocelular (N=1). VHR standardizat (sVHR) pentru segmentele 2-3 înainte de intervenția chirurgicală în stadiul 1 ar fi fost în medie de 11,6%. PsALPPS a obținut chiar și dublarea sVHR la etapa 1, rezultând o creștere a ps-sVHR de la o medie de

POD: Postoperative day;
 psALPPS: Parenchyma sparing ALPPS;
 ps-FLR: Parenchyma spared future liver remnant;
 PSS: Parenchyma sparing surgery;
 PVE: Portal vein embolization;
 PVL: Portal vein ligation;
 RAPID: Resection and partial liver segment 2–3 transplantation with delayed total hepatectomy;
 RAVAS: Heterotopic transplantation of segments 2 and 3 using the splenic Vein and Artery after Splenectomy and with delayed total hepatectomy;
 RBC: Red blood cell;
 RCT: Randomized controlled trial;
 RPV: Right portal vein;
 S: Liver segment.

22,7% (la etapa 1) la 34,0% (la etapa 2), după un interval median între etape de 15 zile. Toți pacienții au tolerat bine intervenția chirurgicală și nu au fost înregistrate complicații majore.

Concluzii: Aplicarea principiilor chirurgiei rezective conservatorii la ALPPS oferă avantajul maximizării volumului hepatic restant, reducând în același timp afectarea ischemică și excludere biliară a segmentului 4, în comparație cu ALPPS convențional. În acest fel, psALPPS poate crește semnificativ rezecabilitatea, reducând în același timp morbiditatea.

Cuvinte cheie: rezecția hepatică în doi timpi, chirurgia rezectiva conservatorie, ALPPS, volum restant hepatic, chirurgia regenerativă

Abstract

Background: Associating liver partition and portal vein ligation (ALPPS) has evolved as a treatment strategy for patients with liver tumors who are not amenable for upfront hepatectomy because of an insufficient future liver remnant (FLR). Aim of this study was to test the applicability of ultrasound guided parenchyma sparing surgery to ALPPS concept, by non-anatomically shifting the plane of transection in favor of FLR, resulting in a new technical variant of ALPPS, entitled parenchyma sparing ALPPS (psALPPS).

Materials and Methods: Patients who could not safely undergo right trisectionectomy ALPPS because of insufficient FLR were considered eligible for psALPPS, consisting in liver partition through segment 4 using ultrasound guidance.

Results: Between April 2017 and April 2021, five patients with median age of 68 years (range: 66-78), four male and one female, underwent psALPPS for colorectal liver metastases (N=2), intra-hepatic cholangiocarcinoma (N=2), and hepatocellular carcinoma (N=1). Standardized FLR (sFLR) for segments 2-3 before stage 1 surgery would have been a median of 11.6%. PsALPPS could double the sFLR at stage 1 resulting in an increase of ps-sFLR from a median of 22.7% (at stage 1) to 34.0% (at stage 2) after a median interstage interval of 15 days. All patients tolerated surgery well and no major complications were recorded.

Conclusions: Applying the principles of parenchyma sparing surgery to ALPPS offers the advantage to maximize FLR and simultaneously reduce ischemic injury of segment 4 compared to conventional ALPPS. In this way, psALPPS may markedly increase resectability while reducing morbidity.

Key words: two stage liver resection, parenchymal sparing liver resection, ALPPS, future liver remnant, regenerative surgery

Introduction

Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) is a two-stage hepatectomy strategy introduced in 2012 by Schnitzbauer et al. aiming to improve resection rates of liver tumors leaving a too small future liver remnant (FLR) (1,2). Combining portal vein ligation (PVL) and parenchymal splitting in preparation of resection induces accelerated liver hypertrophy making completion hepatectomy possible in 1-2 weeks. This concept of regenerative liver surgery complements conventional PVL and portal vein embolization (PVE), which induces much slower hypertrophy making resection possible in approximately 6 weeks (3). The key problem of “conventional” two-stage hepatectomy is that the percentage of patients ultimately undergoing hepatectomy is only 60-70% (3). Chief reasons for drop-out are tumor progression and failure of FLR to grow sufficiently (3). In contrast, ALPPS can raise resection rates well above 90% (4-7). Tumor progression is the short interstage-interval is rarely seen and ALPPS offers a valid option for patients with failing PVE (Rescue ALPPS) (8,9). First series of ALPPS, however, cut this initial enthusiasm. Early short-term mortality rates of ALPPS were in an unacceptable range, even in experienced centers up to 20% (10-13). It turned out, that candidates for ALPPS need an appropriate risk analysis before undergoing such an extensive procedure (5,6,14). Besides patient selection, ALPPS has undergone a technical evolution and became apparent that less invasive variants, in the sense of minimizing the hit of stage 1 surgery, offer a more favorable complication profile while maintaining a comparable growth stimulus (15). Currently, a long list of variants exist, including delayed ALPPS (16,17), partial ALPPS (18), segment IV portal pedicle-sparing ALPPS (19), PVE – ALPPS. (20), RALPPS) (21), Tourniquet ALPPS (22), minimally invasive ALPPS (23-25) ALPPS with ligation of the middle hepatic vein (26), monosegment ALPPS (27,28), and rescue ALPPS (29).

Meanwhile, ALPPS is a valid option in the

treatment in a variety of liver tumor entities including colorectal liver metastases (CRLM) (4,7,30,31), intrahepatic cholangiocarcinoma (IHCC)(32), and neuroendocrine liver metastases (33). The situation in hepatocellular carcinoma (HCC), particularly in cirrhosis (34, 35), and perihilar cholangiocarcinoma (36,37) is less clear and needs further investigation.

Besides raising resection rates, i.e. progression to stage 2 surgery, an improvement of overall resectability, which comprises patients with a very small FLR and/or impaired parenchymal quality (e.g. chemotherapy injured liver) has not been proposed so far. It has been shown that ALPPS induced liver hypertrophy of FLR is effectively pushing hepatocytes into the cell-cycle, but maturation of the freshly regenerated liver may not be sufficient and may lead to a temporary liver insufficiency of liver failure (38). This becomes particularly apparent when FLR is very small and the interstage interval short. Most surgeons would agree, that a FLR or standardized FLR (sFLR) $\leq 15\%$ are not amenable for resection. With the exception of transplantation, this issue of resectability has not been addressed surgically, so far. Lessons learned from parenchymal sparing liver surgery (PSS)(39-41) including intraoperative ultrasound (IOUS) guided non-anatomic resection of meticulously identified lesions and accepting minimal required surgical margins of at least 1 mm (41) do have the potential to be integrated in the concept of regenerative liver surgery to further advance resectability. Therefore, aim of this study was to test the combination of advantages of PSS and ALPPS as a modified ALPPS technique that increases FLR and safety of this procedure - parenchymal sparing ALPPS (psALPPS).

Patients and Methods

Study Population

All consecutive patients scheduled for liver surgery for HCC, IHCC and CRLM at the Department of General Surgery and Liver Transplantation at Fundeni Institute Bucharest,

Romania, a tertiary center for HPB surgery, were assessed for eligibility between April 2017 and April 2021. All patients underwent volumetric and functional hepatic assessment according to institutional standard protocol and were discussed at the multidisciplinary tumor board. Inclusion criteria included a sFLR for segments (S) 2-3 $\leq 15\%$ in non-cirrhotic and $\leq 20\%$ in cirrhotic livers, which were interdisciplinary judged to qualify for a right trisectionectomy. Exclusion criteria were patients with significant comorbidities not qualifying for right trisectionectomy and liver tumor entity of perihilar cholangiocarcinoma. The study was approved by our institutional ethics board (NO. 53320/2021). Informed consent was obtained in all cases.

Primary and Secondary Endpoints

The primary endpoint was completion of hepatectomy (i.e. successful progression to stage 2). Secondary endpoints included assessment of volumetric growth of FLR, liver functional assessment, and development of inter-stage and post-stage 2 complications.

Liver Volumetry

Computed tomography (CT) based liver volumetry was performed prior and after stage 1 ALPPS using a semi-automated method (Hepatic VACR[®], GE Healthcare, USA) on the venous phase with 6 mm section thicknesses (42,43). A clear definition of ps-FLR (S2-3 and part of S4) was performed manually, as the virtual transection plane through S4 was customized for each patient, using a 5-mm oncological margin.

Measurements were determined by the radiologist assisted by the surgeon. Standardized total liver volume (sTLV) was estimated on the basis of the body surface area (BSA) of the patients according to following formula: $sTLV (cm^3) = 706 \times BSA (m^2) + 2.4$ (44). The sFLR was calculated according to Vauthey et al ($sFLR = FLR / sTLV$) (45). The target sFLR volume prior to stage 2 was $\geq 25\%$ on non-cirrhotic liver and $\geq 35\%$ on liver cirrhosis.

Close liver functional assessment using was performed in the interstage interval and post-stage 2 using peak serum markers of liver injury and liver function as well as the Model of End-stage Liver Disease (MELD) (46). Complications were graded according the Dindo-Clavien classification system of surgical complications and complications $\geq 3a$ were considered major complications (47).

ALPPS Variant and Technical Setup

Stage 1 surgery

Patients considered eligible underwent exploratory J-shaped laparotomy. Resectability was assessed using IOUS, that confirmed the pre-operatively known lesions and scanned for new lesions and/or satellite nodules, mapping the tumors in relation to liver segments and major vessels. The liver was almost fully mobilized by dissecting the ligaments, except for the tip of the left coronary ligament, which was preserved to facilitate FLR fixation. The liver was almost fully mobilized from the inferior vena cava (IVC) by sectioning most of the accessory hepatic veins. The rationale was based on safety, as controlling all hepatic veins (HVs) was facilitated in this way, and also on efficacy, as partial venous deprivation obtained in this way should boost the regeneration of FLR. Right HV and common trunk of the middle and left HVs were controlled by placing tourniquets. The hanging maneuver was routinely performed.

After cholecystectomy and hilar lymphadenectomy, the hilar structures were exposed only on the right side to avoid extensive dissection of the hilum. The right hepatic artery was encircled with a vessel loop, facilitating the dissection of the right portal vein (RPV), which was likewise encircled with a vessel loop. The level of the RPV ligation was confirmed at IOUS Doppler. Whenever considered risky (e.g. large tumor compression of the portal bifurcation), portal vein occlusion was carried out using Hem-o-lok[®] clips, avoiding the sectioning and suture (*Fig. 1*). A tourniquet was placed on the liver hilum for a Pringle maneuver on demand.

The transection plane through the S4

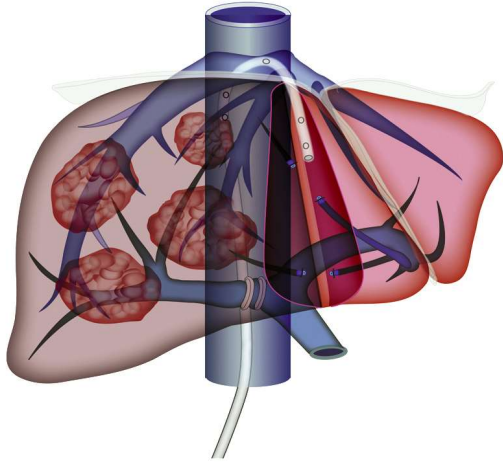


Figure 1. Schematic presentation of the psALPPS technique. Under IOUS guidance liver segment 4 is non-anatomically transected with the aim of preserving as much FLR on the left as possible, while respecting tumor margins and major vascular and biliary structures. With the exception of one case, the vessel was clipped and not transected. Note the positioning of a retrohepatic drain at the end of stage 1 surgery, which helps as an anatomical landmark and sling for the hanging maneuver at stage 2 surgery

2-1-81.pdf&EntryID=922974) was carefully evaluated using IOUS with the goal to preserve as much as possible of the left part of this segment while respecting oncological resection margins of at least 1 mm. The transection plane was curved or straight, depending on which part of S4 was preserved. When tumor was in contact with a major intrahepatic vessel (e.g. the left portal pedicle), a partial transection avoiding exposure of the tumor was performed. Parenchymal transection was performed mainly using the Kelly-crush technique under IOUS-guidance; we used energy device (Harmonic®, Ethicon Endo-Surgery) only for the first 1-2 cm. All cases were performed as partial ALPPS (15,48) avoiding the division of the middle HV. Intermittent clamping was used on demand, in case of significant bleeding during transection. When needed, tumor clearance of FLR was also performed during stage 1 surgery. Perihepatic spaces and the transection surface were drained. Particularly, a drain on the retrohepatic IVC was placed, through the

(Fig. 2 C-E and Supplementary video - <https://www.revistachirurgia.ro/pdfs/?art=202>

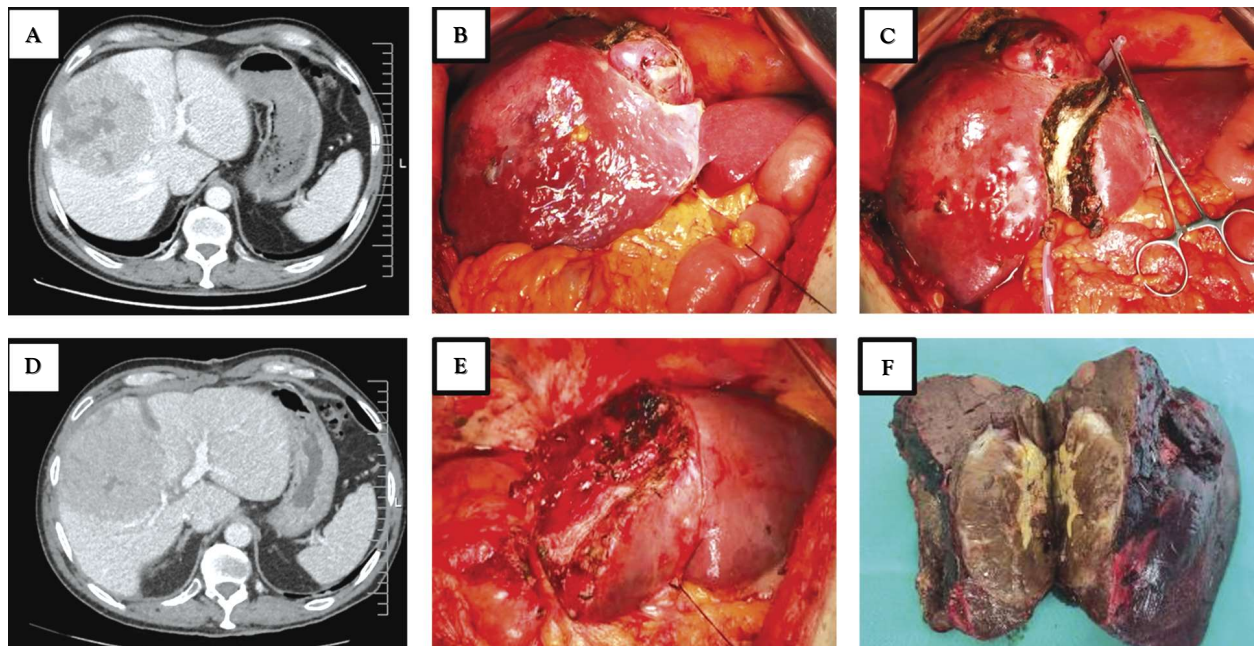


Figure 2. PsALPPS performed for a patient with a large HCC in the right liver with invasion to segment 4 on a HBV-associated liver cirrhosis Child A (case #5). Volumetry of S2-3 revealed an sFLR of 17.6% for a right trisectionectomy (A, B). Definition of a non-anatomic S-shaped transection plane through segment 4 using IOUS (C) could revealed a ps-sFLR of 29.4% making a staged resection with psALPPS possible. After an interstage interval of 14 days the ps-sFLR increased to 40.9% (D) making a completion hepatectomy possible (E). Panel F depicts the resected specimen with sufficient margins.

space between the right HV and the common trunk of the middle and left HV with the tip onto the cut surface (*Fig. 2C* and *Supplementary video*), to prevent adherence of IVC to the liver and to be used for the hanging maneuver during stage 2 of psALPPS.

Interstage interval

A minimum interstage interval was set to 14 days. The day before, a CT-volumetry of FLR was performed, and if insufficient, this was re-evaluated every other week. Patients were carefully monitored throughout this period.

Stage 2 surgery

After relaparotomy and adhesiolysis, the drain placed on the retrohepatic IVC was used as a sling for the hanging maneuver (*Fig. 2C* and *Supplementary video*). The right anterior and posterior pedicles were controlled, sectioned and sutured with the extraglissonian technique, combining the anterior and posterior approach. Liver transection was completed using the same technique as in stage 1. Finally, the right HV was sectioned and sutured. Vessel patency of the FLR was verified using Doppler IOUS. FLR was additionally fixed to the falciform ligament, if needed. Finally, a drain was placed on the cut surface and the abdomen was closed.

Results

Patient characteristics and liver volumetry

Five patients, four male and one female,

fulfilled above mentioned inclusion criteria for psALPPS (*Table 1*). Two patients had IHCC, two patients CRLM, and one patient HCC. Tumor details are presented in *Table 2*. Median age was 68 years (range: 66-78) and none had relevant comorbidities precluding major liver resection. While two patients presented with healthy liver parenchyma, the patient with HCC had hepatitis B virus (HBV) related Child A cirrhosis, another one HBV chronic hepatitis, and one patient had steatosis. Calculated sFLR for S2-3 before stage 1 surgery aiming for anatomic right trisectionectomy were 18% in the cirrhotic liver, and 11% in the patients with normal liver background. In the other two patients an sFLR of 12% was calculated. Given this volumetry and the liver parenchymal quality, none of these patients were judged resectable with conventional ALPPS. Re-calculating liver volumetry manually using the principles of PSS, a non-anatomic ps-sFLR pre-stage 1 of at least 20% (median: 25, range: 20-28), and pre-stage 2 of at least 25% (median: 34, range: 25-39) was determined (*Table 1*).

Stage 1 surgery

Median operative time for stage 1 was 250 min (range: 225-445 min) with a median blood loss of 900 ml (range: 750-1450 ml) requiring transfusion in two cases (*Table 3*). The Pringle maneuver was performed on demand in the two cases in which transfusion was needed. Considerable bleeding was encoun-

Table 1. Patient characteristics and liver volumetry

Patient	Age	Gender	Liver quality	Stage 1 volumetry				Interstage interval (days)	Stage 2 volumetry		Procedure completed	Delta	
				FLR (S2/3) (%)	sFLR (S2/3) (%)	ps-FLR (%)	ps-sFLR (%)		ps-FLR (%)	ps-sFLR (%)		Yes	ps-FLR (%)
#1	66	M	Steatosis	11.3	11.6	20.0	20.5	20	26.1	31.6	Yes	6.0	11.1
#2	68	F	Chronic hepatitis (HBV)	11.6	12.5	25.9	27.7	14	33.9	42.7	Yes	8.0	15.0
#3	78	M	Normal liver	11.7	10.7	24.8	22.7	15	34.0	34.5	Yes	9.3	11.8
#4	74	M	Normal liver	10.4	10.6	20.1	20.6	-	-	-	No	-	-
#5	67	M	Child A cirrhosis (HBV)	16.7	17.6	27.8	29.4	14	38.5	40.9	Yes	10.7	11.6

Table 2. Tumor characteristics

Patient	Tumor entity	Total tumor number	Maximum tumor diameter (cm)
#1	CRLM	6	7.5
#2	IHCC	1	12
#3	IHCC	1	8
#4	CRLM	26	6
#5	HCC	1	9

tered in case #2 after transection of the middle HV during parenchymal transection of S4. Cause of this bleeding was the cut surface of the deportalized lobe, most probably due to the sudden congestion induced by division of the middle HV. This event led to 900 ml blood loss in 20 min, requiring transfusion (that otherwise would have not been needed). Therefore, in the following cases, parenchymal transection was performed avoiding the division of the middle HV and exposing it on the cut surface. All cases, with the exception of case #1, who underwent RPV sectioning, only underwent ligation of the RPV. In case #4 the posterior RPV emerged separately from the main portal vein, that was sectioned in order to provide access to the right anterior portal vein, which was subsequently clipped. Tumor clearance of FLR, which was considered in pre-operative liver volumetry was required only in case #4. Details of operative data on stage 1 are depicted in *Table 3*.

Interstage Interval

After stage 1, patients spent a median time of one day (range: 1-2 days) on the intensive care unit (ICU) for close observation and stayed hospitalized until completion hepatectomy.

The median interstage interval was 15 days (range: 14-20 days) (*Table 1*). The only complication occurring in the interstage interval was a self-limiting drainage bleeding in case #3 requiring one unit of red blood cell (RBC) transfusion (grade 2 complication according to the Dindo-Clavien system of surgical complications(47) (*Table 5*). Four of the five patients were able to successfully proceed to stage 2. However, one patient (case #4) experienced intrahepatic disease progression, with new lesions in FLR occurring during the interstage interval. This patient was referred to palliative chemotherapy without completing hepatectomy (drop-out).

Stage 2 Surgery

Median operative time for stage 2 was 240 min (range: 200-300 min) with a median blood loss of 575 ml (range: 400-1350 ml) requiring transfusion in one case (*Table 3*; Pringle maneuver was only performed in this case (case #1). During stage 2, the drain placed on the retrohepatic IVC at stage 1 turned out to be very useful, as it facilitated the re-mobilization of the right hemiliver by preventing the adherence of IVC to the liver. The separate extraglissonian approach of the anterior and posterior right portal pedicles avoided the dissection of the fibrotic tissue formed on the right side of the liver hilum (due to previous dissection during stage 1) eliminating the risk of intraoperative injuries of the main vascular and biliary structures of the remnant liver. Consequently, no adverse events were recorded intraoperatively. In the postoperative course of stage 2 patients spent a median of 2 days (1-2 days) on ICU with a total median

Table 3. Operative data of psALPPS

Patient	Stage 1 surgery				Stage 2 surgery			
	Time (h)	Blood loss (ml)	Transfusion	Pringle	Time(h)	Blood loss (ml)	Transfusion	Pringle
#1	4:45	850	No	No	5:00	1350	Yes (1 unit)	Yes
#2	3:45	1450	Yes (1 unit)	Yes	5:00	500	No	No
#3	4:10	750	No	No	3:20	650	No	No
#4	7:25	950	Yes (1 unit)	Yes	-	-	-	-
#5	3:50	900	No	No	4:20	400	No	No

hospitalization time of 29 days (range: 22-30 days) (*Table 5*). Post-stage 2 complications occurred in three patients; the highest grade was a Dindo-Clavien grade 2 complication. Two patients had ascites (treated with diuretics), and one patient developed *C. difficile* colitis (treated with adequate antibiotics).

Liver Function

Preoperative liver function, interstage, and postoperative liver function were monitored closely clinically and using laboratory parameters giving a validated reflection of liver function (*Table 4*). Starting with a normal liver function at stage 1, none of the patients developed liver failure this stage (*Table 4*). Likewise, after stage 2, none of the patients developed liver failure as shown in *Table 4*. None of the patients fulfilled the 50-50 criteria after stage 1 and 2, maximum median MELD after stage 1 was 10, and after stage 2 was 12. Peak aspartate transaminase (ASAT), alanine transaminase (ALAT), and bilirubin were 321 U/L, 372 U/L, and 2.5 mg/dL, respectively (*Table 4*). Except ascites mentioned above, no further clinical signs of postoperative liver dysfunction occurred.

Follow-up

After completed hepatectomy, two of 5

patients (CRLM only) underwent adjuvant chemotherapy. The median follow-up was 6 months (range: 3-23 months) with no hepatic and extrahepatic recurrence in this period. The patient with the longest follow-up (case #1) died at 23 months after surgery with hepatic and extrahepatic recurrence diagnosed at 17 months after surgery (*Table 6*). All the other patients are alive without recurrence.

Discussions

The current analysis is a consecutive series of patients with extensive malignant liver tumors (HCC, IHCC and CRLM), who underwent liver resection with an sFLR $\leq 15\%$ using psALPPS. Concept of this novel technique is to maximally shift the liver transection plane towards the deportalized hemiliver, saving a significant amount of liver tissue on the side of FLR. This novel ALPPS technique uses principles of PSS with exact ultrasound-guided definition of transection planes, while ensuring the required oncological margins.

Patients included were judged non-resectable, neither by regenerative liver surgery, including conventional two-stage hepatectomy, bi-embolization and ALPPS, nor by PSS. A potential alternative to overcome the dilemma of the too small FLR could be liver transplantation (LT), either full graft LT,

Table 4. Main lab data on the postoperative course. No dialysis required in all patients

Patient	Peak bilirubin (mg/dL)	Bilirubin (mg/dL) Day 5	Peak ASAT (U/L)	Peak ALAT (U/L)	Prothrombin time Day 5	Peak INR	50-50 criteria fulfilled	Peak MELD
<i>Post-stage 1 surgery (interstage interval)</i>								
#1	0.6 (0.4-0.7)	0.55	91.0 (65.0-117.0)	104.5 (61.0-159.0)	15.5	1.14	no	8
#2	0.4 (0.2-0.6)	0.42	137.0 (49.0-225.0)	59.0 (38.0-372.0)	14.8	1.32	no	10
#3	1.2 (1.2-1.2)	0.92	283.0 (245.0-321.0)	156.5 (96.0-257.0)	14.2	1.43	no	11
#4	0.7 (0.7-0.8)	0.70	127.0 (63.0-256.0)	101.5 (74.0-216.0)	16.2	1.33	no	10
#5	0.7 (0.5-0.9)	0.66	191.0 (157.0-261.0)	154.0 (138.0-185.0)	17.5	1.42	no	11
<i>Post-stage 2 surgery</i>								
#1	1.0 (0.8-2.3)	0.9	52.0 (47.0-123.0)	38.5 (35.0-42.0)	18.8	1.81	no	13
#2	0.9 (0.5-1.3)	0.6	37.5 (24.0-101.0)	44.5 (24.0-72.0)	16.3	1.52	no	11
#3	1.6 (1.5-2.0)	1.5	50.0 (38.0-83.0)	56.0 (45.0-58.0)	15.9	1.31	no	10
#4	*	*	*	*	*	*	*	*
#5	1.2 (0.9-2.5)	1	67.0 (52.0-198.0)	93.0 (88.0-169.0)	18.2	1.78	no	16

Table 5. Clinical data on the postoperative course

Patient	Post-stage 1 (Interstage Interval)			Post-stage 2			Total hospital stay (days)
	ICU stay (days)	Complications	Dindo-Clavien Classification	ICU stay (days)	Complications	Dindo-Clavien Classification	
#1	1	none		4	C. difficile colitis	II	30
#2	1	none		2	Ascites (max. 900 ml on POD 2)	II	26
#3	2	drainage bleeding requiring blood transfusion	II	2	none		29
#4	1	none		-	-	-	22
#5	1	none		1	Ascites (max. 800 ml on POD 2)	II	29

Resection and partial liver S2–3 transplantation with delayed total hepatectomy (RAPID) (49,50), or heterotopic transplantation of S2-3 using the splenic Vein and Artery after Splenectomy and with delayed total hepatectomy RAVAS (51). Benefits of RAPID and RAVAS have been demonstrated in a very limited number of cases in CRLM, but, to our knowledge, not in IHCC. Besides safety, feasibility, and immunosuppression, the availability of donor organs needs to be considered in these scenarios. Acknowledging the worldwide scarcity of donor organs, we instead aimed to optimize staged, regenerative liver surgery with maximization of the starting size and growth of FLR.

Increased portal hyperperfusion and consecutive arterial hypoperfusion of FLR because of contralateral PVE may cause a stealing phenomenon of the left hepatic artery and could contribute to increased morbidity and mortality rates after ALPPS (5,52) However, there is limited data available on the hemodynamic consequences of ALPPS (53).

Following this hypothesis, extra liver volume rescued by psALPPS would counteract the impact of portal hyperperfusion, protecting FLR.

Since the introduction of ALPPS, a series of variants were devised to refine the initial technique, including partial ALPPS (48), hybrid ALPPS (54), mini-ALPPS (55), tourniquet ALPPS (22), and S4 portal pedicle-spared ALPPS (19). All these modified techniques also use different transection planes than initially described, but stick to anatomic transection planes. S4 portal pedicle-sparing ALPPS has some similarity to psALPPS, as it avoids the division of the portal pedicles of S4 in order to prevent necrosis, but uses the anatomic conventional transection plane for right trisectionectomy as initially described. Proponents of the “classical” in-situ split for right trisectionectomy argue that partial devascularization of S4 is chiefly responsible for the accelerated hypertrophy. This hypothesis, however, could not be confirmed in series of non-right trisectionectomy ALPPS

Table 6. Follow-up after psALPPS

Patient	Follow-up period (months)	Hepatic recurrence	Extrahepatic recurrence	Alive
#1	23	Yes (at 17 months)	Yes (lung and brain at 17 months)	No (Dead at 23 months)
#2	7	No	No	Yes
#3	5	No	No	Yes
#4	-	-	-	Yes
#5	3	No	No	Yes

(6,28). Saving functional liver parenchyma on the side of FLR should be considered the number one priority to improve safety and push resectability in ALPPS. This series of psALPPS has shown that with a median ps-sFLR of 22.7%, the delta ps-sFLR of 11.7% is moderate and the median interstage interval of 15 days is longer than in large ALPPS registry series (5-7,52) and the Scandinavian randomized-controlled trial (RCT) (4). Precisely these two features of psALPPS may avoid a too strong FLR volume gain with a lag in metabolic function (56) corresponding to immature regenerated hepatocytes (38). Critiques may argue that longer interstage interval and a flatter volume gain would be appropriately addressed by pre-operative PVE. However, this series shows that the median interstage interval of 15 is certainly half of PVE and delta sFLR of 11.7% with a starting median standard volume of 22.7% cannot be achieved by PVE.

Besides the avoidance of S4 necrosis, that is a source of complication when using conventional ALPPS, a significant advantage of psALPPS is the avoidance of major bile leaks at the transection surface. Transection for conventional ALPPS is associated with a complete exclusion of S4 from the biliary tree, commonly leading to infected biloma before stage 2. Moreover, completion hepatectomy in psALPPS can be considered technically easier as the transection line is closer to the main portal bifurcation, particularly when major part of S4 inferior is preserved (*Fig. 2E*). This lowers the risk of injury to the main bile duct and the portal vein feeding FLR. Indeed, in our series we did not encounter bile leaks, not even with small output.

The main reason for using ALPPS has been the fast liver regeneration of FLR and short interval time before final hepatectomy. However, even though ALPPS induces a fast volumetric regeneration of FLR after Stage 1, its function often does not correspond to the actual liver volume increase (57,58). Moreover, neoadjuvant chemotherapy significantly impairs hypertrophy of FLR after ALPPS without impact on morbidity or in-hospital

mortality (59). If so, psALPPS should not be used only when ALPPS is not feasible because of too small FLR, but it should be chosen over conventional ALPPS whenever feasible, especially in case of neoadjuvant chemotherapy. In this way, FLR would have an improved function making the procedure safer. Furthermore, it would allow further local treatments in case of tumor recurrence, according to PSS policy.

Strength of this series is, that it first demonstrates the value of routine use of IOUS in ALPPS. IOUS enables a complete tumor mapping, which may change the surgical strategy as shown in case #1. Even in cases of large single lesions, when psALPPS can be safely performed without ultrasound guidance, IOUS is strongly recommended for optimal diagnosis and resection guidance.

The customized transection plane, through the S4, could be judged as a technically more demanding and time consuming, as it is wider, more vascularized and may require IOUS-guidance, particularly in case of deep located tumors in S4, when compared to conventional ALPPS. The customized transection plane and the care for implementing the innovative elements to insure both, safety and resectability, explain the relatively long operative times.

IOUS was a very useful tool during psALPPS. First, IOUS assessed the resectability by confirming known lesions and by scanning for new lesions and/or satellite nodules, and by mapping all tumors in relation to liver segments and major vessels. Second, IOUS Doppler assisted in establishing the optimal level of the RPV ligation. Third, IOUS helped to establish the transection plane through the S4 preserving as much as possible of the left part of this segment while respecting oncological resection margins of at least 1mm. Parenchymal transection was performed under IOUS-guidance. Finally, Doppler IOUS verified vessel patency of the FLR at the end of liver resection.

PSS using IOUS requires a certain learning curve and is difficult to standardize (39-41). The transection plane through S4 is customized for

each patient, and the partitioning is likely more difficult compared to the avascular, anatomic transection at the falciform ligament. Following the concept of partial ALPPS, the partitioning through S4 may be incomplete, as limiting the partitioning at the level of the middle HV was shown to be sufficient for inducing the optimal hypertrophy of FLR (15,48,55). As learned from case #2, the division of the middle HV was subsequently avoided for reasons of safety. More so, for completion hepatectomy, an extraglissonian approach of the anterior and posterior portal pedicles was used, thus avoiding the difficult and therefore risky hilar dissection. This approach was particularly useful when the liver hilum was affected by inflammation and fibrosis. Our procedure was also improved by the use of hanging maneuver during both stages and the extraglissonian approach during the 2nd stage. The hanging maneuver fulfilled two purposes. First, it facilitated the liver partitioning by offering external guidance, by superficializing the deeper part of the cut surface and by reducing bleeding through retrograde compression. Second, we prevented adherence of the IVC to the liver during interstage period, by converting the tube used for hanging maneuver into a drain placed on the IVC. This tube was re-converted in stage 2 surgery to facilitate an easy and safe completion hepatectomy.

Tumor recurrence after ALPPS in CRLM seems not be accelerated as shown by translational evidence and in the LIGRO RCT (31,60). In case of liver recurrence, patients after ALPPS are well able to undergo repeated hepatectomy if there is no diffuse tumor spread (7). As oncological results for PSS are not inferior compared to other resection techniques (61), an inferiority of psALPPS cannot be assumed, as all current oncological principles are fulfilled by this novel technique. However, long-term outcome remains to be further studied.

A limitation of this study is that it presents a single-institutional experience in a limited number of patients within a limited period, which currently cannot be extrapolated to all patients meeting the proposed inclusion

criteria. However, the complete lack of major morbidity and mortality proves its safety and feasibility and should be considered as a technical variant in patients with a very low FLR.

Conclusion

In conclusion, psALPPS successfully combines two concepts of major liver surgery, regenerative and parenchyma-sparing liver surgery, which synergistically achieve a resectability otherwise not possible with either technique or any other resection technique. Parenchyma sparing ALPPS offers the advantage to maximize FLR and simultaneously reduce ischemic injury of segment 4 compared to conventional ALPPS. In this way, psALPPS may markedly increase resectability while reducing morbidity.

Author Contributions

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Manuscript writing: all authors.

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Conflicts of Interest

The authors have no related conflicts of interest to declare.

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Ethical Statement

The present study was approved by the Ethical Committee of Fundeni Clinical Institute, Bucharest.

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