

ALPPS Procedure. The New Frontier in Advanced Liver Surgery. Single Centre Experience and Literature Review

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Rezumat

Procedura ALPPS. Noua frontieră în chirurgia hepatică avansată. Experiența unui singur centru și review literaturii

Introducere: Prezentarea primei experiențe a unui centru de chirurgie hepatică în aplicarea unei proceduri inovatoare – ALPPS (Associating Liver Partition and Portal vein ligation for Staged hepatectomy – asocierea partiției hepatice și ligaturarea venei portă pentru hepatectomie stadializată) pentru tumori hepatice masive. Această metodă a fost efectuată în clinica chirurgie 2 din 2018 la pacienți cu tumori hepatice primare sau metastatice masive, al căror volum al viitorului ficat rezidual - este considerat prea mic, pentru a efectua rezecție hepatică curativă în condiții de siguranță. Până nu de mult condițiile acestea repartizau tumorile voluminoase, ce ocupau mai mult de 75-90% de ficat, în grupa tumorilor nerezecabile. În mod prospectiv procedura ALPPS a fost evaluată pentru a efectua conversia tumorilor hepatice nerezecabile, din cauza volumului mic de ficat rezidual, în cele rezecabile. Datele literaturii au fost revizuite sistematic folosind PubMed, Scopus, Google Scholar.

Materiale și Metode: Din iunie 2018 au fost efectuate 18 proceduri ALPPS, la pacienți cu vârsta 62 ± 8 ani. Indicațiile pentru rezecția chirurgicală au fost metastaze hepatice ale cancerului colorectal în 7 cazuri, cololangiocarcinom perihilar în 4 cazuri, carcinom hepatocelular în 6 cazuri și metastaze GIST 1 caz. Din datele literaturii am analizat articole din 2014 până în 2019.

Rezultate: Volumul ficatului rezidual a fost calculat pe angiografie CT folosind programul inclus în soft-ul aparatului Siemens® și a fost de 252 ± 115 ml ($19,4 \pm 6,2\%$) înainte de ALPPS-1 și 542 ± 165 ml ($30,7 \pm 6,5\%$) înainte de ALPPS-2 ($P < 0,001$). Creșterea volumului ficatului rezidual între cele două proceduri a fost de $60,4 \pm 38\%$

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(interval: 31-110%, $p < 0,001$). Timpul mediu dintre prima și a doua procedură a fost de $9,4 \pm 2,3$ zile. Media de spitalizare a fost de $28,4 \pm 9,2$ zile. Morbiditatea postoperatorie 34,8%, mortalitatea zero. Supraviețuirea la 18 luni a fost de 100%.

Concluzie: Tehnica ALPPS ne permite să mărim rata rezecabilității la pacienți cu tumori hepatice inițial nerezecabile, cu rezultate postoperatorii favorabile. Selecția atentă a pacienților pentru o intervenție de complexitate majoră, cum este ALPPS, ne-a permis să evităm mortalitate postoperatorie. Ciroză hepatică, colestază și hemoragia intraoperatorie sunt factori principali pentru dezvoltarea morbidității postoperatorii.

Cuvinte cheie: tumori hepatice nerezecabile, volum ficat rezidual, volumetria hepatică, rezecție hepatică, ligaturarea ramului drept a venei portă, insuficiență hepatică posthepatectomie

Abstract

Introduction: Presentation of the first experience of a liver surgery center in applying an innovative procedure - ALPPS (Associating Liver Partition and Portal vein ligation for Staged hepatectomy) for massive liver tumors. This method has been performed in the surgery clinic 2 since 2018 in patients with massive primary or metastatic liver tumors, whose future residual liver volume is considered too small to perform curative liver resection safely. Until recently, these conditions assigned large tumors occupying more than 75-90% of the liver to the group of unresectable tumors. Prospectively, the ALPPS procedure was evaluated to convert unresectable liver tumors due to the small residual liver volume into resectable ones. Literature data were systematically reviewed using PubMed, Scopus, Google Scholar.

Materials and methods: Since June 2018, 18 ALPPS procedures were performed in patients aged 62 ± 8 years. Indications for surgical resection were liver metastases of colorectal cancer in 7 cases, perihilar cholangiocarcinoma in 4 cases, hepatocellular carcinoma in 6 cases, and GIST metastases 1 case. From the literature data we analyzed articles from 2014 to 2019.

Results: Residual liver volume was calculated on CT angiography using the program included in the Siemens® machine software and was 252 ± 115 ml ($19.4 \pm 6.2\%$) before ALPPS-1 and 542 ± 165 ml ($30.7 \pm 6.5\%$) before ALLPS-2 ($P < 0.001$). The increase in residual liver volume between the two procedures was $60.4 \pm 38\%$ (range: 31-110%, $P < 0.001$). The mean time between the first and second procedure was 9.4 ± 2.3 days. Average hospital stay was 28.4 ± 9.2 days. Postoperative morbidity 34.8%, mortality 0. Survival at 18 months was 100%.

Conclusion: The ALPPS technique allows us to increase the resectability rate in patients with initially unresectable liver tumors with favorable postoperative outcomes. Careful selection of patients for a major complex procedure such as ALPPS allowed us to avoid postoperative mortality. Liver cirrhosis, cholestasis, and intraoperative hemorrhage are major factors for the development of postoperative morbidity.

Key words: unresectable liver tumors, residual liver volume, liver volumetry, liver resection, right portal vein ligation, post-hepatectomy liver failure

Introduction

Surgical resection of bulky liver tumors is the only method with a potentially curative effect in primary and metastatic liver tumors. A residual liver volume (RLV) less than 25-30%

should be avoided in morphologically normal liver, 35-40% in liver after chemotherapy, 40-45% in liver fibrosis, and 45-50% in a cirrhotic liver to exclude post-hepatectomy liver failure caused by a small functional liver volume (*Figs. 1, 2*) (1). Over the years, different

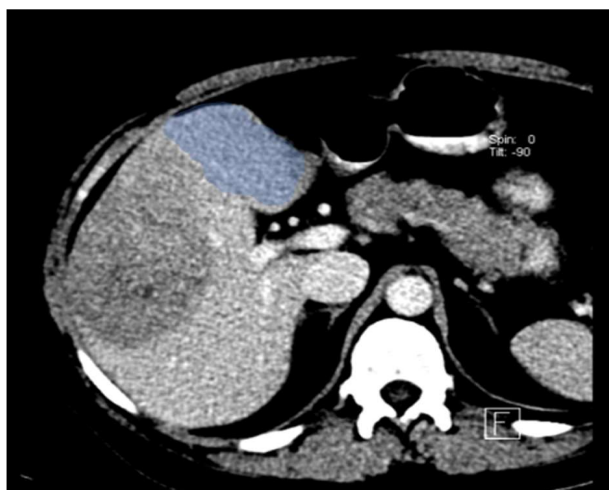


Figure 1. CT abdominal. Residual liver volume 21%

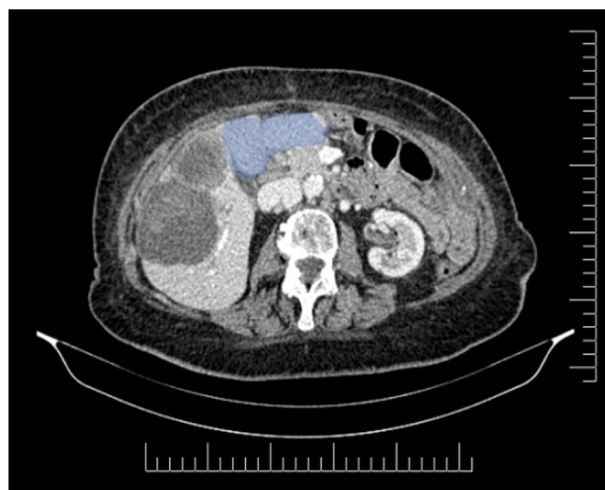


Figure 2. CT abdominal. Residual liver volume 18%

strategies have been developed to increase the resectability of advanced tumors to be resected, leaving sufficient VRL. Preoperative embolization of the portal branch of the portal vein (EVP) or intraoperative ligation of the right portal branch of the portal vein (LVP) is based on occlusion of flow in one of the main branches of the portal vein which induces atrophy of the ipsilateral liver lobe and subsequent hypertrophy of the contralateral lobe (residual future lobe); usually the right branch of the portal vein is occluded, due to the larger volume of the right liver to increase the volume of the left hemifield. This maneuver induces compensatory left lobe hypertrophy, which averages 40% in about 4-8 weeks (2). Although the described method has developed considerably and favorable results have been obtained in rapidly growing tumors, the time required to achieve the necessary compensatory hypertrophy is often too long to ensure tumor operability, and the degree of compensatory hypertrophy is often less than expected (3). To address such problems, recently, a new liver resection technique has been described, which is performed in two stages - called Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS). ALPPS is an innovative surgical technique, which allows to extend the indication of hepatectomy to liver tumors considered un-

resectable by other techniques due to insufficient liver parenchyma - volumetrically and functionally. The first stage of this procedure associates intraoperative ligation of the right portal branch and division of the liver, usually following the scheme of an extended straight hepatectomy. Unlike a classic hepatectomy, the diseased part of the liver (tumor-bearing) is left in situ and remains vascularized only by the right hepatic artery, again drainage through the right bile duct and hepatic veins are preserved (4).

In the second stage of the procedure, which is usually performed within 7-14 days of the first, the diseased part of the liver is removed by sectioning the right hepatic artery, right hepatic duct, and systemic venous pedicles. This innovative procedure allows for rapid and significant hypertrophy of the VRL, thus ensuring greater operability than previous techniques.

ALPPS is touted as one of the most revolutionary surgical procedures in liver surgery in the last decade and has generated tremendous interest in recent years for the worldwide HPB community reflected in consensus, debates, and medical publications.

Surgical Technique

For a better understanding of this surgical

technique, performed in two stages with an interval between them, it is important to define some terms: "diseased hemiliver (DH)" is the part of the liver with tumor burden that will be removed in that second step; "VRL - volume of residual liver" is the hemiliver comprising the liver segments (without tumor burden) that will remain after both procedures; "clean-up" is the resection of all tumor lesions in the VRL during the first step of this technique.

Stage 1.

A bilateral subcostal laparotomy is preferred. To exclude some extrahepatic lesions not detected preoperatively, a thorough exploration of the organs of the abdominal cavity should be performed. Intraoperative ultrasonography (USIO) is mandatory and is performed accurately to assess the number, location, and relationship of tumor lesions to vascular structures. The first surgical gesture consists of perihilar lymph node highlighting not only for oncological reasons, but also for better identification of the anatomical structures of the hepatic pedicle. The lymph nodes are investigated by extemporaneous histopathological examination.

Identification of the elements of the hepatoduodenal ligament: portal vein, right branch of the portal vein and branch of segment 4 (or branch of segments 5, 8 in case

of left trisectionectomy) of the portal vein, right and left hepatic artery, choledochus and common hepatic duct. After ligation and protection of all hilar structures a complete "clean-up" of the tumors in the VRL will be performed. Subsequently, the portal branch of the diseased hemifield and the portal branch for segment 4 (or branch of segments 5, 8 in case of left trisectionectomy) is sectioned and sutured (*Fig. 3*). The affected hemifield is mobilized from its ligaments (right coronary ligament, right triangular), dividing the accessory hepatic veins to the necessary posterior limit. After completion of mobilization, we routinely perform an open cystic duct cholecystectomy for a transcystic test and subsequent transcystic hydraulic test and intraoperative cholangiography. Total or almost total partition (division) of the liver up to the level of the inferior vena cava. Thus, right hepatectomy or right trisectionectomy (segments 4-8 ± segment 1) or left trisectionectomy (segments 1-5 + segment 8) is performed, depending on the patient and the local extension of the disease (*Fig. 4*). For liver transection, we prefer the CUSA (Cavitron Ultrasonic Surgical Aspirator) device. Hanging maneuver is used on a case-by-case basis. It is important to avoid any damage to the right hepatic artery during the parenchymal transition, as this is the only source of vascular flow to this hemifield and therefore essential to avoid liver

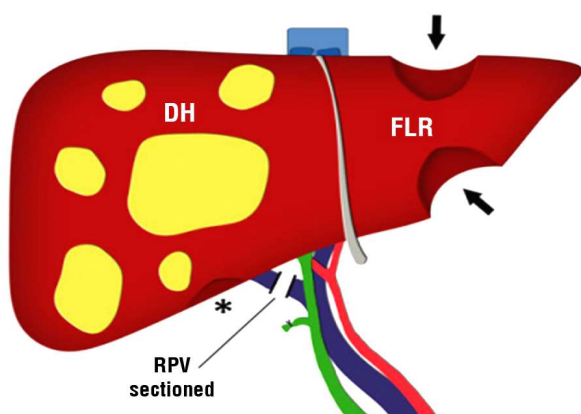


Figure 3. After complete resection of the tumor nodule in the residual future liver. The right branch of the portal vein sectioned. Cholecystectomy

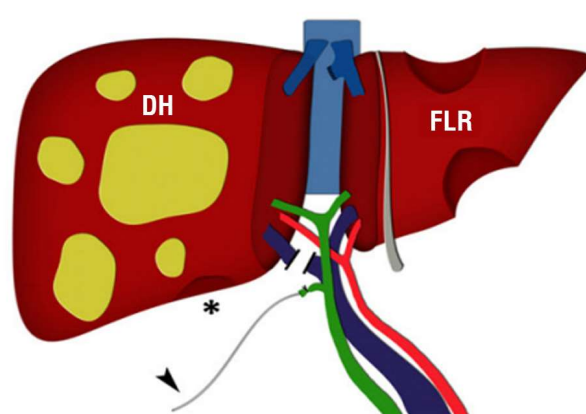


Figure 4. Catheterized cystic duct to perform hydraulic test and intraoperative cholangiography

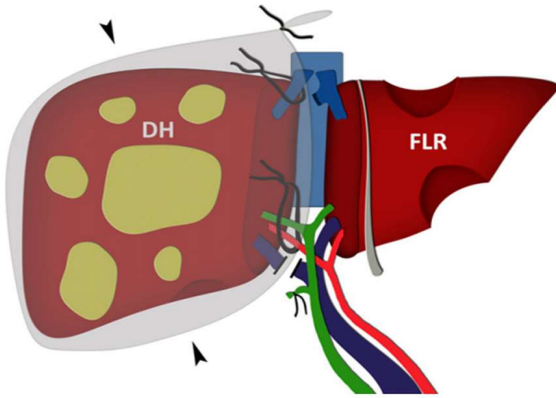


Figure 5. End of first stage. Vascular and biliary structures marked with black thread. Affected hemifield placed in bag

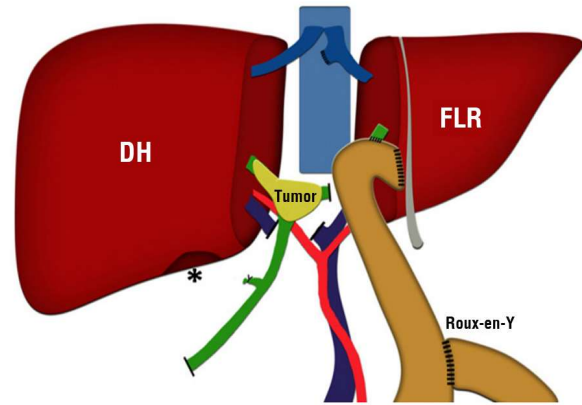


Figure 6. Biliodigestive anastomosis with left lateral section liver duct (SII-III), performed at the end of stage I. Klatskin perihilar cholangiocarcinoma IIIA

necrosis. A complete hemostasis and bilio-stasis of both liver surfaces is a prerequisite in liver resections. After performing the hydraulic test and repairing the biliary fistula, the hepatic artery, cystic duct, and hepatic vein of the diseased hemifield are marked with black thread or vascular loop to facilitate their identification in the second stage. The diseased hemifield is wrapped with a plastic bag to facilitate the second procedure by minimizing postoperative adhesions and avoiding biliary peritonitis (*Fig. 5*). Drains are placed in the right subphrenic space and the other between the liver surfaces.

When a hilar cholangiocarcinoma is operated on and a right trisectionectomy is to be performed, the common bile duct and left

bile duct are transected with R0 surgical margins to be removed en-bloc with the liver parenchyma during completion surgery. Biliodigestive anastomosis should be performed in the first stage immediately after liver division to achieve optimal positioning of the hepaticojejunodigestive anastomosis (*Fig. 6*) (5).

Stage 2.

On 6-7th postoperative day CT or MRI was performed with assessment of the degree of hypertrophy and absence of tumor in the future residual liver. If sufficient volume is demonstrated and the patient does not represent contraindications for surgery the 2nd stage of ALPPS will be performed the following day (*Figs. 7, 8, 9*).

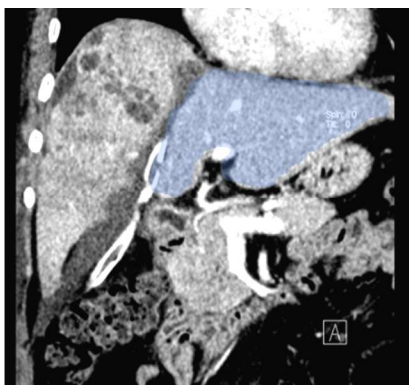


Figure 7. CT after 1 stage. Hypertrophy S2,3. VFR 42%

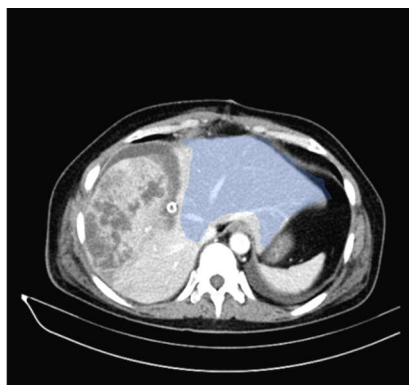


Figure 8. CT after 1 stage. Hypertrophy S2,3. VFR 47%

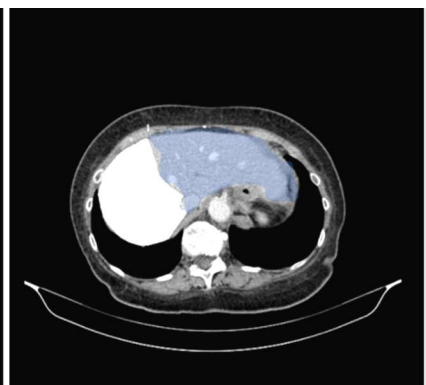


Figure 9. CT after 1 stage. Hypertrophy S2,3,4 VFR 53%

Relaparotomy will be performed through the anterior incision, after viscerolysis, the bag will be evacuated from the peritoneal cavity. The hepatic artery, and the bile duct should be carefully highlighted due to hypertrophy of the caudate lobe the anatomy of these anatomical structures is altered. USIO is also mandatory at the 2nd stage to identify the presence or absence of tumors in the residual liver, determining the vascular structures - hepatic artery, left, hepatic veins, after they are sectioned using the vascular stapler (*Fig. 10*). The cystic duct is carefully identified, which is cannulated and intraoperative cholangiography is performed, this gesture is extremely important as the intrahepatic biliary anatomy is diverse and requires particular accuracy in identification and sectioning. The affected liver is removed from the abdominal cavity, which in turn is retracted (*Fig. 11*).

Pathophysiology of Liver Regeneration

The liver has an intense regenerative capacity, which is achieved by both hyperplasia and cellular hypertrophy. As early as 12 hours after surgery, the intensity of liver regeneration reaches its maximum through substantial changes in gene expression (6). The type of regeneration largely depends on the volume of liver resection. In 1/3 liver resections, cellular

hypertrophy is induced, in 2/3 liver resections, cellular hypertrophy is induced hepatic hyperplasia, in resections greater than 80% the mechanism of dedifferentiation of biliary epithelial cells (BECs) into hepatic progenitor cells (HPCs) is triggered and repopulates the liver (*Fig. 12*) (7). Studies have shown that liver cell replication after hepatectomy is mediated by hepatocyte growth factor (HGF), tumor necrosis factor (TNF), interleukin-6, transforming growth factors (TGF), epidermal growth factors (EGF) (8). ALPPS is associated with more accelerated increase in residual liver volume along with all markers of hepatocyte proliferation compared with portal vein ligation (9). Several data may elucidate the mechanisms that generate the accelerated and remarkable hypertrophy observed during ALPPS. Among the mechanisms that trigger and support liver regeneration, it is the redistribution of portal blood flow and hepatotrophic factors to the residual liver induced by portal vein ligation that plays the most important role (10); arterialization of the diseased hemifield acts as an auxiliary liver which allows the residual liver to tolerate portal hyperinflux by modulating double vascular flow (11). An important role is also played by liver partitioning, which disrupts intrahepatic portal collaterals (12) and may induce an inflammatory response with the release of growth factors, which is itself a stimulus for

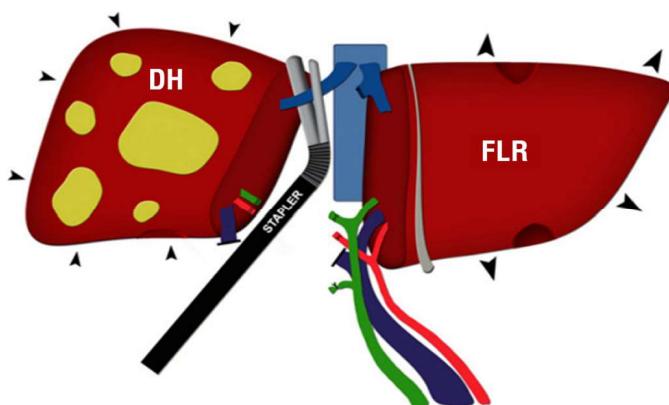


Figure 10. End of the second stage. Vascular structures sectioned using the vascular stapler.

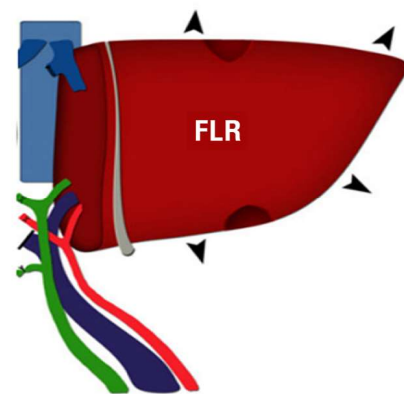


Figure 11. Final aspect

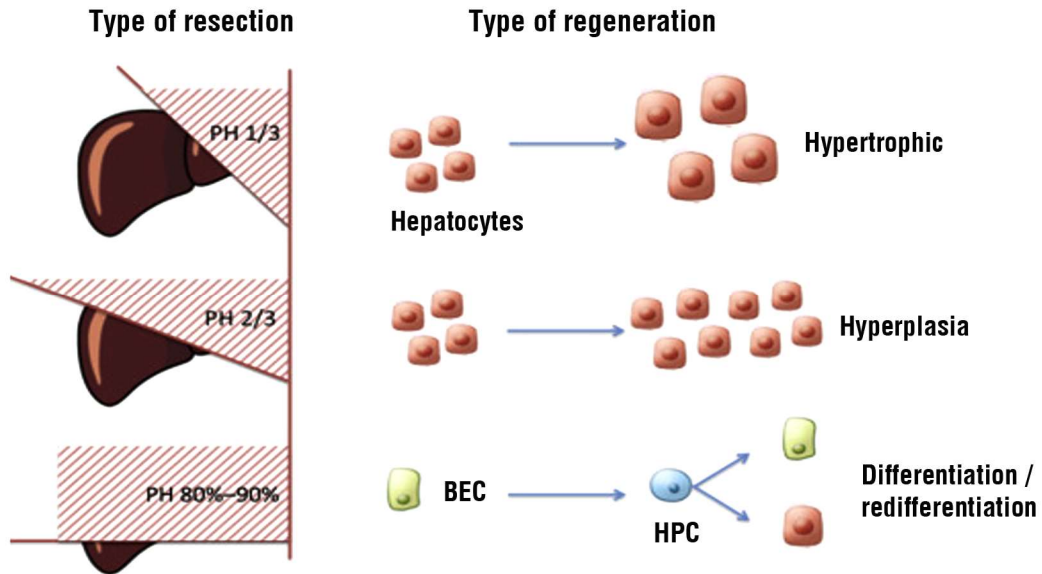


Figure 12. Dominant type of regeneration depending on resection volume

regeneration (9). Another study compared histological findings in the future residual liver in ALPPS with those in hepatectomy after portal vein embolization and it was determined that hepatocyte density is higher with smaller sizes after ALPPS than after portal vein embolization. They also confirmed that residual liver hepatocytes in ALPPS are more immature than in portal vein embolization (13).

Experimental Models

The ALPPS technique induces a rapid increase in VRL four times faster than embolization or portal vein ligation strategies. For a better understanding of the basic principles of ALPPS-triggered regeneration, some experimental animal models have been developed in recent years. Schlegel et al. (9) described the first model of ALPPS in mice. The result confirmed much faster regeneration of the VRL in the ALPPS group compared with the group in which only portal branch ligation was performed and provides evidence suggesting that the ability of accelerated VRL regeneration is due to increased afferent venous circulation with the interruption of afferent and intra-

hepatic venous circulation between the affected hemifield and the residual hemifield after liver transection. Markers of hepatocyte proliferation were tenfold higher after ALPPS compared with control groups (14-16). Recently, a porcine model for ALPPS has also been introduced, with kinetic growth rates similar to those seen in humans (17). Histological studies and molecular models in animals are a valuable tool to explain many of these mechanisms involved in the physiology of this complex surgical procedure. However, human patients undergoing the ALPPS procedure are complex patients with advanced cancer disease and prolonged chemotherapy, such situations are difficult to reproduce in animal models.

Liver Volumetry

Future residual liver volume (FRV%) is estimated as the ratio of FRV to total functional liver volume (excluding tumor volume). We performed liver volumetry in patients scheduled for surgery for primary and metastatic liver tumors. We used a CT-3D liver reconstruction method with calculation of each section using Siemens SOMATOM® Definition 128 multi-slice CT in angiography mode (*Fig. 13*).

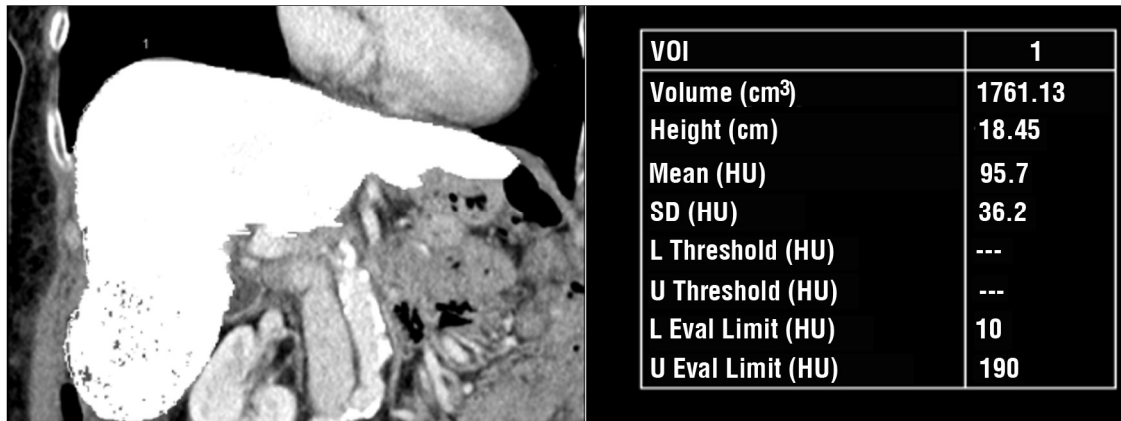


Figure 13. Total liver volume (VTF - 1761 cm³). Volumetry protocol

$$\text{VFR (\%)} = 100 \times \frac{\text{VRL (cm}^3\text{)}}{\text{Total liver volume (cm}^3\text{)} - \text{Tumor volume (cm}^3\text{)}}$$

Perioperative Management

Preoperative management includes appropriate liver CT or MRI evaluation with volumetric determination, determination of liver functional reserve, especially in patients with cirrhosis, cholestasis, in case of cholangiocarcinoma, and patients after chemotherapy. Postoperative management, after the first and second stage, becomes essential as many of these patients are nutritionally deficient, with expressed catabolism, high tumor burden, have undergone chemotherapy, suffer from cholestasis or postoperative infectious complications. In the interval between both stages, antibiotic prophylaxis is maintained due to the presence of an ischemic liver fragment and that foreign body in the abdomen. Also, from the first postoperative day sequential parenteral-enteral nutrition is initiated and maintained during the first postoperative period to ensure satisfactory metabolism of the organ and also of the future residual liver during this crucial week of regeneration. After the second procedure, parenteral nutrition is discontinued to avoid metabolic overload for the remaining liver. Similarly, a daily assessment of liver function, occurrence of complications and their treatment is strictly necessary (18).

Interval Between the First and Second Surgical Stage

Accurate knowledge of liver functional reserve is essential, as post-hepatectomy liver failure is an important cause of mortality after major liver resection (19). The majority of deaths and the development of post-hepatectomy liver failure in ALPPS occurs after stage 2 complete hepatectomy (20). Therefore, the interval between both surgical stages is essential. Liver volume does not always correlate with functionality. Some previous studies have shown discrepancies between volumetric assessment, liver functional tests (21). The liver volume required for safe liver resection varies from patient to patient. The following liver volumetric values have been accepted to perform the 2nd stage: residual liver volume 30% or a ratio of VRL to body weight (VRL/GC) - 0.5% in a patient with a morphologically normal liver, VRL 40% or VRL/GC - 0.8% in a liver with moderate steatosis (20-50%) or post-chemotherapy and a VRL 50% or a VRL/GC index - 1% in a patient with liver cirrhosis (22). Regarding the safety of the ALPPS procedure, the quality of the liver parenchyma and its function are the main directions of evaluation to improve patient selection, as well as the timing of the second

stage, both of which are determinants of outcome (23). Experts recommend that the first CT scan after the 1st stage should be performed on day 7 and repeated weekly for 4 weeks if VRL is insufficient (22). The international ALPPS registry demonstrated that the majority of patients (86%) tolerate rapid hypertrophy without developing liver dysfunction after stage 1. Using the liver function criteria proposed by the International Study Group for Liver Surgery (ISGLS) (24) defined liver failure on day 5 after stage 1 and MELD score at least 10 points immediately before stage 2 as independent predictors of unfavorable outcome after ALPPS stage-2 (25).

This technique was initially associated with high perioperative morbidity in up to 68% of patients, with varying degrees of complications and a 90-day mortality rate of 12% (26). To improve these outcomes, the classical technique has been continuously modified. ALPPS has now evolved into various forms designed by different surgeons around the world. To date, there is a large number of technical modifications of the ALPPS procedure.

ALPPS performed for right adjusted hepatectomy

It has been used at early stages with favorable results. After the resection line was extended from the Cantle line (right adjusted hepatectomy including bisectionectomy or resection of segments 5, 6, 7, 8) to the round-phalciform ligament to perform trisectionectomy (resection of segments 4, 5, 6, 7, 8) (*Fig. 14*) (27).

Laparoscopic ALPPS

At the initial stage it was proposed to perform the first stage ALPPS by laparoscopic approach to avoid excisional trauma and excessive adhesion formation, allowing to perform the second stage more easily (28). In the following years, ALPPS was performed totally laparoscopically in different institutions (29). Recently, a modified form of laparoscopic ALPPS has been described, called laparoscopic microwave ablation and portal vein ligation for staged hepatectomy (LAPS). LAPS has 2 stages: in stage 1 laparoscopic right vein occlusion and microwave ablation of

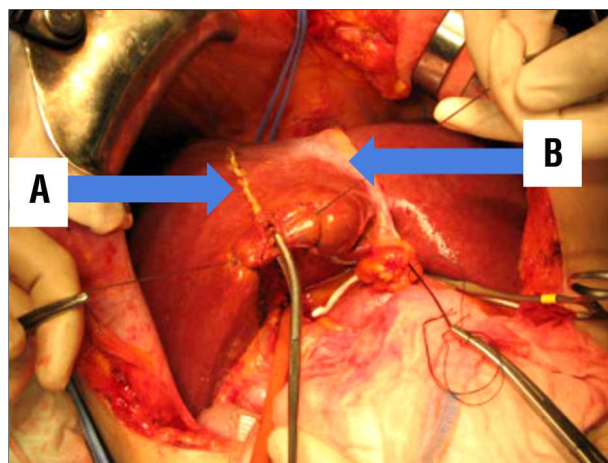


Figure 14. (A) - Cantle line; (B) - the Round-Falciform Ligament

tumors is performed in the bolical hemifield and, if tumors are present in the RVF, stage 2 consists of a laparoscopic total right trisectionectomy (30). In addition, the first fully robotic ALPPS procedure has been reported in Spain (31). The results of these studies indicate that ALPPS can be performed safely with minimal invasiveness. However, most of these studies were only single case reports with a lower level of evidence, and advanced laparoscopic skills are required to perform the procedure.

Left ALPPS

Extended left S 5.8 left adjusted hepatectomy (or left trisectionectomy) includes ligation of the left portal branch and right anterior sectional branch and liver transection along the main portal fissure (*Fig. 15*). Salvage ALPPS - is performed classic method in patients in whom portal vein embolization has been performed, but no necessary hypertrophy has occurred. Right ALPPS - ligate the right posteriolateral branch of the portal vein and transect the liver along the main portal fissure (*Fig. 16*) (32).

ALTPS - associating liver tourniquet and portal ligation for staged hepatectomy

It is a modification of the ALPPS procedure - associating liver tourniquet and right portal ligation for staged hepatectomy. Instead of liver transection a tourniquet is placed on the umbilical ligament (in case of right trisec-

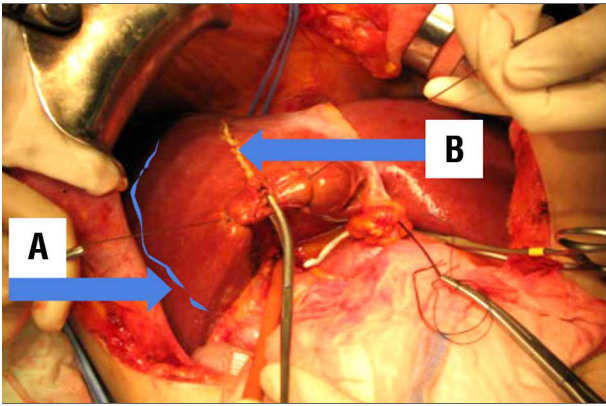


Figure 15. (A) - Main portal fracture; (B) - Cantle line

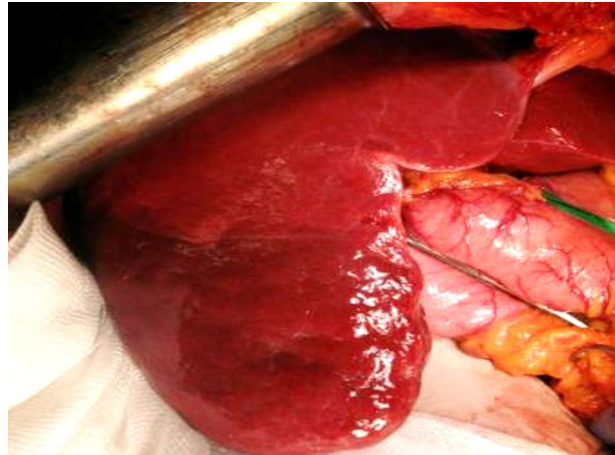


Figure 16. Main portal fracture. Demarcation of the right posterior section

tionectomy) or on the Cantle line (right staged hepatectomy), further it is pulled between the left hepatic vein and the middle hepatic vein continuing through the Rex recess to the pedicle of the left portal vein branch where it is rolled using the extragligionic approach. The distal ends of the tourniquet are swollen, thereby compressing the tributary vessels of segments 2, 3, and 4 (Figs. 17, 18). This approach allows to decrease intraoperative bleeding (33). Similarly, there is also the sequential ALTPS method, which involves only placement of the tourniquet without ligation of the portal branch, which is embolized on postoperative day 4. This modification is indicated in perihilar tumors to perform "non-

touch" approach to liver tumor (Staged liver resection for perihilar liver tumors using a tourniquet in the umbilical fissure and sequential portal vein embolization on the fourth postoperative day (a modified ALTPS) (35).

ALPPS by previous approach

Liver transection performed in the first stage is performed without prior mobilization of the right hemiphysis or visualization of the vena cava. This approach is usually used in massive right lobe tumors. This technique is widely used, and analysis of the worldwide ALPPS

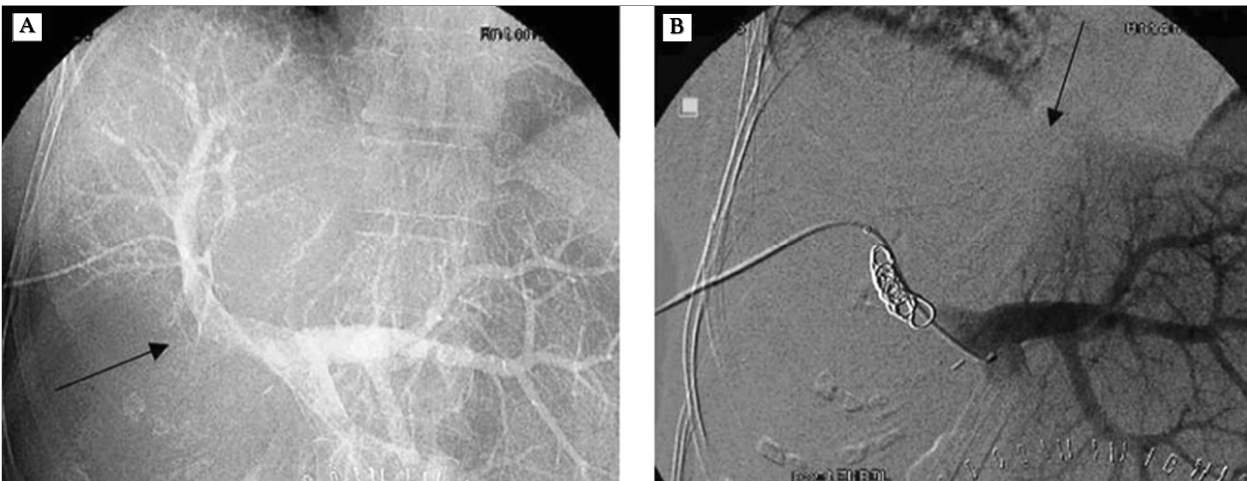


Figure 17. Sequential ALTPS. Right portal branch embolization on the 4th postoperative day. (A) - contrasted right portal branch, (B) - embolized right portal branch.

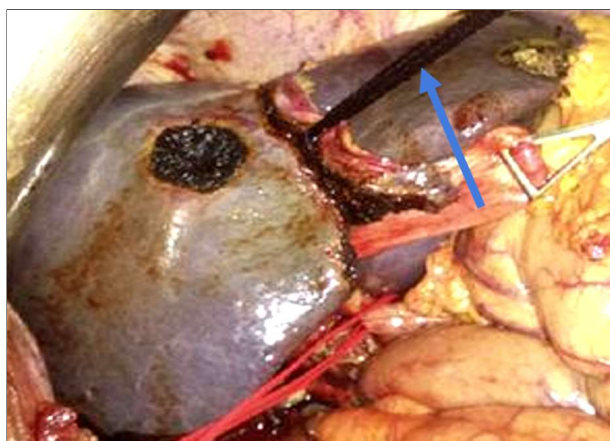


Figure 18. ALPPS. Tourniquet placed along the round-falciform ligament

registry found that it was used in 36% of cases (36).

Hybrid ALPPS

Li et al. (36) described a new approach to ALPPS. The main goal of this technique is "non-touch" tumor to increase the oncological efficacy of surgical treatment, especially, it is the method of choice in tumors with infiltration of the right portal branch or biliary bifurcation. Hybrid ALPPS consists of 3 stages: surgical exploration and in situ division of the liver via an "anterior approach", right portal branch embolization on 1 postoperative day, and complete hepatectomy in the 2nd stage. This modified approach was termed "hybrid ALPPS" or "Non-touch ALPPS" (parenchymal transection in the first stage and portal vein embolization 1 day later). This hybrid ALPPS could improve oncological outcomes (37).

Mini-ALPPS

This method is similar to the Hybrid technique, the only difference is the intraoperative embolization of the right branch of the portal vein (38). The same has been proposed and described by performing this method by laparoscopic approach - Laparoscopic Mini-ALPPS (39).

Partial ALPPS

In 2015, Petrowsky et al. (40) described their experience with a modified form of ALPPS

which they named partial ALPPS (p-ALPPS). Partial (50-80%) but not complete liver splitting was performed. The initial objective was to expose at least 50% of the liver parenchyma along the transection line. An attempt was made to preserve the mid hepatic vein during stage 1, thus the location of the hepatic vein or tumor determined the extent of partial transection ranging from 50% to 80%. The data obtained indicated that p-ALPPS is associated not only with zero mortality but also with a more favorable postoperative complication profile, especially after stage 1 surgery (40). Subsequently, objective boundaries for the classification of liver transection were provided: partial division is defined as transection to the middle hepatic vein, whereas total transection is dissection to the inferior vena cava.

Radio-frequency assisted liver partition with portal vein ligation - RALPP

After ligation of the right portal branch, the radiofrequency ablation probe is applied into the liver parenchyma along the line of demarcation with the aim of producing avascular necrosis. This technique stops the blood flow from the future residual liver to the diseased hemifield without a physical division of the liver parenchyma, which will be performed in stage 2 (33, 41).

Laparoscopic microwave ablation and portal vein ligation for staged hepatectomy (LAPS)

Similar to the previous modification, but laparoscopically applied microwave energy is used (33, 42).

Advantages of the ALPPS Procedure

The biggest advantage and most important moment is the rapid hypertrophy in a short time of the future residual liver, therefore, ALPPS allows surgical resection of liver lesions that were initially considered unresectable. According to the literature, ALPPS results in an increase in VRL from 47% to 93% within 7 to 14 days, which is an impressive result, as other methods of converting initially

unresectable tumors to resectable ones (two-stage hepatectomy TSH) require a median of 99 days (range: 32-210 days) to induce sufficient hypertrophy before the second operation. (43) The reason for this rapid hypertrophy is still debated. Although key factors that initiate liver regeneration include 2 major factors: after partial hepatectomy, a stress signal is generated due to increased energy requirement per unit liver volume and the second factor is altered hemodynamics. Although there is a clear correlation between blood flow and liver regeneration, the specific role of blood flow in liver regeneration remains unclear. In addition, cytokines and growth factors also play a triggering role. Another important advantage is the feasibility and resection of R0. It has been determined that ALPPS is a highly feasible method of treatment in initially unresectable liver tumors (44). It has been reported that ALPPS has a 97% feasibility compared to TSH, which in turn has a feasibility of only 77%. The short interval between the first and second stage of surgery does not allow for progression of the cancerous disease. After all, the ultimate goal of liver resection is R0 resection. The aggressive tactics of the ALPPS procedure allow to achieve an R0 resection rate at 83%-100% (45).

Disadvantages

Certainly, the highly aggressive approach to liver tumors using ALPPS cannot be considered safe. Morbidity and mortality rates are very high compared with other liver resection methods. The main argument against this approach at the initial stage was 68% morbidity and 12% mortality. However, ALPPS has not been abandoned, and its disadvantages have led to refinement of the operative technique. There are already publications with a 36% complication rate and 0% mortality rate (46,47). Another disadvantage of the ALPPS procedure, perhaps the most important one, is that ALPPS is likely to promote tumor growth. A recent study by Oldhafer et al. (48) found that 6 out of 7

patients experience tumor recurrence within a median of 8 months after ALPPS. A previous study noted increased proliferative activity in colorectal cancer liver metastases (a Ki-67 labeling index) after portal branch embolization of the embolized and unembolized lobe. (49) However, Shindoh reported that patients with colorectal cancer liver metastases who were appropriately selected based on oncologic tumor activity and underwent portal branch embolization had overall and recurrence-free survival rates equivalent to those of patients who did not undergo embolization (50). Fukami (51) presented further evidence for ALPPS, biopsied from the same liver metastasis immediately after the first and second laparotomies. The Ki-67 labeling index for tumor cells was 60% during the first operation, but increased to 80% during the second operation. Unfortunately, this evidence is insufficient as it comes from a small series. The mechanism by which ALPPS stimulates tumor growth is still unclear and different tumors have different characteristics. Better designed studies are needed for a single tumor type to determine whether there is any relationship between ALPPS and early tumor recurrence.

The aim of the study: is to describe our first experience in the treatment of massive liver tumors, applying the procedure of extended staged hepatectomy - ALPPS, we also performed systematic review of literature data to highlight the operative indications, surgical techniques.

Literature study. Relevant articles were searched in PubMed, Medline, Google Scholar databases from January 2007 to November 2019. The search was limited to articles published in English and Romanian languages.

Material and methods: From June 2018 to June 2021, we performed 18 ALPPS surgeries in the 2nd IP surgery clinic of Nicolae Testemitanu USMF. All patients were evaluated by a multidisciplinary team which included surgeons, radiologists, gastroenterologists, oncologists. VRL evaluation is mandatory in all patients requiring right hepatectomy and right hepatectomy extended to s IV. Over the years VRL \leq 30%

is considered to be insufficient to perform liver resection safely, therefore these patients were initially considered unresectable and ligation of the right branch of the portal vein was performed, subsequently, after 4-6 weeks, they were evaluated on CT-volumetry if they achieved hypertrophy of the VRL. Patients who did not develop sufficient hypertrophy or suffered from disease progression during this rather long period were considered as absolutely unresectable patients. To overcome these limits, since June 2018, all patients with a VRL $\leq 30\%$ were evaluated for the ALPPS procedure. To achieve success in the immediate and late post-operative period, but especially in the initiation period of this innovative procedure, patient selection is a prerequisite. Exclusion criteria are: age >75 years, extrahepatic spread of disease, portal hypertension, subcompensated and decompensated liver cirrhosis, hepatic steatosis $>50\%$, decompensated associated diseases. Data from patients undergoing ALPPS were collected prospectively.

Results

Indications for surgical resection were liver metastases of colorectal cancer in 7 cases, perihilar cholangiocarcinoma in 4 cases, hepatocellular carcinoma in 6 cases, and GIST metastases in 1 case. All patients with cholangiocarcinoma were diagnosed with IIIA tumor according to Bismuth-Corlette classification, likewise in all of them, endobiliary stents were placed. All 7 patients with liver metastases of colorectal cancer had metachronous metastases, all 6 patients with HCC suffered from Child A stage liver cirrhosis, the patient with metachronous GIST metastases had undergone gastrectomy for gastric GIST in the past. The mean age of the patients was 62 ± 8 ,

Table 1. Liver volumetry in pre- and post 1 stage ALPPS patients

Pre-operative volumetry		P
VTH (cm ³)	1672 \pm 240 (1284-1942)	<0.001
VRL (cm ³)	252 \pm 115 (214-564)	0.0002
VRL/VTH % VRL/VTH	19.4% \pm 6.2%	<0.001
Volume between 2 stages		
VRL (cm ³)	642 \pm 165 (390-792)	<0.001
Volume rate obtained %	60.4 \pm 28%	<0.001
VRL/VTH % VRL/VTH	38.7 \pm 6.5%	<0.001
Time between volumes (days)	9.4 \pm 1.3	<0.001
Time between operations	10.2 \pm 2.3 (390-792)	<0.001

female/ male ratio - 6/12. No patient suffered from decompensated comorbid conditions having good performance status. Four patients underwent neoadjuvant chemotherapy. Liver function tests were within normal limits.

In all cases we performed volumetric measurements using liver CT angiography on the same device before the 1st stage and 2nd stage with determination of total liver volume (THV) and future residual liver volume (FRV). Residual liver volume was calculated on CT in angiography mode using the program included in the Siemens[®] device software and was 252 ± 115 cm³ ($19.4 \pm 6.2\%$) before ALPPS-1, and 642 ± 165 cm³ ($38.7 \pm 6.5\%$) before ALLPS-2 ($P < 0.001$). The increase in VRL between the two procedures was $60.4 \pm 28\%$ (range: 31-110%, $P < 0.001$). The mean time between the first and second procedure was 9.4 ± 1.3 days (*Table 1*).

The average duration of the first stage was 360 minutes (310-410 min), and 130 minutes (100-350 min) for the second stage. Mean intraoperative hemorrhage 850 ± 150 (400-2500 ml) in the first stage, and 350 ± 70 (200-1000 ml) (*Table 2*). Resection of another organ was not performed in any patient, need for hemotransfusion - 66%.

In 8 cases we performed classical ALPPS,

Table 2. Intraoperative data

	First stage ALPPS	Second stage ALPPS	P
Average duration of operation (min)	360 \pm 60 (310-410)	130 \pm 20 (100-350)	< 0.0001
Intraoperative hemorrhage (ml)	850 \pm 150 (400-2500)	350 \pm 70 (200-1000)	< 0.0001
Need for hemotransfusion n (%)	5 (55%)	1 (11%)	0.4629

Table 3. ALPPS method performed

Classic ALPPS	8
Classic ALPPS + hepaticojejunostomy	4
ALPPS by previous approach	4
Partial ALPPS // Partial ALPPS	2

in 4 cases classical ALPPS was completed with Roux-en-Y hepaticojejunostomy, in 4 cases we performed anterior approach ALPPS, and in 2 cases partial ALPPS (*Table 3*).

Right trisectionectomy was performed on 8 patients, right trisectionectomy extended to S I - 6 patients, right hepatectomy extended to S IV - 4 patients. Roux-en-Y hepaticojejunostomy performed in patients with perihilar carcinoma during the first stage.

Histopathological analysis in all cases confirmed preoperative diagnosis (HCC, MHCCR, perihilar cholangiocarcinoma, GIST). R0 margin obtained in 100% of cases.

Postoperative period. Postoperative morbidity

In 14 patients 22 complications occurred of which 6 were grade 3 and higher after Clavien-Dindo. Posthepatectomy liver failure was confirmed in 2 patients on the 5th day after the second stage, treated in the intensive care unit with favorable outcome. Biliary fistula after stage 1 was present in 8 patients and in 4 patients after stage 2. All were treated conservatively by longer exposure of drain tubes. Transient ascites was present in 4 cases (*Table 4*). Four patients had pulmonary complications (pleural effusion). No patient died postoperatively.

Conclusions

Safely performed liver resections of large liver tumors remain a major challenge for liver surgeons. However, current preoperative examinations accurately estimate tumor resectability and VRL volume. In fact, liver surgery changes the oncological paradigm and the resectability of liver tumors does not depend on what was resected, but rather on what will remain after resection. This shift

Table 4. Postoperative period

Patients with complications	14 (77%)
Biliary fistula	12 (66%)
Ascite	4 (22%)
Lung complications	4 (22%)
Liver failure	2 (11%)
Clavien-Dindo classification	
	1 8
	2 4
	3 4
	4 2
	5 0
Postoperative mortality	0

has generated increased attention to VRL, giving rise to new treatment tactics and techniques.

Even though there is limited clinical experience with ALPPS, this revolutionary (two-stage) surgical procedure has attracted the attention of many surgical leaders and cancer centers around the world. This method prevents post-hepatectomy liver failure and allows for a complete resection (R0) during one hospitalization in patients with a locally advanced liver tumor previously declared unresectable. This strategy has been shown to be feasible and safely performed by experienced hepatobiliary surgeons in high-volume liver surgery centers.

In the history of liver resection, ALPPS is like a child. It still needs enough time to grow and mature. Although ALPPS has been reported as a novel approach with high morbidity and mortality rates, this technique offers a chance to cure malignant liver disease that could not be resected with other techniques. Modifications to the ALPPS technique have allowed us to decrease morbidity and mortality rates. The advantages of ALPPS are rapid VRL hypertrophy, feasibility and a high R0 resection rate.

Conflict of Interest Declaration

The authors declare no conflict of interest, financial or non-financial, associated with this work.

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