

# Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS): Tips and Tricks

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## Abstract

**Background** Posthepatectomy liver failure is the most severe complication after major hepatectomies and it is associated with an insufficient future liver remnant (FLR). Associating liver partition and portal vein ligation (PVL) has recently been described as a revolutionary strategy to induce a rapid and large FLR volume increase. We aim to describe our surgical technique, patient management, and preliminary results with this new two-stage approach.

**Technique** During the first stage, liver partition and PVL of the diseased hemiliver are performed. The completion surgery is carried out after volumetric studies have demonstrated a sufficient FLR and provided the patient is in good condition. This is usually achieved after 7 days. In the second step, the patient undergoes a completion surgery with right hepatectomy, right trisectionectomy, or left trisectionectomy.

**Results** Fifteen patients with advanced liver tumors were treated. Nine patients were males and the mean age was 54 years old. The mean difference between the preoperative and postoperative FLR volume was 303 ml ( $p < 0.001$ ), which represented a mean volume increase of 78.4 %. All resections were R0. Morbidity and mortality rates were 53 and 0 %, respectively. The average hospital stay was 19 days.

**Conclusions** The presented technique was feasible and safe in the hands of experienced hepatobiliary surgeons, with satisfactory short-term results. It induces rapid liver hypertrophy and at the same time it offers the possibility of cure to patients previously declared unresectable.

**Keywords** Portal vein ligation · Liver tumors · Metastases · Surgical technique · Hypertrophy

## Introduction

Resection of liver tumors with curative intent remains the treatment of choice for patients with malignant disease that

offers long-term survival.<sup>1</sup> Unfortunately, at diagnosis, many patients have multiple liver lesions which often preclude a complete resection.<sup>1,2</sup> During the last years, new multidisciplinary therapies have been proposed to increase safely the resectability rate in patients with initially non-resectable liver tumors. However, the intent to preserve an adequate liver remnant to avoid posthepatectomy liver failure (PHLF) represents the main limitation to achieve a tumor-free margin after resection of primary or metastatic liver lesions.<sup>1,2</sup> To minimize the risk of PHLF in patients with a marginal future liver remnant (FLR), portal vein embolization or portal vein ligation (PVL) in combination or not with two-stage procedures has been widely used to increase FLR volume and therefore expand the potentially resectable pool of patients.<sup>2,3</sup>

Associating liver partition and PVL for staged hepatectomy (ALPPS) has recently been described as an advantageous strategy to induce a rapid and marked increase in FLR volume with promising preliminary results.<sup>4–8</sup> In the present manuscript, we aim to describe in detail our current surgical

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technique and results with the ALPPS procedure, adding some surgical tips and tricks learned after our initial experience with this new two-stage approach.

### Indications and Contraindications

The indications for this technique include patients with marginally resectable or primarily non-resectable locally advanced liver tumors of any origin with an insufficient FLR either in volume or quality. On preoperative MRI- or CT scan-based volumetric planning, a FLR of less than 30 % in healthy livers or less than 40 % in patients with cholestasis, macrosteatosis, fibrosis, or pathologic changes associated with chemotherapy is used as indication to perform the procedure. In addition, the need to perform major liver resections combined with synchronous resection of other organs (i.e., colorectal cancer and liver metastases, gallbladder cancer that invades the duodenopancreas, neuroendocrine pancreatic, or intestinal tumors with massive liver metastases) could also be considered a potential indication to perform the procedure.

Unresectable liver metastases in the FLR or unresectable extrahepatic metastases, severe portal hypertension, high anesthesiological risk, medical contraindications to major hepatectomy, impossibility to achieve negative margins, or unresectable primary tumor of other locations still constitute contraindications to performing this procedure.

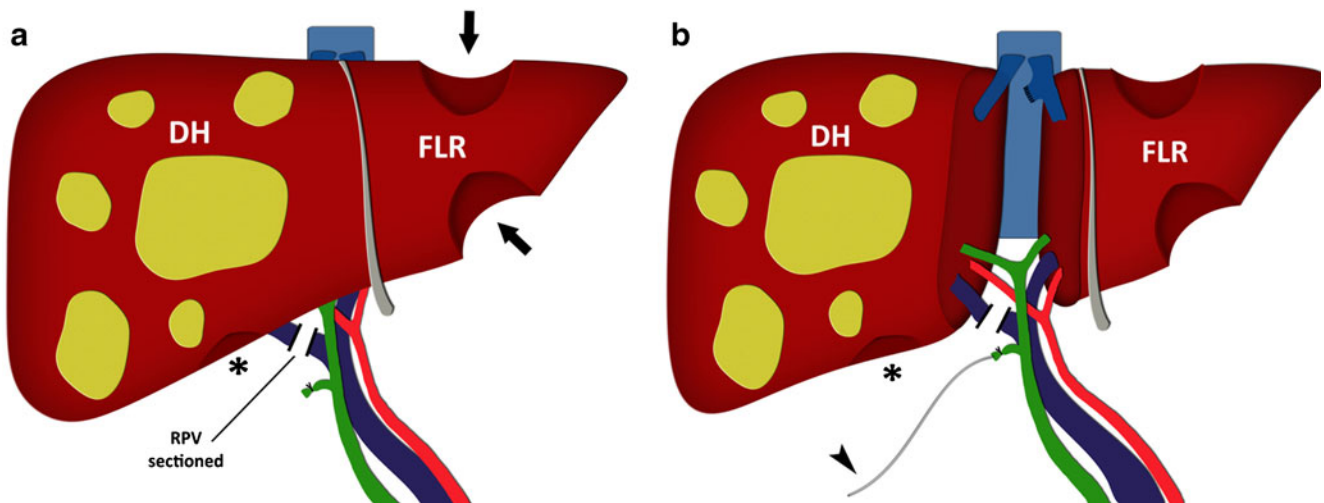
### Surgical Technique

For a better understanding of this two-step technique that divides the liver parenchyma in two hemilivers with an interval period between both procedures, it is important to define some terms: “diseased hemiliver (DH)” is the liver with tumor load that will be resected in the second step; “FLR” is the hemiliver comprising the segments of the liver (with or without tumor load) that will remain after both procedures; “clean-up” is the resection of all tumor lesions in the FLR during the first step of this technique.

#### Stage 1

The abdominal cavity is approached by a bilateral subcostal incision with midline extension. If a simultaneous resection of a primary colorectal tumor in association with the liver metastases is planned, we prefer to perform the resection of the primary tumor during this stage through a midline laparotomy. To rule out extrahepatic lesions, a thorough exploration of the abdominal cavity is carried out. Intraoperative ultrasound (IOUS) of the liver is performed to accurately assess the number, size, and location of all lesions and to

determine their relation with the vasculobiliary structures of the liver. The first surgical gesture is to perform a complete lymphadenectomy of the hepatic pedicle not only for oncological reasons but also for a better identification of all hilar structures that need to be recognized during this complex procedure. In the presence of primary or secondary bilateral liver disease, the next step is to achieve a complete tumor resection (clean-up) of the FLR. Subsequently, the portal vein of the DH is identified, sectioned, and sutured (Fig. 1). The right hemiliver must be mobilized before parenchymal transection, including the right coronary ligament and the suspensory ligament, dividing all accessory hepatic veins until the desired posterior limit of future transection is reached. Once mobilization is complete, we routinely perform a cholecystectomy and the cystic duct is repaired for further transcystic hydraulic test and cholangiography after liver transection. Total or nearly total liver partition to the level of the inferior vena cava (IVC) is carried out as a right hepatectomy, right trisectionectomy (segments 4–8 ± segment 1), or left trisectionectomy (segments 1–5 + segment 8), depending on the patient and on the local extension of the disease (Fig. 1). When performing a right hepatectomy, other resections may be performed simultaneously in the FLR. We prefer the cavitron ultrasonic surgical aspirator in combination with the harmonic scalpel for parenchymal transection but other techniques could be used. If preferred, the hanging maneuver is an alternative that could also be applied to help liver transection. It is of paramount importance to avoid any damage to the hepatic artery of the DH during parenchymal transection because this is the only vascular inflow of this hemiliver and therefore it is essential to avoid hepatic necrosis. A complete hemostasis and biliostasis of both raw surfaces must be achieved. In order to detect remaining biliary leaks, we place a catheter in the cystic duct and perform a hydraulic test. At the end of the procedure, the hepatic pedicle of the DH, the hepatic veins, and the cystic duct are encircled with a black silk or vessel-loop to facilitate their identification during the second stage. The diseased-ischemic liver is wrapped in a hermetic plastic bag with a drain inside it in order to facilitate the second procedure by minimizing postoperative adhesions and avoiding a choleperitoneum due to the higher risk of biliary leaks (Fig. 2). Two more drains are placed, one in the right subphrenic space and the other at the raw surfaces. When operating a hilar cholangiocarcinoma and a right trisectionectomy has to be performed, the distal common bile duct and the distal stump of the left bile duct are sectioned with tumor-free surgical margins and sutured to be removed en bloc with the liver parenchyma during the completion surgery. The biliodigestive anastomosis of the FLR’s proximal bile duct should be performed during this step, after liver partition is complete in order to achieve an optimal positioning of the hepaticojejunostomy (Fig. 3). In these patients, the right



**Fig. 1** **a** After a complete tumor resection (*arrows*) of the future liver remnant (*FLR*) is achieved, the right portal vein (*RPV*) is sectioned and sutured. Cholecystectomy is routinely performed (*asterisk*). **b** A

catheter is placed in the cystic duct (*arrow head*) to perform a hydraulic test and cholangiography after liver partition is carried out as a right trisectionectomy. *DH* diseased hemiliver

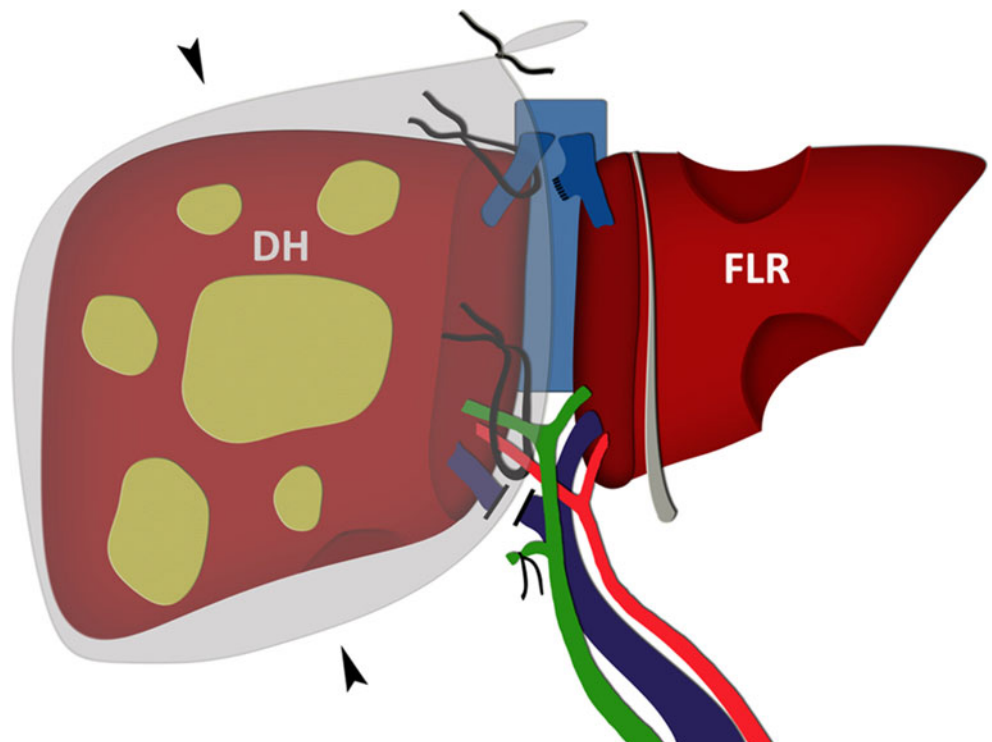
biliary system should always be drained by an external drainage in order to avoid cholestasis, infection, and bile leaks.

## Stage 2

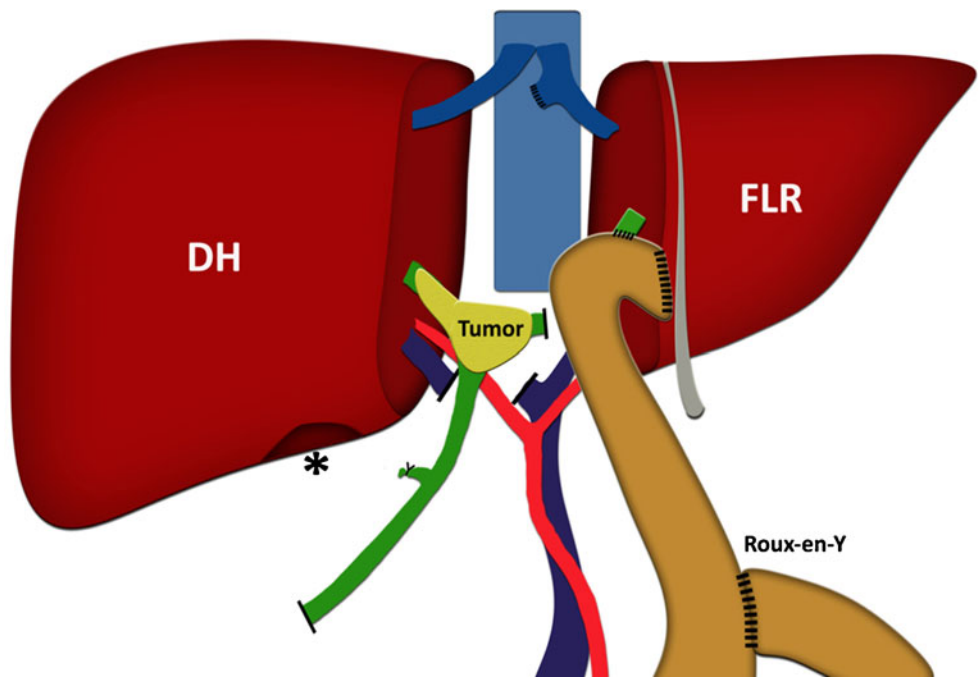
At postoperative day 6, we perform a volumetric CT or MRI to assess FLR hypertrophy and to confirm a tumor-free FLR. If a sufficient FLR is demonstrated and the patient is in good condition, the completion surgery is carried out the

following day. The abdominal cavity is entered using the previous incision. After releasing lax adhesions, the plastic bag is removed including any fluid collections inside it and submitted for routine microbiological examination. The vasculobiliary structures of the DH are easily recognized by identifying the black silk around them. However, the FLR hypertrophy, especially the one of the caudate lobe, might frequently modify the local anatomy with dislodgement of the hepatic pedicle. IOUS is applied in the FLR in order to

**Fig. 2** At the end of the first step, the vasculobiliary structures of the diseased hemiliver (*DH*) are encircled with black silks or vessel-loops. Finally the *DH* is wrapped in a plastic bag (*arrow heads*). *FLR* future liver remnant



**Fig. 3** Right trisectionectomy during the first stage of ALPPS in hilar cholangiocarcinoma. The bile ducts are sectioned with tumor-free surgical margins and sutured to be removed en bloc with the diseased hemiliver (DH) during the completion surgery. The biliodigestive anastomosis of the future liver remnant (FLR) is performed in this stage. *Asterisk* gall bladder bed

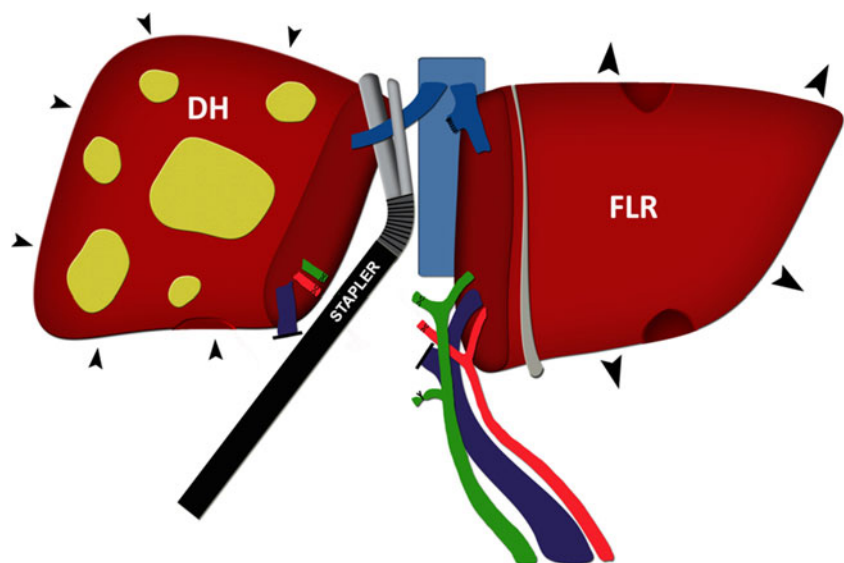


detect any growing tumor that might have escaped preoperative studies. If new lesions are found, either resection or ablation therapy could be performed at this stage of the procedure. The resection of the DH is achieved using vascular staplers for all vasculobiliary structures and the remaining liver parenchyma, if present, in contact with the IVC (Fig. 4). Finally, the cystic duct is cannulated and an intraoperative cholangiography is performed. When a right trisectionectomy is performed, the FLR (segments 2–3) is fixed to the anterior aspect of the abdominal wall using the falciform ligament. Finally, two drains are placed, one in the right subphrenic space and the other at the raw surface.

**Perioperative Patient Management**

Preoperative work-up does not differ from any other programmed major liver resection, in which an adequate volumetric study, either by CT or MRI, is mandatory for the correct selection of patients. On the other hand, the management of these patients during the postoperative course of both surgical procedures is crucial and different from other conventional major hepatectomies because many of these patients have a poor nutrition, a high tumor burden, have received much chemotherapy, have cholestasis, or are infected. After the first procedure, the patient is managed at

**Fig. 4** During the second stage of ALPPS, a marked hypertrophy of the future liver remnant (FLR) is seen (*large arrow heads*) as well as an atrophic diseased hemiliver (DH). The resection of the DH is achieved using vascular staplers





the intensive care unit (ICU). At ICU admission, early extubation is applied. Once stabilized and without the need of such close observation, the patient is transferred to general ward. During the interval period between both steps, antibiotic prophylaxis is maintained due to the presence of an ischemic DH (segments 5 to 8, partial “portal” ischemia, and segment 4, total “arterial and portal” ischemia when included in the resection) and a foreign body in the abdomen. Also, sequential parenteral–enteral nutrition is initiated on the first postoperative day and maintained during the interval period in order to ensure satisfactory nourishment of the FLR during this crucial week of regeneration. We use parenteral nutrition after the first step because the contralateral DH helps the FLR to deplete all nutrients/metabolites. After the second procedure, even though the FLR has grown, we discontinue parenteral nutrition in order to avoid a metabolic overload for the FLR. Daily clinical evaluation and laboratory tests including liver function are performed. If a complication occurs, we record it according to the Dindo–Clavien Classification of surgical complications<sup>9</sup> and postoperative liver failure classified according to the definition proposed by the International Study Group of Liver Surgery.<sup>10</sup>

### Statistical Analysis

Continuous variables were expressed as mean (range). Paired *t* test was used to compare the FLR volume prior to and following the first surgical procedure. A  $p < 0.05$  was considered significant. Due to the short follow-up time in our series, survival and disease-free survival was calculated as percentage of alive or disease-free patients at the end of the study. Our results with this technique were statistically analyzed using Primer of Biostatistics, 4.02, 1996 McGraw Hill.

### Results

Between June 2011 and June 2012, this technique was successfully applied in 15 patients with primary or secondary liver tumors (one with a hepatocellular carcinoma, ten with colorectal liver metastases, one with a Klatskin tumor, two with neuroendocrine liver metastases, and one with non-neuroendocrine non-colorectal liver metastases). Nine were males and the mean age was 54 years old (range=35–78). The preoperative mean FLR volume was 403 ml (range=237–572) and the mean FLR/TLV was 27 % (range=15–44). The mean postoperative volume of the FLR at 6 days was 706 ml (range=468–1,030) and the mean FLR/TLV before reoperation was 46.9 % (range=31.7–67). The mean difference between the preoperative and postoperative FLR volume was 303 ml ( $p < 0.001$ ), which

represented a mean volume increase of 78.4 % (range=21–139). All patients successfully underwent the two stages and had R0 resections confirmed by pathology (100 % feasibility). Biopsies taken from the FLR during both procedures in eight patients demonstrated hepatocyte proliferation with increased mitosis and less apoptosis at the time of completion surgery. The mean operative time of the first stage was 326 min (range=195–480) and the second stage was 139 min (range=75–300). Intermittent Pringle maneuver was applied only during the first stage in 5 of 15 cases for a median of 25 min (range=7–50 min). The overall morbidity and mortality rates were 53 and 0 %, respectively. Only two patients developed a grade A PHLF and one a grade B PHLF. The mean hospital stay was 19 days (range=11–54). Patients were followed up for a median of 188 days (range=18–410). Current median overall survival is 100 %, and disease-free survival, 73 %. Patient’s details are summarized in Table 1.

### Discussion

The safe removal of extensive tumor load in the liver has been a major challenge for hepatobiliary surgeons for decades.<sup>1–4</sup> Even though current preoperative studies accurately estimate tumor resectability and FLR volume, many times in patients with an apparently sufficient FLR, the surgical scenario turns out to be different. Therefore, if resection is carried out, the patient might end up suffering the consequences of PHLF. This is the main cause of death after major hepatectomy, being FLR volume and quality determining factors directly related with this complication. In fact, in many cases, resectability is not determined by what it is resected but rather by what will remain after resection. This paradigm shift has generated greater attention in the FLR, giving rise to new tactics and techniques for treatment. These new strategies can be grouped into those that tend to decrease tumor size (such as neoadjuvant chemotherapy and endovascular treatments) and those that tend to preserve or enhance the remaining healthy parenchyma such as two-stage surgery, local ablation treatment, and preoperative portal vein occlusion. In the early 1980s, Makuuchi and coworkers introduced portal vein embolization (PVE) as a method to induce hypertrophy of a putative FLR, enabling a safer removal of large or multiple liver tumors.<sup>11</sup> A decade later, Adam and his colleagues introduced the concept of sequential two-stage hepatectomies allowing the liver to regenerate between both procedures.<sup>2</sup> Soon after, Jaeck et al. developed another two-stage approach for bilateral tumor involvement, combining right PVE after the initial removal of tumors located in the left hemiliver.<sup>12</sup> Finally, based on the evidence that PVL triggers a regenerative response similar to that of PVE, this approach

**Table 1** Patients characteristics and results

Patient no.	Diagnosis	Sex	Age	FLR/TLV (%)	Preop treatment	1st step additional procedures	Type of resection	FLR volume (ml)	Hypertrophy (%)	Complications <sup>9</sup> (grade)	Treatment	Hospital stay	
													Preop
1	CRLM	Female	40	44	CAPOX–bevacizumab	FLR clean-up + simultaneous CR resection (LC)	Right hepatectomy	452 <sup>a</sup>	690	53	None	11	
2	CRLM	Male	55	27	PVL, PVE, FOLFOX + cetuximab	None	Right hepatectomy	471	776	65	Biliary leakage, pleural effusion (3a)	Chest tube	24
3	Hilar-CC	Male	59	20	Bilateral PBD	HJ	Right hepatectomy	285	521	83	None	None	13
4	HCC	Female	78	30	None	Right hepatic artery reconstruction	Right hepatectomy	412	541	31	None	None	13
5	CRLM	Male	48	21	FOLFOX	FLR clean-up	Right hepatectomy	352 <sup>a</sup>	828	135	None	None	17
6	NCNNELM	Male	74	24	None	Diaphragm resection	Right hepatectomy	330	724	119	Biliary leakage (2)	2	17
7	CRLM	Male	53	25	FOLFOX	None	Right hepatectomy	572	853	49	None	None	12
8	CRLM	Female	57	35	CAPOX + bevacizumab	FLR clean-up	Right hepatectomy	380 <sup>a</sup>	538	42	Bleeding (2)	Blood Transfusion	16
9	CRLM	Male	39	25	None	Simultaneous CR resection (UAR)	Right hepatectomy	430	1,030	140	Pleural effusion (3a)	Chest tube	17
10	CRLM	Female	50	27	FOLFOX + bevacizumab FOLFIRI–cetuximab	FLR clean-up	Left hepatectomy	400 <sup>a</sup>	832	108	None	None	20
11	NELM	Female	69	30	None	FLR clean-up + distal pan-creatotomy	Right hepatectomy	465 <sup>a</sup>	565	22	Pancreatic fistula, biliary leakage (3b)	Endoscopic stent	54
12	CRLM	Male	35	15	FOLFOX–cetuximab	None	Right hepatectomy	237	525	122	None	None	16
13	CRLM	Male	76	37	None	None	Right hepatectomy	500	879	76	Abdominal pain (3b)	Blank laparotomy	19
14	NELM	Female	56	18	Plakitaxel + gemcitabine	PBD	Right hepatectomy	265	468	77	PV thrombosis (3b)	Laparotomy	27
15	CRLM	Male	63	26	FOLFIRI–cetuximab	FLR clean-up	Right hepatectomy	445 <sup>a</sup>	830	87	Abdominal pain, ARI, RPS necrosis (3b)	Blank laparotomy	21

FLR future liver remnant, TLV total liver volume, CRLM colorectal liver metastases, LC left colectomy, PVL portal vein ligation, PVE portal vein embolization, CC cholangiocarcinoma, PBD percutaneous biliary drainage, HJ hepaticojunostomy, HCC hepatocellular carcinoma, NCNNELM non-colorectal non-neuroendocrine liver metastases, UAR upper anterior resection, NELM neuroendocrine liver metastases, PV portal vein, ARI acute renal insufficiency, RPS right posterior segment

<sup>a</sup> In those patients with metastasis in the FLR that were cleaned up during the first procedure, the volume corresponding to those lesions was discounted in the preoperative volumetric studies

was modified by applying concomitant right PVL with wedge resections of all left-sided tumors during the first surgery.<sup>3,13,14</sup> Despite this evolution, the drawback lies in the need for long intervals between the two surgeries (up to 8 weeks), with the potential disease progression in the meantime.<sup>15–17</sup> Other shortcomings include the insufficient hypertrophy of a putative remnant liver, preventing curative resection, or if performed, leading to PHLF.<sup>18</sup> The amount of the remnant liver is crucial, but its quality is also very important (presence of steatohepatitis, sinusoidal obstructive syndrome, cirrhosis, etc.). In the setting of an abnormal liver parenchyma, even a FLR that macroscopically appears enough might end up not being sufficient. In these patients, in whom volumetric studies do not necessarily correlate with functionality, studies such as the HIDA test, the LiMAX test or the indocyanine green test, might be of paramount help. However, except for the HIDA test, most functional studies imply full liver functionality without discriminating the FLR.

The technique described in this manuscript, originally developed by Dr. Hans Schlitt from Regensburg, Germany, prevents PHLF and has preliminary encouraging results in terms of FLR hypertrophy (40–160 %) and time interval between procedures (7 days).<sup>4–8</sup> The exact physiopathological events involved in such enhanced liver hypertrophy are still unknown. This phenomenon could be possibly explained by mainly four mechanisms that work in collaboration: (1) PVL creates a redistribution of hepatotrophic factors to the FLR.<sup>19</sup> This produces an active and necessary phenomenon of FLR hypertrophy; (2) liver partition, which causes local surgical trauma that per se might represent an important regeneration stimulus; (3) the impairment of bilateral cross portal circulation, allowing a more dramatic increase in portal flow to the FLR; (4) unlike one-stage major hepatectomies, in which the liver remnant has to deal with hyperflow and portal hypertension, in this technique the diseased arterialized hemiliver allows the FLR to tolerate this hemodynamic stress modulating the double hepatic vascular inflow. In addition, the diseased hemiliver acts as a transitory auxiliary liver that assists the growing FLR in metabolic, synthetic, and detoxifying functions for the first and critical week after resection.<sup>4,7,20</sup> Later, it may be removed with impunity, or if regeneration is not appropriate, the second step can be delayed.

This two-stage surgical approach might offer many advantages: a rapid and superior amount of FLR hypertrophy, an early definitive liver resection with a short interval period allowing a less demanding procedure, unlikely tumor progression, and a faster recovery for the patient with early restart of chemotherapy.<sup>4–8</sup> Furthermore, this new strategy offers additional significant benefits. This technique might allow performing simultaneous resections of other organs during the first stage of the procedure, including the tumor cleaning of the FLR, thus minimizing the risk of

complications associated with PHLF.<sup>7,8</sup> Moreover, in the case of hilar cholangiocarcinoma (hilar CC), PVE predetermines the resection side, creating a difficult surgical scenario if the embolized side does not match the intraoperative findings. This technique allows changing the resection side intraoperatively without the concern of a mismatched PVE. Many patients with hilar CC have a small FLR, are cholestatic, and sometimes infected, even with prior percutaneous biliary drainage. In these cases, this approach might offer the advantage of tolerating infection and resection due to a transitory auxiliary liver.

Recently, Schnitzbauer and coworkers reported the largest series to date with the ALPPS approach in a multicenter experience including 25 patients with extensive tumor load.<sup>5</sup> In their series, they performed a right trisectionectomy and only patients with a tumor-free left lateral section (segments 2–3) were included. In contrast, we also performed left trisectionectomies and removed tumors from the FRL. However, we believe that this technique could be extended to any major liver resection that results in an insufficient FLR either in volume or in quality. Even though the German multicenter study described that a 74 % volume increase of the remnant liver was achieved in a mean of 9 days, they reported waiting times of up to 28 days.<sup>5</sup> In our experience, the second step was usually completed by postoperative day 7 with a mean FLR volume increase of 78 %. All patients successfully underwent the two stages and had R0 resections (100 % feasibility) with a morbidity and mortality of 53 and 0 %, respectively.

Regarding specifically technical considerations, even though there are only few published experiences,<sup>4,5,7,8</sup> many surgical leaders in the field of hepatobiliary surgery have exposed some preliminary results of their own at several recent international meetings and as letters to editor that have raised controversies.<sup>21</sup> The main disadvantage of using a plastic bag or sheet during the first stage is that if the second stage cannot be performed for any reason, the patient will still require a reoperation to remove the foreign body. Some authors advocate the resection of the ischemic segment 4 to avoid septic complications such as abscess or fistula related to its eventual necrosis. The rationale for this appears valid only if the second procedure is delayed for a long period of time. Even though other authors have reported these complications, we have not observed any abscesses of segment 4, probably because the antibiotics used during the interval period contributed to avoiding this septic complication. We believe the resection of segment 4 is unnecessary in ALPPS and we advise against this additional maneuver, since the patient will be reoperated on within a week. Besides, if an eventual bile leak is present in the DH, the bile is contained in the plastic bag and the fistula solved after the second operation when this hemiliver is removed. In addition, the routine ligation of the DH bile duct should not be performed; it leads to increased morbidity and mortality due to bile leaks and to the possibility of injuring the right hepatic

artery during dissection, without hypertrophic advantage. Finally, even though there have been remote cases of a laparoscopic ALPPS,<sup>21</sup> since laparoscopic liver resection is a method in development, ALPPS should not be performed by laparoscopy at least during the learning curve of this procedure. Furthermore, laparoscopy lacks palpation, which is essential to diagnose occult lesions after chemotherapy during both surgical steps.

The present report represents an original contribution to the present literature, since it is the first technical report concerning this novel strategy and, to the best of our knowledge, based on the largest ALPPS experience in a single center without mortality. During our practice performing this procedure, we have learned and developed some valuable technical tips and tricks that were included in this manuscript and that, in our opinion, contribute to facilitating this complex procedure. This strategy emerges as a tempting alternative to be considered in the surgical armamentarium of an already experienced HPB surgeon.

## Conclusion

Even though there is limited clinical experience, this revolutionary two-stage surgical procedure has attracted the attention of many surgical leaders and cancer centers around the world. It prevents PHLF and allows a complete resection (R0) during a single hospitalization in patients with locally advanced liver disease previously declared unresectable. This strategy has demonstrated to be feasible and safe in the hands of experienced hepatobiliary surgeons at high-volume centers and by means of a multidisciplinary team effort. Despite the encouraging results obtained so far, this new technique is still in its infancy and, due to the lack of certified long-term benefits, only increased experience and further research will define the fate of this novel surgical approach.

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