Our initial experience with ALPPS technique: encouraging results

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Our initial experience with ALPPS technique: encouraging results

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Abstract Surgical resection is the best option for prolonged survival in patients with primary or secondary liver tumors. A sufficient future liver remnant (FLR) volume is needed to prevent post-hepatectomy liver failure (PHLF). With the aim of increasing FLR, a new two-step technique has been recently developed. Our aim is to report our initial experience with associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) technique. Analysis was conducted of ten patients previously considered locally unresectable because of small FLR. During first surgical step liver parenchymal partition and portal vein ligation was performed. Seven days after the first procedure, once volumetric and functional studies have demonstrated an appropriate FLR volume, the resection of the deportalized hemiliver was achieved. This technique was successfully performed in all ten patients (feasibility 100 %). Six were male with mean age of 55.2 years (range 39–77). Mean preoperative FLR volume and FLR/total liver volume were 408.4 ml and 27.8 %. Mean postoperative FLR volume was 733 ml representing a mean volume increase of 325 ml or 82 % (range 31–140) \( (p < 0.0001) \). All resections were R0 (4 right hepatectomies, 5 right trisectionectomies and 1 left trisectionectomy). There were two grade A post-hepatectomy liver failures. Morbidity was 40 % and mortality 0 %. With a mean follow-up of 187 days, disease-free survival and overall survival were 80 and 100 %, respectively. ALPPS induces a great and fast FLR hypertrophy allowing R0 resections in patients otherwise considered unresectable because of small FLR volume, without severe PHLF and low mortality in experience centers. Further experience is needed to determine long-term outcomes.

Keywords ALPPS · Postoperative liver failure · Liver tumors · Future liver remnant · Liver partition

Introduction

Surgical resection with curative intent for primary and secondary liver tumors, with or without neoadjuvant chemotherapy, is the treatment of choice to enhance long-term survival [1].

Improvements in anesthesia, perioperative care and advances in surgical techniques have decreased morbidity and mortality of major liver resections. These developments have led to a change in the resectability criteria in recent years, from being defined by what is resected to be defined on the basis of what remains after resection. This paradigm shift implies that the surgeon has to focus his attention on the functionality and volume of the future liver remnant (FLR) and not only in the size and number of lesions [2].

Post-hepatectomy liver failure (PHLF) is the most feared and severe complication after extended liver resections and recovery from major hepatic resection relates primarily to the quality and volume of liver that remains after resection [3–5]. In case of normal hepatic function, a FLR of approximately 25 % of total liver volume (TLV) is considered to be sufficient to maintain liver function after...
resection. For patients with hepatic dysfunction or earlier liver injury (e.g., due to chemotherapy), a higher FR (approximately 40%) is recommended [6]. Several authors report different percentages of FR necessary to perform a safe hepatic resection avoiding PHLF in normal and diseased livers. But in the clinical practice, mostly due to the use and abuse of preoperative chemotherapy drugs, this percentage is not so easy to determinate [3, 7].

Furthermore, the remaining liver volume is a very important limiting factor for performing major liver resections. This gave rise to new tactics and techniques to prevent postoperative liver failure. In the early 1980s, Makuuchi introduced portal vein embolization (PVE) as a method to induce hypertrophy of a putative FR. Soon after other authors introduced several techniques combining portal vein occlusion with stage hepatectomies [1, 4, 8–10].

A new two-step technique has been developed in 2007 by Schnitzbauer et al. and coworkers in Germany consisting on the combination of partition of liver parenchyma with portal vein ligation (PVL) [11]. de Santibañes and Clavien have proposed to rename it “associating liver partition and portal vein ligation for staged hepatectomy” (ALPPS) [12].

Although there are many alternative techniques to enhance growth of FR, none of them have showed so far neither the same degree of liver hypertrophy (with ranges between 40 and 160%) nor as fast (7–9 days) as ALPPS [11, 13, 14].

The aim of this manuscript is to report our initial experience employing the ALPPS technique in ten patients with primary and secondary liver tumors who were previously considered locally unresectable because of insufficient FR volume.

Materials and methods

Since June 2011 to March 2012 we have performed the ALPPS technique in ten patients previously considered locally unresectable because of insufficient FR.

Inclusion criteria for this approach were main right tumor with compromise of the left hemiliver, tumor invasion of the right portal vein, previous PVL or PVE with unsatisfying results, tumors at high risk of rapid progression with potential compromise of vascular structures, and big tumors with little amount of homolateral parenchyma and hypertrophy of contralateral hemiliver conditioning a poor response to PVE or PVL.

CT images were obtained preoperatively and 6 days after the first surgical step by using 64-row MDCT (Aquilion; Toshiba Medical Systems) to determine the FR volume. A baseline unenhanced scan was obtained and then a biphasic technique was performed. Volumetric reconstruction was performed by a single experienced radiologist. The TLV was calculated using the formula: −794.41 + 1,267.28 × body surface area (BSA) [15]. The mean absolute FR and also the FR/TLV ratio were calculated before each step to determine the degree of hypertrophy.

All patients underwent a two-stage hepatectomy. During the first step a detailed exploration of the abdominal cavity was carried out and intraoperative ultrasound (IOUS) of the liver was performed. The first surgical gesture was 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 necessarily need to be recognized during this complex procedure. In the presence of primary or secondary multifocal liver disease, a complete tumor resection (clean-up) of the FR was performed. Subsequently, the portal vein of the diseased hemiliver was identified, sectioned and sutured. Once liver mobilization was complete, total or nearly total liver partition to the level of the inferior vena cava (IVC) was carried out as a right hepatectomy, right trisectionectomy or left trisectionectomy depending on the patient and the local extension of the disease. The deportalized liver was wrapped in a hermetic plastic bag with a drain inside in order to facilitate the second procedure minimizing postoperative adhesions and avoiding a choleperitoneum due to international publications on ALPPS which report a high incidence of biliary leakage and associated mortality [11].

Postoperative course was completed in the intensive care unit (ICU). Prophylactic antibiotics treatment and total parenteral nutrition were administrated.

Six days after surgery, a new MDCT scan examination was performed to determine the FRL volume. If the FR was considered sufficient and the patient was stable, a completion surgery was performed the following day.

The abdominal cavity was entered using the previous incision. The resection of the deportalized hemiliver was achieved using vascular staplers for all vascular and biliary structures and the remaining liver parenchyma, if present, in contact with the IVC. Finally, the cystic duct was cannulated and a hydraulic test and intraoperative cholangiography were performed.

Laboratory findings regarding prothrombin time (PT), factor V (FV) and serum bilirubin among others were registered day by day to evaluate liver function. Postoperative complications were evaluated according to the Dindo–Clavien classification [16]. PHLF was defined as postoperative acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions (which are characterized by decrease in PT and concomitant hyperbilirubinemia) on or after postoperative day 5. PHLF was classified as grade A, B and C according to the International Study Group of Liver Surgery definition [17].
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age</th>
<th>FLR/TLV</th>
<th>Preop. treatment</th>
<th>1st step additional procedures</th>
<th>Type of resection</th>
<th>Preop FLR/TLV vol.</th>
<th>Postop FLR vol.</th>
<th>Hypertrophy (%)</th>
<th>Complications</th>
<th>Grade</th>
<th>Hospital stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CRLM</td>
<td>Female</td>
<td>40</td>
<td>44</td>
<td>Capox–bevacizumab</td>
<td>Clean-up FLR, simultaneous CR resection (LC)</td>
<td>Right hepatectomy</td>
<td>452&lt;sup&gt;a&lt;/sup&gt;</td>
<td>690</td>
<td>53</td>
<td>None</td>
<td>11</td>
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<tr>
<td>2</td>
<td>CRLM</td>
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<td>55</td>
<td>27</td>
<td>PVL, PVE, Folfox + cetuximab</td>
<td>None</td>
<td>Right hepatectomy</td>
<td>471</td>
<td>776</td>
<td>65</td>
<td>Biliary leakage, pleural effusion</td>
<td>3a</td>
<td>24</td>
</tr>
<tr>
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<td>Hilar CC</td>
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<td>20</td>
<td>Bilateral PBD</td>
<td>HJ</td>
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<td>Right hepatic artery reconstruction</td>
<td>Right trisectionectomy</td>
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<td>31</td>
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<td>21</td>
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<td>Clean-up FLR</td>
<td>Right trisectionectomy</td>
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<td>135</td>
<td>None</td>
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<td>74</td>
<td>24</td>
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<td>Right trisectionectomy</td>
<td>330</td>
<td>724</td>
<td>119</td>
<td>Biliary leakage</td>
<td>2</td>
<td>17</td>
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<td>25</td>
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<td>Clean-up FLR</td>
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<td>Right hepatectomy</td>
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<td>1030</td>
<td>140</td>
<td>Pleural effusion</td>
<td>3a</td>
<td>17</td>
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<tr>
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<td>50</td>
<td>27</td>
<td>Folfox + bevacizumab</td>
<td>Folli–cetuximab</td>
<td>Clean-up FLR</td>
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<td>832</td>
<td>108</td>
<td>None</td>
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</tbody>
</table>


<sup>a</sup> The volume of the CRLM located in the FLR has been subtracted from the preoperative volumetry of the FLR
Continuous variables are expressed as mean (range). Paired \( t \) test was used to compare the FLR volume previous and posterior to the first surgical procedure. A \( p < 0.05 \) was considered significant. Due to the short follow-up time in this work, survival and disease-free survival were calculated as percentage of alive or disease-free patients at the end of the study. Statistical analysis was performed with Primer of Biostatistics, 4.02, 1996 McGraw Hill.

Results

This technique was successfully performed in all ten patients; seven had colorectal liver metastases (CRLM), one hepatocellular carcinoma, one hilar cholangiocarcinoma and one non-colorectal non-neuroendocrine liver metastases (Table 1). Six were males and the mean age was 55.2 years (range 39–77). Six patients with CRLM had preoperative chemotherapy. One patient had a previous metastasis resection associated with PVL, afterwards a PVE was performed because of an insufficient growth in the FLR. Finally due to insufficient growth in spite of these two previous tactics, ALPPS was indicated.

Five patients with CRLM had previous surgery of the primary colorectal tumor. The remaining two had simultaneous colorectal resections (left hemicolecctomy and upper anterior rectal resection) during the first stage of the hepatectomy. In the patient with the upper anterior rectal resection, an ileostomy was performed due to hypoalbuminemia and poor general condition associated to a long course of chemotherapy.

The mean preoperative FLR volume was 408.4 ml (range 285–572 ml) and mean FLR/TLV was 27.8 % (range 19–44 %). One patient had a preoperative FLR/TLV of 44 %, in this case the patient had CRLM and had received over fourteen cycles of chemotherapy and biological agents.

The mean operative time for the first intervention was 303 min (range 195–360) and for the second 121 min (range 60–180).

Three patients required red blood cell (RBC) transfusion during the first surgery (mean 1.5 RBC packs per patient). Six patients required blood transfusion during the second procedure (mean 2 RBC packs per patient). Only one patient required blood transfusion during both procedures.

Intermittent Pringle maneuver was performed in two patients during the first surgery. The first one had three Pringle maneuvers of 20, 15 and 15 min to resect two lesions in segments II and III and for parenchymal transection. The other patient had one clamping of 15 min to transect the liver parenchyma.

The mean postoperative FLR volume 6 days after the first procedure was 733 ml (range 521–1,030 ml) being the mean difference between preoperative and postoperative FLR volume 325 ml (\( p < 0.0001 \)) and representing a mean volume increase of 82 % (31–140 %) (Fig. 1).
All patients succeeded in the completion of the second stage hepatectomy 7 days after the first procedure which translates into a feasibility rate of 100 %.

Two of the patients developed grade A PHLF during their hospital stay. Postoperative serum bilirubin and PT daily values are detailed in Figs. 2 and 3. Postoperative morbidity in our series was 40 % with four patients with complications grade II and IIIa (two biliary leakages and two pleural effusions) after the second procedure. There were no complications registered following the first procedure. Mortality rate was 0 %. Mean hospital stay was 15.5 days (range 11–24).

With a mean follow-up of 187 days (range 77–343), disease-free survival and overall survival was 80 and 100 %, respectively. One patient with CRLM developed lung metastasis after 116 days and is undergoing chemotherapy.

Discussion

Post-operative liver failure is the main cause of death after major hepatic resections and it is strictly related to the volume and quality of the FLR.

This gave rise to new tactics and techniques to prevent postoperative liver failure. Masatoshi Makuuchi in 1980s introduced PVE to induce FLR hypertrophy of around 10–40 % in 4–8 weeks [8]. A decade later, Adam and colleagues introduced the concept of sequential two-stage hepatectomy allowing the liver to regenerate between both procedures [1]. Soon after, Daniel Jaeck developed another two-stage approach combining right PVE after the initial removal of tumors located in the left hemiliver [9]. Finally, this approach has being modified by applying concomitant right PVL [4, 18]. These four developments led to the successful removal of multiple, often bilateral, liver lesions otherwise felt to be unresectable. However, a sufficient hypertrophy is not always achieved and there is concern about the potential simultaneous and faster growth of the tumor during the period of time prior to resection [19–21].

In 2007, Prof. Hans Schlitt from Regensburg, Germany, performed the first ALPPS in a patient with a hilar cholangiocarcinoma. This technique has been described as an advantageous strategy to induce a rapid and marked increase in FLR volume, unparalleled by current methods [11]. Unlike PVE, which enhances liver growth approximately 20–35 % in 30–45 days, ALPPS technique allows a FLR growth of 40–160 % in only 6–9 days [11, 13, 14].

Although long-term oncological results with this new technique are still not completely evaluated, the short period between the two interventions could avoid the risk of tumor progression in the meantime. The time window between two steps of treatment was pointed as an important period that allows observing oncological behavior of the tumor and therefore exclude patients with tumor growth during the treatment. This concept was highlighted in patients who underwent neoadjuvant therapies for colorectal liver metastases. We think that performing the two steps of the treatment within 7 days does not carry any disadvantage because first of all, ALPPS is a strategy that may be used in patients with different primary or secondary liver tumors (e.g. HCC, Gallbladder Cancer, Cholangiocarcinoma, etc.) in whom chemotherapy does not have a central role in its management. Concerning patients with CRLM, these were previously unresectable patients who have been rescued with an intense chemotherapy scheme, which reduced tumoral load and had an acceptable biological response. In these patients, ALPPS appears as a feasible strategy for surgical rescue and to achieve a R0 resection.

Despite the lack of long-term evidence, in our opinion this technique could have several surgical and oncological advantages. On one hand, the exploration of the abdominal cavity allows to reliably exclude intra and extrahepatic disease, which might have escaped the preoperative work-up and preclude resectability, which is not possible in cases of PVE. On the other hand, intensive cleaning of the FLR can be performed without the fear that a small FLR will result as a consequence of this radical procedure considering the diseased hemiliver left in place acts as an auxiliary liver to assist the FLR during the first week after the partition. Recently, we postulated this important concept after calculating the postoperative liver functioning volume by scintigraphy. Surprisingly, we found that the contralateral diseased liver remained functioning and represented up to 60 % of total liver function 6 days after the first surgery [14].

In our experience, this approach also allows simultaneous primary tumor resection, mainly colorectal. However, in unpublished series of ALPPS not in our case, an increase in morbidity and mortality has been reported when associating both procedures. Finally, the rapid recovery of the patient after ALPPS allows the early restoring of chemotherapy.

To date, the largest clinical experience with ALPPS is the Cooperative German Experience recently published [11]. They treated 25 patients with primary and secondary liver tumors and reported a 74 % mean increase of FLR in 9 days. They had a 64 % morbidity and 12 % in-hospital mortality with an overall survival of 86 % at 6 months. These preliminary results appear promissory for this new method. In Buenos Aires we started to perform the ALPPS in June 2011. Since then, we have operated 10 patients. As the German group, we found a mean of 82 % FLR increase in only 7 days. We had 40 % morbidity. None of our
patients developed severe PHLF or died. At a median follow-up of 187 days our overall survival is 100 % and the disease-free survival is 80 %.

ALPPS is a new and revolutionary tool that allows achieving R0 resections in patients otherwise considered unresectable in a single hospital stay without postoperative liver failure. Due to the complexity of the procedure and postoperative management, this technique must be limited to experienced HPB surgeons in high-volume centers.

Nevertheless, further experience is needed to determine long-term outcomes.

Conflict of interest  None.

References