Salvage parenchymal liver transection for patients with insufficient volume increase after portal vein occlusion — An extension of the ALPPS approach

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Abstract

Background: Portal vein ligation (PVL) or embolization (PVE) are standard approaches to induce liver hypertrophy of the future liver remnant (FLR) prior to hepatectomy in primarily non-resectable liver tumors. However, this approach fails in about one third of patients. Recently, the new “ALPPS” approach has been described that combines PVL with parenchymal transection to induce rapid liver hypertrophy. This series explores whether isolated parenchymal transection boosts liver hypertrophy in scenarios of failed PVL/PVE.

Methods: A multicenter database with 170 patients undergoing portal vein manipulation to increase the size of the FLR was screened for patients undergoing isolated parenchymal transection as a salvage procedure. Three patients who underwent PVL/PVE with subsequent insufficient volume gain and subsequently underwent parenchymal liver transection as a salvage procedure were identified. Patient characteristics, volume increase, postoperative complications and outcomes were analyzed.

Results: The first patient underwent liver transection 16 weeks after failed PVL with a standardized FLR (sFLR) of 30%, which increased to 47% in 7 days. The second patient showed a sFLR of 25% 28 weeks after PVL and subsequent PVE of segment IV, which increased to 41% in 7 days after transection. The third patient underwent liver partition 8 weeks after PVE with a sFLR of 19%, which increased to 37% in six days. All patients underwent a R0 resection.

Conclusion: Failed PVE or PVL appears to represent a good indication for the isolated parenchymal liver transection according to the newly developed ALPPS approach.

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Introduction

Despite recent advances in multimodality treatment of colorectal liver metastases many patients suffer from extensive bilobar disease, which prevents the performance of a single procedure due to an insufficient future liver remnant (FLR).1–3 To minimize the risk of postoperative liver failure, occlusion (via embolization or ligation) of portal vein branches feeding the part of the liver to be resected has been widely used over the past two decades to increase FLR volume.4

Previous reports have demonstrated that about one third of patients undergoing portal vein occlusion do not proceed to liver resection due to insufficient hypertrophy of the FLR.
or interval tumor progression (Table 1).2,5–10 Associating liver partition and portal vein ligation for staged hepatectomies with portal vein occlusion (ALPPS) has recently been introduced as a strategy to induce a rapid and extensive increase in FLR volume.4,11 Despite promising results in obtaining FLR growth, initial reports have described high perioperative mortality and morbidity, limiting its widespread application outside of studies and registries.11

When the conventional portal vein occlusion strategies fail to induce a sufficient FLR (generally 30–40% of the total liver volume) within 4–8 weeks, longer waiting times may ensue with the risk of tumor progression and ultimately loss of resectability. Some authors have suggested not to perform major liver resections at all in patients with low kinetic growth rate because these patients have a strongly increased risk of postoperative liver failure.12 Isolated parenchymal liver transection following the ALPPS paradigm may, however, offer a salvage strategy in patients with insufficient hypertrophy by boosting FLR growth and still allow for a potentially curative approach.13,14 The present report suggests that after both PVE and PVL, conversion to ALPPS may lead to salvage of the curative approach.

Patients and methods

Patients

A database of 170 patients with liver tumors resected after portal vein manipulation including 48 cases of ALPPS between 2002 and 2012 maintained by the University Hospital in Zurich, Switzerland, Western University Medical Center in London, Canada, Italian Hospital in Buenos Aires, Argentina and University Hospital Mainz, Germany, was searched for patients who underwent salvage parenchymal transections following the ALPPS paradigm after failed portal vein occlusion. Clinical outcome and complications were assessed.15 Three patients were identified (Table 2). All three patients had colorectal liver metastasis with bilobar lesions and insufficient FLR volume growth after previous portal vein occlusion. Patient 1 underwent right PVL and resection of segment III during the first stage of a two-stage hepatectomy. After 8 weeks the patient did not fulfill criteria for resection despite a sFLR of 31% because of a low kinetic growth rate and extensive chemotherapy. Patient 2 underwent right PVL in conjunction with a right hemicolectomy during a first stage. After interval chemotherapy, the patient did not fulfill criteria for resection due to a sFLR of 18%. Therefore, subsequently the patient underwent a segment IV embolization in addition to a right hepatic vein embolization in an attempt to boost growth of the FLR with a resulting increase to a still low sFLR of 25%. At surgical exploration, the patient’s liver showed signs of SOS and instead of the planned resection an isolated parenchymal transection was performed. Patient 3 underwent a laparoscopically assisted sigmoid colectomy with synchronous segment III resection during a first stage. Two weeks after the first stage PVE was performed with a volume increase after 8 weeks to a sFLR of 19%, not fulfilling resection criteria. No progression of disease was seen after PVE or PVL.

Surgical technique

The surgical technique of conventional liver resections after PVE or PVL have been previously described.1,3,4,10 Isolated parenchymal liver transection was performed between the FLR and the part of the liver to be resected at a later stage following the techniques described for the ALPPS procedure. The hepatic arterial flow and biliary drainage of the previously deportalized liver were preserved during the transection. The transection lines were placed to the left of the tumor involvement of segment 4, frequently resulting in partial devascularisation of segment 4. After sufficient hypertrophy of the FLR was obtained, the hepatectomy was performed by transection of the right hepatic artery, hepatic duct, portal vein and hepatic veins.

Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Second stage completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam et al.2</td>
<td>2000</td>
<td>16</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Kianmeh et al.5</td>
<td>2003</td>
<td>20</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Jaeck et al.6</td>
<td>2004</td>
<td>33</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Tsai et al.7</td>
<td>2010</td>
<td>35</td>
<td>10 (29%)</td>
</tr>
<tr>
<td>Wicherts et al.8</td>
<td>2008</td>
<td>59</td>
<td>19 (31%)</td>
</tr>
<tr>
<td>Narita et al.9</td>
<td>2011</td>
<td>90</td>
<td>30 (33%)</td>
</tr>
<tr>
<td>Brouquet et al.10</td>
<td>2011</td>
<td>65</td>
<td>18 (33%)</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Gender/age</th>
<th>BMI (kg/m²)</th>
<th>Disease</th>
<th>TNM</th>
<th>Liver disease</th>
<th>Strategy</th>
<th>Chemotherapy</th>
<th>sFLR0</th>
<th>sFLR1</th>
<th>KGR %/week</th>
<th>Time to transection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F</td>
<td>43</td>
<td>40</td>
<td>CRLM</td>
<td>pT4 pN0 M1</td>
<td>Steatosis</td>
<td>PVE</td>
<td>FOLFIRO/Cetuximab</td>
<td>21%</td>
<td>30%</td>
<td>0.56</td>
<td>16 weeks</td>
</tr>
<tr>
<td>2 M</td>
<td>55</td>
<td>28.4</td>
<td>CRLM</td>
<td>pT3 pN(ni) pM1</td>
<td>No</td>
<td>PVE + PVE</td>
<td>FOLFOX/Cetuximab</td>
<td>10%</td>
<td>25%</td>
<td>0.54</td>
<td>28 weeks</td>
</tr>
<tr>
<td>3 M</td>
<td>65</td>
<td>23.3</td>
<td>CRLM</td>
<td>pT4 pN2b M1</td>
<td>SOS</td>
<td>PVE</td>
<td>FOLFOX/Bevacizumab</td>
<td>15%</td>
<td>19%</td>
<td>0.5</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

Pt: patient; F: female; M: male; BMI: body mass index; CRLM: colorectal liver metastases; SOS: sinusoidal obstruction syndrome; PVE: portal vein ligation; PVE: portal vein embolization; sFLR0: standardized future liver remnant prior to conventional PVO; sFLR1: standardized future liver remnant after conventional PVO; KGR: kinetic growth rate.
Liver volumetry

In each patient, baseline FLR volume (FLR0, i.e. prior to PVE/PVL), FLR1 (prior to transection) and volume prior to removal of the diseased hemiliver (FLR2) was measured based on computer tomography (CT) or magnetic resonance imaging (MRI) studies using dedicated volume rendering software to compare the increase in FLR volume. Standardized total liver volume (sTLV) was calculated according to Vauthey et al.16 The Mosteller formula was used to calculate body surface area. sFLR was calculated accordingly as FLR/sTLV*100%. Increase of sFLR after PVE/PVL (sFLR1−sFLR0) as well as increase after parenchymal transection prior to removal of the diseased hemiliver (sFLR2−sFLR1) was calculated. Kinetic growth rate (KGR) was calculated as increase of sFLR in percent after the intervention divided by the weeks between performed volumetry (sFLR2−sFLR1/weeks). Figures were made using Graph Pad Prism (Graph Pad Software, La Jolla, CA).

Results

Volume increase after isolated parenchymal transection and after hepatectomy

Patient 1 experienced an increase of the sFLR from 31% to 47% within one week and subsequently underwent hepatectomy according to the 2nd stage in the ALPPS procedure. Patient 2 experienced an increase of the sFLR from 25% to 41% within one week. Patient 3 experienced a sFLR increase from 19 to 37%. Posthepatectomy liver volumetry in all three patients showed sustained increase of the remnant liver volume one week after hepatectomy (Fig. 1a−c). Interestingly volume increase continued with the same velocity as after isolated parenchymal transection (Fig. 2). The kinetic growth rates were between 12.3 and 18% (Table 3) and compared favorably to the 0.50−0.56%/week achieved by PVE and PVL.

Clinical outcomes and complications

Patient 1 developed posthepatectomy ascites and was discharged 17 days after resection. She developed peritoneal carcinomatosis 1 year after the procedure with the liver still free of tumor. Patient 2 developed a postoperative biliary leak and right pleural effusion and underwent a percutaneous abdominal drain and chest tube placement. She was discharged on POD 13 and developed pulmonary metastases after one year without evidence of liver recurrence. Patient 3 developed a grade 1 postoperative liver insufficiency after the criteria of the ISGLS but recovered well and was discharged after 14 days.17 She has no recurrence at 12 months after resection (Table 3).15

Figure 1. a: Liver remnant (LR) increases in volumetric assessment in patients 1−3. The arrows depict the increase in volume. b: Increase of volume measured in cc of the future liver remnant (FLR) after portal vein embolization/ligation (PVE/PVL) (black and blue), and after transection (red). (*For visual purposes the growth between time points is depicted as linear; however in reality the growth is certainly not linear.). c: Increase of volume computed as standardized future liver remnant (sFLR) after portal vein embolization/ligation (PVE/PVL) (black and blue) and after transection (red). The interrupted line shows the common clinical cut-off of 30% for safer liver surgery. (*For visual purposes the growth between time points is depicted as linear however in reality the growth is certainly not linear.)
Discussion

This report suggests that isolated parenchymal liver transection like during ALPPS may be used successfully after failed portal vein occlusion. By boosting hypertrophy of the FLR it enables a safe resection. Failure to achieve adequate hypertrophy and a sufficient kinetic growth rate with conventional portal vein occlusion does not select for an intrinsic lack of regenerative potential. Selection based on inadequate growth has been used by some authors as a guide to exclude patients from resection. The introduction of ALPPS and isolated parenchymal transection might avoid this negative selection based on growth failure of the FLR.

Hypertrophy induced by isolated parenchymal transection appears more effective than other strategies proposed to salvage inadequate FLR growth. Nagino et al. reported two patients with cholangiocarcinoma with successful arterial embolization to salvage insufficient FLR hypertrophy after PVE with a 46% and 22% volume increase after 2 and 3 weeks, respectively. Gruttaduria et al. reported two patients with colorectal cancer metastases with arterial embolization to salvage insufficient FLR hypertrophy with volume increases of 140% and 72% three weeks after arterial embolization. The ALPPS approach induces a similar degree of hypertrophy within 1 week. Sequential arterial embolization induces necrosis of the completely de-vascularized parenchyma, whereas the arterial blood flow to the part of the liver planned to be resected, remains intact after parenchymal liver transection. If any necrosis develops, it is generally limited to a small area of segment 4.

Another salvage strategy is hepatic vein embolization with vascular plugs to prevent migration of coils to salvage insufficient hypertrophy after PVE has been proposed and tested prospectively. It has been shown to be effective in nine of twelve patients to induce additional hypertrophy of 27.6% ± 8.6% two weeks after embolization and allows resection of liver tumors. However, it is uncommonly used and the hypertrophy induced appears mild as shown in patient 2 in our report. Additional embolization of the portal branches to segment IV has been reported to result in more overall hypertrophy than embolization of the unilateral portal vein only as long as it is performed simultaneously. Whether repeated portal vein embolization or additional embolization of segment IV branches is effective as a salvage strategy is unclear due to lack of published data.

Our preliminary experience suggests that isolated parenchymal liver transection might be the best salvage strategy applicable to all scenarios of previous failed portal vein occlusions. Indeed, more hypertrophy is induced in a shorter period of time than with any other salvage strategy proposed so far. Our data suggest that failure to grow to a ‘safe’ volumetric resection cut-off or not reaching a certain kinetic growth rate, does not automatically imply that these patients should be indefinitely excluded from liver resection. We propose to consider isolated liver parenchymal transection 6–9 weeks after PVE if either kinetic growth rate or volumetric cut-off are felt to be too low to proceed with resection. Failed growth of the FLR has been shown to be the cause for half of the cases of non-proceeding to curative resection after PVE. Indeed, in cases of slow hypertrophy that can be attributed to liver parenchymal damage due to chemotherapy, parenchymal liver transection remains a salvage option, as shown in patient 2. The other half of patients not proceeding to liver resection after PVO has been attributed to tumor progression that is also often related to longer waiting times after PVO. It remains, however, to be proven if an early application of isolated liver parenchymal transection to boost FLR growth will also translate into better long-term oncologic outcomes for these patients.

Table 3
Clinical outcomes and complications for patients 1–3.

<table>
<thead>
<tr>
<th>Pt</th>
<th>sFLR1 %</th>
<th>sFLR2 %</th>
<th>KGR %/week</th>
<th>Time to resection</th>
<th>Bilirubin POD 5</th>
<th>INR POD 5</th>
<th>Liver failure (ISGLS)</th>
<th>Complications (Clavien Dindo)</th>
<th>Tumor recurrence at 12 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30%</td>
<td>47%</td>
<td>17</td>
<td>7 days</td>
<td>6 umol/l</td>
<td>1</td>
<td>—</td>
<td>Posthepatectomy ascites (II)</td>
<td>Peritoneal, not hepatic</td>
</tr>
<tr>
<td>2</td>
<td>25%</td>
<td>41%</td>
<td>12.3</td>
<td>9 days</td>
<td>49 umol/l</td>
<td>1.5</td>
<td>—</td>
<td>Bile leak and pleural effusion (IIa)</td>
<td>Pulmonary, not hepatic</td>
</tr>
<tr>
<td>3</td>
<td>19%</td>
<td>37%</td>
<td>18</td>
<td>7 days</td>
<td>83 umol/l</td>
<td>1.7</td>
<td>A</td>
<td>Liver insufficiency (IV)</td>
<td>—</td>
</tr>
</tbody>
</table>

Pt: patient; PVL: portal vein ligation; PVE: portal vein embolization; sFLR1: standardized future liver remnant after conventional PVO; sFLR2: standardized future liver remnant prior to resection; KGR: kinetic growth rate; POD: postoperative day; Complications: according to the Clavien Dindo Classification; Liver Failure: according to the ISGLS definition.
Parenchymal transection results in rapid liver growth. However, the amount of hypertrophy might not necessarily reflect functional capacity of the liver, especially in patients with underlying parenchymal liver disease as exemplified in patient 3, who developed transient liver failure after resection. Although a widely accepted safety margin for primary liver resection, 30% sFLR, after rapid hypertrophy might not guarantee sufficient postoperative liver function. With respect to this, functional, not just volumetric, assessments of the FLR have become a priority.

It is remarkable that hypertrophy after parenchymal transection continues at a similar pace one week after liver resection as shown in Fig. 2. It has been suggested that the FLR growth rate after ALPPS stage one or after isolated parenchymal transection is similar to the growth rate of the liver after resection.²⁵ Our finding that hypertrophy continues after resection at the same rate as after parenchymal transection supports the hypothesis that ALPPS simulates a major hepatectomy as far as the growth rate is concerned. There are however shortcomings to our study. First, we report only three individual cases, albeit as the result of screening a database of 170 patients with PVE/PVL. Second, all patients had CRM L thereby limiting the generalizability of our findings to other types of liver tumors. Indeed, it has been shown that ALPPS should be applied with caution in patients with cholangiocarcinoma because of its high morbidity and mortality according to recent reports.²⁶ Third, due to the retrospective character of our analysis the intervals between PVE/PVL, parenchymal liver transection and resection were standardized for the cases reported.

In order to elucidate possible benefits and dangers of the ALPPS procedure to achieve complete tumor resection in patients with small FLRs a registry was implemented (www.alpps.net) and a multicentric RCT initiated (www.clinicaltrials.gov; NCT 01775267).

Conclusion

This report suggests the efficacy and safety of isolated parenchymal liver transection in patients with insufficient future liver remnant hypertrophy following portal vein occlusion. We recommend isolated parenchymal liver transection according to the ALPPS procedure as a salvage strategy in order to maintain a curative intent in these selected patients.

Conflict of interest statement

The authors declare to have no conflict of interest.

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References

21. Hwang S, Lee SG, Ko SY, et al. Sequential preoperative ipsilateral hepatic vein embolization after portal vein embolization to induce


