Radiological aspects of portal vein embolization
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Chapter 3

Outcomes of portal vein embolization and extensive resection in predamaged livers

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D.J. Gouma
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T.M. van Gulik
Abstract

Objectives: To assess efficacy and safety of portal vein embolization (PVE) in relation to pre-existing liver cirrhosis, steatosis, cholestasis, chemotherapy, and clinical outcomes.

Methods: Between January 2005 and July 2011, 56 consecutive patients underwent PVE, at least three weeks before extensive liver resection. Volumes of total liver, tumour and future remnant liver (FRL) were analyzed. Outcomes were assessed in relation to pre-existing liver cirrhosis, cholestasis and chemotherapy.

Results: All patients underwent successful embolization. A serious adverse event occurred in one patient (1.7%), consisting of contralateral portal vein thrombosis, rendering the patient unresectable. The mean increase of the FRL was 51% (0-305%). Insufficient hypertrophy response precluding surgical resection was seen in only one patient (1.7%). There were no significant differences in hypertrophy response of FRL after PVE between patients with and without chemotherapy (p=0.51), fibrosis/steatosis (p=0.43) or patients with and without cholestasis (p=0.58) and there are no significant differences in regeneration three months after liver resection.

Conclusions: PVE is a safe and efficient technique in patients with compromised liver function due to fibrosis, cholestasis or liver damage after chemotherapy. There were no significant differences in post-PVE hypertrophy response nor in post-resectional liver regeneration between patients with predamaged and normal livers.
Introduction

In patients with metastatic liver disease or with primary hepatic or biliary malignancy, surgical resection is the only option to achieve long-term survival. As almost half of these patients need at least a hemihepatectomy to ensure margin-negative resection, many patients are found unresectable because of an anticipated, small future remnant liver (FRL). The function and volume of the FRL are important determinants for predicting postoperative liver failure, which is a life-threatening complication after resection.[1]

Makuuchi et al. clinically introduced in 1990 the technique of portal vein embolization (PVE) to induce liver hypertrophy, rendering patients with a small FRL resectable.[2] Since then, many studies have demonstrated the augmenting effect and safety of this procedure. In patients with normal liver parenchyma, the minimum volume of the FRL is considered to be at least 25% to avoid liver failure after major liver resection. However, in predamaged livers (fibrosis/cirrhosis, steatosis, cholestasis, post-chemotherapy), the minimum volume of the FRL is rather chosen at 40%.[3]

PVE increases the opportunities for patients to undergo resection and allows surgeons to perform more extensive liver resections, exploring the limits of what is technically possible. Since patients are increasingly included in neoadjuvant chemotherapy regimens, the influence of chemotherapy on the hypertrophy response of the FRL is under debate.[4,5] Some authors reported that chemotherapy does not affect the hypertrophy response at all [4,5,6,7], whereas others concluded that chemotherapy negatively influenced the rate of hypertrophy.[8,9]

The role of cholestasis in regeneration of the FRL after PVE also remains controversial. It is stated by some authors that longstanding cholestasis, as is often encountered in patients with cholangiocarcinoma, impedes the hypertrophy response of the FRL, emphasizing the need for pre-procedural biliary drainage.[10,11] This notion however, has not been confirmed in other studies.[6,12]

The aim of this study was to assess our results of PVE in patients with compromised liver function and to compare these with the results in patients with normal liver function, including regeneration of the liver remnant 3 months after resection.

Materials and methods

Patients

Between January 2005 and July 2011, 56 consecutive patients underwent PVE prior to liver resection. Patient characteristics, indications for PVE, volumetric changes, hypertrophy response, complications after PVE, surgical outcome and surgical complications were evaluated.

The influence of pre-existing liver cirrhosis/fibrosis, steatosis, cholestasis and chemotherapy on the hypertrophy response was examined in particular. Data concerning cirrhosis, fibrosis and steatosis were extracted from pathology reports, radiology reports and patient records.
All patients with extensive intrahepatic cholestasis caused by cholangiocarcinoma or colorectal liver metastasis (CRLM) were evaluated separately. More than half of the patients with CRLM, received pre-operative chemotherapy according to locale treatment strategies (mostly 5-FU/Leucovorin combined with Oxaliplatin or Irinotecan). As data concerning interruption of chemotherapy between PVE and resection were inconsistent, these were not taken into account.

PVE

All procedures were performed using the percutaneous, ipsilateral approach as described by Madoff[12] to prevent complications of the contralateral, usually the left portal vein and left liver lobe. The procedure was performed under conscious sedation by midazolam (Midazolam, Actavis 5mg/ml, Actavisgroup PTC ehf, Iceland), fentanyl (Fentanyl 50 microgram/ml, Bifarma pharmaceuticals, Hameln, Germany) and local infiltration of the skin with lidocaine (Lidocaine HCL 2%, B. Braun AG, Melsungen, Germany). After ultrasound-guided puncture of an anterior branch of the right portal vein, a 5 French sheath was inserted. Following portography, all right branches of the portal vein were selectively catheterized using a reverse curved catheter, and embolized with PVA particles (300-500 μg, Cook Incorporated, Bloomington, United States of America) and multiple 6 to 12 mm platinum coils (Tornado Embolization Coils, Cook Incorporated, Bloomington, USA). The procedure was completed with a check portogram to confirm total occlusion of the right portal system and normal flow through the left, future remnant portal system. Finally, the puncture tract was closed with a gelfoam plug (Spongostan Standard, Ferrosan A/S, Soeborg, Denmark). In patients with cholestasis, complete percutaneous or endoscopic drainage of the obstructed bile ducts was performed prior to PVE.

Technical success was defined as complete occlusion of the right portal venous system at the end of the embolization procedure. Clinical success was defined as an uncomplicated procedure and adequate hypertrophy response after a minimum of 3 weeks after PVE, making resection possible.

Biochemical follow-up after PVE

Biochemical tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AF), γ-glutamyltransferase (γGT) and total bilirubin were performed before PVE, immediately following PVE, and 1, 2 and 21 days after PVE. These tests were repeated 6 hrs after surgery, and on day 1, 2, 3, 4, 5, 6, 7, 8 and 14 after resection.

Measurement of liver volume

A multiphase computed tomography (Mx 8000 or Brilliance, Philips, Eindhoven, the Netherlands) with intravenous injection of contrast medium (Ultravist-300, Bayer Schering Pharma, Bayer BV, Mijdrecht, the Netherlands) was performed in all patients before PVE,
approximately three weeks after PVE and three months after surgery, to calculate the maximum hypertrophy response after PVE and after resection. The portal phase or the 4-minutes late enhancement phase of the CT-scan was used to visualize the right, middle and left branches of the hepatic vein, as well as the portal vein, to delineate the individual liver segments according to Couinaud.

CT-data were post-processed and evaluated on a MxView – Independent Multi-Modality Diagnostic Workstation (Version 3.52 B2, August 2002, Philips Medical Systems, Eindhoven, the Netherlands). Five millimetre Multi Planar Reconstructions were made. Segmental anatomy of the left and right liver segments, as well as the tumour were manually delineated after which total liver volume (TLV), future remnant liver volume (FRLV) and tumour volume (TV) were calculated.

The percentage FRL before and three weeks after PVE were calculated, using the following equation:

\[
\% \text{ FRL} = \frac{FRLV}{TLV - TV} \times 100\
\]

Liver hypertrophy after PVE was defined as

\[
1 - \frac{FRL\text{ prePVE}}{FRL\text{ postPVE}} \times 100\%
\]

The same calculation was made with the FRL volumes after surgery:

\[
1 - \frac{FRL\text{ 3months after surgery}}{FRL\text{ postPVE}} \times 100\%
\]

Measurement of liver function using hepatobiliairy scintigraphy

Hepatobiliary scintigraphy (HBS) was performed with $^{99m}$Tc-labeled 2,4,6 trimethyl-3-bromo aminodiacetic acid ($^{99m}$Tc-mebrofenin [Bridatec]; GE Healthcare) to evaluate liver function and to calculate function of the FRL, as described previously.[13] Images are obtained in supine position, with a large-field-of-view (FOV) SPECT/CT camera (Infinia II; GE Healthcare), equipped with low-energy high-resolution collimators, positioned over the liver and heart region. Firstly, a dynamic acquisition (36 frames of 10 s/frame, 128 matrix) immediately after the intravenous administration of 200 MBq of $^{99m}$Tc-mebrofenin was obtained for calculation of the hepatic uptake function. Subsequently, a fast SPECT acquisition was performed (60 projections of 8 s/projection, 128 matrix) centered on the peak of the hepatic time–activity curve, which was used for the 3-dimensional assessment of liver function and calculation of functional liver volume. Immediately after SPECT, a low-dose non–contrast-enhanced CT scan was obtained for attenuation correction and anatomic mapping on the same gantry, without moving the patient. Finally, a second dynamic acquisition (15 frames of 60 s/frame, 128 matrix) was obtained to evaluate biliary excretion. Data were processed on a workstation (MultiModality; Hermes Medical Solutions).

The scintigraphy was performed approximately 14 days before and three weeks after PVE. It was also performed, three months after surgery. Scintigraphy, combined with CT-volumetry, was used to determine the volumetric and functional reserve of the liver. Patients were considered to have sufficient residual liverfunction with an uptake of at least 2.7%/min./m$^2$ and a functional FRL of 25-40%.
Liver resection

All patients elected for PVE were scheduled for either hemihepatectomy (3 or 4 Couinaud segments) or extended hemihepatectomy (4 or 5 Couinaud segments). Surgery was performed if the FRL was at least 25% in patients with normal liver parenchyma and 40% in patients with predamaged livers.

Time of surgery, postoperative course and complications were assessed. The Clavien classification was used for evaluation of complications.[14] Morbidity and mortality were compared in 56 patients who had undergone liver resection without PVE in the same period.

Statistic analysis

SPSS Statistics version 17.0 and GraphPad Prism Version 5.0 was used for statistical analysis. Increase of FRL-volume for each diagnosis was analyzed using the Wilcoxon signed rank test. To compare FRL growth in patients with and without compromised liver, as well as in patients with and without chemotherapy, the Wilcoxon Mann-Whitney U-test was used. A difference with a $P$ value < 0.05 was considered significant.

Results

PVE was performed in 56 patients, 36 men and 20 women, with a mean age of 60 ± 12 yrs (range 31-78). The majority of patients (n=40) were diagnosed with CRLM, in which 18 patients had bilobar disease. A compromised liver, defined by pre-existing fibrosis, steatosis, previous chemotherapy or long-standing cholestasis, was documented in 22 patients. A detailed description of the patient characteristics is given in Table 1.

Table 1: patient characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>36/20</td>
</tr>
<tr>
<td>Age at PVE (yr)</td>
<td>60 (31-78)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Colorectal metastasis</td>
<td>40</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>8</td>
</tr>
<tr>
<td>Hepatocellular adenoma</td>
<td>4</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Neuroendocrine tumour</td>
<td>1</td>
</tr>
<tr>
<td>Gallbladder carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Compromised liver</td>
<td>22/56</td>
</tr>
<tr>
<td>Previous Chemotherapy</td>
<td>26/56</td>
</tr>
</tbody>
</table>
Technical and clinical success of PVE

The technical success rate of the procedure was 100%. Clinical success was achieved in 54 of 56 patients (96.3%). In one patient, portal vein thrombosis of the (left) FRL was found at surgery 4 weeks after PVE, causing unresectability despite exploration of the left portal vein and thrombectomy. This was the only patient in whom a contralateral portal venous access was chosen. After this event, all subsequent patients were managed by ipsilateral right portal access. In one patient PVE was considered to have failed because there was no hypertrophy response at all, despite technical success of the procedure. Therefore, resection in this patient was deferred.

PVE related complications

One patient developed skin rash during the procedure, caused either by the contrast medium or by pre-procedural antibiotics. Embolization of the portal vein could be continued after administration of an antihistamine drug, clemestine (Tavegyl, Novartis Consumer Health BV, Breda, Netherlands) and subsequently was successful. Except for some self-limiting, mild abdominal discomfort, no other complications were seen in the remaining 54 patients. There was no PVE related mortality.

Follow-up of liver function after PVE

An initial elevation in levels of AST, ALT, AF, γGT and total bilirubin was seen, which returned to almost normal in two days. No significant differences in liver enzymes were observed between any of the groups.

Liver volume

In all 56 patients, CT-scans were performed to calculate liver volumes pre and post PVE. The CT-scans were made with a mean of 34 ± 29 days before PVE and a mean of 24 ± 10 days after PVE.

Increase of FRL

As shown in table 2, FRL-volumes significantly increased after PVE as well as after resection (both p<0.0001), compared to pre-PVE volumes. Also the percentage FRL significantly increased from 28.4 ± 8 % to 41.0 ± 9 % (p<0.0001). The FRL volume increased with a mean of 51 ± 50 %.

Table 2: liver volumes before PVE, after PVE and after surgery.

<table>
<thead>
<tr>
<th>Mean volumes (± sd)</th>
<th>TLV-tumour (ml)</th>
<th>Tumour volume (ml)</th>
<th>FRL volume (ml)</th>
<th>FRL (%)</th>
<th>RLV (ml)</th>
<th>RLV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before PVE</td>
<td>1943 ± 713</td>
<td>224 ± 457</td>
<td>507 ± 238</td>
<td>28 ± 8</td>
<td>1263 ± 332</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>After PVE</td>
<td>2009 ± 747</td>
<td>274 ± 534</td>
<td>741 ± 316</td>
<td>41 ± 9</td>
<td>1060 ± 321</td>
<td>59 ± 9</td>
</tr>
<tr>
<td>After surgery</td>
<td>1487 ± 495</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

TLV: Total liver volume; RLV: right liver volume (total liver volume – tumour volume – FRL)
The volume of the embolized segments to be resected (RLV) corresponding with the right liver lobe, decreased significantly after PVE showing a mean decrease of 16% (range 0 - 66%), as well as the percentage of right liver volume (both p<0.05). Total liver volume did not change significantly (p=0.17).

**Cholestasis**

Comparison of patients with cholestasis (n=7) and without cholestasis (n= 49) showed no significant differences in FRL-volumes before PVE (p=0.74) and after PVE (p=0.76; Table 3). Neither were there any significant differences in increase of FRL after PVE (p=0.58).

<table>
<thead>
<tr>
<th>Table 3: increase of FRL-V in patients with and without cholestasis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FRL volume (ml) before PVE</strong></td>
</tr>
<tr>
<td>Percentage FRL (%) before PVE</td>
</tr>
<tr>
<td>FRL volume (ml) after PVE</td>
</tr>
<tr>
<td>Percentage FRL (%) after PVE</td>
</tr>
<tr>
<td>Increase after PVE (%)</td>
</tr>
</tbody>
</table>

**Chemotherapy**

Comparison of patients receiving (n=26) or not receiving (n=30) chemotherapy before PVE, showed no significant differences in FRL-V before PVE (p=0.12) nor after PVE (p=0.46). The increase of FRL in mL/days was also not significantly different (p=0.51 ; Table 4).

<table>
<thead>
<tr>
<th>Table 4: increase of FRL-V in patients with and without chemotherapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FRL volume (ml) before PVE</strong></td>
</tr>
<tr>
<td>Percentage FRL (%) before PVE</td>
</tr>
<tr>
<td>FRL volume (ml) after PVE</td>
</tr>
<tr>
<td>Percentage FRL (%) after PVE</td>
</tr>
<tr>
<td>Increase after PVE (%)</td>
</tr>
</tbody>
</table>

**Compromised liver**

There were no significant differences between patients with a compromised liver (consisting of steatosis, fibrosis/cirrhosis or a combination (n=12)) and patients with a non-compromised liver (n=44) as regards FRL-volumes before PVE (p=0.33); FRL-volumes after PVE (p=0.53) and increase of the FRL in time after resection (p=0.57 ; Table 5).
Hepatobiliary scintigraphy

Hepatobiliary scintigraphy was performed in 51 patients, approximately 14 ± 21 days before and at least three weeks after PVE (mean of 21 ± 5 days). Before PVE, total liver uptake was 16 ± 9.5 % per minute. The FRL showed an uptake of 27 ± 7 %, representing the functional fraction of this part of the liver. A control scintigraphy was performed at least three weeks after PVE in 51 patients. Total liver uptake was then 14 ± 3 % per minute whereas the functional contribution of the FRL had significantly increased to 42 ± 14 % (p=0.027).

Total liver uptake did not change significantly (p=0.27). The uptake by the left liver segments did increase significantly after right PVE, showing a mean of 4.21 ± 3 % per minute before PVE, and a mean of 5.66 ± 2 % per minute after PVE (p<0.0001). Hence, PVE resulted in a significant increase in function of the hypertrophic FRL, three weeks after PVE.

Patients with cholestasis, showed a significantly lower total liver uptake pre- and post-PVE as compared to patients with normal livers (p=0.002), but there were no significant differences in liver function of the FRL pre- (p=0.37) and post-PVE (p=0.63).

There were also no significant differences in uptake of the non-embolized, left liver segments before PVE (p=0.96) or after PVE (p=0.46) in patients after chemotherapy as compared to normal livers. HBS showed a lower increase in uptake of the FRL three weeks after PVE in patients with a compromised liver (9.7%) as compared to patients with a normal liver (54.9%), but this difference is not statistically significant.

Table 5: Increase of FRL-V in patients with and without compromised liver.

<table>
<thead>
<tr>
<th></th>
<th>Non-compromised liver (n=44)</th>
<th>Compromised liver (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRL volume (ml) before PVE</td>
<td>478 ± 186</td>
<td>588 ± 303</td>
</tr>
<tr>
<td>Percentage FRL (%) before PVE</td>
<td>29 ± 8</td>
<td>29 ± 9</td>
</tr>
<tr>
<td>FRL volume (ml) after PVE</td>
<td>711 ± 294</td>
<td>808 ± 353</td>
</tr>
<tr>
<td>Percentage FRL (%) after PVE</td>
<td>42 ± 9</td>
<td>42 ± 9</td>
</tr>
<tr>
<td>Increase after PVE (%)</td>
<td>52 ± 59</td>
<td>44 ± 47</td>
</tr>
</tbody>
</table>

Hepatobiliary scintigraphy was performed in 51 patients, approximately 14 ± 21 days before and at least three weeks after PVE (mean of 21 ± 5 days). Before PVE, total liver uptake was 16 ± 9.5 % per minute. The FRL showed an uptake of 27 ± 7 %, representing the functional fraction of this part of the liver. A control scintigraphy was performed at least three weeks after PVE in 51 patients. Total liver uptake was then 14 ± 3 % per minute whereas the functional contribution of the FRL had significantly increased to 42 ± 14 % (p=0.027).

Total liver uptake did not change significantly (p=0.27). The uptake by the left liver segments did increase significantly after right PVE, showing a mean of 4.21 ± 3 % per minute before PVE, and a mean of 5.66 ± 2 % per minute after PVE (p<0.0001). Hence, PVE resulted in a significant increase in function of the hypertrophic FRL, three weeks after PVE.

Patients with cholestasis, showed a significantly lower total liver uptake pre- and post-PVE as compared to patients with normal livers (p=0.002), but there were no significant differences in liver function of the FRL pre- (p=0.37) and post-PVE (p=0.63).

There were also no significant differences in uptake of the non-embolized, left liver segments before PVE (p=0.96) or after PVE (p=0.46) in patients after chemotherapy as compared to normal livers. HBS showed a lower increase in uptake of the FRL three weeks after PVE in patients with a compromised liver (9.7%) as compared to patients with a normal liver (54.9%), but this difference is not statistically significant.

Surgery

Of the initial 56 patients, six patients were deemed unresectable on the post-PVE CT-scan. Five patients because of tumor progression (two of them also developed metastases in the future remnant, left liver) and one patient showed insufficient hypertrophy of the FRL. Of the remaining 50 patients, 5 patients were found to be unresectable at laparotomy because of portal vein thrombosis in the left portal vein (n=1, as described above), metastases discovered in the FRL, not detected on preoperative CT-scan (n=1), gross tumor invasion in the bifurcation of the portal vein and segment four (n=1) and extrahepatic metastases found during exploration (n=2). A sixth patient, with a gallbladder carcinoma, proved to have no liver metastasis at laparotomy, and therefore a cholecystectomy sufficed.
The types of resection in the 44 patients undergoing resection is summarized in table 6. The mean duration of the operation was 327 ± 123 minutes. Postoperative complications were seen in 23 patients (46%). Most patients showed minor complications (Clavien grade II-IIIa), such as self-limiting bile leakage, hypertension, pulmonary embolism, intra-abdominal abscess, or urinary tract infection. Major complications (Clavien grade IIIb-IVb) occurred in 4 patients (leakage of the hepatico-jejunostomy (n=1), abdominal wound dehiscence (n=1), transient liver failure (n=2)).

Three patients died of liver failure within 30 days after surgery (mortality 6.8%). One patient with CRLM had an uncompromised liver but developed liver failure despite pre-operative FRL of 37.5% after right PVE. A specific cause for the postoperative liver failure and encephalopathy was not found. The second patient who had undergone a right hemihepatectomy including segment 1 for hilar cholangiocarcinoma developed postoperative portal vein thrombosis of the liver remnant, causing liver failure. This patient had a pre-operative FRL of 29.7% on CT scan and a functional FRL of 53% (uptake of 10.5%/min./m²). The third patient had undergone a right hemihepatectomy for CRLM, leaving a FRL of 29.3% after PVE. The procedure was complicated by massive intraoperative and postoperative bleeding, and the patient died two weeks later of multiple organ failure.

In the same period 56 patients underwent liver resection without pre-operative PVE. The procedures consisted of 8 right hemihepatectomies, 2 left hemihepatectomies, 1 right extended hemihepatectomy, 1 left extended hemihepatectomy, 28 multiple segment resections, 13 metastasectomies and 3 hilar resections. The 30 days mortality in this group was 3.6%.

**Table 6: overview of liver resections.**

<table>
<thead>
<tr>
<th>Type of resection</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hemihepatectomy</td>
<td>16</td>
</tr>
<tr>
<td>Extended right hemihepatectomy</td>
<td>10</td>
</tr>
<tr>
<td>Right hemihepatectomy + metastatectomy</td>
<td>12</td>
</tr>
<tr>
<td>Extended right hemihepatectomy + metastasectomy</td>
<td>4</td>
</tr>
<tr>
<td>Segment/metastasis/hilar resection</td>
<td>2</td>
</tr>
<tr>
<td>No resection possible</td>
<td>12</td>
</tr>
</tbody>
</table>

**Follow-up after surgery**

AST levels in the blood initially increased after surgery with peak concentrations on day 1 until day 2 (NS). After three days, these values returned to normal. ALT levels also increased after surgery (NS). In one patient, the AST levels progressively increased up to 3000 U/L in the first days after resection with concomitant liver failure, which finally became fatal (Figure 1,2).

Postoperative liver enzyme levels were not significantly correlated with FRL-V. There were no significant differences in levels of AST, ALT, AF, γGT and total bilirubin within 14 days after surgery.
Growth of the remnant liver after surgery

CT-scans 3 months after resection were available in 30 of the 44 resected patients. The mean volume of the remnant liver had increased to 1487±495ml which was significantly larger than the volume of FRL after PVE (741±315 (p<0.0001)). Table 7 and Figure 3 show the future remnant liver volumes and percentages before and after PVE, and the eventual liver volumes 3 months after resection.

There were no significant differences in the remnant liver volumes three months after surgery in patients with or without cholestasis (mean volume of 1844 ± 456 ml versus 1333±285 ml, p=0.11), in patients with or without chemotherapy (mean volume 1429 ± 367 ml versus 1546 ± 398 ml, p=0.66) and in patients with or without a compromised liver (mean volume 1334 ± 368 ml versus 1605 ± 465 ml, p=0.23).

Table 7: Volumes and increase of FRL before and after PVE, and after resection.

<table>
<thead>
<tr>
<th></th>
<th>FRL volume (mL)</th>
<th>FRL (%)</th>
<th>Increase of FRL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before PVE</td>
<td>509 ± 238</td>
<td>28.5 ± 8</td>
<td></td>
</tr>
<tr>
<td>After PVE</td>
<td>741 ± 315</td>
<td>41 ± 9</td>
<td>51 ± 51</td>
</tr>
<tr>
<td>After surgery</td>
<td>1487 ± 495</td>
<td>100</td>
<td>105 ± 67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[compared to volume after PVE]</td>
</tr>
<tr>
<td>After surgery</td>
<td></td>
<td></td>
<td>207 ± 124</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[compared to volume before PVE]</td>
</tr>
</tbody>
</table>

Figure 1: Concentration of AST after surgery.  
Figure 2: Concentration of ALT after surgery.

Figure 3: Regeneration of the FRL, after PVE and after resection.
HBS after surgery
14 patients underwent hepatobiliary scintigraphy approximately three months after surgery (87 ± 8 days), in conjunction with CT-volumetric assessment. The mean percentage uptake of the FRL per minute was 11.3 ± 4%, compared to 5.7 ± 2% three weeks after PVE. The total liver uptake and function of the liver remnant after surgery was significantly increased compared to the uptake of the FRL before PVE (p=0.001) and after PVE (p=0.002). Differences in regeneration of the liver remnant three months after surgery between normal and compromised livers could not be established because of the small number of patients.

Discussion

Our findings that PVE proved to be a safe and efficient procedure to induce hypertrophy of the FRL is in line with many previous studies. [11,15,16,17,18,19] In literature, many techniques have been described and many types of embolization materials are used. In our experience, an ipsilateral puncture and the use of PVA particles and coils is a safe technique. The only patient in our study treated by contralateral approach unfortunately became unresectable because of subtotal portal vein thrombosis in the FRL. Giraudo [7], de Baere [9] and Elias[20] all described large groups treated by contralateral access and only Giraudo [7] experienced this complication only once.

Post procedural fever was not seen in our patients as has been described many times in patients embolized with N-butyl-cyanoacrylate (NBCA). Elias[20] described such an inflammatory response in 90% of patients. Covey et al[5] also reported pyrexia in 45% of patients embolized with PVA particles. All cases were transient and self-limiting.

The influence of pre-existing compromised liver on regeneration and the hypertrophy response as in patients with cirrhosis, fibrosis or steatosis, is unclear. Previous studies reported a significantly poorer response to PVE [21,22], although other reports showed no significant difference in regeneration compared to uncompromised livers. [7,6,23] The same applies to patients who received chemotherapy. Some studies report an impaired hypertrophy response [8,9], whereas others mention no significant differences. [4,5,6,7,24,25] Our study shows no significant differences in increase of FRL volumes in patients with compromised livers (p=0.77) or in patients without cholestasis (p=0.19). In all patients with cholestasis, adequate drainage of the biliary system was performed prior to undertaking PVE, to facilitate post-PVE regeneration and to avoid infectious biliary complications as cholangitis. The regenerative responses after PVE and subsequently after liver resection were not significantly different compared to patients with uncompromised livers, probably owing to this policy.

Many studies find no significant differences in growth of the FRL when comparing patients with and without chemotherapy. De Baere et al., however, reported a lesser hypertrophy response in patients who had received platin agents, whereas the use of other chemotherapeutic agents did not influence hypertrophy of the FRL. [9] No differences in hypertrophy response in patients with and without chemotherapy were reported by Nafidi [25]. Beal et al. [8] evaluated a group of 15 patients after PVE who all had received pre-PVE
chemotherapy, and compared patients who continued chemotherapy with patients who stopped chemotherapy in the regeneration period between PVE and resection. No significant growth of tumour volume was seen, but a significant reduction in hypertrophy response was observed in patients receiving chemotherapy after PVE. In our series, no significant differences in hypertrophy response or in post-operative liver regeneration were seen in patients with or without chemotherapy. It therefore seems that chemotherapy given before PVE does not affect the hypertrophy response of the FRL, nor has a limiting influence on surgical treatment options. Continuing chemotherapy after PVE therefore, potentially avoids PVE-related tumour progression without significantly influencing the hypertrophy response, although this notion awaits further clinical assessment.

We evaluated the results of PVE not by volumetric data only, but also by quantitative assessment of function of the FRL, obtained by $^{99m}$Tc-mebrofenin hepatobiliary scintigraphy (HBS) as has been validated by de Graaf et al. [26] Functional uptake of the left liver segments did increase after PVE ($p<0.0001$) whereas the uptake rate of the embolized, right liver segments decreased. Three months after surgery, the functional uptake had increased with 194% compared to the uptake of the FRL before surgical resection, demonstrating the inexhaustive power of the liver cells to regenerate. The uptake function was ultimately almost 84% of total liver function before resection (mean 11.3 ± 3.6% per minute). In our experience, HBS is a valuable tool in the preoperative work-up to improve risk assessment in patients requiring extensive liver resection. De Graaf concludes that functional assessment using HBS is of more value than morphological evaluation using CT volumetry, especially in patients with a compromised liver. [26]

Major hepatectomies still have significant morbidity and mortality, ranging from 4 to 8%, depending on the extensiveness and complexity of the procedure. [27,28] Postoperative liver failure is associated with increased morbidity and mortality and its pathogenesis is related to the amount of functional liver mass remaining after resection. [1,29] Three patients died within 30 days after surgery because of progressive liver failure. One of them had an un-compromised liver with post-PVE FRL of even 37.5%. The other two patients, also with sufficient post-PVE FRL volume of almost 30%, developed liver failure because of septic complications culminating in multiple organ failure.

The high mortality rate (6.8%) reported in our study is in part explained by patient selection as all patients subjected to preoperative PVE had increased tumor burden, and required more complex procedures. A relatively high proportion of patients in our series had hilar cholangiocarcinoma requiring large resections in combination with biliary anastomoses, carrying an increased risk of postoperative morbidity, liver failure and mortality, the latter reported up to 10%. After introduction of PVE in our institution, an increased number of patients who would initially have been considered unresectable, did undergo resection in spite of extensive liver tumor(s). These patients obviously had an increased operative risk. For comparison, the overall postoperative mortality in patients undergoing liver resection without PVE in the same period in our institution ($n=56$), was 3.6%.
PVE is safe and efficient in patients with normal livers, as well as patients with compromised livers or patients receiving preoperative chemotherapy. There were no significant differences in the hypertrophy response in patients with pre-existing liver cirrhosis/fibrosis, steatosis, cholestasis, or after chemotherapy. Also post-resectional liver regeneration was not influenced by these factors.
References


