Original article

Increase in future remnant liver function after preoperative portal vein embolization

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Background: **Preoperative portal vein embolization (PVE) is performed in patients with insufficient future remnant liver (FRL) to allow safe resection. Although many studies have demonstrated an increase in FRL volume after PVE, little is known about the increase in FRL function. This study evaluated the increase in FRL function after PVE using ^{99m}Tc-labelled mebrofenin hepatobiliary scintigraphy (HBS) with single photon emission computed tomography (SPECT) and compared this with the increase in FRL volume.**

Methods: **In 24 patients, computed tomography volumetry and ^{99m}Tc-labelled mebrofenin HBS with SPECT were performed before and 3–4 weeks after PVE to measure FRL volume, standardized FRL and FRL function. A hypothetical model was used to assess safe resectability after PVE. The limit for safe resection for FRL function was set at an uptake of 2·69 per cent per min per m^2. For FRL volume and standardized FRL, 25 or 40 per cent of total liver volume was used, depending on the presence of underlying liver disease.**

Results: **After PVE, FRL function increased significantly more than FRL volume. The correlation between the increase in FRL volume and FRL function was poor. Using the hypothetical model, seven patients did not achieve a sufficient increase in FRL function to allow safe resection 3–4 weeks after PVE, compared with 12 and nine patients based on FRL volume and standardized FRL respectively.**

Conclusion: **The increase in FRL function after PVE is more pronounced than the increase in FRL volume, suggesting that the necessary waiting time until resection may be shorter than indicated by volumetric parameters.**

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Introduction

Future remnant liver (FRL) volume, measured by computed tomography (CT) volumetry, is currently the standard method for determining whether a patient can safely undergo liver resection. Although there are no formal guidelines, a FRL volume (expressed as a percentage of total liver volume, or as standardized FRL) larger than 25–30 per cent is considered sufficient in patients with normal liver parenchyma, whereas more than 40 per cent is preferred in patients with parenchymal disease[1,2]. A large proportion of livers are deemed unresectable owing to insufficient FRL volume[3,4].

Preoperative portal vein embolization (PVE) is used to increase the number of resectable patients. It induces atrophy of the embolized, tumour-bearing liver segments, while compensatory hypertrophy occurs in the non-embolized lobe, thereby increasing FRL volume and, supposedly, FRL function. PVE reduces the risk of postoperative liver insufficiency[5,6] and enables resection of livers previously considered unresectable owing to a marginal FRL[4,7–10]. CT volumetry is the established method of assessing the increase in FRL volume after PVE.

Little is known about the improvement in FRL function after PVE, because few liver function tests have the ability to measure FRL function selectively. Quantitative liver function tests, such as the indocyanine green (ICG) clearance test and the galactose elimination capacity test, measure overall liver function and are used widely as preoperative predictors of postoperative outcome[11–13]. CT volumetry is sometimes combined with total liver function

measured by the ICG clearance test to calculate FRL function; however, this is potentially inaccurate in livers with an inhomogeneous functional distribution, which is the case after PVE. Therefore, these tests are probably not suitable for assessing the relative increase in FRL function after PVE.

Clinical studies from Japan have demonstrated that the functional increase in FRL measured by ^{99m}Tc-labelled galactosyl–human serum albumin (^{99m}Tc-GSA) scintigraphy exceeds the increase in volume after PVE[14–16]. This implies that the recommended waiting time until operation may be shorter than suggested by volumetric studies, providing a potential benefit in light of the risk of tumour progression after PVE[17]. These results, however, have not been confirmed using other quantitative liver function tests.

^{99m}Tc-labelled mebrofenin hepatobiliary scintigraphy (HBS) with single photon emission CT (SPECT) has recently been validated as a quantitative method for evaluating liver function as well as liver functional volume[18]. ^{99m}Tc-mebrofenin HBS measures both total liver (uptake) function as well as FRL function, and can be used before surgery to predict postoperative liver failure[19–21]. ^{99m}Tc-GSA scintigraphy and ^{99m}Tc-mebrofenin HBS are both nuclear imaging techniques, but are based on different principles[20]. ^{99m}Tc-GSA scintigraphy measures the binding of ^{99m}Tc-GSA to its receptor, which is expressed on functional hepatocytes. ^{99m}Tc-mebrofenin HBS measures the kinetic process of uptake and excretion of ^{99m}Tc-mebrofenin by hepatocytes. The aim of this study was to compare the increase in FRL function, measured by ^{99m}Tc-mebrofenin HBS, with the increase in FRL volume, measured by CT volumetry, after preoperative PVE.

Methods

Between 2005 and 2008, 28 patients underwent PVE before liver resection. In 24 patients, ^{99m}Tc-mebrofenin HBS and CT volumetry were performed before, and 3–4 weeks after PVE. These patients were analysed with the approval of the institutional review board and after informed consent had been obtained. Post-PVE ^{99m}Tc-mebrofenin HBS and CT volumetry were performed on the same day. The FRL was delineated according to the planned resection. When FRL hypertrophy proved insufficient, the interval until resection was extended by 2 weeks.

The histopathology of the resection specimens and/or perioperative biopsies was assessed by an experienced pathologist, taking into account cholestasis, steatosis, fibrosis and chronic inflammation. A compromised liver was defined as: severe fibrosis (marked portoportal bridging or cirrhosis); steatosis of more than 30 per cent; moderate to severe cholestasis; or a combination of diseases, that is mild fibrosis (fibrous expansion of portal areas or incomplete portoportal septa) combined with mild cholestasis and/or steatosis (5–30 per cent) in combination with mild or moderate inflammation.

Portal vein embolization

PVE was indicated when the anticipated FRL volume was less than 25–30 per cent of total liver volume. In patients with biliary obstruction or an expectedly compromised liver, a cut-off value of 40 per cent was applied. All patients underwent embolization of the right portal system. In 23 patients, a percutaneous transhepatic ipsilateral approach was used as described previously[22]. In one patient, a contralateral approach was employed. The branches of the right portal trunk were embolized using polyvinyl alcohol particles (300–500 nm; Cook Medical, Bloomington, Indiana, USA) and coils (Tornado® Embolization Microcoil; Cook Medical). Additional embolization of segment IV was performed in two patients.

Computed tomography volumetry

Multiphase contrast-enhanced CT was carried out with a multislice helical scanner (Philips Medical Systems, Eindhoven, The Netherlands). Total liver, tumour mass(es) and FRL were delineated manually by an experienced radiologist in collaboration with a hepatobiliary surgeon according to the anticipated resection[19] (*Fig. 1a*,*e*). Integrated software (Mx-View 3·52; Philips Medical Systems) was used to calculate total liver volume (TLV), tumour volume (TV) and FRL volume (FRLV) (*Fig. 1b*,*f*). Percentage FRL volume before PVE was calculated using the formula:

$$\%\mathrm{FRLV}_{\text{pre-PVE}} = \frac{\mathrm{FRLV}_{\text{pre-PVE}}}{(\mathrm{TLV}-\mathrm{TV})_{\text{pre-PVE}}} \times 100\%.$$

Percentage FRL volume after PVE was calculated by dividing FRL volume after PVE by pre-PVE total liver volume. Pre-PVE total liver volume was used because atrophy of the embolized liver segments can influence individual post-PVE total liver volume, affecting percentage FRL volume independently of FRL increase.

Standardized future remnant liver measurements

Standardized FRL is a frequently used alternative way of expressing FRL volume (measured by CT volumetry)

as percentage of calculated total liver volume (^{cal}TLV), determined using a formula based on body surface area (BSA)[23]:

$$^{cal}\text{TLV} = -794{\cdot}41 + 1267{\cdot}28 \times \text{BSA}$$

where $\text{BSA} = \sqrt{\text{height (cm)} \times \text{weight (kg)}}/3600$.

Scintigraphic imaging and data acquisition

HBS was performed with ^{99m}Tc-labelled (2,4,6 trimethyl-3-bromo) iminodiacetic acid (^{99m}Tc-mebrofenin, Bridatec; GE Healthcare, Eindhoven, The Netherlands), as reported previously[18]. Briefly, a dynamic acquisition (36 frames at 10 s/frame, 128 matrix) was made using an Infinia^{TM} II SPECT/CT camera (GE Healthcare) immediately after intravenous administration of 200 MBq ^{99m}Tc-mebrofenin, which was used for the calculation of hepatic uptake function. Subsequently, a fast SPECT acquisition was performed (60 projections at 8 s/projection, 128 matrix) followed by low-dose non-contrast-enhanced CT for attenuation correction and anatomical mapping on the same gantry without moving the patient. Finally, a second dynamic acquisition was performed to evaluate biliary excretion. Data were processed on a Hermes workstation (Hermes Medical Solutions, Stockholm, Sweden).

Calculation of dynamic planar hepatobiliary scintigraphy parameters

Hepatic ^{99m}Tc-mebrofenin uptake rate (per cent per minute) was calculated on an anterior and geometric mean ($\text{Gmean} = \sqrt{\text{anterior} \times \text{posterior}}$) data set using time–activity curves from the liver, the heart/large vessels within the mediastinum (serving as blood pool) and around the total field of view, with scanned radioactivity values acquired between 150 and 350 s after injection[18]. To compensate for differences in individual metabolic requirements, total liver ^{99m}Tc-mebrofenin uptake rate (per cent per minute), representing total liver function, was divided by the BSA and expressed as per cent per minute per square metre. FRL (uptake) function was calculated by dividing the summed counts (150–350 s after injection) within the delineated FRL by the total liver counts within the same time frame, and multiplying this factor by total liver ^{99m}Tc-mebrofenin uptake rate expressed as per cent per minute per square metre (*Fig. 1c,g*). Total liver function and FRL function were calculated using both the anterior and Gmean data sets. The anterior data set was used because it has been correlated with clinical outcome after partial liver resection[19,21], whereas Gmean is a more precise parameter[18]. The uptake of mebrofenin per litre of FRL liver tissue was calculated by dividing the FRL function (not corrected for BSA) by FRL volume and expressed as per cent per minute per litre.

Calculation of single photon emission computed tomography parameters

SPECT acquisition was centred around the peak of the hepatic time–activity curve because the amount of radioactivity within the liver is relatively stable during this phase. SPECT was used for three-dimensional assessment of liver function and calculation of functional liver volume[18]. Briefly, an outline extraction method (with a threshold of 30 per cent of the maximal voxel count value) was applied automatically to outline the liver and calculate total functional liver volume. In patients with a fast hepatic uptake, accumulation of radioactivity in the small bile ducts disturbs the calculation of total and regional liver function and volume. Therefore, the activity within the extrahepatic bile ducts was removed manually and the intrahepatic bile ducts were automatically replaced by the average count density of normal liver tissue. Subsequently, the FRL was outlined manually on the CT images linked to the SPECT images (*Fig. 1d,h*), with the contrast-enhanced CT image as a constant reference (*Fig. 1a,e*).

Before PVE, FRL functional volume was expressed as a percentage of total liver functional volume. As with CT volumetry, percentage FRL functional volume after PVE was calculated by dividing FRL functional volume after PVE by pre-PVE total functional liver volume.

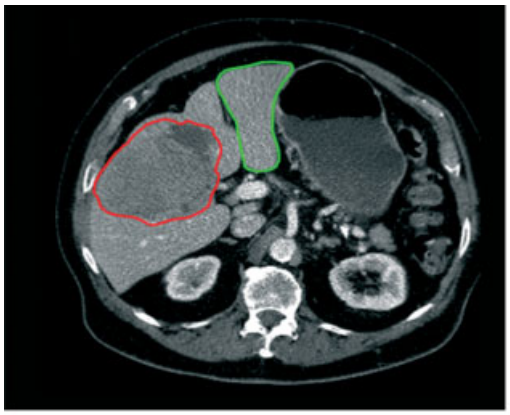
For calculation of actual SPECT FRL function (^{SPECT}FRLF), the percentage of counts within the FRL was multiplied by the total liver ^{99m}Tc-mebrofenin uptake rate as measured by the Gmean data set of the dynamic HBS.

Hypothetical model for resectability

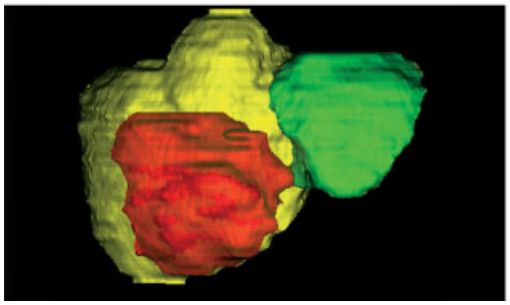
In this study, liver resection was not performed exactly 3–4 weeks after PVE in all patients, and some patients had a less extensive resection than anticipated, making it impossible to correlate FRL function, measured at 3 weeks after PVE, with actual clinical outcome. To determine whether the more pronounced increase in FRL function could eventually be translated into a shorter time interval between PVE and resection, a hypothetical model was derived to assess resectability 3 weeks after PVE.

Patients were divided into those with a normal liver parenchyma and those with a compromised liver parenchyma based on preoperative diagnostic findings.

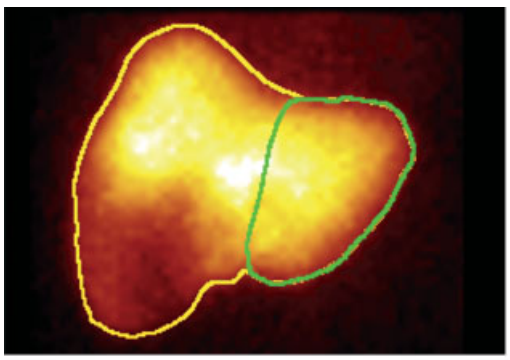
Before PVE



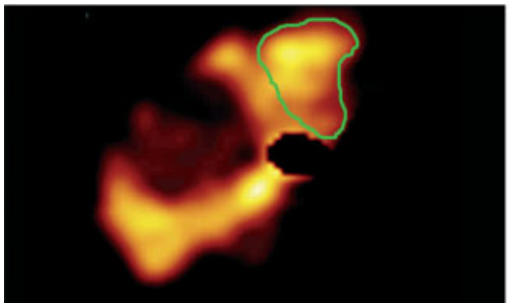
a Contrast-enhanced CT before PVE



b CT reconstruction before PVE



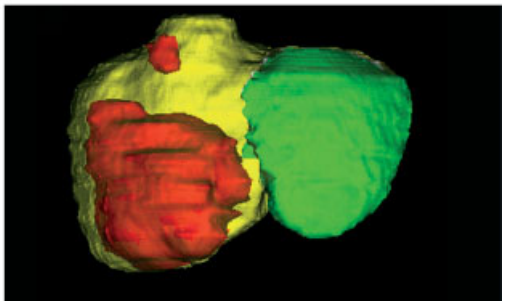
c HBS before PVE



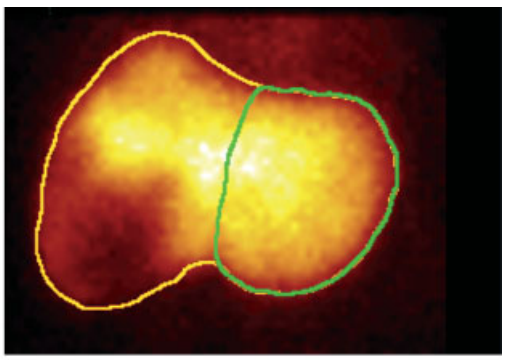
d SPECT before PVE

After PVE

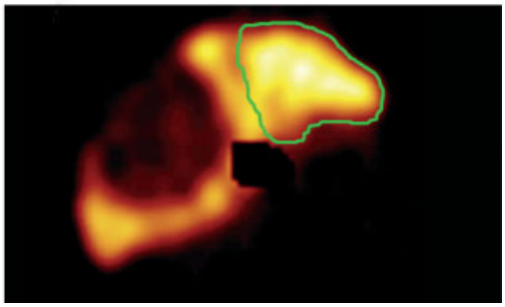
e Contrast-enhanced CT after PVE



f CT reconstruction after PVE



g HBS after PVE



h SPECT after PVE

Patients with hilar cholangiocarcinoma and preoperative chemotherapy were considered to have a compromised liver parenchyma. In six patients the presence of parenchymal liver disease was assessed by preoperative biopsy. In five patients magnetic resonance spectroscopy was used for non-invasive assessment of steatosis. Thirteen patients were considered to have a compromised liver before operation, two of whom were subsequently found to have normal liver parenchyma on histopathological evaluation of the resection specimen or perioperative biopsy. Eleven patients were considered to have normal liver parenchyma, of which two ultimately had evidence of compromised liver parenchyma.

The limit for safe resection for percentage FRL volume and standardized FRL was set at 25 per cent in patients with anticipated normal liver parenchyma[1,24] and 40 per cent for those with a compromised liver parenchyma[2,25,26]. For FRL function, a cut-off of 2·69 per cent per min per m^2 was used as the limit for safe resection, using the anterior data set of the dynamic HBS. A cut-off value for FRL function of 2·69 per cent per min per m^2 was able to identify patients with an increased risk of postoperative liver failure in a study of patients undergoing major liver resection[19].

Statistical analysis

Continuous data were expressed as mean(s.d.) and compared by independent-samples *t* test or paired *t* test. Correlation between variables was tested using the Pearson correlation coefficient. All statistical tests were two-tailed and differences were considered significant at $P \leq 0{\cdot}050$. Statistical analysis was performed with GraphPad® Prism 4.01 (GraphPad Software, San Diego, California, USA) and SPSS® version 14.02 (SPSS, Chicago, Illinois, USA).

Results

Patient characteristics are shown in *Table 1*. The PVE procedure was uncomplicated in 23 patients. One patient, in whom segment IV was additionally embolized, developed a thrombus in the left portal vein which became apparent during surgery and the planned extended right hepatectomy was abandoned. Laparotomy was performed in all patients. Five further patients did not undergo liver resection, four because of intrahepatic or extrahepatic tumour progression; in the fifth patient a non-infiltrating gallbladder carcinoma was identified on exploration for which a cholecystectomy sufficed. Of all patients who underwent liver resection, one developed remnant liver failure and eventually died 1 month after extended hemihepatectomy from postoperative portal vein thrombosis. Two patients had transient liver insufficiency.

Table 1 Patient characteristics

	No of patients*
Age (years)†	60·0(11·1) (32–74)
Sex ratio (M : F)	14 : 10
Compromised liver	13
Biliary fibrosis	1
Cholestasis	4
Steatosis	5
Combined disease	3
Diagnosis	
Liver metastases	14
Cholangiocarcinoma	5
Benign lesion	3
Gallbladder carcinoma	1
Neuroendocrine tumour	1

*Unless indicated otherwise; †values are mean(s.d.) (range).

Thirteen patients had evidence of a compromised liver parenchyma in the resection specimen or perioperative biopsy, including biliary fibrosis (1), severe cholestasis (4), steatosis (5) or a combination of these (3). In one patient, no liver tissue was available for histological evaluation.

Increase in liver volume and liver functional volume after portal vein embolization

^{99m}Tc-mebrofenin HBS and CT volumetry were performed 23·0(4·9) days after PVE. Total liver volume and total functional liver volume (measured by SPECT) were not significantly affected by PVE ($P = 0{\cdot}622$ and $P = 0{\cdot}160$

Fig. 1 Examples of images produced by the different techniques **a–d** before and **e–h** after portal vein embolization (PVE). **a,e** Portal and hepatic veins were used as landmarks for delineation of the future remnant liver (FRL) on contrast-enhanced computed tomography (CT) images. **b,f** The anterior projection of the CT reconstruction was used as a guideline for delineating the FRL on **c,g** planar dynamic ^{99m}Tc-labelled mebrofenin hepatobiliary scintigraphy (HBS) images. In addition, the round ligament was used as the border between segments III and IV. The line, projected on the liver surface as a plane between the middle of the gallbladder fossa (visible in the late phase of the scintigraphy) and the inferior caval vein, was used as a border between the right and left liver lobes. The delineated FRL on the contrast-enhanced CT images was used as a constant reference for delineation of the FRL on **d,h** single photon emission CT (SPECT) images

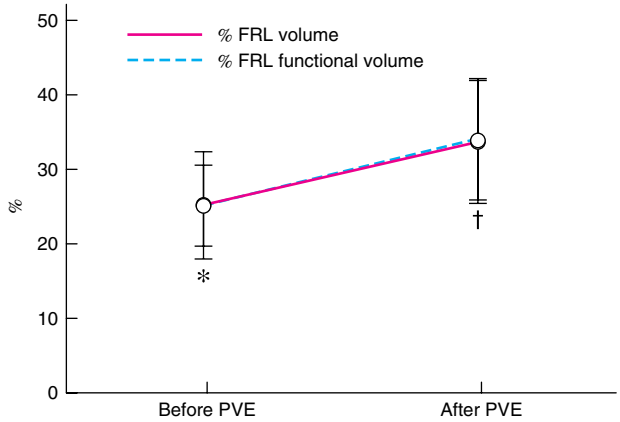


Fig. 2 Effect of portal vein embolization (PVE) on mean(s.d.) percentage future remnant liver (FRL) volume and percentage FRL functional volume. *$P = 0{\cdot}940$, †$P = 0{\cdot}678$ for comparison of percentage FRL volume *versus* functional volume (paired *t* test)

respectively). The percentage FRL volume measured by CT volumetry increased from 25·2(7·2) per cent before PVE to 33·7(8·2) per cent after embolization ($P < 0{\cdot}001$). The percentage FRL functional volume measured by SPECT increased from 25·1(5·4) to 34·0(8·1) per cent ($P < 0{\cdot}001$) (*Fig. 2*). There was no significant difference between percentage FRL volume and percentage FRL functional volume before ($P = 0{\cdot}940$) or after ($P = 0{\cdot}678$) PVE. Standardized FRL increased from 27·6(10·4) to 36·8(11·5) per cent.

As a result of PVE, FRL volume and FRL functional volume increased by 35·8(14·7) and 35·7(12·3) per cent respectively. For compromised and normal livers, the increase in both FRL volume (37·5(13·8) *versus* 34·7(16·8) per cent respectively; $P = 0{\cdot}666$) and FRL functional volume (34·0(12·0) *versus* 38·7(14·7) per cent; $P = 0{\cdot}382$) was similar.

Increase in liver function after PVE measured by planar dynamic hepatobiliary scintigraphy

Total liver function before PVE was significantly less in compromised compared with normal livers for both the anterior data set (5·7(1·7) *versus* 7·8(1·2) per cent per min per m^2; $P = 0{\cdot}005$) and the Gmean data set (7·1(2·5) *versus* 8·9(1·2) per cent per min per m^2; $P = 0{\cdot}048$). Total liver function was not significantly changed by PVE ($P = 0{\cdot}601$ and $P = 0{\cdot}085$ for anterior and Gmean respectively).

The effect of PVE on FRL function is shown in *Fig. 3*. FRL function was increased by 51·9(25·7) per cent (anterior data set) and 54·5(22·8) per cent (Gmean data set), with a similar increase in patients with compromised *versus* normal liver parenchyma ($P = 0{\cdot}392$ and $P = 0{\cdot}609$ respectively). Overall, the increase in FRL function was significantly greater than the increase in FRL volume ($P < 0{\cdot}001$, anterior data set; $P = 0{\cdot}003$, Gmean data set). The uptake of ^{99m}Tc-mebrofenin in the FRL increased from 9·2(3·3) per cent per min per litre liver tissue before PVE to 10·3(3·1) per cent per min per litre after PVE based on the anterior data ($P < 0{\cdot}001$), and from 8·5(3·2) to 9·7(3·1) per cent per min per litre based on the Gmean data ($P = 0{\cdot}001$). In the majority of patients, PVE resulted in a more pronounced increase in FRL function than in FRL volume (18 of 24 for anterior data, 17 of 24 for Gmean). Based on the anterior data set, the FRL function increase exceeded the FRL volume increase in both normal and compromised livers ($P = 0{\cdot}047$ and $P = 0{\cdot}027$). The Gmean data set showed a significant difference in favour of FRL function for compromised liver ($P = 0{\cdot}004$), but not for normal liver ($P = 0{\cdot}083$).

The increase in FRL volume resulting from PVE correlated poorly with the increase in FRL function in patients with a normal liver ($r = 0{\cdot}15$, $P = 0{\cdot}068$) as well as in those with a compromised liver parenchyma ($r = 0{\cdot}53$, $P = 0{\cdot}062$), indicating that the functional increase of the FRL was at least partially independent of the volumetric increase.

Increase in liver function after portal vein embolization measured by SPECT

Although planar dynamic HBS parameters have been validated extensively in the clinical setting, ^{SPECT}FRLF recently proved to be a better predictor of postoperative remnant liver function[18]. Similar to the planar dynamic HBS parameters, PVE induced a significantly greater increase in ^{SPECT}FRLF compared with FRL volume ($P = 0{\cdot}001$) and FRL functional volume ($P = 0{\cdot}002$) (*Fig. 4a*). In 19 of the 24 patients, the increase in ^{SPECT}FRLF exceeded the increase in FRL volume. The increase in ^{SPECT}FRLF was similar in compromised and normal liver (62·1(35·7) *versus* 66·1(37·9) per cent; $P = 0{\cdot}799$). Again, no significant correlation was found between increases in FRL volume and ^{SPECT}FRLF in normal liver ($r = 0{\cdot}05$, $P = 0{\cdot}889$). A poor correlation was found for compromised liver parenchyma ($r = 0{\cdot}58$, $P = 0{\cdot}0363$) (*Fig. 4b*). The uptake of ^{99m}Tc-mebrofenin in the FRL increased from 7·8(2·4) per cent per min per litre liver tissue before PVE to 9·2(3·0) per cent per min per litre after embolization ($P = 0{\cdot}001$).

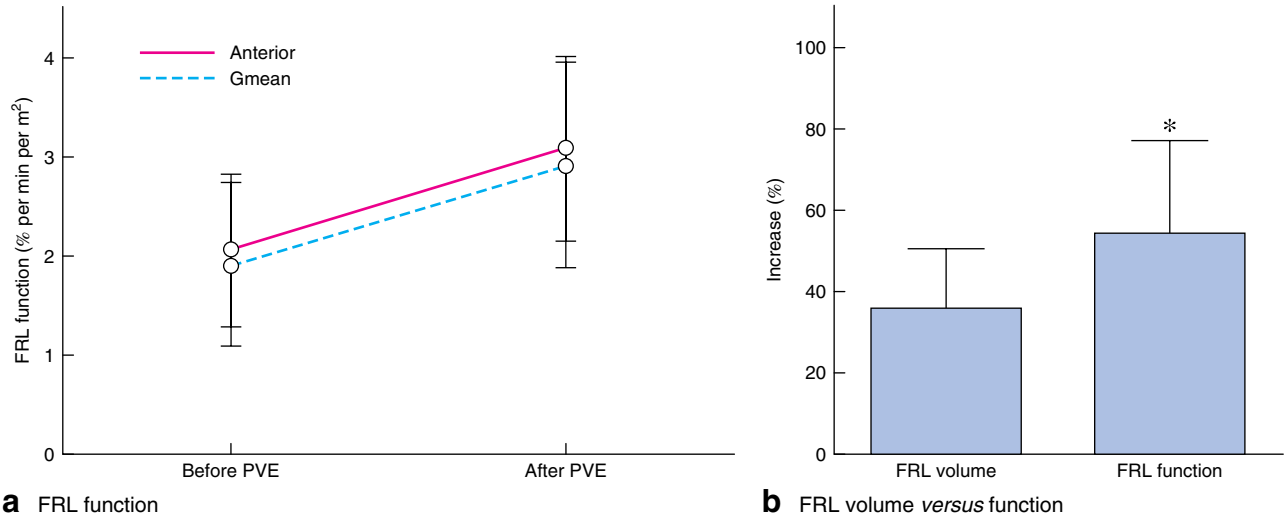


Fig. 3 **a** Effect of portal vein embolization (PVE) on mean(s.d.) future remnant liver (FRL) function, measured by dynamic hepatobiliary scintigraphy (HBS), based on anterior and Gmean data sets (both $P < 0{\cdot}001$ after *versus* before PVE; paired *t* test). **b** Mean(s.d.) increase in FRL function measured by HBS *versus* FRL volume measured by computed tomography volumetry in the anterior data set. *$P < 0{\cdot}001$ *versus* FRL volume (paired *t* test). The Gmean data set showed the same pattern

Hypothetical model for resectability

To determine whether the significantly more pronounced increase in FRL function could eventually be translated into a shorter time interval between PVE and resection, the hypothetical model described above was used. One patient with severe steatosis and a large adenoma, which was difficult to delineate from the surrounding tissue, underwent preoperative PVE despite a percentage FRL volume just above 40 per cent. When using the cut-off value for FRL function, three patients would not have needed preoperative PVE. Seven patients did not achieve a sufficient increase in FRL function to allow

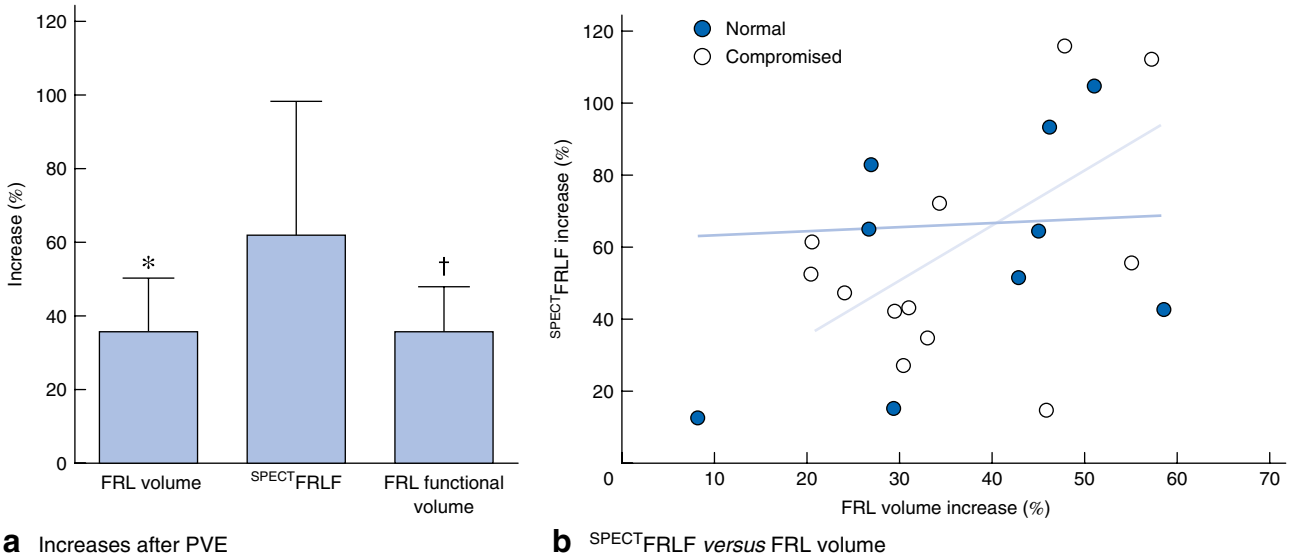


Fig. 4 Effect of portal vein embolization (PVE) on mean(s.d.) increase in future remnant liver (FRL) function measured by single photon emission computed tomography (^{SPECT}FRLF), FRL volume and FRL functional volume. *$P = 0{\cdot}001$, †$P = 0{\cdot}002$ *versus* ^{SPECT}FRLF (paired *t* test). **b** Correlation between ^{SPECT}FRLF and FRL volume increases in patients with normal ($r = 0{\cdot}05$, $P = 0{\cdot}889$) and compromised ($r = 0{\cdot}58$, $P = 0{\cdot}0363$) liver parenchyma

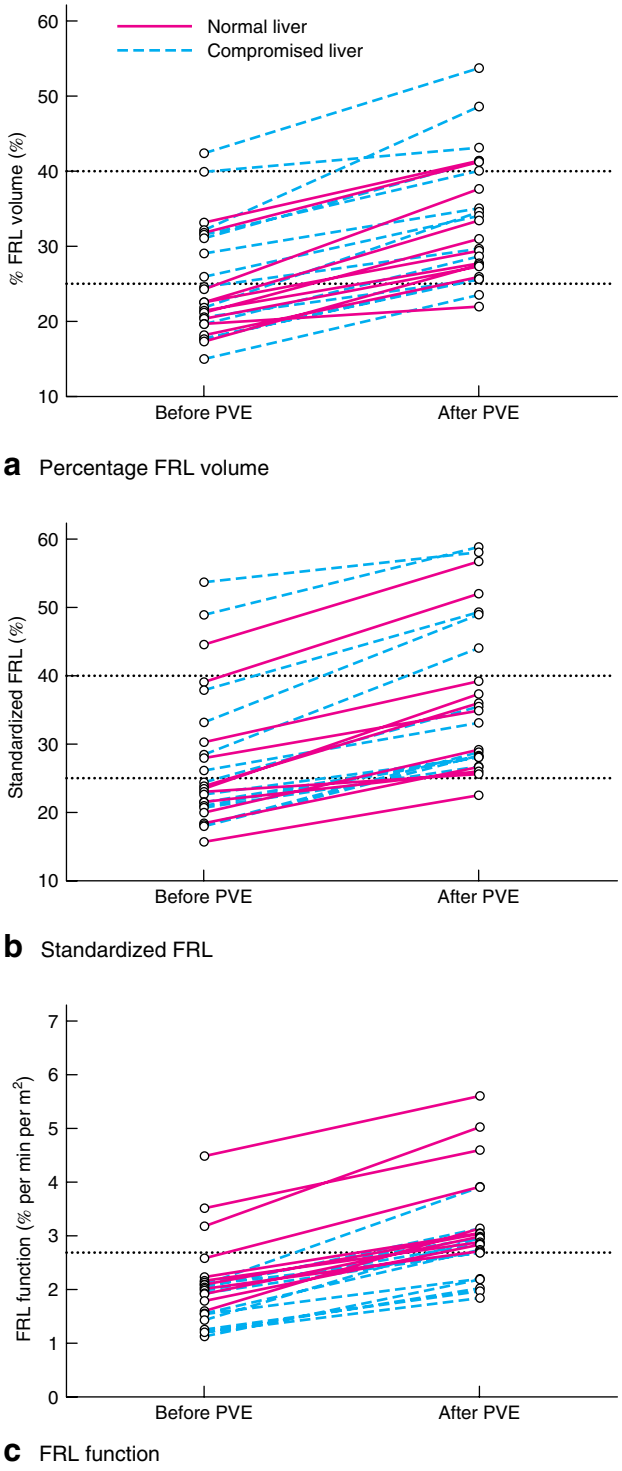


Fig. 5 Resectability 3 weeks after portal vein embolization (PVE) based on **a** percentage future remnant liver (FRL) volume, **b** standardized FRL and **c** FRL function. Limits of safe resection are shown by dotted lines (in **a** and **b** the lower and upper lines represent limits for normal and compromised livers respectively)

safe resection 3 weeks after PVE, compared with 12 and nine patients based on FRL volume and standardized FRL respectively (*Fig. 5*). These data indicate that the waiting time to resection may be shorter than indicated by the volumetric parameters.

Discussion

Although the increase in FRL volume after PVE has been investigated in many studies, few have described the increase in FRL function[14,15,27]. In this study the increase in FRL function induced by PVE was measured by ^{99m}Tc-mebrofenin HBS and compared with the increase in FRL volume measured by CT volumetry.

The liver has multiple roles including metabolic, synthetic and detoxifying functions. The ideal liver function test representing the multiple aspects of liver function has not yet been identified. Several quantitative liver function tests have been developed, each reflecting a separate component of the broad spectrum of liver functions. Although ^{99m}Tc-mebrofenin is not metabolized, it is taken up by organic anion transporting polypeptides and subsequently excreted into the bile by multidrug resistance proteins[28]. It follows a path of intracellular transit that is similar to that of various endogenous and exogenous substances, including bilirubin, hormones, drugs and toxins, and therefore represents an important liver function. Clinically, preoperative ^{99m}Tc-mebrofenin HBS has been correlated with the ICG clearance test, and accurately predicts postoperative liver function and outcome after liver resection[19–21]. ^{99m}Tc-mebrofenin HBS with SPECT therefore offers a valuable clinical liver function test.

Among studies that have investigated the improvement in FRL function after PVE, one investigated the biliary excretion of ICG in patients with multiple biliary drains, which enabled the assessment of ICG excretion in the non-embolized and embolized liver segments separately[27]. The functional gain in the non-embolized lobes was of greater magnitude than the volumetric increase. This method is, however, suitable only for patients with percutaneous biliary drains and is not applicable in the general patient population. Three Japanese studies used non-invasive dynamic ^{99m}Tc-GSA SPECT as a liver function test and showed that FRL function increased to a greater extent than FRL volume in patients with and without cirrhosis[14–16]. The present study has confirmed that the increase in FRL function is more pronounced than the increase in FRL volume after PVE. The uptake function in the FRL per litre of liver tissue increases after PVE. The increased liver function per gram or millilitre of liver tissue has been

described previously during liver regeneration after partial hepatectomy in both humans and rats[29,30].

Combination of the ICG clearance test and the percentage FRL volume derived by CT volumetry has been described for the assessment of FRL function after PVE[8]. This method, however, is based on the assumption that the increase in FRL volume is related to the increase in FRL function, and that liver function is distributed homogeneously within the liver volume. However, only a weak correlation between the increase in FRL volume and FRL function was found, and so combination of the ICG clearance test with the percentage FRL volume derived from CT volumetry may not accurately measure FRL function after PVE. This indicates the importance of additional quantitative functional assays that specifically measure FRL function after PVE.

In this study, the hypertrophic response of the FRL (both liver volume and liver function) after PVE was similar for patients with a compromised liver and those with a normal liver parenchyma. However, no patients with liver cirrhosis were included. Controversy exists regarding the effect of parenchymal liver disease on the hypertrophic response after PVE. Several large single-centre studies have shown a similar increase in FRL volume in patients with parenchymal liver disease[25,31]. Others, however, have demonstrated that patients with cirrhosis in particular have a smaller hypertrophic response[32].

Tumour progression has been reported after PVE in patients with colorectal metastases or primary liver tumours[17]. In addition, high rates of unresectable disease have been described after PVE, ranging from 6·4 to 33 per cent[17]. In the present study, in four of the 21 patients with malignant disease, the tumour was unresectable after PVE as a result of intrahepatic or extrahepatic tumour progression. Tumour progression after PVE creates a dilemma in terms of optimal waiting time until resection. The possible risk of tumour growth obviously demands a waiting time as short as possible. The interval is mainly determined by the time required to attain sufficient FRL volume or FRL function. The reported waiting time to resection after PVE varies considerably, from 2 weeks to several months, with most of the hypertrophy occurring within the first 3 weeks[9,33].

To determine whether the significantly greater increase in FRL function could eventually be translated into a shorter interval between PVE and resection, a hypothetical model was used to assess resectability 3 weeks after PVE. The model was based on cut-off values associated with the limits for performing safe liver resection. This study was not designed to correlate FRL function with actual clinical outcome. Three weeks after PVE, more patients reached sufficient FRL function to allow safe resection compared with standardized FRL and FRL volume, indicating that the waiting time until resection may be shorter than indicated by volumetric parameters. This model is hypothetical and requires correlation with actual postoperative outcome.

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Commentary

Increase in future remnant liver function after preoperative portal vein embolization (*Br J Surg* 2011; 98: 825–834)

Understanding the relationship between liver volume and liver function is key to the safe practice of liver surgery. In recent years attention has focused on what is being left behind rather than what is being removed. Portal vein embolization (PVE) has become a commonly used adjunct to our armamentarium, whereby blocking the portal vein on the side of the liver to be removed can be used to stimulate increased growth of the future remnant liver. Here de Graaf and colleagues have demonstrated that, following PVE, improvement in liver function precedes increase in volume of the future remnant liver. This rapid change in metabolic capacity of the liver was first shown in the context of major liver resection in relation to urea synthesis[1]; in patients with otherwise healthy livers, hepatic resection was accompanied by an almost instantaneous increase in metabolic capacity per gram of remaining tissue.

This study from de Graaf and co-workers brings into question whether it is strictly necessary to wait 4–6 weeks for a change in liver volume of the future remnant liver before embarking on surgery. In patients with healthy background liver it may be that early metabolic enhancement arising from PVE is sufficient to permit safe early resection. On a cautionary note, it should be remembered that many people use PVE as a challenge for regeneration, and failure to demonstrate regeneration in the future remnant liver after PVE may indicate an intrinsic problem with the liver that will make resectional surgery dangerous[2]. Further studies are required to examine the functional and regenerative responses to standard PVE in healthy and, more importantly, diseased liver, and also to explore whether other interventions such as infusion of stem cells might enhance the functional and regenerative capacity of the future remnant liver.

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