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Liver

Functional and volumetric assessment of liver segments after portal vein embolization: Differences in hypertrophy response

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ABSTRACT

Background: Patients considered for liver resection with insufficient volume or function of the future remnant liver are candidates for portal vein embolization to allow safe resection. The aim of this study is to analyze the volumetric and functional responses after portal vein embolization and to evaluate predictors of the hypertrophy response.

Methods: All patients who underwent portal vein embolization before liver resection 2006-2017 were included. Patients who did not undergo computed tomography–volumetry and functional assessment with technetium-99m mebrofenin hepatobiliary scintigraphy before and after portal vein embolization were excluded. The functional and volumetric response rates were calculated. Multiple regression analysis was conducted to examine the relationship between the hypertrophy response and potential predictors.

Results: A total of 90 patients underwent portal vein embolization of the right liver. After 3 weeks, there was a significant increase in both volumetric and functional share of the future remnant liver (both $P < .01$). The increase in functional share exceeded the increase in volumetric share ($P < .01$). The median functional contribution of segment 4 after portal vein embolization was 41.5% (31.7%–48.7%) of the nonembolized lobe. Preoperative chemotherapy was not a significant predictor of the increase in function or volume. Compared with benign lesions, malignant diseases were significant negative predictors of the functional response.

Conclusion: A total of 3 weeks after portal vein embolization, the functional response exceeded that of the volumetric response, meaning that the waiting time to resection potentially can be decreased. Segment 4 had a significant share of both volume and function, enabling surgical strategies only leaving segment 4 as a monosegment. Neoadjuvant chemotherapy had no negative influence on the hypertrophy response.

Introduction

Liver resection remains the only curative option for many patients with primary or metastatic liver cancer. Because of advances in surgical techniques and postoperative management, major liver resection (defined as 3 or more Couinaud segments) can be performed with limited mortality.[1] Nevertheless, the loss of functional liver mass after hepatectomy increases the risk of posthepatectomy liver failure, which is the main cause of mortality.[2] To prevent posthepatectomy liver failure, preoperative assessment of the future remnant liver (FRL) is part of the standard workup of patients scheduled for liver resection. This assessment can be performed using computed tomography (CT)-volumetry or quantitative liver function tests, such as technetium-99m (^{99m}Tc) mebrofenin hepatobiliary scintigraphy (HBS). CT is used as a surrogate measure of liver function based on volume rather than function and, therefore, is potentially unreliable in patients with undetermined parenchymal quality and function.[3] HBS yields direct representation of liver function with the possibility to quantify total and segmental liver function using a cutoff value applicable to both patients with normal or compromised liver parenchyma.[4]

Patients with too small of an FRL to undergo safe resection are candidates for preoperative portal vein embolization (PVE).[5,6] PVE

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induces atrophy of the embolized lobe and a compensatory hypertrophy response of the nonembolized lobe, resulting in both volumetric and functional increase of the FRL. PVE is usually performed on the right side of the liver, corresponding to segments 5–8 (S5–8). In patients planned for extended right hemihepatectomy in which segment 4 (S4) is additionally resected, however, a right PVE brings about an unfavorable effect in these cases, because a hypertrophy response is induced in S4, resulting in growth stimulation of tumors within this segment. Additional selective embolization of the portal venous branches to S4 has been shown to significantly improve the hypertrophy of segments 2–3 (S2–3) in comparison with right PVE alone.[7,8] In contrast, additional S4 embolization is technically more difficult because it bears the risk of accidental occlusion of the FRL portal branches to S2–3 because of backflow of the embolized material. When performed by experienced interventional radiologists,however, embolization of S4 has been shown to be a safe procedure, with no additional associated risk of complications compared with a standard right PVE.[8,9]

Little data are available about the functional response after PVE nor about how volume increase correlates with the increase in function. Furthermore, the hypertrophy response in each liver segment after PVE has not been defined, despite the fact that such an assessment can aid in the selection of potential surgical strategies.

The aim of this study was to analyze the volumetric and functional responses after a PVE to determine the relationship between the function and volume of the hypertrophy response. In addition, the regional, segmental response in function and volume of S2–3 as compared withsegments 2–4 (S2–4) was assessed in conjunction with predictors of the hypertrophy response of the FRL.

Methods

All consecutive patients who underwent PVE between 2006 and 2017 before anticipated liver resection for any indication were included in this retrospective study. Patients who did not undergo both HBS and CT volumetry before and after PVE were excluded from this analysis. The need for written informed consent and ethical approval was waived by the institutional review board of the Academic Medical Center, Amsterdam, The Netherlands.

PVE

PVE was believed to be indicated when the anticipated FRL function was insufficient (<2,7 %/min/m^2) or FRL volume was < 30%. All patients underwent embolization of the right portal system using a percutaneous, transhepatic approach, a total of 81 (90%) patients underwent embolization by an ipsilateral approach, and, in 9 (10%) patients, a contralateral approach was employed for access after ultrasonographic examination. The branches were embolized using polyvinyl alcohol particles (300–500 nm, Cook Group, Bloomington, IN) and coils (Tornado Embolization Microcoil, Cook Group).

CT-volumetry

Multiphase, contrast-enhanced CT was carried out before and after PVE (MX-8000 or Brilliance, Philips Research, Eindhoven, The Netherlands). The arterial phase images were acquired 35 seconds and the portovenous phase 70 seconds after injection of contrast. The portal-venous phase was used for volumetric assessment. The liver was outlined on an axial scan in a semiautomated fashion, with manual adjustment to ensure that all extrahepatic structures were excluded. The volume of the tumors was calculated by manual delineation.

Several landmarks were used to delineate the segments of the FRL, according to Couinaud's functional segmentation of the liver.[10] The falciform ligament was used as the border between segments 2/3 and 4 and the gallbladder and middle hepatic vein for the border between segments 4 and 5/8 (Cantlie's line; Fig. 1).

Total liver volume (TLV), tumor volume (TV), and future remnant liver volume of segments 2-3 ($FRLV_{2-3}$) and segments 2-4 ($FRLV_{2-4}$) were obtained. The volumetric share of the FRL was calculated using the following formula:

$$\text{FRL volumetric share } (\%) = \frac{\text{FRLV}}{\text{TLV} - \text{TV}} \times 100\% \quad (1)$$

Hepatobiliary scintigraphy

Patients underwent ^{99m}Tc-mebrofenin HBS before and after PVE. The acquisition and processing were performed in the same manner as described in recent studies.[4,11,12] Total liver function (TLF) is represented by the mebrofenin uptake rate (MUR; %/min/m^2). Briefly, regions of interest (ROI) were drawn around the left ventricle (representing the blood pool), liver, and total field of view on the geometric mean dynamic datasets. From these ROIs, three time-activity curves were generated. The MUR was calculated based on these parameters, according to the formula described by Ekman et al[12] and corrected for body surface area (BSA, m^2) to compensate for individual metabolic requirements.[11] Subsequently, S2-3 and S2-4 were delineated on the single proton emission computed tomography data sets (Fig. 2). Contrast-enhanced diagnostic CTs were used to assist in anatomic information where the same landmarks were used as for the volumetry. The functional share was calculated as the ratio between the counts on the delineated segments and the total liver representing the functional share according to the following formula:

$$\text{Functional share } (\%) = \frac{\text{Counts FRL}}{\text{Counts total liver}} \times 100\% \quad (2)$$

The function of the segments 2-3 ($FRLF_{2-3}$) and segments 2-4 ($FRLF_{2-4}$) were calculated using the following formula:

$$\text{FRLF } \left(\%/\text{min}/\text{m}^2\right) = \text{MUR} \times \text{Functional share} \quad (3)$$

Statistical analysis

Continuous data were expressed as median and interquartile range (IQR) or means and standard deviations (SD) when appropriate. Differences in continuous variables were analyzed using a paired *t* test, Wilcoxon signed rank test, or Mann-Whitney *U* test. The Pearson correlation test was used to analyze the correlation between normally distributed variables. Multiple regression analysis was conducted to examine the relationship between the hypertrophy response and various potential predictors. Statistical analysis was performed using SPSS (SPSS 24.0, IBM, Chicago, IL).

Results

Patients

A total of 90 patients underwent embolization of S5-8. Patient characteristics are presented in Table 1. The median time between PVE and HBS was 22 (21–23) days and did not differ from the median time between PVE and CT-volumetry of 22 (21–25) days.

Of the 90 patients, 85 had an FRL function <2.7 %/min/m^2 and underwent PVE. Of these, 65 had an FRL volumetric share <30%, and the remaining 20 had an FRL volumetric share > 30%. A total of 5 patients who underwent PVE had an FRL function >2.7 %/min/m^2 but an FRL volumetric share <30%. These patients were treated before 2012. At that time, the need for PVE was assessed in our department on the basis of both CT and HBS.

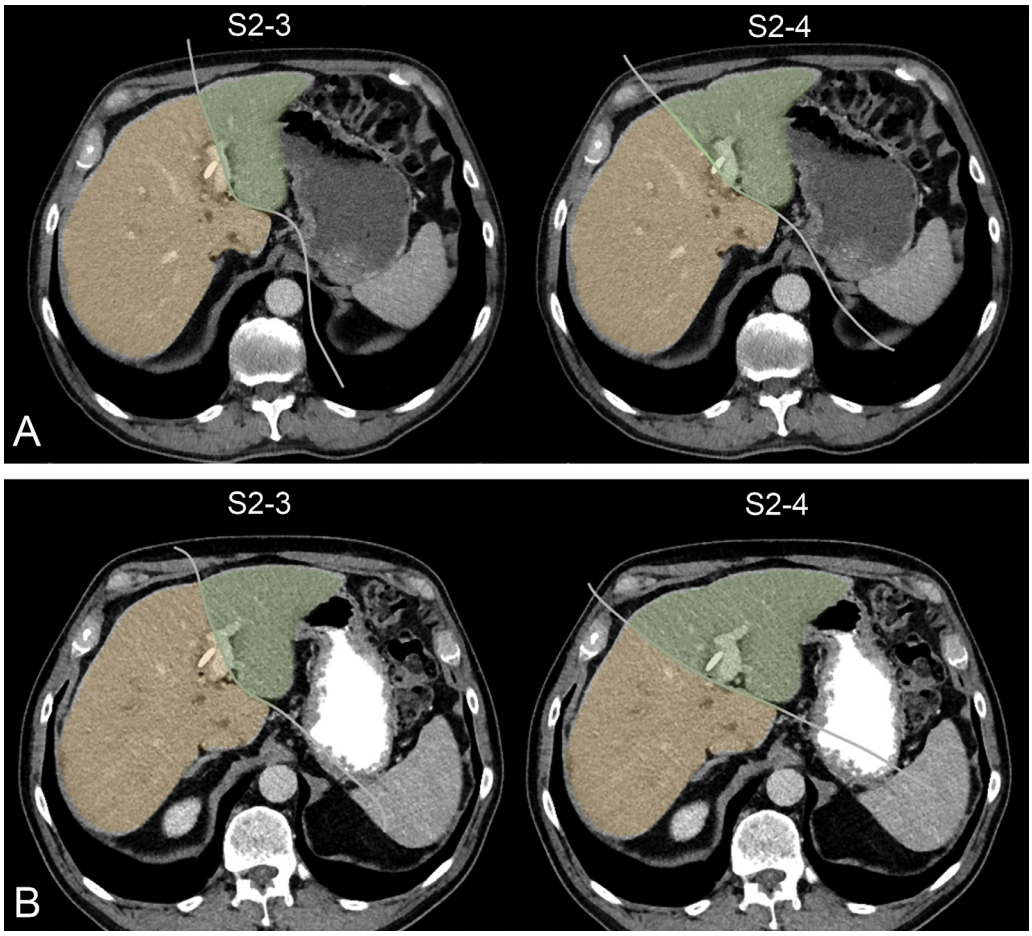

Fig. 1. CT-volumetry, delineation of S2-3 + S2-4, pre-PVE and post-PVE.

Functional and volumetric changes

The functional and volumetric changes are presented in Table 2, and the increase in $FRLF_{2-3}$ and $FRLF_{2-4}$ are presented in Table 3. After PVE, both the median TLF and TLV remained similar to baseline values.

The median (IQR) functional share of S2-3 increased from 17.2% (12.1%–22.8%) to 30.2% (25.4%–35.9%; $P < .01$) and that of S2-4 from 31.6% (24.9%–36.7%) to 51.6% (44.6%–61.1%; $P < .01$). This increase corresponds with an increase of 77.6% (39.8%–112.2%) and 61.4% (38.1%–104.9%), respectively ($P < .01$).

The median (IQR) FRL volume% of S2-3 increased from 16.7% (12.6%–21.2%) to 23.8% (18.5%–27.9%) ($P < .001$) and that of S2-4 from 30.1% (23.6%–34.8%) to 40.8% (34.2%–45.4%; $P < .001$), corresponding to an increase of 41.8% (29.6%–56.3%) and 36.8% (24.0%–60.7%), respectively (Fig. 3).

The median (IQR) functional share of S4 was 13.0% (9.9%–16.8%) before PVE and increased to 20.5% (15.4%–27.7%) after PVE ($P < .001$), and the median (IQR) volumetric share of S4 was 12.3% (10.0%–14.9%) before PVE and increased to 16.5% (13.2%–20.1%) after PVE ($P < .001$).

After right PVE, the median contribution of segment 4 to the total nonembolized lobe (S2-4) was 41.5% (31.7%–48.7%) of the function and 41.6% (37.4%–48.5%) of the volume.

Volumetric versus functional share

At baseline, the ratio between functional and volumetric share of the nonembolized lobe was equal: 17.2% (12.1%–22.8%) vs 16.7% (12.6%–21.2%); however, after a median time of 22 days after PVE, the ratio had shifted in favor of function rather than volume: 51.6% (44.6%–61.1%) vs 40.8% (34.2%–45.4; Fig. 4).

Tumor volume

The changes in tumor volume after PVE are presented in Table 4. Significant tumor growth was observed in patients with colorectal liver metastasis from 37.5 (8.5–108.1) to 60.0 (21.8–166.8) mL ($P < .01$), and a nonsignificant increase was noted in tumor size of hepatocellular carcinoma from 467.9 (43.3–1243.8) to 626.8 (36.7–1905.5) mL ($P = .12$). Remarkably, there was a decrease in tumor size in patients with benign tumors. In all groups, there was no correlation between the increase in tumor volume and increase in volume of the nonembolized lobe.

Neoadjuvant chemotherapy

A total of 40 (44%) patients with colorectal liver metastasis underwent neoadjuvant chemotherapy before PVE (Table 1). A total of 3 patients received chemotherapy during the interstage period after PVE. In the total group, neoadjuvant chemotherapy did not influence the median increase in liver function: 56.4% (27.8%–91.8%) and 54.7% (34.3%–93.3%) in the chemotherapy and the no-chemotherapy group, respectively ($P = .858$). Similarly, neoadjuvant chemotherapy did not affect the median increase in liver volume of the nonembolized lobe: 43.6% (29.9%–63.2%) and 33.4% (22.4%–52.5%), respectively ($P = .081$).

Table 1
Patient characteristics.

Patient characteristics, N = 90	
Age (years)	64.3 (57.4–70.4)
Male sex	55 (61%)
BMI, kg/m^2	24.7 (22.7–27.3)
BSA, m^2	1.94 (1.76–2.07)
Diagnosis:	
Colorectal liver metastasis	49 (54%)
Hepatocellular carcinoma	7 (8%)
Perihilar cholangiocarcinoma	20 (22%)
Intrahepatic cholangiocarcinoma	4 (4%)
Intraductal papillary neoplasm of the bile duct	1 (1%)
Gallbladder carcinoma	1 (1%)
Neuroendocrine tumor	2 (2%)
Benign lesion	6 (7%)
Parenchymal assessment of patients with hepatocellular carcinoma ($n = 7$):	
No—mild fibrosis	4
Severe fibrosis—cirrhosis	3
Biliary drainage (ERC or PTBD) in patients with perihilar cholangiocarcinoma ($n = 20$):	
Drainage	17
No drainage	3
Neoadjuvant chemotherapy before PVE	40 (44%)
Number of cycles	5 (3–6)
Oxaliplatin	*32*
Capecitabine	*28*
5-Fluorouracil	*6*
Irinotecan	*3*
Bevacizumab	*18*
Panitumumab	*3*
Other agents	*3*
Missing data: 6 patients	
Resected	65
Right hemihepatectomy	32 (49%)
Right hemihepatectomy with partial S4 resection	11 (17%)
Extended right hemihepatectomy	22 (34%)

ERC, endoscopic retrograde cholangiography with endobiliary stent; *PTBD*, percutaneous transhepatic biliary drainage.

Table 2
Functional and volumetric share increase pre-PVE and post-PVE.

	Pre-PVE	Post-PVE	Change %	*P* value
Functional share S2-3 (%)				
All ($n = 90$)	**17.2 (12.1-22.8)**	**30.2 (25.4-35.9)**	**77.6 (39.8-112.2)**	**<.01**
CRLM ($n = 49$)	15.2 (10.0-19.0)	26.9 (20.4-31.3)	82.5 (45.6-111.6)	<.01
PHC ($n = 20$)	22.4 (16.0-28.2)	33.1 (29.4-41.1)	47.8 (17.9-105.8)	<.01
HCC ($n = 7$)	20.9 (20.0-28.0)	36.0 (30.2-47.5)	66.7 (44.3-145.0)	.02
Benign ($n = 6$)	16.0 (9.9-21.2)	28.6 (21.8-35.1)	93.0 (32.7-195.3)	.03
Other ($n = 8$)	21.5 (16.0-26.6)	35.6 (31.6-47.9)	94.2 (22.0-148.4)	.02
			$P = .39$	
FRLV S2-3 (%)				
All ($n = 90$)	**16.7 (12.6-21.2)**	**23.8 (18.5-27.9)**	**41.8 (29.6-56.3)**	**<.01**
CRLM ($n = 49$)	14.2 (10.9-19.2)	20.8 (15.7-24.6)	46.0 (33.3-65.7)	<.01
PHC ($n = 20$)	18.4 (13.8-21.6)	26.7 (21.4-30.2)	41.8 (27.6-56.0)	<.01
HCC ($n = 7$)	22.2 (15.3-24.7)	26.2 (24.1-35.2)	42.8 (20.6-47.2)	.02
Benign ($n = 6$)	15.7 (11.1-26.4)	24.5 (18.6-35.0)	49.1 (30.9-97.0)	.03
Other ($n = 8$)	21.1 (19.4-24.9)	28.6 (25.1-32.0)	30.0 (22.9-37.8)	.01
			$P = .63$	
Funcunctional share S2-4 (%)				
All ($n = 90$)	**31.6 (24.9-36.7)**	**51.6 (44.6-61.1)**	**61.4 38.1-104.9**	**<.01**
CRLM ($n = 49$)	30.3 (24.1-34.0)	48.4 (40.3-57.7)	62.2 39.8-101-6	<.01
PHC ($n = 20$)	36.6 (29.2-49.6)	56.8 (50.6-64.9)	57.2 31.7-87.6	<.01
HCC ($n = 7$)	41.3 (31.0-46.3)	58.0 (48.7-65.1)	40.4 21.7-122.6	.02
Benign ($n = 6$)	29.9 (23.2-37.2)	53.9 (41.6-67.0)	76.4 29.5-185.7	.03
Other ($n = 8$)	31.7 (24.6-42.1)	57.3 (45.1-61.6)	75.0 30.5-145.8	.01
			$P = .62$	
FRLV S2-4 (%)				
All ($n = 90$)	**30.1 (23.6-34.8)**	**40.8 (34.2-45.4)**	**36.8 (24.0-60.7)**	**<.01**
CRLM ($n = 49$)	26.4 (22.2-32.7)	38.5 (30.7-43.4)	41.6 (28.4-63.1)	<.01
PHC ($n = 20$)	32.6 (28.5-36.0)	43.6 (38.1-48.9)	35.9 (18.6-65.5)	<.01
HCC ($n = 7$)	33.0 (25.9-38.6)	44.7 (34.2-53.0)	32.2 (24.1-47.1)	.02
Benign ($n = 6$)	32.7 (23.8-46.5)	41.1 (36.5-49.6)	28.1 (0.1-0.74)	.12
Other ($n = 8$)	31.5 (28.2-40.7)	52.1 (36.3-50.2)	032.4 (20.3-40.1)	.02
			$P = .59$	

CRLM, colorectal liver metastasis; *PHC*, perihilar cholangiocarcinoma; *HCC*, hepatocellular carcinoma.

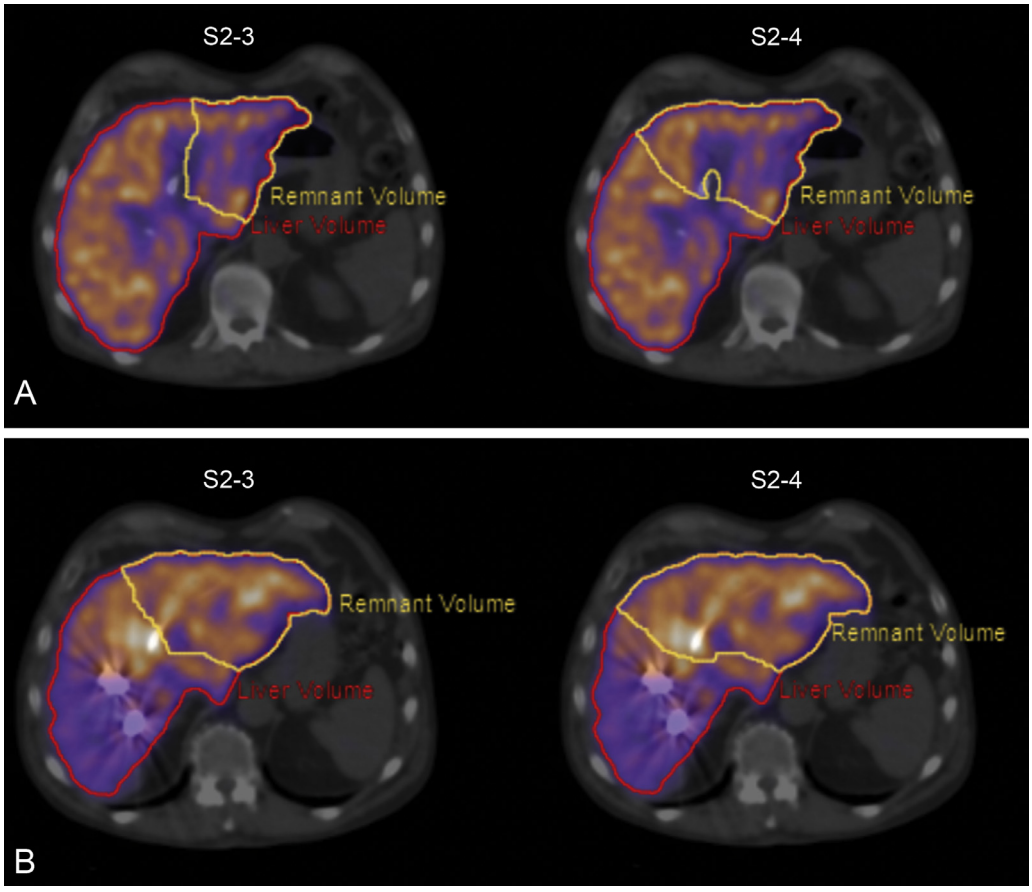

Fig. 2. SPECT delineation of S2-3 + S2-4 (*A*) pre-PVE and (*B*) post-PVE.

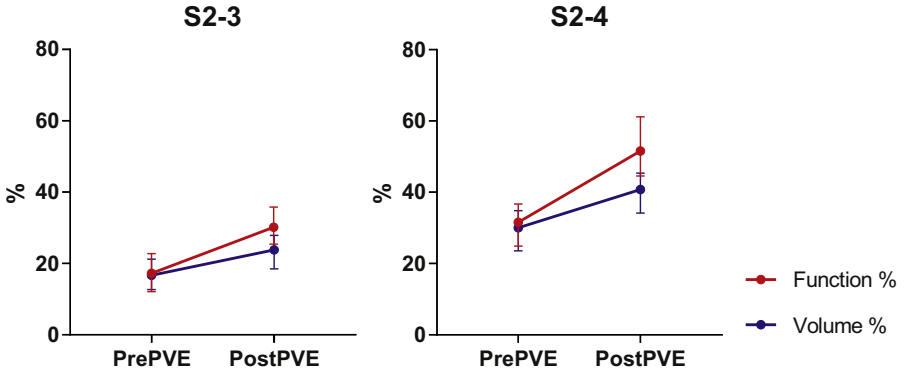

Fig. 3. Change in volumetric and functional share of S2-3 + S2-4.

Complications

Two patients developed complications after PVE. One patient developed a subcapsular liver hematoma that resolved over time and one patient developed an allergic rash.

Predictors of PVE response

A multiple regression analysis was conducted to predict the functional and volumetric increase of the nonembolized liver segments based on age, sex, neo-adjuvant chemotherapy, initial liver function, and tumor type (Table 5).

Initial TLF was a significant negative predictor of the functional response, but not for volumetric response, indicating that patients with relatively good baseline liver function might benefit less after PVE compared with patients with a lesser function at baseline. Preoperative chemotherapy was not a significant predictor of both the functional and volumetric response. Compared with benign lesions, all malignant diseases (hepatocellular carcinoma, colorectal liver metastases, and biliary tumors) were significant negative predictors of the functional response.

Operative outcome

Of the total population, 65 patients went on to liver resection (72%). The median time between PVE and liver resection was 41 days (32–52 days).

Of the 23 patients who did not undergo liver resection, 18 (20%) were unresectable because of tumor progression (colorectal liver metastasis $n = 9$, perihilar cholangiocarcinoma, $n = 7$, hepatocellular

Table 3
FRL function of S2-3 and S2-4 (%/min/m^2) pre-PVE and post-PVE.

	Pre-PVE	Post-PVE	Change %	*P* value
Total liver function	15.5 (12.1-17.5)	14.8 (12.0-16.1)	−2.2 (−16.9-73)	.06
Total liver volume	1719.6 (1462.8-2165.0)	1702.4 (1932.2-2127.1)	1.1 (−6.9-8.5)	.39
$FRLF_{S2-3}$ (%/min/m^2)				
All (*n* = 90)	**1.3 (0.9-1.7)**	**2.2 (1.6-2.8)**	**69.5 (42.6-108.5)**	**<.01**
CRLM (*n* = 49)	1.2 (0.9-1.6)	2.1 (1.5-2.8)	61.3 (44.8-107.3)	<.01
PHC (*n* = 20)	1.3 (0.9-1.9)	2.3 (1.6-3.2)	72.9 (28.1-113.5)	<.01
HCC (*n* = 7)	1.5 (1.1-1.6)	2.1 (1.7-2.6)	67.4 (5.7-90.4)	.03
Benign (*n* = 6)	1.2 (0.9-1.8)	2.3 (2.0-2.7)	93.8 (40.7-159.0)	<.01
Other (*n* = 8)	2.1 (1.2-2.7)	3.1 (2.7-3.6)	64.2 (10.8-112.0)	.01
			P = .64	
$FRLF_{S2-4}$ (%/min/m^2)				
All (*n* = 90)	**2.4 (1.9-3.0)**	**3.9 (2.8-4.8)**	**54.7 (30.0-92.6)**	**<.01**
CRLM (*n* = 49)	2.3 (1.9-2.7)	3.7 (2.6-4.8)	53.7 (32.8-91.0)	<.01
PHC (*n* = 20)	2.4 (1.8-3.0)	3.8 (2.7-5.1)	68.2 (38.6-93.1)	<.01
HCC (*n* = 7)	2.5 (2.3-3.1)	3.5 (2.3-4.2)	37.7 (0.0-73.0)	.10
Benign (*n* = 6)	2.3 (1.8-3.3)	4.2 (3.6-5.5)	64.4 (37.4-181.9)	.03
Other (*n* = 8)	2.8 (1.9-4.2)	4.7 (3.8-4.8)	43.0 (0.1-109.8)	.02
			P = .29	
$FRLV_{2-3}$ (mL)				
All (*n* = 90)	**274.2 1 (89.4-371.5)**	**256.5 (284.6-533.8)**	**43.0 (25.8-61.4)**	**<.01**
CRLM (*n* = 49)	214.0 (161.1-294.5)	317.2 (239.5-385.1)	46.2 (30.2-63.2)	<.01
PHC (*n* = 20)	340.2 (254.4-399.2)	492.6 (322.8-630.1)	42.5 (16.3-72.2)	<.01
HCC (*n* = 7)	397.3 (230.0-482.0)	544.5 (286.0-771.2)	30.0 (22.6-37.1)	.02
Benign (*n* = 6)	297.3 (148.3-898.9)	410.8 (273.1-906.5)	38.4 (8.1-91.3)	.05
Other (*n* = 8)	317.7 (275.3-421.3)	464.3 (388.5-552.7)	39.3 (30.3-54.2)	.01
			P = .47	
$FRLV_{2-4}$ (mL)				
All (*n* = 90)	**488.7 (366.8-644.8)**	**639.9 (512.7-802.9)**	**35.0 (21.1-60.2)**	**<.01**
CRLM (*n* = 49)	403.9 (312.8-529.5)	560.2 (447.9-721.9)	36.4 (27.4-61.7)	<.01
PHC (*n* = 20)	538.1 (505.6-751.5)	791.9 (614.1-1031.3)	37.5 (15.2-65.7)	<.01
HCC (*n* = 7)	648.5 (453.8-722.0)	752.6 (530.4-1020.0)	16.9 (15.7-34.4)	.02
Benign (*n* = 6)	521.9 (404.4-1479.8)	750.8 (472.6-1357.8)	23.3 (0.0-53.3)	.46
Other (*n* = 8)	464.9 (389.3-682.5)	659.8 (614.1-830.5)	40.4 (27.3-53.6)	.01
			P = .25	

CRLM, colorectal liver metastasis; *PHC*, perihilar cholangiocarcinoma; *HCC*, hepatocellular carcinoma.

Table 4
Tumor volume.

Tumor volume (mL)*n* = 47	Pre-PVE median (IQR)	Post-PVE median (IQR)	Change%	*P* value
Colorectal liver metastasis*n* = 37	37.5 (8.5-108.1)	60.0 (21.8-166.8)	28.1 (−18.3-146.5)	.002
Hepatocellular carcinoma*n* = 6	467.9 (43.3-1243.8)	626.8 (36.7-1905.5)	28.6 (−18.3-47.5)	.116
Benign tumors*n* = 4	550.0 (92.0-1853.2)	313.0 (64.7-2434.3)	−39.2 (−55.0-23.3)	.715

carcinoma *n* = 1, intrahepatic cholangiocarcinoma *n* = 1). Regarding the 9 patients with colorectal liver metastasis who were unresectable because of tumor progression, 7 had developed new lesions in the nonembolized lobe and only 3 also showed further tumor growth in the embolized lobe.

Furthermore, 4 patients (4%) did not undergo resection because of too small of an FRL (colorectal liver metastasis *n* =2, hepatocellular carcinoma *n* = 1, perihilar cholangiocarcinoma *n* = 1), and 1 patient with gallbladder carcinoma had no apparent liver involvement on further assessment.

Of the patients who underwent liver resection, 43 (66%) underwent right hemihepatectomy. Of these, 11 patients underwent partial resection of S4 (S4A *n* = 8, S4B *n* = 3). The remaining 22 patients (34%) underwent extended right hemihepatectomy with complete resection of the nonembolized S4. Data for 2 patients were missing.

Complications and mortality

Postoperatively, 16 patients (25%) developed severe complications (Clavien-Dindo grade 3a or greater), 7 of whom after extended right hemihepatectomy and 9 after right hemihepatectomy (of whom 3 also had partial S4 resection).

Of the 3 patients who had chemotherapy during the interstage period, 2 did not undergo resection because of tumor progression, whereas 1 had undergone resection without further complications.

Overall, 5 patients died postoperatively (90-day mortality 8%), 1 after extended right hemihepatectomy and 4 after right hemihepatectomy (of whom 1 with partial S4 resection).

A total of 4 patients sustained severe postoperative complications, ultimately leading to posthepatic liver failure (PHLF; International Study Group of Liver Surgery grade B or C), subsequently leading to their death. Only 1 patient developed deterioration of liver function immediately after resection attributable to an apparent insufficient FRL, despite sufficient predicted FRL function and volume. All of these patients had sufficient FRL function (>2.7 %/min/m^2) preoperatively. Further details about these patients are presented in Table 6.

Discussion

In this study, the segmental functional and volumetric increase after PVE were calculated in patients with insufficient FRL who were being evaluated for a major liver resection. A total of 3 weeks after PVE of the right liver, the functional response was greater than the volumetric response. This observation has been reported p in a smaller cohort.[13] The waiting time after PVE until resection

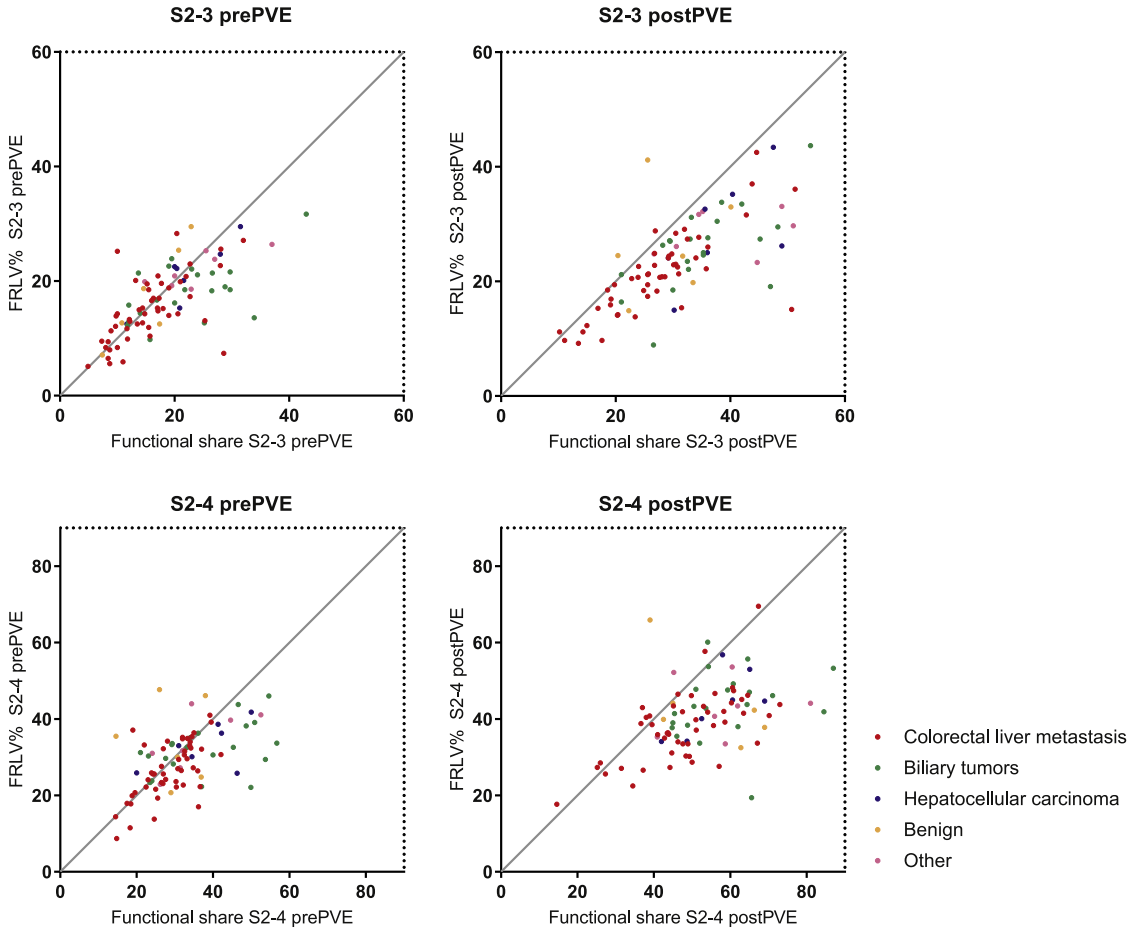

Fig. 4. Comparison functional + volumetric share of S2-3 / S2-4.

Table 5
Multiple linear regression with predictors of PVE response.

	Functional response (percentage increase in liver function of the nonembolized lobe)				Volumetric response (percentage increase in liver volume of the nonembolized lobe)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Predictor	β coefficient	*P* value	β coefficient	*P* value	β coefficient	*P* value	β coefficient	*P* value
Age (years)	0.083	.435	0.01	.145	−0.016	.884	−0.002	.588
Female sex	−0.022	.011	−0.103	.485	−0.158	.137	−0.108	.126
Neoadjuvant chemotherapy	−0.023	.829	0.049	.779	0.225	.033	0.101	.233
Total liver function pre-PVE	−0.374	**<.001**	−0.076	**<.001**	−0.140	.189	−0.002	.847
Benign			Reference				Reference	
Hepatocellular carcinoma	−0.147	.167	-1.297	**.001**	−0.086	.421	−0.043	.806
Colorectal liver metastasis	−0.021	.842	−0.777	**.017**	0.204	.054	0.036	.813
Biliary tumor	−0.061	.567	−0.973	**.001**	−0.120	.261	0.018	.896
Other tumors	0.278	**.008**	0.631	.126	−0.059	.581	0.020	.917

might be decreased if function rather than volume is used to assess the hypertrophy response, taking into consideration that posthepatectomy liver failure is caused mainly by a loss of functional reserve. The finding that the ratio between the functional and volumetric share of the FRL shifts in favor of function after PVE indicates that the functional capacity per mass of tissue of the hypertrophied liver parenchyma is greater than before PVE. The main risk factor for developing PHLF is the loss of functional mass. CT volumetry only shows the morphologic increase of the FRL, which does not always correlate with the functional increase. Considering the discrepancy between function and volume presented in this cohort, we propose the use of a functional assessment, rather than a volumetric assessment, of hypertrophy response after PVE.

Since approximately the year 2012, we have relied mainly on functional assessment, using HBS for the assessment of FRL sufficiency in contrast with CT volumetry and for the decision to perform PVE. In this cohort, 20 patients had insufficient FRL function (<2.7 %/min/m^2) but sufficient FRL volumetric share ($>30\%$). These

Table 6
Characteristics of patients developing posthepatectomy liver failure.

Patient	Liver disease	Resection	FRL function pre-PVE (%/min/m^2)	FRL function preoperative (%/min/m^2)	FRL volume% pre-PVE (%)	FRL volume% preoperative (%)	Initiating factor	Clinical details
1	CRLM	Right hemihep-atectomy	1.2	3.0	9	27	Infectious	Intra-abdominal abscesses leading to septic shock, acute kidney failure, abdominal dehiscence and multi-organ (including liver) failure and death
2	CRLM	Extended right hemihepatec-tomy	2.2	3.6	27	37	Excessive blood loss	Intraoperatively, the patient had 14 liters blood loss due to injury to the vena cava. After initial recovery, the patient developed progressive liver and multi-organ failure and death
3	CRLM	Right hemihep-atectomy	2.2	3.7	17	34	Insufficient FRL	Postoperatively, the patient developed encephalopathy and further deterioration of liver functions. This was further complicated by pneumonia, hepato-renal syndrome, hemodynamic instability, multi-organ failure and death
4	PHC	Right hemihep-atectomy	0.90	2.7	31	48	Infectious	After initial recovery, the patient became septic due to intra-abdominal abscesses followed by an intra-abdominal bleeding from the left hepatic artery, which was surgically resolved. Postoperatively, the patient developed progressive deterioration of liver functions with hemodynamic and respiratory instability and further multi-organ failure leading to death.
5	CRLM	Right hemihep-atectomy	2.5	2.7	37	34	Infectious	Septic complications ultimately lead to liver failure and death

CRLM, colorectal liver metastases; *PHC*, perihilar cholangiocarcinoma; *FRL*, future remnant liver.

patients would not have undergone PVE if we had made the decision to resect based only on volumetry. The association between the implementation of HBS for the decision to perform PVE and a decrease in PHLF and PHLF-related mortality has been reported earlier.[14]

No consensus has been reached concerning the optimal waiting time after PVE.[15] The waiting time should be long enough to achieve sufficient hypertrophy and short enough to evade excessive tumor progression. Ribero et al[16] reported that the initial volumetric growth in the first 3 weeks after PVE is followed by a plateau phase, during which the FRL increases only slightly. In the present cohort, the functional growth exceeded the volumetric growth by which the functional cutoff of the FRL was reached earlier. The peak of functional regeneration is possibly achieved in less than 3 weeks. Consequently, the waiting time to resection can be shortened, thereby potentially decreasing the risk of tumor progression after PVE. Nevertheless, 18 patients (20%) did not undergo hepatic resection because of tumor progression detected 3 weeks after PVE.

The Associating Liver Partition and Portal vein Ligation for Staged (ALPPS) hepatectomy procedure was introduced to induce an accelerated increase in FRL volume exceeding that of PVE, thereby decreasing interstage time.[17] On functional assessment early after stage 1, however, the increase in function of the FRL was less pronounced than the volumetric increase.[18,19] The overestimation of liver function by measurement of only liver volume in ALPPS could partly explain the high complication rate after completion of ALPPS, further underscoring the importance of interstage assessment of liver function.

In the early proliferative stage after ALPPS-stage 1, the increase in volume is the result of proliferation of hepatocytes that are enlarged but have not yet undergone full maturation.[20,21] As hepatocytes mature, the functional increase will likely catch up with the volume increase. Of note, the differentiation of hepatocytes in ALPPS appears to be more prolonged than after hepatectomy.[20] Whether the dynamics of these growth patterns are comparable in patients undergoing PVE remains unknown. In this study, the first measurement of both volume and function was conducted 3 weeks after PVE. To substantiate the optimal waiting time to resection after PVE, future studies are needed to measure the functional response in in the early regeneration phase after PVE to provide more insight into the functional hypertrophy response.

After right PVE, the contribution of S4 to total volume and function of the nonembolized lobe (S2-4) was considerable. Additional embolization of the left portal vein branches in cases of planned extended right hemihepatectomy may translate into an enhanced hypertrophy response of the left lateral segments. This has been shown in multiple studies in which additional embolization of S4 resulted in a larger volume gain of S2-3 than right PVE alone.[7,8] Extending right PVE to S4, however, remains controversial in view of potential procedure-related complications as mentioned earlier in this report.

In cases of extensive, bilobar tumor distribution, where patients are initially considered unresectable because of insufficient FRL, a two-stage hepatectomy combined with PVE can provide a salvage to achieve curative resection.[22] Considering the substantial functional contribution of S4 after right PVE, this segment can have the functional capacity to act as a monosegment after two-stage resection.[23,24] In this case, a left lateral resection, with possible additional metastectomy of S4, can be performed in the first stage, followed by right PVE to allow hypertrophy of S4. In the second

stage, right hemihepatectomy is then performed.[23] This strategy can provide an alternative to extended right hemihepatectomy, thereby increasing resectability in selected cases.[25]

Neoadjuvant chemotherapy is used extensively for patients with colorectal liver metastasis to decrease the tumor burden and facilitate resection. Oxaliplatin combined with capecitabine or 5-Fluorouracil or folinic acid are the agents used most commonly. Targeted molecular therapy with bevacizumab may be added to this regimen. There have been concerns that these agents may damage the hepatic parenchyma, thereby negatively influencing the hypertrophy response after PVE. Several studies, however, have demonstrated that chemotherapy does not influence the volume increase after PVE.[26,27] In the present study, we showed that neoadjuvant chemotherapy was not a predictor of the functional response after PVE.

In this study, we did not find differences in the hypertrophy response between the different pathologies. This finding may be attributable to the selection criteria of patients potentially eligible for liver resection, which excluded most patients with a low parenchymal quality. For instance, patients with hepatocellular carcinoma are only considered for resection in an early stage with preserved liver function (Child Pugh A).[28] This approach accounts for only a minority of all patients with hepatocellular carcinoma, as is reflected by their small number in this cohort. The same applies to patients with perihilar cholangiocarcinoma in whom the selection criteria for resection are relatively strict. For example, patients are only eligible for PVE or hepatobiliary surgery after appropriate biliary drainage, further contributing to the homogeneous patient population undergoing PVE in this study.[29,30] Another explanation for the lack of differences in the hypertrophy response between tumor types is the small sample size of this study; however, in the multivariable analysis, patients with hepatocellular carcinoma and biliary tumors showed a more negative association with the functional gain compared with patients with colorectal liver metastasis or benign disease. This observation can be a reflection of the fact that the former group of patients tend to have a more compromised liver parenchyma either attributable to chronic liver disease in hepatocellular carcinoma (3 of the 7 had severe fibrosis to cirrhosis) or cholestasis in biliary tumors (occurring in 17 of the 20 patients with perihilar cholangiocarcinoma), which can compromise regeneration.

This study has several limitations. First, the study population is heterogeneous and includes patients with a variety of liver diseases, preoperative chemotherapy regimens, and the quality of the liver parenchyma. Subgroup analysis did not indicate significant differences between tumor type (Table 2 and 3), although resulting in small sample sizes per group. There was also heterogeneity in the type of resections carried out. Some patients underwent a standard right hemihepatectomy, and others underwent extended right hemihepatectomy. Another limitation is the retrospective design of this study, resulting in some missing data such as the exact timing of chemotherapy.

In conclusion, 3 weeks after PVE, the functional response of the FRL exceeded the volumetric response, potentially decreasing the time to resection. S4 had a substantial share (41%) of both volume and function after right PVE and, therefore, S4 can be used as a monosegment in selected cases. Furthermore, PVE induced accelerated tumor growth in the nonembolized lobe. Like with volume, neoadjuvant chemotherapy did not negatively influence the functional response after PVE.

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