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FULL PAPER

Identification of cofactors influencing hypertrophy of the future liver remnant after portal vein embolization—the effect of collaterals on embolized liver volume

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Objective: The purpose of this retrospective study was to monitor hypertrophy of future liver remnant following portal vein embolization (PVE) before planned extended right hepatectomy. However, because individual responses to PVE are highly variable, our focus was to identify cofactors of successful hypertrophy.

Methods: 28 patients with primary or secondary liver tumours, mean age 64.1 ± 12.9 years, underwent PVE. Volumetric analysis of hypertrophy before and after PVE (median 39.0 ± 15.7 days) was performed. The embolized liver segments were investigated for occurrence of reperfusion of their portal branches. Blood parameters before PVE were additionally investigated.

Results: Patients were divided into responders (21/28) and non-responders (7/28) by post-PVE standardized future liver remnant being above or below 25%, respectively. No significant differences between the groups

were found regarding biometric and volumetric parameters before PVE. In the entire group after PVE, the mean absolute increase of Segments 2 and 3 was $196.0 \pm 84.7 \text{ cm}^3$ and the median relative increase was $46.6 \pm 98.8\%$. The formation of left to right hepatic portoportal collaterals exhibited a negative correlation to successful hypertrophy ($p = 0.004$) as well as low plasma total protein ($p = 0.019$). Successful embolization of Segment IV showed only a trend to significance ($p = 0.098$).

Conclusion: Cofactors associated with a favourable outcome regarding hypertrophy were the absence of collaterals in the control CT scans and high plasma total protein.

Advances in knowledge: Portoportal collaterals negatively influence hypertrophy after PVE. On the other hand, plasma total protein is a positive prognostic indicator on hypertrophy of the liver in our cohort.

INTRODUCTION

In extensive malignant liver disease, the prognosis of the patients has usually been limited, as surgery was applicable only to a small subgroup of patients. However, recent advances in hepatobiliary surgery and the possibility of safely removing larger portions of the liver have improved the percentage of potentially resectable patients and therefore improved outcomes in this patient group. This was especially true for the possibility of extended right liver resection in cases with hilar cholangiocarcinoma^{1,2} and other primary and secondary malignancies affecting large portions of the right liver, which may even include segment IV.³

However, an extended right hepatectomy (ERH) leaves a residual liver volume of $<20\%$ of the total liver volume (TLV) in $>75\%$ of all cases;^{4,5} this poses a risk in itself, as

patients with a small future liver remnant (FLR) volume are likely to experience post-operative liver insufficiency. Therefore, as resection safety is dependent on the volume and function of the FLR,⁶ appropriate pre-operative procedures are warranted to enlarge the (left) FLR.

It is well known that other factors such as parenchymal liver function also determine the outcome in ERH. Consequently, in recent literature, a residual volume, the “standardized FLR” (sFLR) of 25–30% has been described as the benchmark in patients with normal liver function⁷ and volumes of at least 40% in patients with parenchymal liver disease.^{8,9}

Three methods to enlarge FLR are possible in this situation before ERH: (1) surgical right-sided portal vein ligation

(PVL),^{10,11} (2) portal vein embolization (PVE) as an interventional approach used by various centres^{12–14} and (3) the surgical approach of “associating liver partition with PVL for staged hepatectomy”.^{15–17}

However, as hypertrophy following PVE is necessary but highly variable, we retrospectively analyzed data from our patient cohort for differences in those with good hypertrophy (increase to >25% of the sFLR) and those with a less beneficial increase in size of sFLR.

The aim of this study was therefore to find determinants for acceptable hypertrophy in a population with right hepatic cancer and PVE as a pre-operative method for planned ERH (trisegmentectomy).

METHODS AND MATERIALS

Patients

All consecutive patients who underwent PVE before ERH between June 2010 and May 2014 were included in the study if they matched the following criteria.

Inclusion criteria consisted of a plan on extended right hemihepatectomy based on the approval of the local tumour board. All included patients underwent PVE. Pre- and post-interventional CT scans, laboratory parameters and biometric data had to be available to be included. Pre-PVE metastasectomy was allowed previous to PVE if all metastases were resectable ($n = 3$).

Exclusion criteria were the inability to perform PVE due to extensive extrahepatic or the presence of left-sided hepatic metastases. Also, a technical failure of PVE, as in one patient in whom the sonographic approach to the right portal vein was not available, due to a large right central tumour was excluded.

Three of the patients had had previous external PVLs, with failure to show sufficient hypertrophy. All three patients showed insufficient PVL with blood flow to >90% ligated right-sided liver despite previous PVL. Therefore, they were considered unembolized and were treated in the same fashion as the other patients and not excluded from our study.

28 patients were recruited in our study, 10 females and 18 males. The mean age was 64.1 ± 12.9 years and range was 30–82 years. For histopathological data, please refer [Table 1](#), and for biometric data, please refer [Table 2](#).

Imaging

In all patients with potentially resectable disease, pre-interventional CT was performed on multislice scanners [either on a GE Optima 660 (GE Healthcare, Pittsburgh, PA) or a Philips Brilliance 40 (Philips Healthcare, Best, Netherlands)] with 120 kV and adaptive mAs adjusted to the patient's body weight; the primary slice thickness was 0.625 and 1.25 mm, respectively. Usually 110 ml of contrast media (Imeron® 400; Bracco, Milano, Italy) was administered. Pre-operative CT scans were performed as described above.

Table 1. Distribution of primary tumours in our patient cohort

Primary tumour	Number of patients
Colorectal carcinoma	9
Hepatocellular carcinoma	6
Intrahepatic cholangiocarcinoma	6
Hilar cholangiocarcinoma	4
Breast cancer	1
Ewing's sarcoma	1
Hepatic adenomatosis	1

Volumetry

Images were processed on an Advantage Workstation 4.1.2 (GE Healthcare). For volumetric evaluation, the venous phase was chosen. Volumetry was performed on CTs directly prior to PVE and on the last and final CT before ERH. The FLR was calculated by outlining Segments 2 and 3 of the liver on axial planes. In this process, tumours >1 cm in diameter were excluded from volumetry. Portal branches and bile ducts were excluded by thresholding the outlined volume. The total estimated liver

Table 2. Biometric and volumetric patient data

Biometric data	
Female	10/28 (36%)
Male	18/28 (64%)
Age (years)	64.1 ± 12.9
BMI	27.1 ± 5.8
BSA (m ²)	1.96 ± 0.25
ERH performed	18 (64%)
Median interval of PVE to ERH (days) ^a	77 ± 46
Median interval of PVE and CT control (days)	59 ± 26
Volumetric data	
Mean TLV (cm ³)	1702 ± 407
Mean TELV (cm ³)	1696 ± 314
Mean FLR1 (cm ³)	341 ± 151
Mean FLR2 (cm ³)	532 ± 179
Mean sFLR1 (%)	20.3 ± 9.2
Mean sFLR2 (%)	32.0 ± 11.2
Mean absolute increase of FLR2 (cm ³)	191 ± 85
Mean relative increase of FLR2 (%) ^b	82.5 ± 98.8
DH (%)	11.7 ± 6.5

BMI, body mass index; BSA, body surface area; DH, degree of hypertrophy; ERH, extended right hepatectomy; FLR1, future liver remnant before PVE; FLR2, future liver remnant after PVE; PVE, portal vein embolization; TELV, total estimated liver volume; sFLR1, standardized future liver remnant before PVE; sFLR2, standardized future liver remnant after PVE; TLV, total liver volume.

^aFour cases of prolonged time to surgery with 130, 160, 168 and 217 days respectively.

^bMedian $46.6 \pm 98.8\%$.

volume (TELV) was calculated using the formula published by Vauthey et al¹⁸ based on the body surface area (BSA) best suited for calculation in a western population:

$$\text{TELV}(\text{cm}^3) = -794.41 + 1267.28 \times \text{BSA}(\text{m}^2).$$

Based on TELV, sFLR was calculated in each individual at both time points: before PVE (sFLR1) and before resection (sFLR2):¹⁸

$$\text{sFLR}(\%) = [\text{FLR}(\text{cm}^3) / \text{TELV}(\text{cm}^3)] \times 100.$$

The cutoff level for sufficient hypertrophy of the sFLR after PVE (FLR2) was set to 25% of TELV. This value was chosen owing to the fact that the study population underwent prior systemic chemotherapy ($n = 25/28$) or had pre-existing cirrhosis ($n = 3/28$). Our collective was then dichotomized according to the threshold of sFLR2 25% in two groups, (1) responders (sFLR $\geq 25\%$) and (2) non-responders (sFLR $< 25\%$).

Portal vein embolization

PVE was performed under general anaesthesia. We used the ultrasound-guided transcutaneous transhepatic approach as a standard measure (Toshiba Aplio XV; Toshiba Medical Systems Europe GmbH, Neuss, Germany). Owing to an agreement in our centre, we exclusively used the right-sided approach to prevent damage to the FLR. A 4-French pigtail catheter (Cook Medical, Bloomington, IN) was introduced into the central portal vein, and direct portography was performed. After that, a 5- or 6-French S1 Sidewinder Catheter (Cook Medical) was routinely introduced to selectively access the right portal vein branches. Embolization was performed selectively with PVA particles (Contour™ PVE Particles, 250–355 μm ; Terumo, Tokyo, Japan) until a near-complete stasis in the selected vessel was apparent by fluoroscopy. The particle embolization was, in all cases, followed by fibred coil embolization (spiral sizes 3–10 mm) (Cook Medical) to prevent central recanalization. This procedure was repeated until all accessible right portal branches were completely embolized. In four patients, Segment 4 branches were accessible and were selectively embolized. Depending on individual anatomies Amplatzer™ Vascular Plugs (St Jude Medical, Saint Paul, MN) were used in selected patients ($n = 2$). At the end of the procedure, success was analyzed by direct portography.

Statistics

Statistical analysis was performed by SPSS® v. 22 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). To evaluate differences between groups, Student's *t*-test, Mann–Whitney *U* test, χ^2 test or Fisher's exact test was used depending on the type of variable examined. The degree of hypertrophy was defined as sFLR before PVE (sFLR1) subtracted from sFLR at the time of control CT (sFLR2).

Ethical approval

The study complied with the declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

RESULTS

The 28 patients included in this study had a median hospitalization after PVE of 2 days. Post-PVE CT scans were scheduled in the sixth to eighth week after PVE and were carried out at a median on Day 39 ± 15.7 days (range 21–89 days).

Volumes

The mean TELV was $1696 \pm 314 \text{ cm}^3$. The mean volume of FLR1 was $341 \pm 151 \text{ cm}^3$ and of sFLR1 was $20.4 \pm 9.2\%$. At the time of the last post-PVE CT, mean FLR2 volumes measured $532 \pm 178 \text{ cm}^3$ and mean sFLR2 was calculated as $31.9 \pm 11.3\%$.

At the time of CT controls, the median absolute increase in Segments 2 and 3 volumes was $191.4 \pm 84.7 \text{ cm}^3$ in the entire group, with a median relative increase of $46.6 \pm 98.8\%$ (mean $82.5 \pm 98.8\%$, range 18.5–500.0%). In the one patient with hypertrophy of 500%, Segments 2 and 3 accounted for only 54 cm^3 (3.7%) prior to PVE. The mean degree of hypertrophy was $11.7 \pm 6.5\%$. The mean growth rate of the entire group (calculated by the absolute increase divided by the number of days) was $3.7 \pm 2.4 \text{ cm}^3$ per day (Table 2).

Groups

21/28 (75%) patients were sorted into the responder group, and 7/28 patients (25%) were classified as non-responders.

Predictors

We analyzed laboratory intervention-related parameters, blood parameters and biometric data for independent risk factors divided between the two groups. *Intervention-related parameters* were the additional embolization of Segment 4 branches and the formation of new portoportal collaterals to the embolized right liver with the effect of reperfusion to the embolized liver volume. Collaterals were directly detectable cross-perfusion of vessels. On CT scans, detections were aided by maximum intensity projections. Non-visible collateralization was supposed in portal branches with peripheral reperfusion of centrally sufficiently embolized and non-perfused portal branches, most likely by small-sized vessels. Arteriovenous shunts were not observed. *Laboratory blood parameters* were: alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma-glutamyltransferase (GGT), bilirubin, albumin, plasma protein level (PPL), thrombocytes and prothrombin time. *Biometric parameters* consisted of sex, gender, age, cirrhosis, diabetes and hepatic steatosis.

The development of new portoportal collaterals to the embolized liver segments on control CT after PVE was shown to be an independent risk factor for being a non-responder ($n = 7/28$, $p = 0.004$). Five of seven of these patients were non-responders (examples are shown in Figures 1a–d and 2a,b). The remaining two patients had only a marginal sFLR2 above the threshold of 25%, with 25.5% and 26.5%, respectively.

In four patients, embolization of Segment IV portal branches was performed. All of these patients accounted for responders. No statistical significance could be achieved in the two-sided test in this small subgroup ($p = 0.098$).

Figure 1. Images of two patients which showed portal revascularization caused by portal collaterals (arrowheads) distally of the coils in the portal main branches (asterisks). (a, b) show the first patient and (c, d) show the second patient in transversal followed by coronal plane, respectively.

For blood analysis data, the only positive predictor in a univariate correlation towards successful hypertrophy was PPL ($p = 0.019$). ALAT and GGT showed a tendency but with no statistical significance ($p = 0.072$ and $p = 0.080$, respectively). No other single risk factor was identified, specifically none in biometric data. Details are shown in [Tables 2](#) and [3](#).

Complications

No severe complications occurred. During one treatment, a single coil was displaced to the left main branch and was subsequently retrieved in the same session by a Snare® device (Amplatz GooseNeck® Snare Kit; Covidien eV3 Endovascular, Inc., Plymouth, MN). In one patient, despite incremental doses

Figure 2. Images of a patient before (a) and after (b) PVE. The arrowhead in (a) marks an only marginally detectable portal side branch of the main right portal vein which was not detected during angiography. This vessel is depicted in (b) 5 weeks after PVE. The vessel diameter is largely increased and is functioning as a portal collateral which is suspected to impede hypertrophy of the FLR.

Table 3. Cofactors and their predictive value for standardized future liver remnant after PVE (sFLR2) <25%

Cofactors	Number of patients	<i>p</i> -value
CTX prior to PVE	25 (93%)	NS
Cirrhosis	3 (11%)	NS
Steatosis	12 (43%)	0.010
Diabetes	6 (21%)	NS
Embolization of Segment IV	4 (14%)	NS ^a
New portal collaterals to embolized liver	7 (25%)	0.004

NS, not significant; PVE, portal vein embolization.

^aTrend to significance ($p = 0.098$ for sFLR >30%).

CTX = chemotherapy.

of heparin to a total of 5000 IE units, central portal vein stasis occurred and the PVE had to be terminated for safety reasons. Subsequently, a second PVE session was scheduled and the procedure was completed.

DISCUSSION

Our results show that the median hypertrophy of Segments 2 and 3 reached a median relative increase of $46.6 \pm 98.8\%$ /mean relative increase of $82.5 \pm 98.8\%$ and an absolute increase of the FLR of $196.0 \pm 84.7 \text{ cm}^3$ after PVE. These results agree with previous published values, where the average percentage increase in FLR hypertrophy was in the range of 27–69%.^{19–21} In comparison with PVL, as published by van Lienden et al,²² in the group with PVL hypertrophy, a growth rate of only 8.1% was achieved. The same group published the only systematic review available to date, with a pooled analysis of nearly 1800 patients; it exhibited a mean hypertrophy rate of FRL after PVE of 37.9%.²³ The finding of superior hypertrophy was confirmed by another research group in an animal model and in human use.^{24,25} In addition, the inflicted trauma to the patient is much lower in PVE owing its minimally invasive nature.

The concept utilized for volume determination of the FLR was chosen because the determined values of Segments 2 and 3 are anatomically robust and the resulting volume can both be normalized to the TLV or total body surface;²⁶ normalization on the body surface was recommended in this comparison and by multicentre analysis on 292 patients.²⁷

However, adequate functional tests of FLR are lacking, leading to variability in outcomes for any given FLR volume threshold. It has been hypothesized that the rate and overall ability for hypertrophy in response to PVE is an indicator of FLR function that is associated with the avoidance of post-operative liver insufficiency.^{6,28} Recent data support this hypothesis with the use of non-parametric regression and showed that post embolization, no patient with a growth rate >2.66% per week developed liver failure.²⁹

In patients with chronic liver disease, some investigators have adopted algorithms incorporating functional tests, such as the indocyanine green retention rate, which has been proposed as an

adjunct to the volumetric measurements.^{30,31} However, despite encouraging results, widespread clinical acceptance is lacking so far.

There are published recommendations for sFLR2 cutoff values based on ratios of FLR to TLV, or to BSA. However, for Klatskin tumours, recommendations for the FLR was set to >30%.³² Comparing the situation in a large series with previous chemotherapy, Shindoh et al³³ clearly demonstrated that an FLR of only 20% poses a risk for patients being treated with chemotherapy exceeding 12 weeks; for those with “long-duration” chemotherapy, a FLR >30% reduces the rate of post-operative hepatic insufficiency and mortality. Therefore, this group, and others, use a cutoff level of 25–30%, depending on individual patients’ histories.^{4,30,34}

Determinants for a favourable outcome were identified as follows: there was a negative correlation between the detection of collaterals in follow-up CT and successful hypertrophy. Furthermore, there was a statistically significant correlation between “normal” PPLs and successful hypertrophy. There was only a trend of a successful Segment 4 embolization being an indicator for a sufficient hypertrophy ($p = 0.098$) most likely due to a low number of subjects being embolized in this area (4/28 patients). Nagino et al³⁵ measured hypertrophy rates in Segment 2 and 3 PVE compared with those having additional Segment 4 embolization. They saw a 50% vs a 31% increase in hypertrophy. This improvement has been reproduced by a group from the Anderson Cancer Center on a larger patient cohort.³⁶ However, other groups did not report significant improvements by comparing right PVE with right PVE plus Segment 4.³⁷

A strong correlation between the absences of portal collaterals to the embolized right liver and left hypertrophy was shown. In our series on control CT, we detected 7/28 patients who had collateral vessel formation, and all of them had poor hypertrophy of Segments 2 and 3. These findings confirm the data from van Lienden,²² where building of collaterals was detected in 1/18 PVE cases in their series. In a recent publication, a conversion from a PVE to a “rescue” ALLPS was reported by Jackson.³⁸ However, changes in macroarchitecture have been reported earlier in an animal model.²⁵

These findings could imply that earlier CT follow-up has to be made. If collaterals are detected in these early controls paired with a slow increase in FLR, e.g. measured by the kinetic growth rate,⁶ additional measures to improve hypertrophy should be discussed. Therefore, the finding of collaterals and low hypertrophy may in future lead to decisions such as: if a control CT of sufficient quality does not demonstrate collaterals, the effect of added ALLPS may be small. However, if there are collaterals detected on CT, then a “rescue” associating liver partition with PVL for staged hepatectomy procedure will probably have a high chance of supporting the hypertrophy concept and will more likely be of benefit to the patient.

To summarize this part of the discussion, the minimum sFLR and indications for PVE should be tailored to each patient and will depend on many factors, including the complexity of the anticipated resection, simultaneous procedures, patients’ comorbidities and underlying liver disease, as described in the article of Ribero et al.⁴

Other materials can be used; recent work on tetradecyl sulfate foam shows that this material is a safe and effective agent,³⁹ and another recent report demonstrates a safe procedure and an even increased hypertrophy rate using *n*-butyl-cyanoacrylate compared with particles and coils.^{12,13} Recent work published by Geisel et al⁴⁰ shows that results using particles alone can be improved with a combination of particles plus coils and plugs. In the above mentioned systematic review, the use of *n*-butyl cyanoacrylate seems to have a greater effect on hypertrophy, but differences between the other analyzed embolization materials did not reach statistical significance.²³

The interventional approach we used is a treatment with little reported morbidity. The PVE procedure is usually well tolerated, where only small numbers of minor or major complications have been described. Minor complications in a transhepatic approach, such as extrahepatic biliomas, have been reported in the range of 3–8%,⁴⁰ and other minor complications such as fever, abdominal discomfort and pain or nausea have been reported in 20–36% of cases.²³ The only report available to date on morbidity following PVE describes a single lethal pulmonary embolism in 1/146 patients.⁴¹ The meta-analysis from van Lienden et al^{22,23} reports a median published major complication rate of 0.7%, including severe cholangitis, larger abscesses or persistent portal vein or mesentericoportal venous thrombosis³⁴ which, however rarely, led to non-resectability in these patients. None of the latter severe complications occurred in our patient cohort.

There are limitations in our study. The data shown are based on a retrospective single centre observation with a relative small number of patients and with different histological findings. Owing to its nature, the study did not have the same significance as a randomized trial. Further studies are necessary to clearly differentiate between the various materials available for PVE and to especially analyze risks and benefits of different approaches such as PVL, ALLPS and PVE to achieve hypertrophy of the FLR.

Identification of cofactors that predict poor outcome, as in our case the development of portal collaterals, may help to decide when to convert cases with poor hypertrophy to open surgery.

CONCLUSION

In conclusion, PVE of the right portal vein using a combination of particles and coils leads to a large increase in FLR volume. Cofactors for a successful outcome are the absence of collaterals in follow-up CT and a “normal” PPL. Successful portal venous embolization of Segment 4 may also favour higher hypertrophy of the FLR even though significance was not reached due to small sample size in the cohort.

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