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Thiery Chapelle

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Estimation of future liver remnant function to prevent post-hepatectomy liver failure: *a refined tool*

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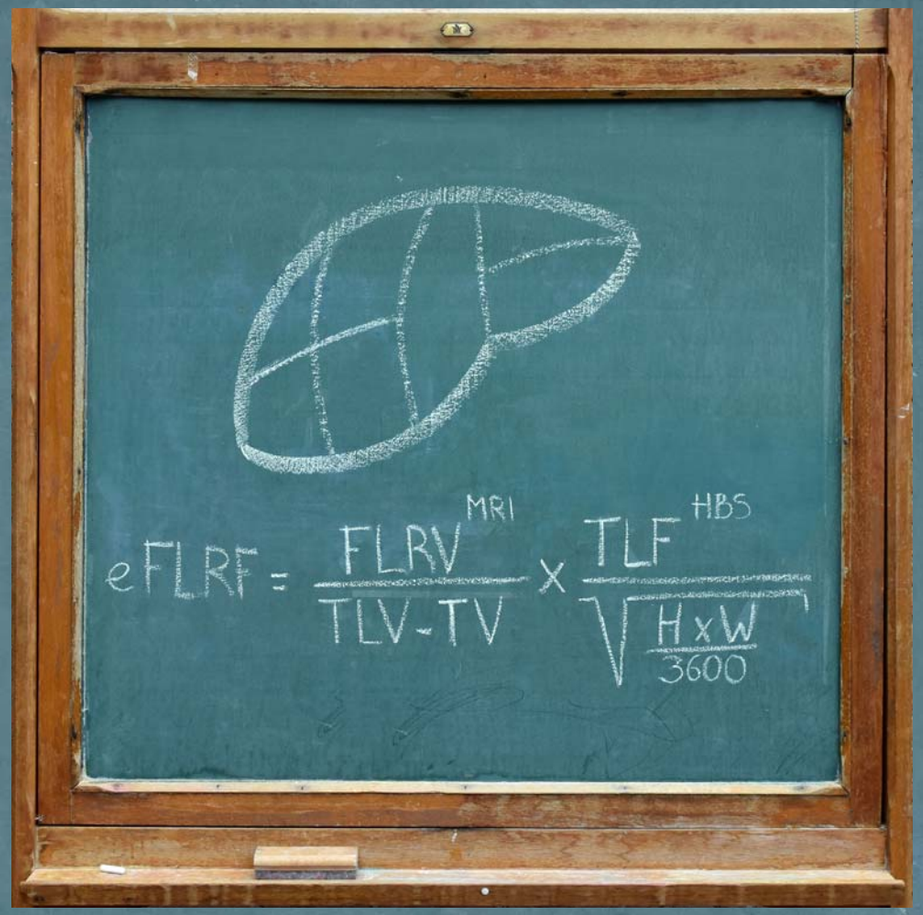
Promotor: Prof. dr. Dirk Ysebaert

Estimation of future liver remnant function

Thiery Chapelle

2017



Estimation of future liver remnant function to prevent post-hepatectomy liver failure: *a refined tool*

Proefschrift voorgelegd tot het behalen van de graad van doctor in de Medische Wetenschappen aan de Universiteit Antwerpen door

Thiery Chapelle

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Prof. dr. Dirk Ysebaert

Medicine is a science of uncertainty
and an art of probability

William Osler, Canadian physician

Chapter 5

Use of future liver remnant function avoids post-hepatectomy liver failure

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Chapter 5: Contents

Abstract

Introduction: Estimation of the future liver remnant function (eFLRF) can avoid post-hepatectomy liver failure (PHLF). In a previous study, a cutoff value of 2.3%/min/m² for eFLRF was a better predictor of PHLF than future liver remnant volume (FLRV%). In this prospective interventional study, investigating a management strategy aimed at avoiding PHLF, this cutoff value was the sole criterion assessing eligibility for hepatectomy, with or without portal vein occlusion (PVO).

Methods: In 100 consecutive patients, eFLRF was determined using the formula: eFLRF = FLRV% x total liver function (TLF). Group 1 (eFLRF >2.3%/min/m²) underwent hepatectomy without preoperative intervention. Group 2 (eFLRF <2.3%/min/m²) underwent PVO and re-evaluation of eFLRF at 4-6 weeks. Hepatectomy was performed if eFLRF had increased to >2.3%/min/m², but was considered contraindicated if the value remained lower.

Results: In group 1 (n=93), 1 patient developed grade B PHLF. In group 2 (n=7) no PHLF was recorded. Postoperative recovery of TLF in patients with preoperative eFLRF <2.3%/min/m² occurred more rapidly when PVO had been performed.

Conclusion: A predefined cutoff for preoperatively calculated eFLRF can be used as a tool for selecting patients prior to hepatectomy, with or without PVO, thus avoiding PHLF and PHLF-related mortality.

Introduction

Posthepatectomy liver failure (PHLF) is a major and potentially life-threatening complication following major hepatectomy in normal livers. It more readily occurs after minor resections in livers compromised by steatosis, steatohepatitis, chemotherapy associated liver injury (CALI) (1) or cirrhosis. Although liver function correlates well with liver volume in uncompromised livers, this relationship is less clear in patients with coexisting parenchymal liver disease (2, 3). Estimation of remnant liver function instead of remnant liver volume is a better predictor of clinical outcome after liver resection in patients with decreased liver function (4). In planning a liver resection, not only should the future liver remnant volume ratio (FLRV%) and total liver function (TLF) be measured, the estimated future liver remnant function (eFLRF) should be calculated. This is particularly important for compromised livers. In a previous pilot study (5), a tool for assessing eFLRF was developed by combining FLRV% (measured by Magnetic Resonance Imaging - MRI) with TLF (measured using ^{99m}Tc-mebrofenin hepatobiliary scintigraphy - HBS). A cut-off value for eFLRF at 2.3%/min/m² was defined by receiver-operating-characteristic (ROC) analysis. This cut-off for eFLRF seemed to be a better predictor for PHLF than FLRV%. In this pilot study, mortality related to PHLF may have been avoided if the eFLRF criterion had been used instead of FLRV%.

Objective of this study

The objectives of this study were to validate the eFLRF cutoff value of 2.3%/min/m² as (a) a criterion of eligibility for hepatic resection and (b) as an indication for portal vein occlusion (PVO), as part of a pre-defined, stepwise hepatic resection strategy, aiming to avoid PHLF and PHLF-related mortality.

Methods

Inclusion criteria

The study was approved by the Medical Ethics Committee of the Antwerp University Hospital. Written informed consent was obtained from each participating patient. Consecutive patients undergoing hepatectomy between April 2012 and January 2014 were included. Indications for liver resection were: benign liver tumor, colorectal and non-colorectal liver metastasis, intrahepatic/perihilar cholangiocarcinoma and hepatocellular carcinoma, all diagnoses being confirmed *post hoc* by pathological examination of the resection specimen. The outlying liver parenchyma was reported as follows: normal, cirrhotic (diagnosed on clinical/biochemical evaluation and/or imaging and/or liver biopsy, if available) and at-risk for chemotherapy-associated liver injury (CALI), based on preoperative administration of chemotherapeutic agents. Cirrhosis Child-Pugh A and suspected CALI were never considered as a contraindication for resection. Exclusion criteria were: cirrhosis Child-Pugh B/C, age under 18 years and pregnancy.

Preoperative evaluation

Age and Body Mass Index (BMI, kg/m^2) were recorded for all patients. The physical status was estimated using the American Society of Anesthesiologists (ASA) score. MRI of the liver, a few weeks prior to surgery, is the standard diagnostic tool in our department. Consecutive slices of this diagnostic MRI examination were used by an expert radiologist to perform liver volumetry. The volume to be resected was delimited in close collaboration with the surgeon.

^{99m}Tc-mebrofenin HBS was performed to measure global liver function and expressed in %/min, regardless of the tumor volume. To compensate for variations in individual metabolic needs, the clearance was normalized by dividing the obtained value by the Body Surface Area (BSA), calculated by the Mosteller formula (BSA^2 = body weight (kg) x body length (cm) / 3600). The liver function measured by HBS, was divided by the body surface area (BSA) and expressed as total liver function (TLF) (5). In this article, TLF refers to this BSA-normalized value.

FLRV% was calculated by dividing the future liver remnant volume (in mL) by the total functional liver volume (in mL). It was expressed as % (FLRV% = FLRV x 100 / TLV). Potential effects of large tumor volume was anticipated by subtracting the tumor volume from TLV.

eFLRF was calculated by multiplying the future liver remnant volume ratio by the total liver function (eFLRF = FLRV % x TLF / 100).

Methodology of MRI volumetry, ^{99m}Tc-mebrofenin HBS, FLRV% and eFLRF calculations were performed as previously described (5).

Portal vein occlusion

When eFLRF was > 2.3%/min/m², hepatectomy was performed without further preoperative intervention (Group 1). When eFLRF was < 2.3%/min/m², PVO was performed (Group 2). PVO could consist of a portal vein embolization (PVE) or a portal vein ligation (PVL). PVE was the treatment of first choice, except when a two-stage hepatectomy was planned: here, PVL was performed during the first procedure.

PVE was performed under general anesthesia by the interventional radiologist. The portal vein was punctured percutaneously with an 18 gauge trocar/needle under ultrasound guidance. The punctured portal vein branch was normally one of the branches intended to be embolized. A short 4 French introducer sheath (Terumo®) was introduced into the punctured portal vein to secure the access. A 0.035 inch guidewire was then used to advance a 4 French Simmons/Sidewinder 1 Glidecath Terumo® catheter through the sheath into the common portal vein, and a diagnostic venogram performed to illustrate the portal vein anatomy. A Progreat 2.7 Terumo® microcatheter was subsequently positioned in the selected branches of the portal vein. Embolization in these selected portal branches was carried out by careful injection of diluted glue, consisting of 1 part Glubran 2 (Gem Italy®) and 5 parts Lipiodol (480 mg/L iodide, Guerbet®). The microcatheter was meticulously flushed with a glucose solution in order to prevent occlusion of the microcatheter lumen by the glue. After successful embolization, the catheters and sheath were carefully removed, simultaneously gluing or gelfoaming the intrahepatic puncture track.

PVL was performed at laparotomy as part of the first step of a two-stage hepatectomy. For example, after resection of tumors in the left liver, the right portal vein was dissected and isolated. Interruption of the portal flow in all right hepatic segments was verified using intraoperative Doppler-ultrasonography by selectively clamping the right portal vein. When portal flow occlusion was confirmed, the right portal vein was sutured and transected. Sclerosis of the right portal vein system was subsequently achieved by injecting 10 mL of ethanol 96% into the right portal vein stump.

Complications related to PVE or PVL were registered according to the Dindo-Clavien classification (6).

Four to 6 weeks after PVO, MRI and ^{99m}Tc-mebrofenin HBS were repeated. FLRV% and TLF were measured and eFLRF was re-calculated. If eFLRF after PVO was > 2.3%/min/m², hepatectomy was performed. If post-PVO eFLRF remained < 2.3%/min/m², hepatectomy was considered to be contraindicated and alternative treatments were proposed.

Intraoperative measurements

The hepatectomy was performed by one of the 3 senior hepatobiliary surgeons in our department, all of whom have a large experience in liver resection surgery. Intraoperative blood loss was measured and reported in mL.

Postoperative evaluation – detection of PHLF

PHLF was diagnosed according to the ISGLS criteria (7), characterized by an increased INR and hyperbilirubinemia on or after postoperative day 5. The severity of PHLF is graded in relation to its impact on clinical management. Grade A PHLF requires no change in the patient's clinical management and was not considered to be clinically relevant in this study. In grade B PHLF, clinical management deviates from the regular course but does not require invasive therapy. The need for invasive treatment defines grade C PHLF. In this study, clinically significant PHLF was recorded as either grade B or C. Perioperative mortality was defined as mortality within 3 months after hepatectomy.

Comparing the interventional and observational studies

The results from the current interventional study were compared with our previously reported observational data (5). In the latter study, FLRV% < 25% was used as a selection criterion for PVO, according to the standard protocol at that time. As outlined previously, in the current interventional study, eFLRF <2.3%/min/m², was used as the selection criterion for preoperative PVO. Therefore, for the purposes of the current analysis, both study cohorts were subdivided into groups according to preoperative eFLRF i.e. > or < 2.3%/min/m² (Figure 5.1). 4 groups were thus created: Group 1, interventional study, including patients with eFLRF >2.3%/min/m² who underwent hepatectomy without PVO; Group 2, including patients with eFLRF <2.3%/min/m² who underwent PVO before hepatectomy. In the observa-

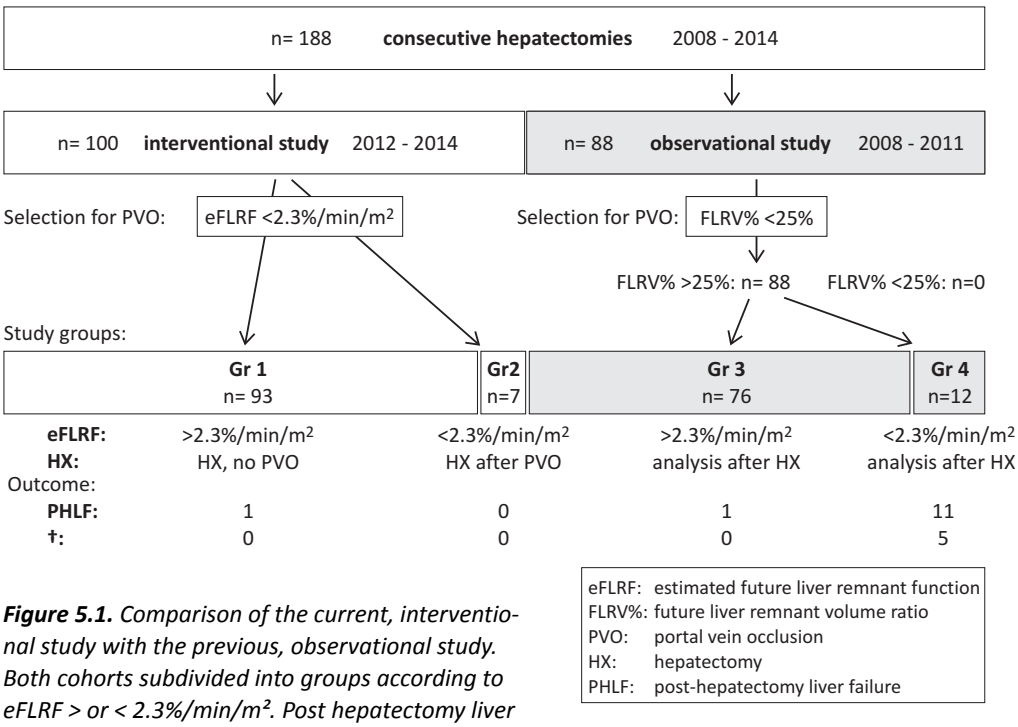

Figure 5.1. *Comparison of the current, interventional study with the previous, observational study. Both cohorts subdivided into groups according to eFLRF > or < 2.3%/min/m². Post hepatectomy liver failure and related mortality was observed almost exclusively in Group 4, in which selection for hepatectomy was made according to FLRV% > 25%, but with a post hoc eFLRF less than 2.3%/min/m².*

tional study, *post-hoc* analysis was used to calculate eFLRF dividing patients into: Group 3, eFLRF > 2.3%/min/m² and Group 4, eFLRF <2.3%/min/m².

Recovery of liver function after hepatectomy

Recovery of liver function after hepatectomy was evaluated by measuring the liver function in all groups at different times. TLF and eFLRF were calculated before hepatectomy or before PVO. In the case of PVO, eFLRF was recalculated 4 to 6 weeks after PVO before deciding on the feasibility of hepatectomy. After hepatectomy, TLF was re-calculated at 14 days and 3 months post-operatively. Evolution and recovery of the liver function in the different groups was reported by means of a time series plot. The data concerning the recovery of liver function in the observational study were previously not reported, but have now been included in the current analysis.

Statistical analysis

Statistical analysis was performed using SPSS (version 21, Chicago, IL). The normal distribution of continuous variables is assessed with the Shapiro-Wilk method. Normally distributed variables are expressed as means with standard deviation and analyzed with the Student T test. Non-parametric continuous variables were expressed as medians with range for non-normally distributed continuous variables and analyzed using the Mann Whitney U test. Categorical data are expressed as numbers (%). For nominal data, Chi-square or Fisher's exact test was performed. Paired metric data are analyzed using the Wilcoxon signed rank test. In all statistical analyses, results were considered significant at a P-value < 0.05.

Results

The baseline characteristics of the 100 patients included in the interventional study, divided according to the preoperatively calculated eFLRF are presented in Table 5.1 (Group 1, eFLRF >2.3%/min/m², Group 2, eFLRF <2.3%/min/m²). The vast majority of patients had eFLRF >2.3%/min/m² and underwent hepatectomy without PVO (Group 1, 93/100 patients). Patients in Group 2 were significantly younger but other demographic factors and indications for liver resection were not significantly different. More segments were resected in Group 2. A total of 7 PVO's were performed: 1/7 for intrahepatic cholangiocarcinoma, 1/7 for benign liver tumor and 5/7 for liver metastases, of which all had neoadjuvant chemotherapy.

In Group 1, 1/97 patients developed grade B PHLF. This patient underwent a liver resection for HCC in a hepatitis B-induced cirrhosis Child-Pugh A. There was portal hypertension with a hepato-veno-portal gradient of 10mmHg, but neither preoperative eFLRF (3.6 %/min/m²) or FLRV% (69.4%) had predicted the risk for PHLF. No mortality was recorded in Group 1.

Table 5.1. *Characteristics of 100 consecutive patients who underwent hepatectomy: an interventional study where the estimated future liver remnant function (eFLRF) was used as sole criterion to assess eligibility for hepatectomy and indication for portal vein occlusion. Portal vein occlusion was performed when eFLRF < 2.3%/min/m². This strategy aimed to avoid post hepatectomy liver failure (PHLF).*

	Units	Group 1	Group 2	P-value
Selection based on eFLRF	**%/min/m²**	**> 2.3 (n= 93)**	**< 2.3 (n= 7)**	
Gender ratio	M / F	58 / 35	0 / 7	0.050
Age	years	62.2 (± 12.2)	48.4 (± 10.1)	0.015
BMI	kg/m²	25.3 (± 3.9)	28.4 (± 6.7)	0.233
ASA	grade	2.4 (± 0.6)	2.2 (± 0.8)	0.158
Indication for liver resection				0.120
Benign liver tumor		6 (6.5%)	1 (14.3%)	
Colorectal liver metastasis		71 (76.3%)	4 (57%)	
Non-colorectal liver metastasis		4 (4.3%)	1 (14.3%)	
Intrahepatic cholangiocarcinoma		5 (5.4%)	1 (14.3%)	
Perihilar cholangiocarcinoma		1 (1.1%)	0 (0%)	
Hepatocellular carcinoma		6 (6.5%)	0 (0%)	
Chemotherapy prior to hepatectomy		49 (46.2%)	5 (71.5%)	0.604
Cirrhosis Child Pugh A		6 (6.5%)	0 (0%)	0.605
Portal vein occlusion		0	7	<0.001
Portal vein embolization		0	5	
Portal vein ligation		0	2	
Complications portal vein occlusion		na.	0	
Segments resected	n	2 (1 - 5)	4 (3 - 5)	< 0.001
Intraoperative blood loss	mL	500 (0 - 8500)	600 (50 - 1500)	0.649
PHLF Grade B/C	n	1 (1.1%)	0 (0%)	0.768
PHLF related mortality	n	0 (0%)	0 (0%)	na.

In Group 2, eFLRF increased to >2.3%/min/m² 4 to 6 weeks after PVO in all 7 patients and hepatectomy could be performed safely. In Table 5.2, the calculation methodology of TLF and eFLRF prior and after PVO is demonstrated. No patient had to be denied hepatectomy due to eFLRF <2.3%/min/m² after PVO. No complications due to PVE or PVL were recorded. No PHLF occurred and there was no mortality.

Table 5.2. *Characteristics of 7 patients with eFLRF < 2.3 and who underwent preoperative PVO.*

Patient	**Units**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Age	y	38	46	50	62	32	51	60
Indication liver resection		BLT	CRLM	non-CRLM	CRLM	CRLM	CRLM	ICCC
Liver parenchyma, clinical estimation		steatosis	CALI	CALI	CALI	CALI	CALI	steatosis
Type PVO	PVE or PVL	PVE	PVE	PVE	PVL	PVL	PVE	PVE
Body length	m	1.57	1.67	1.69	1.58	1.74	1.65	1.59
Body weight	kg	78	75	75	56	86	55	109
BMI	kg/m²	31.7	26.89	26.26	22.43	28.41	20.2	43.03
BSA	m²	1.85	1.87	1.88	1.57	2.04	1.59	2.19
Pre PVO								
HBS	%/min	13.04	12	8.31	15.4	12.45	16.74	10.54
TLF *(= HBS / BSA)*	%/min/m²	7.05	6.42	4.42	9.81	6.10	10.53	4.81
FLRV% *(= 100 x FLRV / TLV)*	%	31.7	35.7	32.1	22.2	34.9	19.7	46.3
eFLRF *(= FLRV% x TLF / 100)*	%/min/m²	2.23	2.29	1.42	2.18	2.13	2.07	2.23
Post PVO								
HBS	%/min	13.5	13.9	12.19	10.8	11.47	17.76	10.64
TLF *(= HBS / BSA)*	%/min/m²	7.30	7.43	6.48	6.88	5.62	11.17	4.85
FLRV% *(= 100 x FLRV / TLV)*	%	38.1	54.3	56.2	40.8	41.8	28.1	48.8
eFLRF *(= FLRV% x TLF / 100)*	%/min/m²	2.78	4.04	3.65	2.81	2.35	3.14	2.37

BSA was calculated by the Mosteller formula (BSA² = body weight (kg) x body length (cm) / 3600). The liver function measured by 99mTc-mebrofenin hepatobiliary scintigraphy (HBS), was divided by the body surface area (BSA) and expressed as total liver function (TLF). The future remnant liver volume ratio (FLRV%) was calculated by dividing the future liver remnant volume (FLRV) by the total functional liver volume (TLV). It was expressed as % (FLRV% = FLRV x 100 / TLV). eFLRF was calculated by multiplying the future liver remnant volume ratio by the total liver function (eFLRF = FLRV % x TLF / 100). All calculations were performed prior to portal vein occlusion (PVO) and 4 to 6 weeks after PVO. All patients had eFLRF < 2.3%/min/m² before and > 2.3%/min/m² after PVO. In this formula, the lower the TLF, the bigger the FLRV% should be in order to avoid eFLRF < 2.3%/min/m². For example in patient 6, high HBS and low BSA resulted in a high TLF with a safe eFLRF-value of 3.14 after PVO, even with a low FLRV% of 28%. At the contrary in patient 7 with high body weight and liver steatosis, TLF is low due to lowered HBS and elavated BSA, resulting in a low eFLRF of 2.23%/min/m² despite a FLRV% of > 40% before PVO.

In Table 5.3, data from the interventional study is compared with data from the observational study. No significant differences in patient characteristics, indications for liver resection, underlying liver disease, number of segments resected or intraoperative blood loss were recorded between the cohorts. Preoperative PVO, PHLF and mortality were significantly different between the cohorts.

Figure 5.2 summarizes the recovery of postoperative liver function (immediate post-resection estimated residual function) in the interventional and observational studies, as subdivided into 4 groups according to the eFLRF cutoff > or < 2.3%/min/m². Full recovery to the preoperative TLF at 14 days after hepatectomy was seen in groups 1 & 3. In group 2 (with initial

Table 5.3. *Data of the interventional study cohort compared with the observational study cohort. Eligibility for hepatectomy was assessed in the interventional study by the estimated future liver remnant function (eFLRF) with cut-off at 2.3 %/min/m². Below this value, portal vein occlusion was performed. Eligibility for hepatectomy was assessed in the observational study by the future liver remnant volume ratio (FLRV%) with cut-off at 25%. Below this value, hepatectomy was not performed. Incidence of post hepatectomy liver failure (PHLF) and PHLF related mortality was significantly higher in the observational study than in the interventional study.*

	Units	**Interventional study (n= 100)**	**Observational study (n= 88)**	**P-value**
Eligibility for hepatectomy		**eFLRF > 2.3%/min/m²**	**FLRV% > 25%**	
Gender ratio	M / F	58 / 42	52 / 36	0.880
Age	years	61 (± 13)	62 (± 11)	0.858
BMI	kg/m²	25.6 (± 4.2)	25.6 (± 4.0)	0.537
ASA	Grade	2.3 (± 0.6)	2.18 (± 0.6)	0.097
Indication liver resection				0.387
Benign liver tumor		7 (7%)	10 (11.4%)	
Colorectal liver metastasis		75 (75%)	48 (54.5%)	
Non-colorectal liver metastasis		5 (5%)	8 (9.1%)	
Intrahepatic cholangiocarcinoma		6 (6%)	5 (5.9%)	
Perihilar cholangiocarcinoma		1 (1%)	5 (5.9%)	
Hepatocellular carcinoma		6 (6%)	12 (13.6%)	
Preoperative chemotherapy		54 (54%)	46 (52%)	0.884
Cirrhosis		6 (6%)	9 (10%)	0.419
Portal vein occlusion		7 (7%)	0	0.007
Segments resected	n	2 (0 - 5)	2 (0 - 6)	0.207
Intraoperative blood loss	mL	500 (0 - 8500)	550 (0 - 6000)	0.140
PHLF Grade B/C	n	1 (1%)	12 (13.6%)	0.001
PHLF related mortality	n	0	5 (5.7%)	0.016

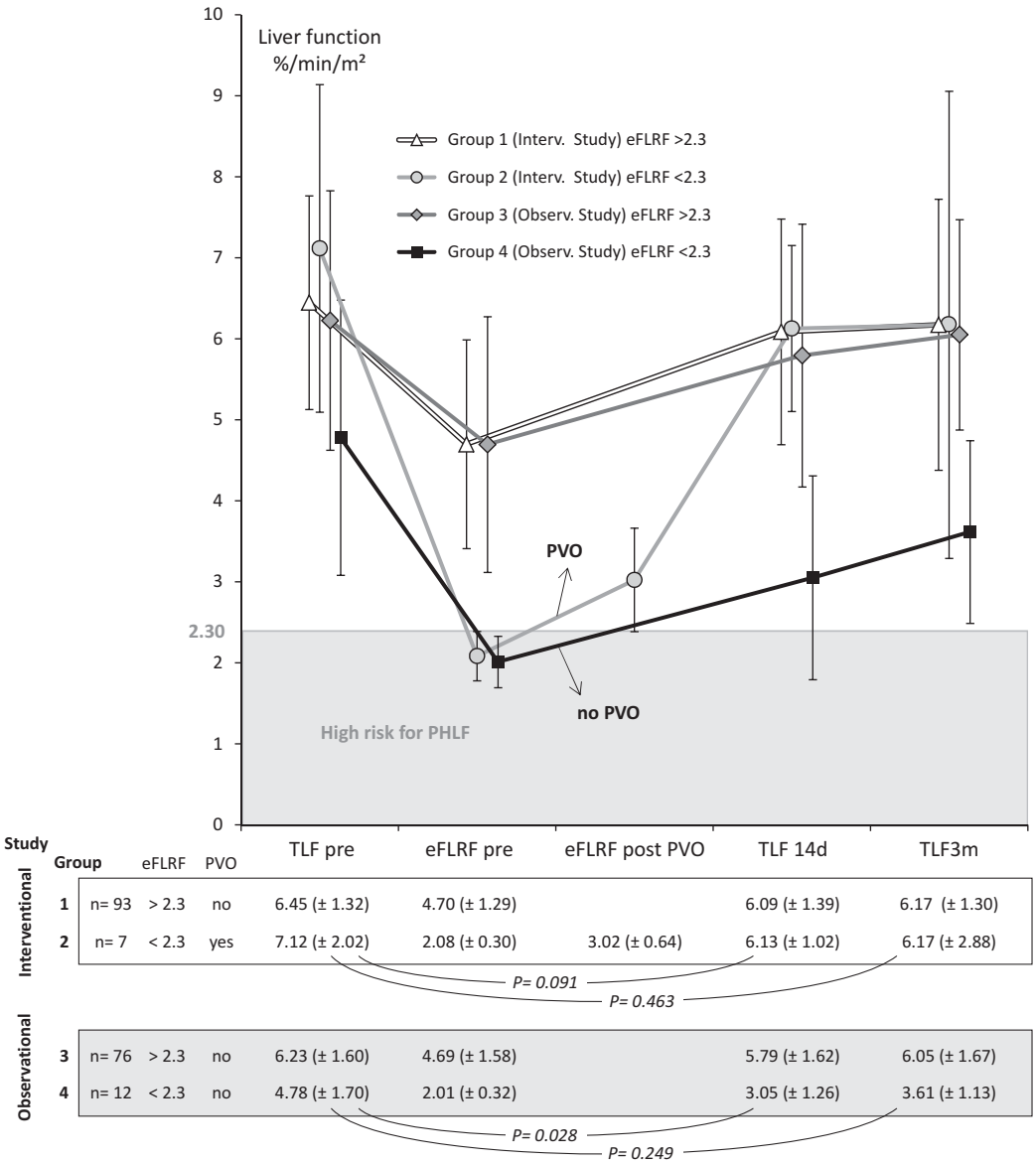

Figure 5.2. *Recovery of liver function after hepatectomy: impact of portal vein occlusion (PVO) in patients with eFLRF < 2.3%/min/m². In all groups, liver function was evaluated by 99mTc-mebrofenin hepatobiliary scintigraphy and future liver remnant function (eFLRF) was estimated preoperatively. In group 2, eFLRF was re-evaluated at 4 to 6 weeks after PVO (eFLRF post PVO). Postoperative liver function was re-evaluated at 14 days and 3 months (TLF 14d & TLF 3m). Liver function at 14 days was lower in patients with eFLRF < 2.3%/min/m² and without PVO (group 4).*

FLRF < 2.3%/min/m² and subsequent preoperative PVO), a full recovery of TLF was also observed at 14 days, similar to the graphics of groups 1 & 3 (TLF pre vs. TLF 14d; P = 0.091). On the contrary, in group 4 (initial eFLRF <2.3%/min/m² but no preoperative PVO), recovery of TLF at 2 weeks post hepatectomy was seen only very slowly (TLF pre vs. TLF 14d; P = 0.028). At 3 months, a tendency towards a slower recovery of liver function could be suggested by the graphics but was not statistically significant (TLF pre vs. TLF 3m; P = 0.249).

Discussion

This interventional study investigated the benefit of eFLRF as a preoperative tool for preventing grade B or C PHLF and PHLF-related mortality. PHLF could be avoided by using a eFLRF cutoff value of < 2.3%/min/m² to select patients for preoperative PVO, with secondary hepatectomy being performed if eFLRF increased above this threshold at 4-6 weeks.

The added value of eFLRF

Calculation of eFLRF was performed by multiplication of the FLRV%, measured by liver volumetry on MRI, with the TLF, measured by ^{99m}Tc-mebrofenin HBS and corrected for BSA. With this formula, it can be assumed that the lower the preoperative liver function on HBS and/or the higher the BSA, the bigger the FLRV% should be in order to avoid PHLF. In Table 5.2, the potential impact of HBS, BSA and FLRV% on eFLRF are exemplified. In a previous observational study our group demonstrated eFLRF to be a better predictor for PHLF than FLRV%. PHLF was observed in almost all cases when preoperative eFLRF lay below the cutoff value of 2.3%/min/m², whereas almost no PHLF was seen above this threshold. The cut-off value for eFLRF at 2.3%/min/m² was defined by receiver-operating-characteristic (ROC) analysis. (5). This value was the premise to perform this prospective study in 100 patients. A slightly different cut-off of 2.69%/min/m² calculated by ROC analysis was found by De Graaf et al. (8). They concluded that preoperative ^{99m}Tc-mebrofenin HBS was more accurate than CT volumetry in predicting PHLF: the cutoff value of 2.69%/min/m² was proposed for both compromised and non-compromised liver parenchyma. De Graaf estimated the eFLRF by delineating ‘regions of interest’ on scintigraphic imaging without using exact volumetry. In our current study, exact volumetry (measured in mL) was performed using MRI scanning. All areas

to be resected were manually delineated on cross-sectional MRI images and added to give a composite measurement of liver volumes. This exact volumetry was included in the calculation of eFLRF (5). The different methodology for volumetric measurements between the current study and the De Graaf analysis can explain the differences between both cut-off values.

As there is now a trend in liver metastasis surgery towards multiple, non-anatomical resections (which cumulatively can result in large volumes of resected liver parenchyma with the attendant risk of PHLF), the authors believe that the approach described here allows for a more precise assessment of the liver remnant when compared to studying 'regions of interest'.

Including measurement of TLF, as well as liver volumetry, before performing liver resection is of particular importance in compromised liver parenchyma. In cirrhosis, the Child-Pugh score classification reflects the liver function: most centers will perform liver resection only in Child-Pugh A, because liver resection surgery is not considered to be safe in Child-Pugh B or C (9). A cutoff of 11 points on the Model for End Stage Liver disease (MELD) score has been shown to be predictive for PHLF when performing liver resections in cirrhosis (10). Makuuchi reported a decision tree based on ascites, serum bilirubin and indocyanine green retention test ($ICGR_{15}$) to assess how much liver parenchyma can be resected safely (11). Our study combines remnant volume and pre-resection function and could therefore be a more refined instrument to assess eFLRF.

Different types of CALI such as chemotherapy associated steatohepatitis, sinusoidal obstructive syndrome and nodular regenerative hyperplasia can compromise liver function and be a risk factor for PHLF in extensive liver parenchymal resections. The presence of chemotherapy associated steatohepatitis is an independent prognostic factor for morbidity and mortality after hepatectomy, whereas sinusoidal obstructive syndrome clearly has an impact on postoperative morbidity and the need for blood transfusion (1). Recently, it has also been reported that PHLF occurs more frequently in nodular regenerative hyperplasia (12). Diagnosis of CALI is based on pathological examination of the resected liver specimen and is hence not available preoperatively, unless a liver biopsy is performed. For this reason, pathological examination is less suitable for preoperative risk assessment of PHLF. In patients treated preoperatively with potentially hepatotoxic chemotherapy (mainly for colorectal liver disease), the risk of reduced liver function post-hepatectomy is not commonly assessed. Globally, Indocyanine Green Retention Test at 15 min ($ICGR_{15}$) is the most widely used functional test in preoperative estimation of liver function (13). Recently, $ICGR_{15}$ has been tested before liver surgery for colorectal liver

metastasis: more complications and liver dysfunction were seen in relation to higher preoperative $ICGR_{15}$ and following a greater number of chemotherapy cycles (14). $ICGR_{15}$ and ^{99m}Tc-mebrofenin HBS have been demonstrated to correlate well (15). Aspartate Aminotransferase to Platelet Ratio Index (APRI) has been recently described as a preoperative liver function assessment. In a multivariate analysis, a low APRI-score was shown to be predictive for PHLF and for the presence of CALI (16). Nevertheless, no quantitative approach determining the safe volume of liver remnant following hepatic resection in the presence of CALI has ever been described. For all of these reasons, we previously developed an approach combining volumetric and functional parameters and were able to identify an eFLRF value of < 2.3%/min/m² as predictive for PHLF.

Main outcome and historical comparison group

The current study was designed to prospectively assess the value of eFLRF as a tool to prevent PHLF. As PVO is an established method of augmenting FRLV%, it was deemed unethical to randomize patients with eFLRF < 2.3%/min/m² to two study groups – with and without PVO. For this reason, data from our previous observational study was included for historical comparison. In the observational study (Table 5.2), patient characteristics, indications for liver surgery, use of preoperative chemotherapy and incidence of cirrhosis were not significantly different from the current interventional study. A significantly higher incidence of PHLF (13.6% vs 1%, P= 0.001) and PHLF-related mortality (5.7% vs 0%, P= 0.016) was observed in the historical group using only a volumetric-based approach (FLRV%). The current study illustrates that eFLRF determines eligibility for hepatectomy, with or without preoperative PVO, and can be used to avoid PHLF and PHLF-related mortality – especially in potentially compromised livers. Of note, it was foreseen in the protocol that patients with eFRLF < 2.3%/min/m² and who remained below this threshold following PVO, were to be denied hepatectomy. However, in all patients eFLRF increased above this threshold. It is also noteworthy that the mean eFLRF was only slightly above 2.3%/min/m² following PVO. Nevertheless, no PHLF occurred, again underscoring the clinical relevance of the previously defined threshold.

Portal vein occlusion

PVO can be performed either by PVE or by PVL. It is a well-tolerated and commonly used technique for preoperatively increasing the future liver

remnant volume. In a recent meta-analysis, single PVL and PVE resulted in comparable percentage increases in future liver remnant, with similar morbidity and mortality rates (17). PVE can be performed with technical success in 98.9 % of patients. Failure of hypertrophy of the future liver remnant, precluding resection, has been seen in 4.8% for PVE and in 7.4% in PVL (18). In our study, 5 patients underwent PVE and 2 patients received PVL with simultaneous injection of ethanol 96% 10mL. PVL was considered easy to perform at the time of the first hepatectomy when two stage hepatectomy was indicated. In all cases, a sufficient response to PVO was observed according to our pre-defined eFLRF-based criterion.

In a recent literature review, the mean complication rate after PVE was 1.2 % (18). Postembolization syndrome with fever and thrombocytopenia, is a major complication. Other complications include necrosis, bile leak, bleeding at the puncture site and abscess formation (19). Migration of coils in portal branches not intended to be embolized has also been described. Morbidity after PVL is 5.7 % (18). In our study, no complications related to PVO were recorded. Tumor progression at the time of the resection has also been described in several studies (20). In our study, tumor progression after PVO, precluding further liver surgery, did not occur.

For all of these reasons, a non-objective approach to PVO in cases at risk of developing PHLF, should be discouraged. A liberal policy of performing preoperative PVO would lead to unnecessary PVO's being carried out. Apart from complications, an unnecessary delay of surgery and the risks of tumor progression, the repercussions on the public health budget also need to be considered.

Selection criteria for PVO are hence of obvious clinical relevance. Currently, no clear guidelines have been defined as to when this should be performed. Volumetric as well as liver function assessments can be used separately, or in combination, to determine the indication for PVO. FLRV% is frequently measured and used as a means of establishing the necessity for PVO. The standardized future liver remnant is a currently used definition based on the ratio of FLRV, as measured on CT and the TLV corrected for BSA (21). Ribero et al found that a standardized future liver remnant of 20% is the absolute minimum in patients without coexisting liver disease. This threshold value increases to 30% in the case of CALI and to 40% for cirrhotic livers (22). If FLRV% lies below these threshold values, PVO is recommended. Although this approach offers clarity, there is a risk of oversimplification, as liver function is not taken into account. There is hence a risk of performing unnecessary PVO in patients with clinically unimportant CALI. On the other hand, PVO may not be performed on patients in whom

CALI is seriously underestimated, or in whom a standardized future liver remnant only slightly exceeds 30%. Moreover, differences of more than 5% were found between the standardized future liver remnant - corrected for BSA - and the FLRV% - measured on imaging - in almost one-third of patients (23). For this reason, standardized future liver remnant cannot be recommended for general use. Furthermore, the volumetric thresholds that should be used in relation to different grades of liver damage have not yet been defined.

In the current study, the gradual approach by liver volume delineation on imaging allows a more precise approach towards FLRV% and consequently towards eFLRF. Using eFLRF as the sole indication for PVO, we were able to avoid all but one grade B PHLF and to completely exclude PHLF-related mortality although the small sample size does not allow to unequivocally exclude any risk of PHLF related mortality. These results were obtained in a patient cohort characterized by individual differences in the number of hepatic segments resected as well as the type of underlying liver disease (Table 5.1). The only patient with a grade B PHLF occurred in the group with eFLRF > 2.3%/min/m². This patient, who therefore underwent hepatectomy without pre-operative PVO, had a cirrhosis with documented portal hypertension. The correct choice regarding the need for preoperative PVO was made in 99/100 patients.

Faster recovery of liver function after PVO

Performing PVO has proven to be beneficial in avoiding PHLF and related mortality (24). The clinical advantage of preoperative PVO is also seen in the more rapid recovery of liver function following hepatectomy in these patients. In a recent study, the serum bilirubin level on postoperative day 3 was 40% lower in PVO pretreated patients when comparing equivalent liver volumes. This suggests that the immediate post-operative hepatic function appears to be better in livers prepared by this treatment (25). It seems that post-PVO upregulated liver regeneration activity has a sustained effect after resection. This was confirmed by our study (Figure 5.2): patients pretreated by PVO showed normalization of their liver function to preoperative values 2 weeks after hepatectomy. At the contrary, in our former observational study of a similar patient cohort that did not receive preoperative PVO, liver function at 2 weeks remained largely below preoperative levels, which explains the higher incidence of PHLF.

Conclusion

In summary, eFLRF can be measured by MRI volumetry combined with ^{99m}Tc-mebrofenin HBS assessment of liver function. A predefined cutoff of 2.3%/min/m² can be used in a stepwise protocol to assess eligibility for hepatectomy and determine the need for preoperative PVO. With this formula, it can be assumed that the lower the preoperative TLF, the bigger the FLRV should be in order to avoid PHLF. The authors suggest the use of the formula prior to all major hepatectomies regardless of the underlying liver condition but also in minor hepatectomies when impaired liver function can be suspected because of steatosis, chemotherapy induced liver injury, fibrosis, or cirrhosis. Although we must acknowledge that the small sample size does not allow enough statistical power to unequivocally exclude any PHLF risk, this protocol successfully avoids PHLF and PHLF-related mortality regardless of underlying liver disease. In patients with impaired liver function, this strategy also results in a faster recovery of postoperative liver function. We have now implemented use of this formula in our current daily practice.

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