99mTc-mebrofenin hepatobiliary scintigraphy and volume metrics before liver preparation: correlations and discrepancies in non-cirrhotic patients

Boris Guiu, Emmanuel Deshayes, Fabrizio Panaro, Florian Sanglier, Caterina Cusumano, Astrid Herrerro, Olivia Sgarbura, Nicolas Molinari, François Quenet, Christophe Cassinotto

Original Article

^{99m}Tc-mebrofenin hepatobiliary scintigraphy and volume metrics before liver preparation: correlations and discrepancies in non-cirrhotic patients

Boris Guiu[1#], Emmanuel Deshayes[2#], Fabrizio Panaro[3], Florian Sanglier[4], Caterina Cusumano[5], Astrid Herrerro[3], Olivia Sgarbura[5], Nicolas Molinari[6], François Quenet[5], Christophe Cassinotto[1]

[1]Department of Radiology, St-Eloi University Hospital, Montpellier, France; [2]Department of Nuclear Medicine, Institut du Cancer de Montpellier (ICM), Montpellier, France; [3]Department of Surgery, St-Eloi University Hospital, Montpellier, France; [4]Department of Radiology, Limoges University Hospital, Limogesr, France; [5]Department of Surgery, Institut du Cancer de Montpellier (ICM), Montpellier, France; [6]IDESP, INSERM, Montpellier Univesity Hospital, Montpellier, France

Contributions: (I) Conception and design: B Guiu, E Deshayes; (II) Administrative support: B Guiu, E Deshayes; (III) Provision of study materials or patients: B Guiu, E Deshayes, F Panaro, C Cusumano, A Herrerro, O Sgarbura, N Molinari, F Quenet, C Cassinotto; (IV) Collection and assembly of data: B Guiu, F Sanglier, E Deshayes; (V) Data analysis and interpretation: B Guiu, E Deshayes, F Quenet, F Panaro, C Cusumano; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Prof. Boris Guiu, MD, PhD. St-Eloi University Hospital, Department of Radiology (Head), 80 Avenue Augustin Fliche, 34295 Montpellier, France. Email: B-guiu@chu-montpellier.fr.

Background: Accurate identification of insufficient future liver remnant (FLR) is required to select patients for liver preparation and limit the risk of post-hepatectomy liver failure (PHLF). The objective of this study was to investigate the correlations and discrepancies between the most-commonly used FLR volume metrics and ^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS).

Methods: In 101 non-cirrhotic patients who underwent HBS before major hepatectomy, we retrospectively analyzed the correlations and discrepancies between FLR function and FLR volume metrics: actual percentage (FLRV%), standardized to body surface area (FLRV%^{BSA}) and weight (FLRV%^{weight}), and FLR to body weight ratio (FLRV-BWR).

Results: Among 67 patients with FLR function ≥2.69%/min/m^2, PHLF was observed in none and 13 patients according to respectively 50-50 and ISGLS criteria. FLRV%, FLRV%^{BSA}, FLRV%^{weight} and FLRV-BWR significantly correlated with FLR function (P<0.001), with Spearman's correlation coefficients of 0.680, 0.704, 0.698, and 0.711, respectively. No difference was observed between the areas under the curve of FLRV%, FLRV%^{BSA}, FLRV%^{weight} and FLR-BWR (all P=ns). Overall, the percentages of patients misclassified by FLRV%, FLRV%^{BSA}, FLRV%^{weight} (thresholds: 30%) and FLR-BWR (threshold: 0.5) versus FLR function (threshold: 2.69%/min/m^2) were 23.8% (95% CI: 15.9–33.3%), 18.8% (95% CI: 11.7–27.8%), 17.8% (95% CI: 11–26.7%), and 31.7% (95% CI: 22.8–41.7%), respectively. FLR volume metrics wrongly classified 1–13.9% of patients with sufficient FLR function (i.e., ≥2.69%/min/m^2), and 9.9–30.7% of patients with insufficient FLR function. FLRV-BWR was the most and the least reliable measure to identify patients with sufficient and insufficient FLR function, respectively.

Conclusions: Despite significant correlations, the discrepancy rates between FLR volume and function metrics speaks in favor of implementing ^{99m}Tc-mebrofenin HBS in the work-up before liver preparation.

Keywords: Hepatectomy; mebrofenin; CT-scan; liver failure

Submitted Nov 09, 2020. Accepted for publication Jan 10, 2021.
doi: 10.21037/atm-20-7372
View this article at: http://dx.doi.org/10.21037/atm-20-7372

Introduction

Liver failure remains the main cause of death after major liver resection (1,2). In recent years, many radiological and surgical advances have been made in liver preparation for surgery (3-7). By inducing hypertrophy of the future liver remnant (FLR), these procedures can reduce the risk of post-hepatectomy liver failure (PHLF), if the patients at risk of hepatic dysfunction have been properly identified at baseline.

The baseline preoperative assessment of the FLR usually relies on computed tomography (CT)-based volumetry to calculate the total liver volume, tumor volume, and FLR volume (8). The FLR volume percentage relative to the total liver size (excluding tumor volume) is the most frequently used metric (9,10), and is referred to as FLRV%. Such ratio can be calculated faster when total liver volume is estimated based on biometric data, rather than being volumetrically determined. Weight, height and body surface area (BSA) have been proposed to estimate the liver volume necessary to meet the metabolic demands, and the ratio of FLR to total liver volume can be standardized according to BSA or body weight (FLRV%^{BSA} and FLRV%^{weight}) (11), or as the FLR volume to body weight ratio (FLRV-BWR) (12). Unlike real volumetric measurements, such approaches do not take into account nonfunctional tumor nodules, dilated bile ducts and occluded vasculature (11).

All these volumetry techniques share the same pitfall: they do not take into account the actual liver functionality. Therefore, the thresholds for identifying patients at risk of PHLF vary widely, from 20% to 40% for FLRV% (actual or standardized), depending on whether the hepatic parenchyma is considered healthy, potentially impaired [steatosis, history of chemotherapy (13,14)], or cirrhotic (15). Similarly, the FLRV-BWR threshold ranges from 0.5% for healthy liver (12) to 1.4% for cirrhotic liver (16). Because histopathological analysis of the liver parenchyma is rarely preoperatively available, many centers use the upper (i.e., 30%) threshold for FLR volume (14,17) in noncirrhotic patients in order to take into account potential liver damage due to the baseline hepatopathy and/or prior systemic therapies.

However, PHLF is not only related to FLR volume but also to many other factors among which several are linked to liver function, such as patient age (18), cholestasis, steatosis, fibrosis, and microvascular damage (19,20). PHLF still occurs in 1–39% of patients despite cautious preoperative volumetric evaluation (21,22). FLR volumetry is supposed to be an indirect measure of FLR function, under the assumption that these metrics are correlated. However, such correlation has never been investigated in an unselected population of patients without cirrhosis, probably because regional function measurement was not routinely available in liver surgery centers.

Recently, hepatobiliary scintigraphy (HBS) with ^{99m}Tc-mebrofenin has emerged as an attractive tool to measure liver function at the regional level, especially in the FLR. By taking into account the volume and also the quality of the underlying parenchyma (23), it has been shown that FLR function (FLR-F) values >2.69%/min/m^2 predict the absence of PHLF with excellent diagnostic performances whatever the liver parenchyma quality (24,25).

Therefore, it is now important to compare the CT-based FLR volumetry techniques with functional FLR evaluation before major hepatectomy. The objective of this study was to investigate in patients without cirrhosis, the correlations and discrepancies between the most-commonly used FLR volume metrics (FLRV%, FLRV%^{BSA}, FLRV%^{weight}, and FLRV-BWR) and ^{99m}Tc-mebrofenin HBS-based FLR-F. We present the following study in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7372).

Methods

This single center retrospective study was performed in accordance with the Declaration of Helsinki (as revised in 2013). Our institutional review board approved the retrospective analysis of their anonymized data (No. ICM-ART2016/02) and waived informed consent.

Patients and study design

According to the policy and standard of care of our hospitals, since 2014 ^{99m}Tc-mebrofenin HBS is systematically performed for the preoperative evaluation before major liver resection. In this study, we retrospectively selected all consecutive patients who underwent ^{99m}Tc-mebrofenin HBS before hepatectomy leaving ≤4 segments (including repeated hepatectomies) between February 2014 and February 2017. Patients with bilirubin level >1.5 times the upper limit of normal (because of competitive uptake of bilirubin and mebrofenin) and/or patients with cirrhosis (biopsy-proven or signs of cirrhosis on preoperative diagnostic imaging) were not included. Blood tests, including prothrombin time, international normalized ratio, creatinine and total bilirubin level, were systematically performed within 1 week before ^{99m}Tc-mebrofenin HBS. For all patients, age, body mass index (BMI, kg/m^2), BSA (m^2) and Model for End-stage Liver Disease (MELD) score were collected and/or calculated at the time of ^{99m}Tc-mebrofenin HBS. For patients who underwent several ^{99m}Tc-mebrofenin HBS exams, for instance before and after portal vein embolization (PVE), only the first scintigraphy performed in the absence of any liver preparation for surgery was used for this study.

Volumetric and functional evaluations

All patients underwent ^{99m}Tc-mebrofenin single-photon emission CT (SPECT)-CT imaging using a hybrid scanner (Discovery NMCT670, GE Healthcare, Milwaukee, USA). After injection of 150 MBq of ^{99m}Tc-mebrofenin (Cholediam, Mediam Pharma, Loos, France), a 6-minute dynamic acquisition was performed to assess the total liver clearance rate (in %/min/m^2) normalized to the BSA. Then, a fast SPECT acquisition was immediately performed as initially described by de Graaf *et al.* (26) with 60 projections (30 per detector) of 8 seconds per projection, view angle of 6°, leading to a total SPECT acquisition of 6 minutes (4 minutes of projections acquisition time +2 minutes of rotation time between angles). Finally, CT images (2.5 mm slice thickness) were acquired at the portal venous phase using the same system. The Volumetrix® software (GE Healthcare, Milwaukee, USA) was used to reconstruct SPECT data using an iterative algorithm to produce attenuation-corrected images. Co-registration between CT and SPECT images was visually and manually checked and corrected when required. On each CT image, the resection margin was jointly planned by the liver surgeon and the nuclear medicine physician. FLR volume and total liver volume (TLV) were automatically calculated by the workstation (OsiriX MD, Pixmeo, Bernex, Switzerland). Tumor volumes were also segmented and subtracted from the TLV and/or FLR, depending on the tumor(s) location(s).

Based on these measurements, the following ratios were calculated:

- FRLV%: the ratio between the FRL and the TLV minus the tumor volume.
- FRLV%^{BSA}: the standardized BSA TLV (^{BSA}TLV) was first calculated using the previously published formula: −794.41+1267.28× BSA (11) with $BSA=\frac{\sqrt{(height\,(cm)\times weight\,(kg))}}{3600}$. Then, FRLV%^{BSA} was defined as FRL/^{BSA}TLV ×100.
- FLRV%^{weight}: the standardized weight TLV (^{weight}TLV) was first calculated using the previously published formula: 191.8+18.51× weight (kg) (11). Then, the standardized FLRV%^{weight} was defined as FRL/^{weight}TLV ×100.
- FLRV-BWR: this ratio was defined as FLR/weight (kg) ×100 (12).

Volumes of interest (VOI) created on CT images were exported to the SPECT attenuation corrected images. The actual ^{99m}Tc-mebrofenin counts in the VOI of FLR and TLV were calculated and the corresponding regional functions were defined as [(total counts in the region of interest VOI/total counts in total liver VOI) × total liver clearance rate] and expressed as %/min/m^2.

Surgery & post-operative outcome

Over the study period, the decision to resect was based on FLR function (>2.69%/min/m^2). Intraoperative ultrasound was systematically performed. Homolateral hepatic artery and portal vein were systematically ligated before the parenchymal transection with an anterior approach. Pringle manoeuvre with intermittent clamping and homolateral hepatic vein control were performed if necessary. The parenchymal phase was done by the aide of CUSA or harmonic scalpel and bipolar forceps.

Liver blood tests were performed the day before and each day after liver resection until the patient's discharge. PHLF occurrence, according to according to the 50-50 (27) and International Study Group of Liver Surgery (ISGLS) criteria (28), as well as grade III to V postoperative complications [according to the Clavien-Dindo classification (29)]. Mortality at day 90 post-surgery was also recorded.

Statistical analysis

The normality of samples was tested using the Shapiro-Wilk test. Categorical data were expressed as numbers (percentages) and compared using the Chi-square test or Fisher's exact test, as appropriate. Quantitative data were expressed as means (± standard deviation) or medians (interquartile range, IQR) and compared using the two-sample *t*-test or the Wilcoxon rank-sum test, according to the data distribution. Data were compared between patients with FLR-F ≥2.69%/min/m^2 ("adequate FLR-F group") and with FLR-F <2.69%/min/m^2 ("insufficient FLR-F group").

Then, the correlations between FLR volume and FLR-F values were assessed using Spearman's correlation

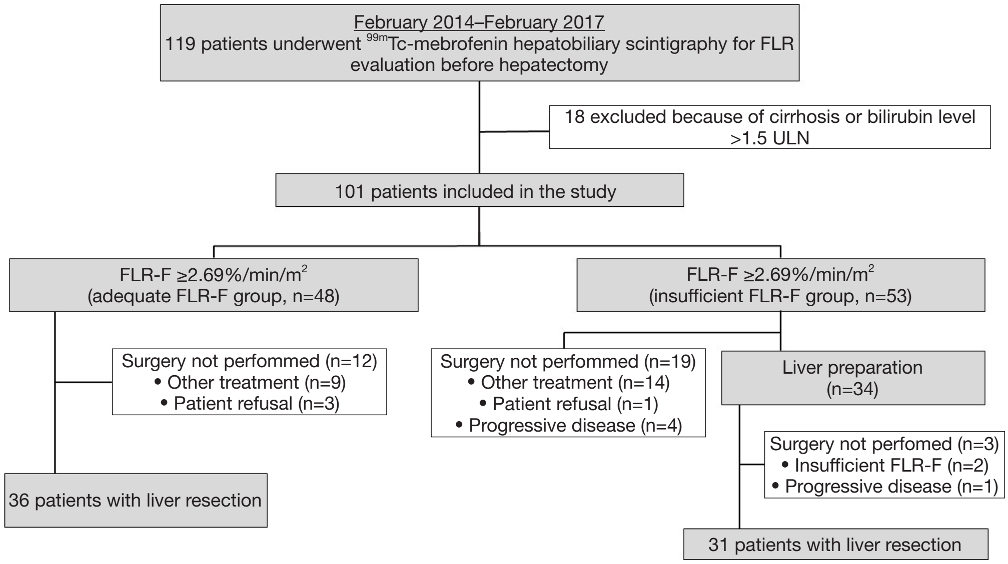

Figure 1 Study flowchart.

coefficients. Receiver operating characteristics curves to predict FLR-F ≥2.69%/min/m^2 were built to estimate the area under the curve (AUC). The R packages cocor and pROC were used to compare correlation coefficients and AUCs, respectively (30).The discriminative abilities (sensitivity, specificity, positive predictive value, and negative predictive value) of FLR volume metrics were estimated using the threshold of 30% for FLRV%, FLRV%^{BSA}, FLRV%^{weight} and of 0.5 for FLRV-BWR.

Finally, the misclassification rates by volumetric and functional metrics were calculated with their 95% confidence intervals (CI) and compared. All statistical analyses were performed using the R (version 3.3.0) programming environment. P values <0.05 were considered significant.

Results

Patients

A total of 101 patients with a median age of 63.9 years (IQR 54–70.2, range, 39–79 years) met the inclusion criteria (*Figure 1*). Tumors were liver metastases from colorectal cancer (64.4% of patients; 65/101), intra-hepatic cholangiocarcinoma (13.9%; 14/101), hepatocellular carcinoma without severe fibrosis or cirrhosis (8.9%; 9/101), and liver metastases from other cancers (12.9%; 13/101). Seventy-four patients (73.3%) underwent at least six cycles of chemotherapy before FLR evaluation. Clinical and laboratory data, liver volumes and function are summarized in *Table 1*. FLR-F was above the threshold of 2.69%/min/m^2 in 48 patients (i.e., 'adequate FLR-F' group) and below 2.69%/min/m^2 in 53 patients (i.e., 'insufficient FLR-F' group). Creatinine level and MELD score were slightly higher in patients with insufficient FLR-F (0.873±0.252 *vs.* 0.777±0.212 mg/dL, P=0.042; and 4.532±1.652 *vs.* 3.865±1.715, P=0.049, respectively). Unlike the raw FLR volume, all FLR volume metrics were significantly higher in the adequate FLR-F group.

Surgery and post-operative outcomes

Finally, 67/101 patients underwent liver resection [leaving 4 segments (n=48), and less than 4 segments (n=19); re-hepatectomy (n=7)]: 36 had upfront surgical resection (FLR-F ≥2.69%/min/m^2) and 31 needed liver preparation (portal and/or hepatic vein embolization) to reach this FLR-F threshold on a second ^{99m}Tc-mebrofenin HBS. None of these 67 patients developed PHLF according to the 50-50 criteria. According to ISGLS criteria, 13 patients developed PHLF, among which PHLF was observed before any complication in 6 patients [grade A (n=5), grade C (n=1)] and was secondary to one/several complication(s) in the 7 others [grade B (n=6), grade C (n=1)]. Grade ≥3 complications according to the Clavien-Dindo classification occurred in 20.9% of patients (14/67): in 8 patients (8/36, 22.2%) after upfront surgery and in 6 patients (6/31, 19.4%)

Table 1 Clinical and biological data, liver volumes and function of the whole study population, and classified in two groups (adequate and insufficient FLR-F) in function of the ^{99m}Tc-mebrofenin HBS threshold value of 2.69%/min/m^2

Variables	Study population (n=101)	FLR-F ≥2.69%/min/m^2 (n=48)	FLR-F <2.69%/min/m^2 (n=53)	P value
Age	63.9 (54–70.2)	59.2 (53.6–69.9)	64.8 (56.2–70.2)	0.489
Male	56 (55.5%)	24 (50%)	32 (60.4%)	0.295
Body mass index (kg/m^2)	25 (±3.9)	24.71 (±4.01)	25,24 (±3.78)	0.494
Body surface area (m^2)	1.84 (±0.23)	1.83 (±0.24)	1.85 (±0.22)	0.638
Prothrombin time (%)	98 [88–100]	97 [87–100]	100 [88–100]	0.543
INR	0.97 (0.96–1.06)	0.98 (0.96–1.07)	0.96 (0.96–1.06)	0.546
Creatinine (mg/dL)	0.827 (±0.238)	0.777 (±0.212)	0.873 (±0.252)	0.042*
Total bilirubin (mg/dL)	0.47 (0.29–0.65)	0.465 (0.265–0.625)	0.470 (0.300–0.700)	0.435
MELD score	4.215 (±1.707)	3.865 (±1.715)	4.532 (±1.652)	0.049*
FLR-F (%/min/m^2)	2.60 (1.90–3.30)	3.50 (3–4.80)	1.90 (1.70–2.30)	<0.001*
FLR volume (mL)	487 (327–698)	554 (359–777)	431 (322–641)	0.136
FLRV% (%)	28.3 (22.5–38.9)	40.9 (28.6–50.1)	24.9 (19.3–28.3)	<0.001*
FLRV%^{BSA} (%)	30.3 (23.5–46.1)	45.9 (32.9–54.2)	24.6 (19.2–28.8)	<0.001*
FLRV%^{weight} (%)	29.90 (23.79–46.20)	45.8 (33–55.7)	24.5 (19.8–29.6)	<0.001*
FLRV-BWR	0.642 (0.505–0.971)	0.968 (0.686–1.194)	0.513 (0.414–0.622)	<0.001*

*, significant P values. The sample normality was tested using the Shapiro-Wilk test. Categorical data were expressed as numbers (percentages), and quantitative data as mean (± standard deviation) or median (interquartile range), according to the data distribution. FLR-F, future liver remnant function; HBS, hepatobiliary scintigraphy; INR, international normalized ratio; MELD, model for end-stage liver disease; FLRV%, future liver remnant volume; FLR, future liver remnant; FLR-F, FLR function.

who had surgery after liver preparation (P=0.77).

The 90-day postoperative mortality rate was 4.5% (3/67). The causes of death were hemorrhagic stroke (n=1), septic and hemorrhagic shock (n=1), and multi-visceral failure (pleural effusion, malnutrition and kidney failure) (n=1).

Relationship between FLR volume and function

The median FLR-F was 2.60 %/min/m^2 (IQR: 1.90–3.30). The median FLRV% FLRV%^{BSA}, FLRV%^{weight}, and FLRV-BWR were 28.3% (IQR: 22.5–38.9), 30.3% (IQR: 23.5–46.1), 29.9% (IQR: 23.8–46.2), and 0.642 (IQR: 0.505–0.971), respectively.

The FLRV%, FLRV%^{BSA}, FLRV%^{weight}, and FLRV-BWR values were significantly correlated with the FLR-F values, with Spearman's correlation coefficients of 0.680 (P<0.001), 0.704 (P<0.001), 0.698 (P<0.001), and 0.711 (P<0.001), respectively (*Figure 2*). No difference was observed among correlation coefficients (all P=ns).

Moreover, the AUC values of FLRV%, FLRV%^{BSA}, FLRV%^{weight}, and FLRV-BWR were comparable (0.85, 0.88, 0.88, 0.88, all P=ns). *Table 2* shows the diagnostic performances of FLRV%, FLRV%^{BSA}, and FLRV%^{weight}, using the threshold of 30%, and of FLRV-BWR with the threshold of 0.5.

Patient misclassification using the FLRV metrics and FLR-F (Figure 2)

Overall, using cut-offs of 30% for FLRV%, FLRV%^{BSA} and FLRV%^{weight}, and of 0.5 for FLRV-BWR, the ratio of misclassified patients (relative to their FLR-F value) was 23.8% (95%CI:15.9-33.3%) for FLRV%, 18.8% (95% CI: 11.7–27.8%) for FLRV%^{BSA}, 17.8% (95% CI: 11–26.7%) for FLRV%^{weight}, and 31.7% (95% CI: 22.8–41.7%) for FLRV-BWR. The number of misclassified patients was significantly higher using FLRV-BWR *vs.* FLRV%^{weight} (P=0.03), whereas the other head-to-head comparisons were not significant (*Figure 3*).

The ratio of patients with insufficient FLR-F (i.e.,

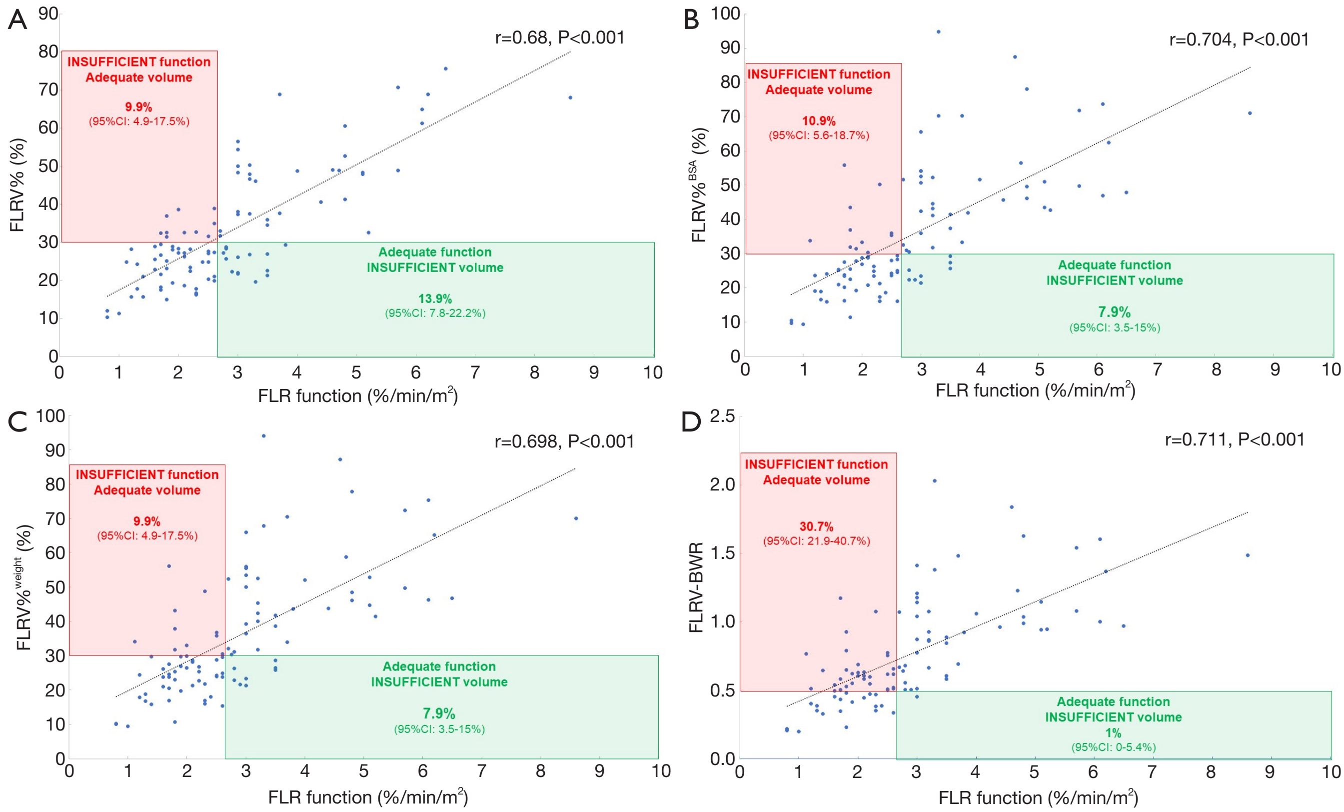

Figure 2 Correlation (Spearman) between FLRV% (A), FLRV%^{BSA} (B), FLRV%^{weight} (C), FLRV-BWR (D) and FLR-F. Red boxes, patients with insufficient FLR-F (<2.69%/min/m^2) despite adequate volume (value ≥30% for FLRV%, FLRV%^{BSA}, FLRV%^{weight}, and ≥0.5 for FLRV-BWR); green boxes, patients with adequate FLR-F and insufficient FLR volume. FLRV%, future liver remnant volume; FLRV-BWR, FLR to body weight ratio; FLR-F, FLR function; BSA, body surface area.

Table 2 Diagnostic performances of FLR volume metrics to predict a FLR-F value ≥2.69%/min/m^2

Variables	FLRV% (threshold: 30%)	FLRV%^{BSA} (threshold: 30%)	FLRV%^{weight} (threshold: 30%)	FLRV-BWR (threshold: 0.5)
AUC (95% CI)	0.85 (0.77–0.92)	0.88 (0.81–0.95)	0.88 (0.81–0.95)	0.88 (0.82–0.95)
Sensitivity (95% CI)	0.71 (0.58–0.84)	0.83 (0.73–0.94)	0.83 (0.73–0.94)	0.98 (0.94–1.01)
Specificity (95% CI)	0.81 (0.71–0.92)	0.79 (0.68–0.90)	0.81 (0.71–0.92)	0.41 (0.28–0.55)
PPV (95% CI)	0.77 (0.65–0.90)	0.78 (0.67–0.90)	0.80 (0.69–0.91)	0.60 (0.49–0.71)
NPV (95% CI)	0.75 (0.64–0.87)	0.84 (0.74–0.94)	0.84 (0.74–0.94)	0.96 (0.87–1.04)
Accuracy (95% CI)	0.76 (0.68–0.85)	0.81 (0.74–0.89)	0.82 (0.75–0.90)	0.68 (0.59–0.77)

FLR, future liver remnant; FLRV%, future liver remnant volume; AUC, area under receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

<2.69%/min/m^2) misclassified by volumetric measurements (i.e., values ≥30% for FLRV%, FLRV%^{BSA} and FLRV%^{weight} and ≥0.5 for FLRV-BWR) were 9.9% (95% CI: 4.9%–17.5%), 10.9% (95% CI: 5.6–18.7%), 9.9% (95% CI: 4.9%–17.5%) and 30.7% (95% CI: 21.9–40.7%), respectively. Patients with insufficient FLR-F were more frequently misclassified by FLRV-BWR than by the other volumetric measurements (*Figure 3*).

The ratio of patients with adequate FLR-F (i.e., ≥2.69%/min/m^2) misclassified by volumetric measurements

	FLRV%	FLRV%^{BSA}	FLRV%^{weight}	FLRV-BWR
FLRV%		7.9% *vs.* 13.9% P=NS	7.9% *vs.* 13.9% P=NS	1% *vs.* 13.9%P=0.001
FLRV%^{BSA}	9.9% *vs.* 10.9% P=NS		7.9% *vs.* 7.9% P=NS	1% *vs.* 7.9% P=0.035
FLRV%^{weight}	9.9% *vs.* 9.9% P=NS	10.9% *vs.* 9.9% P=NS		1% *vs.* 7.9% P=0.035
FLRV-BWR	9.9% *vs.* 30.7% P<0.001	10.9% *vs.* 30.7% P=0.001	9.9% *vs.* 30.7% P<0.001	

Figure 3 Head-to-head comparisons of the misclassification rates using FLRV%, FLRV%^{BSA} FLRV%^{weight} and FLRV-BWR in patients with adequate and insufficient FLR function. The figure highlights the misclassification rate of column *vs.* line. Significant P values are in bold. Green color, adequate FLR function (i.e., ≥2.69%/min/m^2). Red color, insufficient FLR function (i.e., <2.69%/min/m^2). FLRV%, future liver remnant volume.

(i.e., values <30% for FLRV%, FLRV%^{BSA} and FLRV%^{weight} and <0.5 for FLRV-BWR) were 13.9% (95% CI: 7.8–22.2%), 7.9% (95% CI: 3.5–15%), 7.9% (95% CI: 3.5–15%) and 1% (95% CI: 0.03–5.4%), respectively. Patients with adequate FLR-F were less frequently misclassified by FLRV-BWR than by the other volumetric measurements (*Figure 3*).

Discussion

FLR volumetric evaluations have been used for decades for liver resection decision-making, under the assumption that FLR volume is a surrogate of FLR function, although it has never been properly demonstrated. By comparing FLR volume metrics with FLR-F obtained by ^{99m}Tc-mebrofenin HBS in an unselected population of resectable patients without cirrhosis, we found that (I) FLR volume metrics were significantly higher in patients with adequate FLR-F compared with the insufficient FLR-F group; and (II) FLR volume metrics with FLR-F were significantly correlated (Spearman's r between 0.68 and 0.711). To our knowledge, only one study (n=55 patients) investigated the correlation between one FLR volume metric (FLRV%) and FLR-F in resected patients with normal and compromised liver (by histopathology analysis), and reported similar results (r=0.71 and r=0.61, respectively) (24).

^{99m}Tc-mebrofenin HBS is easy to perform, has small interobserver variability, and correlates strongly with postoperative liver function (23,24). Contrary to indocyanine green retention rate which is a global liver functional test (3), ^{99m}Tc-mebrofenin HBS has the ability to quantify liver function at a regional level, and especially in the FLR. PHLF risk in patients with FLR-F above the 2.69%/min/m^2 cut-off (whatever the liver parenchyma quality) is very low (2.4%) (24). We confirmed this finding because none of the 67 patients who underwent surgery developed PHLF according to 50-50 criteria, 5 (7.5%) developed grade A and 1 (1.5%) grade C PHLF according to ISGLS criteria in the absence of prior complication. Post-operative complications remained close to the literature data with a 90-day mortality rate of 4.5% and a major morbidity rate (complication ≥ grade 3a) of 20.8% (21,25,31,32). Interestingly, the different FRL volume metrics showed very similar diagnostic performances to predict sufficient FLR function (AUC of FLRV%, FLRV%^{BSA}, FLRV%^{weight}, and FLR-BWR of 0.85, 0.88, 0.88, 0.88, respectively, all P=ns) and good accuracy (68–82%). Yet, it has been reported that the measured and estimated FLR volumetry substantially (≥5%) differ in ~1/3 patients, thereby affecting clinical decision-making (33). In our series, no significant difference was observed among FLRV%, FLRV%^{BSA}, and FLRV%^{weight}, in terms of correlation and diagnostic performance compared with FLR-F.

FLR volume cut-off values of 20–30% are commonly used as preoperative selection tool before hepatectomy in patients with non-cirrhotic non-cholestatic liver (14,17,19,21,34). The theoretical lower limit (i.e., 20%) for normal liver is usually increased because liver quality is influenced by the baseline hepatopathy or hepatic toxicity caused by systemic treatments. Cirrhosis can be diagnosed using morphological criteria on imaging; conversely, other factors, such as chemotherapy-induced lesions [sinusoidal obstruction syndrome (35), regenerative nodular hyperplasia (36), steatosis, or steatohepatitis (37)], are more difficult to detect despite advances in imaging (38). Chemotherapy-induced lesions increase the risk of post-operative complications (20,39). Liver biopsy is not routinely performed due to unequal distribution of parenchymal damage leading to sampling bias (40) and the risk of complications. Therefore, in most cases, liver quality is only presumed, and therefore many centers tend to use the upper (i.e., 30%) threshold for FLR volume metrics in the pre-operative work-up (14,17,19,21,34,41,42) to limit the risk of PHLF. In a series of 194 patients undergoing right hemi-hepatectomy for colorectal liver metastases, a FLR volume ratio ≤30% independently predicted PHLF (14).

Our study highlighted important differences in FLR volume-function discrepancies in function of the volume metrics. FLRV-BWR values <0.5 strongly predicted insufficient FLR-F, with fewer false negative patients (i.e., insufficient volume, adequate function) than other volumetric measurements (1% *vs.* 7.9–13.9%). Therefore, due to its easy calculation, FLRV-BWR can be used confidently to refer patients for liver preparation when the ratio is <0.5. However, FLRV-BWR also showed the highest number of misclassified patients. Indeed, 30.7% of patients with FLRV-BWR ≥0.5 had insufficient FLR-F. Similarly, Cieslak *et al.* found that 16 of 29 (55%) patients undergoing PVE because of insufficient baseline FLR function had adequate FLRV-BWR (25). Therefore, the FLRV-BWR threshold of 0.5 should probably not be considered sufficient for liver resection decision-making. The high AUC (0.88) indicates that the optimal threshold might be higher than 0.5. The misclassification rate of the other volumetric metrics was lower, but they still led to ~10% (95% CI: 4.9–18.7%) of false-positive patients (i.e., adequate volume, insufficient function). Rassam *et al.* (43) reported that 20/85 patients had FLR function <2.7%/min/m^2 despite FLRV% >30%, even though they included patients with perihilar cholangiocarcinoma (n=20) or cirrhotic liver (n=3), contrary to our study. In a series of 22 resected patients with histologically-proven normal liver, 7/22 (32%) had adequate FLR volume but insufficient FLR function (10). Such discrepancies between volume and functional evaluations could at least partly explain the PHLF incidence rates of 1–39% reported after liver resection in non-cirrhotic patients (21,22,32), even in expert centers (44), where the decision to resect was based on the established FLR volume cut-offs. ^{99m}Tc-mebrofenin HBS as a pre-operative tool can thus potentially extend the number of patients candidate for safe resection.

When considering discrepancies between volume and function evaluations, it is also important to note that 7.9–13.9% of patients were considered as having insufficient FLR using FRLV%, FLRV%^{BSA}, and FLRV%^{weight}, whereas FLR-F was adequate. This misclassification can be regarded as less problematic, but may lead to unnecessary liver preparation, or even contraindication to surgery with a switch to palliative care. Despite the low risk of complications following PVE (45), performing PVE in patients with FLR volume above the thresholds is unnecessary (46,47), particularly if FLR-F is adequate. All these results strongly support adopting ^{99m}Tc-mebrofenin HBS as a routine exam to select patients for safe liver resection.

Several limitations to this work must be acknowledged. First, this study was retrospective. Second, our policy to resect patients with FLR function ≥2.69%/min/m^2, as proposed by de Graaf *et al.* (24), prevented investigating PHLF incidence in patients who underwent resection with insufficient FLR-F. However, Cieslak *et al.* showed a significant decrease in PHLF and PHLF-related mortality by implementing ^{99m}Tc-mebrofenin HBS in the preoperative work-up (25). In addition, PHLF was not the endpoint of our study, but the comparison of FLR volume and function evaluations. Third, function and volume metrics could not be compared in terms of PHLF incidence given the design of the study and our policy to resect only those patients with adequate FLR function. Forth, we selected 30% as the safe threshold for FLR volume metrics [except for FLRV-BWR, for which we used the published cutoff of 0.5 (12)], whereas some centers may use 25% or 40% for patients without cirrhosis. Although the optimal threshold is still debated in this population (21), changing the cutoff value would still result in substantial discrepancies between FLR volume metrics and FLR-F, as easily visualized in *Figure 2*. Fifth, correlations and discrepancies between volume and function metrics after liver preparation were considered out of the scope of this study, mainly because dynamic evaluations such as the kinetic growth rate are usually preferred in this setting.

In conclusion, the commonly used FLR volume metrics correlated well with FLR-F determined by ^{99m}Tc-mebrofenin HBS. However, volume metrics wrongly classified 10–30.7% of patients with adequate FLR-F, and 1–13.9% of patients with insufficient FLR-F. The observed substantial discrepancy rates between FLR volume and function assessments, whatever the volume metrics, speaks in favor of implementing ^{99m}Tc-mebrofenin HBS in the preoperative work-up before major hepatectomy in patients without cirrhosis.

Acknowledgments

The authors thank Elisabetta Andermarcher for revising

the English.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-7372

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-7372

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (http://dx.doi.org/10.21037/atm-20-7372). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This single center retrospective study was performed in accordance with the Declaration of Helsinki (as was revised in 2013). Our institutional review board approved the retrospective analysis of their anonymized data (No. ICM-ART2016/02) and waived informed consent.

References

1. Mullen JT, Ribero D, Reddy SK, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007;204:854-62; discussion 862-4.
2. van den Broek MA, Olde Damink SW, Dejong CH, et al. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. Liver Int 2008;28:767-80.
3. Madoff DC, Odisio BC, Schadde E, et al. Improving the Safety of Major Resection for Hepatobiliary Malignancy: Portal Vein Embolization and Recent Innovations in Liver Regeneration Strategies. Curr Oncol Rep 2020;22:59.
4. Guiu B, Quenet F, Escal L, et al. Extended liver venous deprivation before major hepatectomy induces marked and very rapid increase in future liver remnant function. Eur Radiol 2017;27:3343-52.
5. Memeo R, Conticchio M, Deshayes E, et al. Optimization of the future remnant liver: review of the current strategies in Europe. HepatoBiliary Surg Nutr 2020. doi: 10.21037/hbsn-20-394.
6. Guiu B, Quenet F, Panaro F, et al. Liver venous deprivation versus portal vein embolization before major hepatectomy: future liver remnant volumetric and functional changes. HepatoBiliary Surg Nutr 2020;9:564-76.
7. Panaro F, Giannone F, Riviere B, et al. Perioperative impact of liver venous deprivation compared with portal venous embolization in patients undergoing right hepatectomy: preliminary results from the pioneer center. Hepatobiliary Surg Nutr 2019;8:329-37.
8. Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointest Surg 2003;7:325-30.
9. Olthof PB, van Dam R, Jovine E, et al. Accuracy of estimated total liver volume formulas before liver resection. Surgery 2019;166:247-53.
10. Schindl MJ, Redhead DN, Fearon KC, et al. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut 2005;54:289-96.
11. Vauthey JN, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in Western adults. Liver Transpl 2002;8:233-40.
12. Truant S, Oberlin O, Sergent G, et al. Remnant liver volume to body weight ratio > or =0.5%: A new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. J Am Coll Surg 2007;204:22-33.
13. Asencio JM, Vaquero J, Olmedilla L, et al. "Small-for-flow" syndrome: shifting the "size" paradigm. Med Hypotheses 2013;80:573-7.
14. Shindoh J, Tzeng CW, Aloia TA, et al. Optimal future liver remnant in patients treated with extensive preoperative chemotherapy for colorectal liver metastases. Ann Surg Oncol 2013;20:2493-500.
15. Vauthey JN, Dixon E, Abdalla EK, et al. Pretreatment assessment of hepatocellular carcinoma: expert consensus statement. HPB (Oxford) 2010;12:289-99.

16. Lin XJ, Yang J, Chen XB, et al. The critical value of remnant liver volume-to-body weight ratio to estimate posthepatectomy liver failure in cirrhotic patients. J Surg Res 2014;188:489-95.
17. Chapelle T, Op De Beeck B, Huyghe I, et al. Future remnant liver function estimated by combining liver volumetry on magnetic resonance imaging with total liver function on (99m)Tc-mebrofenin hepatobiliary scintigraphy: can this tool predict post-hepatectomy liver failure? HPB (Oxford) 2016;18:494-503.
18. Cieslak KP, Baur O, Verheij J, et al. Liver function declines with increased age. HPB (Oxford) 2016;18:691-6.
19. Guglielmi A, Ruzzenente A, Conci S, et al. How much remnant is enough in liver resection? Dig Surg 2012;29:6-17.
20. Truant S, Baillet C, Gnemmi V, et al. The Impact of Modern Chemotherapy and Chemotherapy-Associated Liver Injuries (CALI) on Liver Function: Value of 99mTc-Labelled-Mebrofenin SPECT-Hepatobiliary Scintigraphy. Ann Surg Oncol 2021;28:1959-69.
21. Narita M, Oussoultzoglou E, Bachellier P, et al. Post-hepatectomy liver failure in patients with colorectal liver metastases. Surg Today 2015;45:1218-26.
22. Joechle K, Goumard C, Vega EA, et al. Long-term survival after post-hepatectomy liver failure for colorectal liver metastases. HPB (Oxford) 2019;21:361-9.
23. Dinant S, de Graaf W, Verwer BJ, et al. Risk assessment of posthepatectomy liver failure using hepatobiliary scintigraphy and CT volumetry. J Nucl Med 2007;48:685-92.
24. de Graaf W, van Lienden KP, Dinant S, et al. Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. J Gastrointest Surg 2010;14:369-78.
25. Cieslak KP, Bennink RJ, de Graaf W, et al. Measurement of liver function using hepatobiliary scintigraphy improves risk assessment in patients undergoing major liver resection. HPB (Oxford) 2016;18:773-80.
26. de Graaf W, van Lienden KP, van Gulik TM, et al. (99m)Tc-mebrofenin hepatobiliary scintigraphy with SPECT for the assessment of hepatic function and liver functional volume before partial hepatectomy. J Nucl Med 2010;51:229-36.
27. Balzan S, Belghiti J, Farges O, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg 2005;242:824-8, discussion 828-9.
28. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713-24.
29. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
30. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.
31. Shindoh J, Truty MJ, Aloia TA, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. J Am Coll Surg 2013;216:201-9.
32. Viganò L, Torzilli G, Aldrighetti L, et al. Stratification of Major Hepatectomies According to Their Outcome: Analysis of 2212 Consecutive Open Resections in Patients Without Cirrhosis. Ann Surg 2020;272:827-33.
33. Martel G, Cieslak KP, Huang R, et al. Comparison of techniques for volumetric analysis of the future liver remnant: implications for major hepatic resections. HPB (Oxford) 2015;17:1051-7.
34. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-422.
35. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15:460-6.
36. Wicherts DA, de Haas RJ, Sebagh M, et al. Regenerative nodular hyperplasia of the liver related to chemotherapy: impact on outcome of liver surgery for colorectal metastases. Ann Surg Oncol 2011;18:659-69.
37. Robinson SM, Wilson CH, Burt AD, et al. Chemotherapy-associated liver injury in patients with colorectal liver metastases: a systematic review and meta-analysis. Ann Surg Oncol 2012;19:4287-99.
38. O'Rourke TR, Welsh FK, Tekkis PP, et al. Accuracy of liver-specific magnetic resonance imaging as a predictor of chemotherapy-associated hepatic cellular injury prior to liver resection. Eur J Surg Oncol 2009;35:1085-91.
39. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006;243:1-7.
40. Viganò L, Ravarino N, Ferrero A, et al. Prospective

evaluation of accuracy of liver biopsy findings in the identification of chemotherapy-associated liver injuries. Arch Surg 2012;147:1085-91.
41. Abdalla EK. Portal vein embolization (prior to major hepatectomy) effects on regeneration, resectability, and outcome. J Surg Oncol 2010;102:960-7.
42. Torzilli G, Adam R, Viganò L, et al. Surgery of Colorectal Liver Metastases: Pushing the Limits. Liver Cancer 2016;6:80-9.
43. Rassam F, Olthof PB, van Lienden KP, et al. Functional and volumetric assessment of liver segments after portal vein embolization: Differences in hypertrophy response. Surgery 2019;165:686-95.
44. Vibert E, Pittau G, Gelli M, et al. Actual incidence and long-term consequences of posthepatectomy liver failure after hepatectomy for colorectal liver metastases. Surgery 2014;155:94-105.
45. van Lienden KP, van den Esschert JW, de Graaf W, et al. Portal vein embolization before liver resection: a systematic review. Cardiovasc Intervent Radiol 2013;36:25-34.
46. Denys AL, De Baere T, Doenz F. Portal vein embolization: a plea for strict patient selection. AJR Am J Roentgenol 2006;187:W125; author reply 6.
47. Nagino M, Nimura Y, Kamiya J, et al. Right or left trisegment portal vein embolization before hepatic trisegmentectomy for hilar bile duct carcinoma. Surgery 1995;117:677-81.

Cite this article as: Guiu B, Deshayes E, Panaro F, Sanglier F, Cusumano C, Herrerro A, Sgarbura O, Molinari N, Quenet F, Cassinotto C. ^{99m}Tc-mebrofenin hepatobiliary scintigraphy and volume metrics before liver preparation: correlations and discrepancies in non-cirrhotic patients. Ann Transl Med 2021;9(9):795. doi: 10.21037/atm-20-7372