Prevention of post-hepatectomy liver failure after major resection of colorectal liver metastases: is hepato-biliary scintigraphy the optimal tool?

Caterina Cusumano[1#], Emmanuel Deshayes[2#], Boris Guiu[3], Guillaume De Meeus[4], Sébastien Carrère[4], Alix Bouillin[4], Diana Ilonca[2], Marie Claude Éberlé[2], Sophie Guillemard[2], Cyril Fersing[2,5], Olivia Sgarbura[4,6], François Quénet[4]

[1]Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, Strasbourg University Hospital of Strasbourg, Strasbourg, France; [2]Nuclear Medicine Department, Regional Cancer Institute of Montpellier (ICM), Montpellier University, Montpellier, France; [3]Department of Radiology, St-Eloi University Hospital, Montpellier, France; [4]Surgical Oncology Department, Regional Cancer Institute of Montpellier (ICM), Montpellier University, Montpellier, France; [5]Institute for Biomolecules Max Mousseron (IBMM), University of Montpellier, CNRS, ENSCM, Montpellier, France; [6]Institute for Cancer Research of Montpellier (IRCM), INSERM U1194, Montpellier University, Montpellier, France

Contributions: (I) Conception and design: C Cusumano, E Deshayes, F Quénet; (II) Administrative support: F Quénet; (III) Provision of study materials or patients: E Deshayes, F Quénet, S Carrère, O Sgarbura, D Ilonca, S Guillemard, MC Éberlé; (IV) Collection and assembly of data: C Cusumano, G De Meeus; (V) Data analysis and interpretation: C Cusumano, E Deshayes, B Guiu, F Quénet; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: François Quénet. Surgical Oncology Department, Institut Régional du Cancer de Montpellier (ICM), 208 Avenue des Apothicaires, 34298 Montpellier, France. Email: François.quenet@icm.unicancer.fr.

Background: Liver failure is the most threatening complication after hepatectomy for colorectal liver metastases. Recent studies indicate that liver functional evaluation by hepatobiliary scintigraphy (HBS) could be more sensitive than volumetry to predict the risk of post-hepatectomy liver failure (PHLF). The aim of this study was to evaluate the performance of ^{99m}Tc-mebrofenin HBS, when used as the main preoperative assessment before major hepatectomy in patients with liver metastases from colorectal cancer.

Methods: This retrospective study reviewed data from all patients with colorectal liver metastases treated at Montpellier Cancer Institute between 2013 and 2020. Only patients who underwent HBS before surgery were included. The primary aim was to evaluate how the use of this functional imaging modifies the surgical management of patients with colorectal liver metastases.

Results: Among the 80 patients included, 26 (32.5%) underwent two-stage hepatectomy and 13 (16.3%) repeated hepatectomies. Severe postoperative complications occurred in 16 patients (20%) and all-grade liver failure occurred in 13 patients (16.3%). Seventeen patients (21.3%) underwent major liver surgery based on sufficient mebrofenin uptake, although the retrospectively evaluated future liver remnant (FLR) volume was insufficient (<30% of total liver). None of these patients had PHLF.

Conclusions: This study showed the reliability of HBS for the preoperative functional assessment of patients with colorectal liver metastases. Indeed, it allowed performing major hepatectomy safely in 20% more patients who would not have been considered for surgery on the basis of volumetric assessment.

Keywords: Liver metastases; two stage hepatectomy; future liver remnant (FLR); hepatobiliary scintigraphy (HBS); mebrofenin

Submitted Sep 19, 2022. Accepted for publication Feb 03, 2023. Published online Mar 15, 2023.

doi: 10.21037/atm-22-3665

View this article at: https://dx.doi.org/10.21037/atm-22-3665

Introduction

Liver is the most common metastatic site in colorectal cancer. Surgery with systemic chemotherapy remains the best therapeutic strategy for patients with colorectal liver metastases (CRLM) (1). However, liver surgery cannot be performed in up to 80% of patients with CRLM at diagnosis (2).

In the last two decades, the number of patients with resectable CRLM has increased. This increase is partly due to advances in intensified systemic chemotherapy regimens associated with targeted therapy or immunotherapy (3,4), and partly due to technical improvements that increase the size of the future liver remnant (FLR) (5) and facilitate parenchyma-sparing surgery. Moreover, different strategies have been developed to overcome the clinical and technical challenges of bilobar hepatic involvement (6). These strategies include two-stage hepatectomy, associated liver partition and portal vein ligation for staged hepatectomy, and recently, ultrasound-guided enhanced one-stage hepatectomy (7,8). All these approaches have raised concerns about surgical morbidity and mortality; thus, accurate patient selection and rigorous evaluations are required before planning extended resections.

Post-hepatectomy liver failure (PHLF) may occur if the amount of remnant liver is not sufficient for its function. PHLF incidence varies widely, from 1.2% to 32% (9). It can be partially avoided with a reliable estimation of the FLR. Traditionally, FLR has been estimated by computed tomography (CT) volumetry (FLR-V). However, in the presence of chemotherapy-induced liver parenchyma dysfunction, volumetric measurements do not bring information about the future liver function. Consequently, the FLR-to-body-weight ratio has been introduced to obtain individualized volumetry, based on the patient's body weight or body surface area (10,11). The hepatic reserve can be assessed also using indocyanine green clearance that is well correlated with ^{99m}Tc-mebrofenin extraction rate (12). However, indocyanine green clearance cannot be used for FLR estimation. On the other hand, ^{99m}Tc-mebrofenin-based hepatobiliary scintigraphy (HBS) takes into account the spatial distribution of liver function. In addition, ^{99m}Tc-galactosyl human serum albumin scintigraphy seems to be a promising approach for PHLF estimation, but is available only in Asia.

^{99m}Tc-mebrofenin HBS gives quantitative information on liver function at the global and regional levels. HBS has shown better sensitivity than CT volumetry in predicting FLR function and PHLF risk in the presence of liver parenchyma damage (13). After the introduction of a reliable cut-off value (2.69%/min/m^2) for liver function to ensure safe resections (14), HBS has been integrated into preoperative assessments for hepatic surgery (15). However, its use has remained limited to some pioneering centres (16-20).

The primary aim of this retrospective study was to evaluate how the preoperative use of HBS modifies the surgical management of patients with CRLM. The secondary aim was to investigate the short- and long-term outcomes of surgery in these patients. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3665/rc).

Highlight box

Key findings

- This study found that the routinary use of HBS in the pre-operative assessment of liver resection is safe and increases the number of patients amenable to liver surgery in comparison with volumetry.

What is known and what is new?

- HBS has shown better sensitivity than CT volumetry in predicting FLR function and PHLF risk in the presence of liver parenchyma damage. HBS has started been integrated into preoperative assessments for hepatic surgery but its routinary use is still limited.
- This series is a monocentric, homogeneous sample of the routinary and exclusive use of HBS before liver surgery: the results show that this strategy is safe and effective in terms of mortality and morbidity.

What is the implication, and what should change now?

- Before a radical change in the clinical practice, a randomized study comparing volumetry and scintigraphy should be done. Anyway these results should comfort surgeons in the use of scintigraphy in the preoperative assessment.

Methods

Patients and treatments

This retrospective study included data retrieved from a prospectively maintained database of patients who underwent HBS before surgery at our centre between February 2013 and June 2020 (*Figure 1*). The following inclusion criteria were used:

- ❖ Patients with CRLM and planned major hepatectomy (defined as the removal of at least three hepatic segments), or repeated minor hepatectomy in patients who had previously

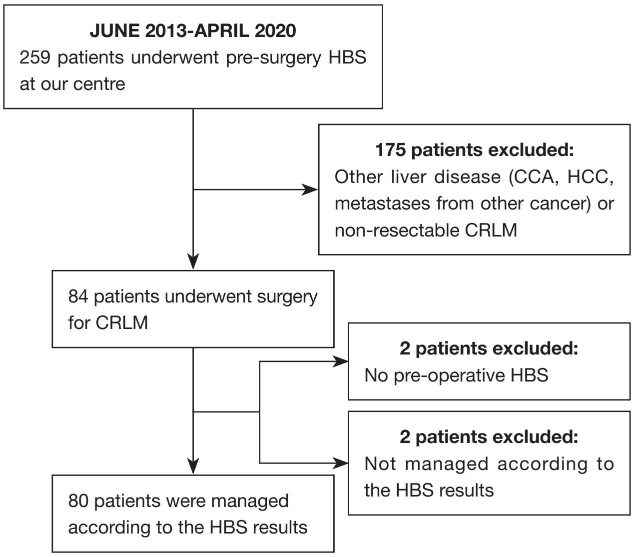

Figure 1 Flowchart of the patient selection process. HBS, hepatobiliary scintigraphy; CCA, cholangiocarcinoma; HCC, hepatocarcinoma; CRLM, colorectal liver metastases.

undergone hepatic resection. The latter situation is considered at higher risk for PHLF compared with primary minor hepatic resection;

- ❖ Validation of the surgery indications by a multidisciplinary tumour board.

Exclusion criteria were:

- ❖ Clinical conditions contra-indicating surgery;
- ❖ Non-resectable liver metastases;
- ❖ Blood bilirubin levels 1.5-fold above the upper limit of the normal range (21);
- ❖ Patients who received chemotherapy or embolization before liver surgery, and did not underwent HBS after these treatments prior to hepatectomy;
- ❖ Patients with liver cirrhosis.

All surgical interventions were performed by three senior surgeons experienced in hepato-pancreato-biliary surgery and intra-operative hepatic ultrasonography was performed in all cases.

The two-stage hepatectomy for bilobar CRLM consisted of two steps: (I) removing the tumours in the FLR before liver venous embolization or ligation, followed by (II) hepatic resection (major hepatectomy in most cases) performed 4–6 weeks later. HBS was systematically performed in the week before hepatic resection. Embolization of the portal vein alone or of the portal and hepatic veins was performed to achieve liver venous deprivation (LVD) or extended liver venous deprivation (eLVD), respectively, as described elsewhere (22).

Imaging procedures: HBS and morpho-functional evaluation with contrast-enhanced SPECT/CT

Pre-surgery liver function assessment with HBS

First, ^{99m}Tc-mebrofenin uptake rate (normalized to body surface area and expressed in %/min/m^2) by the whole liver was assessed, as described by Ekman *et al.* (23). Briefly, patients received an intravenous injection of 150 MBq ^{99m}Tc-mebrofenin (Cholediam®, Mediam Pharma, Loos, France), followed immediately by dynamic planar acquisition for 6 min. Then, fast, single-photon emission computed tomography (SPECT) was performed, as described elsewhere (24). CT images (2.5 mm thickness) were acquired at the portal phase after injection of an iodinated contrast medium. The Volumetrix® software (GE Healthcare, Milwaukee, USA) was used for data reconstruction with an iterative algorithm to generate attenuation corrected images. Co-registration between CT and SPECT images was checked and corrected, if required. The volumes of interest were first delineated on CT (whole liver and FRL) images and then copied to the SPECT images (fused). For all complex cases the volumes of interest were drawn after reaching a consensus between the surgeon and the nuclear medicine physician.

The ^{99m}Tc-mebrofenin counts were calculated in each volume of interest. Pre-surgery FLR function (FLR-F) was defined as follows: (total counts in FLR volumes of interest/total counts in whole liver volumes of interest) × whole liver uptake rate (expressed in %/min/m^2).

Retrospective liver volume evaluation

As evaluation of the PHLF risk is usually based on volumetric calculations, the total liver volume and FLR volume (FLR-V) were retrospectively (post-surgery) calculated for each patient using the CT images of the SPECT/CT data with an OsiriX MD workstation (Pixmeo®, Bernex, Switzerland), according to the surgery plan decided after HBS evaluation. The FLR-V threshold of 30% was used to compare the performances of CT volumetry and HBS, performed before surgery, for PHLF prediction. This threshold was chosen because it should better take into account the chemotherapy-related parenchyma damage.

Data collection and statistical analysis

Demographic, clinical, intraoperative, postoperative, and histopathological variables were included according to previous recommendations in the literature (25).

Post-operative complications were reported according to the Clavien-Dindo classifications (26). Liver-specific complications were described using the definitions established by the International Study Group for Liver Surgery for PHLF and postoperative hepatic haemorrhage (9,26,27) and the 50-50 criteria for PHLF (28). PHLF management included nutritional support, diuretic drug administration, radiological or surgical drainage, infection prevention or aggressive treatment, and laxatives. PHLF was graded as A: no change in the patient management; B: a change in management that did not require invasive therapy; and C: management with invasive therapy. After surgery, patients were monitored by CT imaging every 4 months for the first 3 years; then, every 6 months, until the fifth year; then, yearly.

Patients were followed until 31 August 2020, or until the time of death. Overall survival (OS) and disease-free survival (DFS) were calculated in months. Survival times were evaluated from the time of CRLM surgery to the last available follow-up (OS) or to the first recurrence (DFS).

Continuous data were expressed as the number of events (n), median, and range. Qualitative data were expressed as the number of observations (n) and frequency (%). Quantitative and qualitative data were compared with the Wilcoxon and Chi-2 tests, respectively.

The median follow-up time and 95% confidence interval (95% CI) were calculated by reverse Kaplan-Meier analysis. OS, DFS, and liver and global DFS (L-DFS and G-DFS) and their 95% CI were calculated with the Kaplan-Meier method. Survival curves were compared with the log rank test. Hazard ratios (HRs) and 95% CIs were estimated with Cox proportional hazard models. All perioperative variables that showed associations with the outcomes of interest in the univariate analysis were included in the multivariate analysis. All statistical tests were bilateral, and the significance threshold was fixed at 5% ($P<0.05$). Statistical analyses were performed with SPSS v24.0 (IBM Corporation, Armonk, NY, USA).

Ethical statement

The study protocol (OPTIMEB) was approved by the local Ethics Committee Review Board of the Regional Cancer Institute of Montpellier (No. ICM-ART 2021/01). Individual consent was waived for this retrospective analysis. This study was conducted according to the Declaration of Helsinki (as revised in 2013) and the European Good Clinical Practice requirements.

Results

Patient characteristics

The study population included 80 patients who met the inclusion criteria and underwent surgery for CRLM. Their median age was 64 years (range: 37–85). The preoperative patient characteristics are in *Table 1*. Sixty-eight patients (85%) had synchronous CRLM, and 61 (76.3%) had bilobar liver involvement. Seventy-one patients (88.8%) received neoadjuvant therapy, mainly chemotherapy (5-fluorouracil, oxaliplatin, irinotecan) plus targeted therapy (anti-epidermal growth factor receptor antibodies or bevacizumab) (n=47, 58.8%). The median number of chemotherapy cycles before surgery was 8 (range: 3–41). Nine patients received chemotherapy intensification in which hepatic intra-arterial infusion of oxaliplatin was combined with intravenous FOLFIRI and targeted therapy.

The perioperative characteristics are listed in *Table 2*. Twenty-six patients (32.5%) underwent two-stage hepatectomy, and thirteen patients (16.3%) underwent repeated hepatectomy. Preoperative embolization was performed in patients with borderline HBS values or below the established cut-off of $2.69\%/min/m^2$, (n=42 patients, 52.5%, among whom 27, 33.7%, underwent LVD).

The retrospectively calculated FLR-V showed that seventeen patients (21.3%) underwent major liver surgery despite insufficient volumetry (*Table 3*).

Modification of the surgical strategy based on the pre-surgery functional assessment by HBS

The 80 patients underwent HBS at our centre before surgery to evaluate whether the initial surgical plan was consistent with the FLR-F (*Figure 2*). In the 39 patients (48.7%) with mebrofenin uptake $>2.69\%/min/m^2$, 30 had upfront surgery according to the initial plan. The other 9 patients with borderline mebrofenin uptake (2.69–$2.80\%/min/m^2$) underwent pre-operative liver embolization and then the initially planned surgery.

In the 41 patients (51.3%) with insufficient pre-operative mebrofenin uptake ($>2.69\%/min/m^2$), 33 underwent pre-operative embolization. Moreover, the surgical plan was modified in 23/41 patients: more extensive surgery (after pre-operative embolization) in 9 patients and resized

Table 1 Preoperative characteristics of the study population

Variables	Patients (N=80)
Age at surgery (y)	64 [37–85]
Women/men	36 (45.0%)/44 (55.0%)
Body surface area (m^2)	1.8 (1.3–2.5)
Body mass index (kg/m^2)	24 (15.2–37)
Primary tumour site	
Left colon	37 (46.3%)
Rectum	25 (31.3%)
Right colon	17 (21.3%)
Synchronous liver metastases	68 (85.0%)
Reverse surgical strategy[†]	29 (42.6%)
Other metastatic sites	21 (26.3%)
Mutational status	
RAS mutation	31 (38.8%)
BRAF mutation	6 (7.5%)
Microsatellite instability	1 (1.3%)
Histopathology of primary tumour:	
In situ tumour	1 (1.3%)
T 0/1/2/3/4	2/0/6/47/17 (2.5%, –, 7.5%, 58.8%, 21.3%)
N 0/1/2	22/34/15 (27.5%, 42.5%, 18.8%)
M 0/1	12/68 (15.0%, 85.0%)
Microvascular invasion	23 (28.8%)
Perineural invasion	28 (35.0%)
Liver metastases site	
Right	15 (18.8%)
Left	4 (5.0%)
Bilateral	61 (76.3%)
Histopathology of liver metastases	
Number	4 [1–21]
Size max (cm)	3 (0.6–40)
R0 surgical margin[‡]	52 (65.0%)
Response to chemotherapy[§]	37 (46.3%)
Histopathology of normal liver	
Normal	25 (31.3%)
Sinusoidal dilatation	30 (37.5%)
SOS, minor steatosis	11 (13.8%)
Major steatosis, area of steatohepatitis and or fibrosis	7 (8.8%)
Neoadjuvant chemotherapy	71 (88.8%)
Intra-arterial chemotherapy	9 (11.3%)
Biotherapy	51 (63.8%)
Folfox-only regimen	19 (23.8%)
Folfiri-only regimen	13 (16.3%)
Tri-therapy	47 (58.8%)
Number of cycles	8 [3–41]
Inter-stage chemotherapy[¶]	8 (10.0%)

Values are the median (range) or the number (%), as indicated. †, reverse surgical strategy: liver surgery prior to primary tumour surgery; ‡, R0 margin was defined as >0.1 cm; §, response to chemotherapy: when tumour regression grades: TRG 1–3/Blazer 1 is achieved, which indicated a positive response to chemotherapy; ¶, inter-stage chemotherapy for two stage hepatectomy. SOS, sinusoidal obstruction syndrome.

surgery in 14 (17.5%). The retrospectively calculated FLR-V was <30% in 2/9 patients who had more extensive surgery. For these patients, neither PHLF nor major complications (Clavien-Dindo grade ≥3) were reported. PHLF was significantly more frequent in the group of 14 patients with insufficient mebrofenin uptake and resized surgery.

HBS allowed proposing surgery to 17 patients (21.3%) who would not have been operated if the decision would have been based on volume assessment (FRL-V <30%) (*Table 3*). Two of these patients had severe post-surgery complications (Clavien-Dindo grade ≥3), and one required an emergency laparotomy. No PHLF was reported.

Postoperative outcome

The median hospital stay was 11 days (range: 2–44) (*Table 4*). Sixteen patients (20%) experienced severe complications (Clavien-Dindo grade ≥3): emergency repeated laparotomies for biliary leaks (n=4) and peritonitis (n=3), post-hepatectomy acute Budd Chiari syndrome with inferior vena cava compression (n=2), acute haemorrhage (n=1), and acute necrotizing pancreatitis (n=1). Moreover, in two patients (2.5%) prothrombin time (PT) was reduced

Table 2 Perioperative characteristics

Characteristics	Patients (N=80)
Interval between HBS and surgery, days	21±20.4
Two-stage hepatectomy	26 (32.5%)
Venous liver embolization	42 (52.5%)
Portal vein	15 (35.7%)
Portal vein + 1 HV	12 (28.6%)
eLVD	15 (35.7%)
Previous liver surgery	13 (16.3%)
Mebrofenin uptake	3.66 (0.55–8.6)
FLR-V %	40.6 (17.8–85)
Pringle manoeuvre (intermittent total pedicle clamping)	22 (27.5%)
Mean intra-operative bleeding, mL	951±729
Median (range), mL	700 (50–3,200)
Frequencies	
0–200 mL	3 (3.8%)
200–800 mL	38 (47.5%)
800–1,500 mL	20 (25.0%)
>1,500 mL	16 (20.0%)
Transfusions U/pts	0 (0–6)
Median operative time, min	240 (140–420)
Lasting intra-operative hypotension (>10 min)	7 (8.8%)
Major hepatic resection (>3 segments)	65 (81.3%)
Type of surgery	
Right hepatectomy	26 (32.5%)
Right extended to SIV hepatectomy	24 (30.0%)
Right extended to SI hepatectomy	4 (5.0%)
Right extended to SI and SIV hepatectomy	5 (6.2%)
Left hepatectomy (SI, II, III, IV)	3 (3.7%)
Left extended hepatectomy	4 (5.0%)

Values are the mean ± SD, the median (range), or the number of patients (%), as indicated. HBS, hepato-biliary scintigraphy; HV, hepatic vein; eLVD, extended liver venous deprivation; FLR-V, future liver remnant-volume; U/pts, unit of red blood cells/patient; SIV, segment 4; SI, II, III, IV, segment 1, 2, 3, 4.

Table 3 Patients who underwent liver surgery with FLR-V <30% and mebrofenin uptake >2.69%/min/m^2

Characteristics	Patients (N=17, 21.3%)
Type of surgery	
Right extended to SIV hepatectomy	9 (52.9%)
Right hepatectomy	5 (29.4%)
Right extended to SI hepatectomy	1 (5.9%)
Right extended to SIV + wedge resections	2 (11.8%)
Initial surgical plan	
Maintained	13 (76.4%)
Resized	2 (11.8%)
Extended	2 (11.8%)
Postoperative complications:	
Clavien-Dindo ≥ grade 3	2 (11.8%)
Re-laparotomy	1 (5.9%)
PHLF grade B-C	–

FLR-V, future liver remnant-volume; SIV, segment 4; SI, segment 1; PHLF, post-hepatectomy liver failure.

(<50% of normal) concomitantly with hyperbilirubinaemia (bilirubin serum concentration >50 µmol/L) on post-operative day 5 (POD5). PHLF occurred in 13 patients (16.3%). Abnormal laboratory parameters were observed alone in four patients (5%) and combined with ascites, fatigue, and jaundice in nine patients. Eight patients (10%) received adequate treatment that resulted in satisfactory remission (PHLF-B). No patient required admission to an intensive care unit.

Two patients died in the 90-day postoperative period. One was a 38-year-old patient who died at POD80 from complications related to PHLF, although both HBS and CT volumetry assessments were favourable. The second was a 43-year-old patient with previous right extended hepatectomy who underwent repeated hepatectomy (partial resection of segment 2) with HBS uptake of 3.3%/min/m^2 (FLR-V =40%) before the repeated hepatectomy. Death occurred on POD2 due to acute thrombosis in the left hepatic vein.

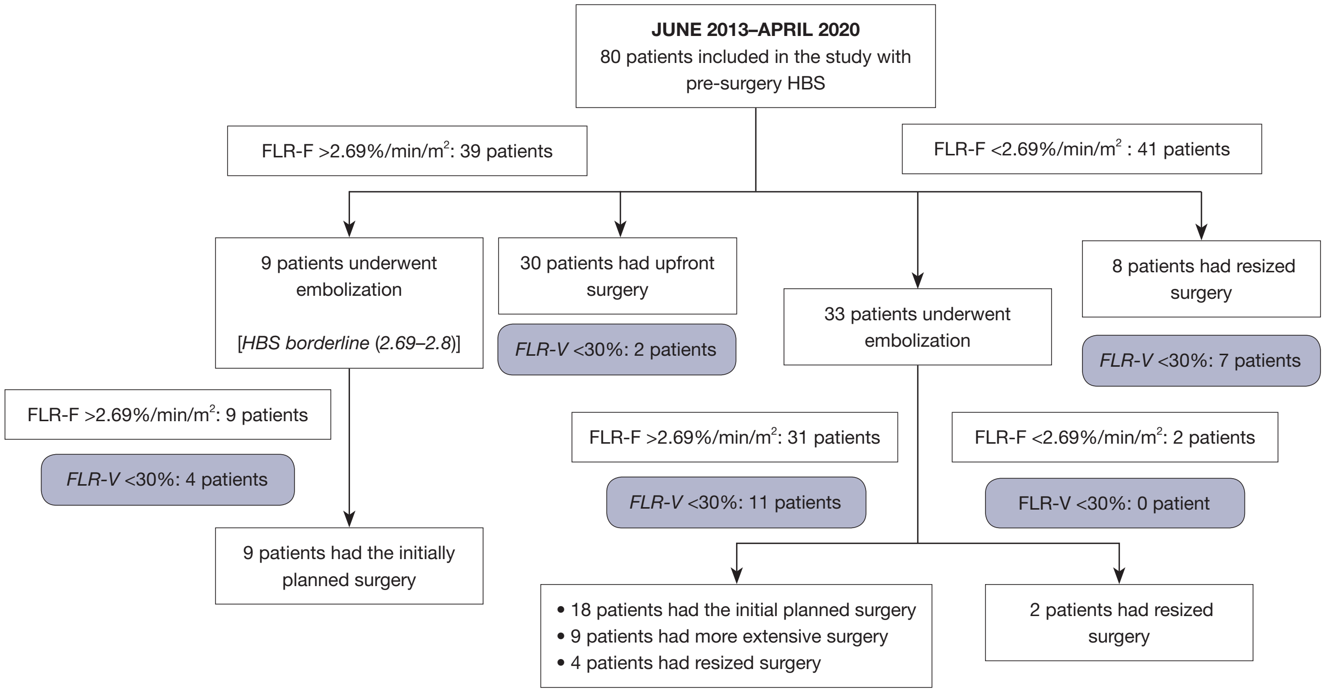

Figure 2 Flowchart showing the modification of the surgical strategy on the basis the HBS results. HBS, hepatobiliary scintigraphy; FLR-F, future liver remnant-function; FLR-V, future liver remnant-volume.

Univariate analysis showed that postoperative complications were associated with decreased PT at POD5, presence of positive margins on histopathological specimens (R1 resection), and previous hepatectomy. In the multivariate analysis, which included only variables that were significant in the univariate analysis, only decreased PT at POD5 remained associated with increased risk of postoperative complications (HR: 0.93, 95% CI: 0.88–0.98; P=0.004) (*Table 5*).

In univariate analysis, PHLF was associated with the interval between HBS and surgery, mebrofenin uptake, intra-arterial chemotherapy, and severe post-operative complications. In the multivariate analysis, PHLF remained significantly associated with intra-arterial chemotherapy (HR: 2.27, 95% CI: 0.72–3.83; P=0.004) and presence of severe complications (HR: 1.83, 95% CI: 0.29–3.38; P=0.020) (*Table 5*).

Survival and oncological outcomes

After a median follow-up of 21.3 months (95% CI: 7.8–32.5) and a mean follow-up of 17.7 months, the median OS of the 80 patients was 63.4 months (95% CI: 27.2–NR). The 1-, 2-, and 3-year OS rates (95% CI) were: 87.7% (76.7–93.7), 72% (57–82.6), and 56.1% (39–70.2), respectively. The median DFS and L-DFS were 7.3 months (95% CI: 6.1–10.5) and 10.5 months (95% CI: 8.2–13.9), respectively. The 1- and 2-year G-DFS rates (95% CI) were 27.7% (17.3–39.1) and 9.9% (3.6–19.9), respectively. The 1-, 2-, and 3-year L-DFS rates (95% CI) were 43.1% (30.7–54.8), 24.6% (14.1–36.7), and 19.7% (9–33.5), respectively.

Univariate analysis found that OS was associated with the HBS cut-off value, R1 resection, post-hepatectomy haemorrhage, and post-surgery hospital stay duration; in the multivariate analysis, the only independent prognostic factor of OS was the HBS cut-off value (HR: 8.37, 95% CI: 2.24–3.12; P<0.001) (*Table 5*).

In univariate analysis, G-DFS was associated with number of metastatic nodules, biliary leak, and PHLF. In multivariate analysis, only PHLF remained an independent risk factor for G-DFS (HR: 1.72, 95% CI: 1.04–2.85; P=0.034).

The univariate analysis showed that L-DFS was associated with FLR-V <30%, interval between HBS and surgery, number of metastatic nodules, biliary leak, and post-hepatectomy haemorrhage. In the multivariate analysis, only biliary leak remained associated with L-DFS (HR: 5.63, 95% CI: 1.36–23.22; P=0.017) (*Table 5*).

Table 4 Postoperative outcomes

Outcomes	Patients, N=80
Hospital stays, days	11 [2–44]
Clavien-Dindo postoperative complications	38 (47.5%)
Severe complications (≥ grade 3a)	16 (20.0%)
Grade 1/2	22 (27.5%)
Grade 3a	6 (7.5%)
Grade 3b	7 (8.7%)
Grade 4a/4b	1 (1.3%)
Grade 5	2 (2.5%)
Ascites/pleural fluid	7 (8.8%)
Biliary leak	6 (7.5%)
Bleeding/need of RBC transfusion	5 (6.3%)
Infected ascites/peritonitis	5 (6.3%)
Biloma	3 (3.8%)
Others[†]	12 (15.0%)
POD5 Bilirubin >50 µmol/L	6 (7.5%)
POD5 PT level <50%	2 (2.5%)
POD5 Bilirubin >50 µmol/L and PT level <50%	2 (2.5%)
Post-hepatectomy hepatic failure	13 (16.3%)
Grade A	4 (5.0%)
Grade B	8 (10.0%)
Grade C	1 (1.3%)
Post-hepatectomy haemorrhage	8 (10.0%)
Grade A	5 (6.3%)
Grade B	–
Grade C	3 (3.8%)

Values are the median (range) or the number (%), as indicated. [†], others included: surgical wound infection, post-operative ileus, urinary infection, venous central line infection, cardiac arrhythmia, post-hepatectomy acute Budd-Chiari syndrome, and acute vascular insufficiency of the lower limbs. RBC, red blood cell; POD5, postoperative day 5; PT, prothrombin time.

Discussion

The present study showed that HBS is clinically relevant for the assessments before liver surgery and that it reliably extends patient selection for hepatic resection, compared with FLR-V. To our knowledge, this study is the first to report the clinical outcomes of a homogenous population of patients with CRLM who had a preoperative risk assessment exclusively based on HBS.

We hypothesized that the PHLF risk was the main limiting factor for extended liver surgery, and that HBS would be more sensitive than CT volumetry to predict PHLF. Therefore, we based the decision to perform preoperative embolization and the whole surgical plan on the pre-validated HBS threshold of 2.69%/min/m^2 (13). Our multivariate analysis confirmed the strength of the association between PHLF and this cut-off value. Moreover, the short- and long-term results after major hepatectomy reported in this monocentric series validated the selection strategy based on HBS results.

The International Study Group of Liver Surgery has defined liver-specific post-hepatectomy complications and their grading to facilitate comparisons among studies (9). However, the rates of severe postoperative complications (20%) and of PHLF that would have required changes in surgical strategy (11.2% for PHLF-B and C) remain difficult to compare, due to differences in the complexity of surgery and in the used classification systems. Nevertheless, we could compare our mortality rates with those of previous studies. A recent, large German study reported 5.8% of mortality for all resections and 10% of mortality for major hepatectomies, compared with 2.5% in our study (29). This lower rate is probably due to the adequate patient selection, based on HBS, and to the expertise of a high-volume centre. Indeed, the German study showed that mortality rates ranged from 4.6% in high-volume centres to 7.5% in low-volume hospitals.

Vibert *et al.* (30) compared the post-surgery complications in 232 patients according to the liver resection extent (147 minor and 85 major hepatectomies). They reported incidences of 7% to 9.4% for bile leakage, 0.6% to 7% for PHLF, and 1.3% to 8.2% for peri-hepatic fluid collection. The definition of peri-hepatic fluid collection is quite generic and in other studies it was defined as a temporary liver dysfunction with ascites, or biloma. This emphasizes the heterogenous terminology among studies. The authors also found that all complications were significantly more frequently after major hepatectomy. Despite some differences in definitions, our results are similar to those reported in other studies on complex hepatic surgical interventions in patients with CRLM (30-33).

In our study, mebrofenin uptake was considered insufficient in 14 patients, and this led to surgery resizing. In this group of patients, PHLF was more frequent, despite the modification of the surgical plan. This can be mainly

Table 5 Multivariate analysis of the variables significant in univariate analysis associated with the indicated outcomes

Outcomes	Variables	HR	95% CI	P value
Post-operative complications	POD5 PT <50%	0.93	0.88–0.98	0.004
	R1 resection	–	–	–
	Previous hepatectomy	–	–	–
PHLF	Mebrofenin uptake	–	–	–
	IAC	2.27	0.72–3.83	0.004
	Clavien-Dindo grade ≥3	1.83	0.29–3.38	0.020
	HBS-surgery interval	–	–	–
OS	R1 resection	–	–	–
	Post-surgery hospital stay	–	–	–
	PHH	–	–	–
	Mebrofenin uptake	8.37	2.24–3.12	0.001
G-DFS	Biliary leak	–	–	–
	Nodule number	–	–	–
	PHLF	1.72	1.04–2.85	0.034
L-DFS	FLR-V <30%	–	–	–
	HBS-surgery interval	–	–	–
	Biliary leak	5.63	1.36–23.22	0.017
	Nodule number	–	–	–
	PHH	–	–	–

POD5, post-operative day 5; PT, prothrombin time; PHLF, post-hepatectomy liver failure; IAC, intra-arterial chemotherapy; HBS, hepatobiliary scintigraphy; OS, overall survival; PHH, post-hepatectomy haemorrhage; G-DFS, global disease-free survival; L-DFS, liver disease-free survival; FLR-V, future liver remnant-volume.

explained by the fact that a new pre-operative HBS was not performed according to the resized surgical plan. Therefore, in some of these 14 patients, liver function might have not allowed even the reduced resection. Moreover, as all 14 patients had bilobar metastases, one could hypothesize that the high tumour burden may have caused a more important liver function impairment.

This analysis found that PHLF had a significant impact on DFS, confirming the postoperative morbidity contribution to survival and relapse in patients with cancer (34).

When we used HBS as the only preoperative assessment, and calculated the FLR-V values retrospectively, we found that 17 patients (21.3%) underwent successful surgery, despite a FLR-V <30%, even after LVD (*Table 3*). We chose a FLR-V cut-off of 30%, like in other studies on patients with CRLM, to take into account the possible effect on liver function of prolonged chemotherapy prior to surgery (33,34). Patients with FLR-V <30% and HBS results above the cut-off had postoperative outcomes similar to patients with concordant HBS and volumetry. Moreover, no PHLF-B or -C was reported in both groups. Our results showed that surgery could be proposed to more patients by using HBS, rather than volumetry, for the preoperative assessment.

The risk of postoperative complications was associated with PT level at POD5, but not with the hepatic resection extent and preoperative chemotherapy. Moreover, our multivariate analysis results showed that mebrofenin uptake <2.69%/min/m^2, intra-arterial neoadjuvant chemotherapy and Clavien-Dindo complications grade ≥3 were risk factors of PHLF. The significant association between PHLF and major post-surgery complications confirmed the idea that septic complications might worsen a mild post-operative hepatic dysfunction, leading to clinically relevant symptoms.

No patient had liver cirrhosis, but almost all (N=71, 88.8%) received neoadjuvant chemotherapy, with a median of 8 cycles, including tri-therapy regimens and intensification chemotherapy (N=9, 11.3%) in which intra-hepatic arterial oxaliplatin infusion was combined with intravenous FOLFIRI. Chemotherapy has been associated with liver dysfunction; it can induce steatosis, sinusoidal obstruction syndrome, and non-alcoholic steatohepatitis. In this setting, HBS is considered a sensitive tool for PHLF prediction (35). Ribeiro *et al.* (36) reported that >8 cycles of pre-operative chemotherapy were associated with nearly a five-fold increase in PHLF risk.

At our centre, HBS is systematically used for pre-operative assessment only in patients with CRLM. Indeed, as mebrofenin transport is impaired in patients with jaundice, we decided to exclude patients with cirrhosis and with primary liver tumours because of the higher frequency of jaundice in these conditions. In these patients, pre-surgery FLR estimation is based on volumetric assessment. Moreover, the inclusion of only patients with CRLM resulted in a more homogeneous sample, avoiding the bias of any other underlying liver disease.

The limited number of surgeons (n=3) with similar skills in hepatobiliary surgery strongly reduced the potential of a bias due to surgical experience, which may have influenced patient outcome.

Our short- and long-term results compared favourably with those reported in previous studies (31,32). Moreover, in the 17 patients we selected for surgery on the basis of HBS, although with retrospective insufficient FLR-V, neither clinically relevant PHLF nor death was recorded. These findings suggested that HBS might be an optimal tool for extending surgery beyond the limits of FLR-V. However, prospective studies are needed to confirm this preliminary conclusion.

This study had some limitations. First, its retrospective and monocentric design resulted in a limited number of patients. Second, the fact that FLR-V was calculated only after surgery could be considered as a limitation, but it reflects the management of patients with CRLM at our centre. Third, this study did not include a control group managed according to volumetry.

Conclusions

In conclusion, this study showed that surgical management of patients with CRLM, based on HBS, is safe and increases the number of patient amenable to major liver resection. In this homogeneous single-centre series of patients with CRLM, HBS allowed the safe surgical management of patients who would have been excluded from surgery on the basis of the standard volumetric assessment. These patients achieved acceptable outcomes, without severe morbidity (including severe PHLF).

Acknowledgments

This work was presented as a poster presentation at the Congress of the French Association of Hepato-Biliary and Transplantation Surgery (ACHBT) in Marne-la-Vallée, France, in 2019. English editing of the article has been done (Dr. Elisabetta Andermarcher, English native speaking, freelance editor).
Funding: This work was supported by the SIRIC Montpellier Grant INCa, Inserm DGOS 12553.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3665/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3665/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3665/coif). OS received honoraria as lecturer at the Seoul International Symposium of Surgical Oncology 2022, and as member in the communication board of the European Society for Surgical Oncology and in the director board for the French Society for Surgical Oncology and the French Network for the Peritoneum (RENAPE). The other 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the European Good Clinical Practice requirements. The protocol (OPTIMEB) was approved by the local Ethics Committee Review Board of the Regional Cancer Institute of Montpellier (No. ICM-ART 2021/01) and individual consent for this retrospective analysis was waived.

References

1. Collins D, Chua H. Contemporary surgical management of synchronous colorectal liver metastases. F1000Res 2017;6:598.
2. Adam R, Kitano Y. Multidisciplinary approach of liver metastases from colorectal cancer. Ann Gastroenterol Surg 2019;3:50-6.
3. Loupakis F, Stein A, Ychou M, et al. A Review of Clinical Studies and Practical Guide for the Administration of Triplet Chemotherapy Regimens with Bevacizumab in First-line Metastatic Colorectal Cancer. Target Oncol 2016;11:293-308.
4. Ychou M, Rivoire M, Thezenas S, et al. A randomized phase II trial of three intensified chemotherapy regimens in first-line treatment of colorectal cancer patients with initially unresectable or not optimally resectable liver metastases. The METHEP trial. Ann Surg Oncol 2013;20:4289-97.
5. Kim D, Cornman-Homonoff J, Madoff DC. Preparing for liver surgery with "Alphabet Soup": PVE, ALPPS, TAE-PVE, LVD and RL. Hepatobiliary Surg Nutr 2020;9:136-51.
6. Adam R, de Gramont A, Figueras J, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev 2015;41:729-41.
7. Torzilli G, Cimino MM. Extending the Limits of Resection for Colorectal Liver Metastases enhanced one stage surgery. J Gastrointest Surg 2017;21:187-9.
8. Memeo R, Conticchio M, Deshayes E, et al. Optimization of the future remnant liver: review of the current strategies in Europe. Hepatobiliary Surg Nutr 2021;10:350-63.
9. 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.
10. 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.
11. 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.
12. Erdogan D, Heijnen BH, Bennink RJ, et al. Preoperative assessment of liver function: a comparison of 99mTc-Mebrofenin scintigraphy with indocyanine green clearance test. Liver Int 2004;24:117-23.
13. 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.
14. 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.
15. Espersen C, Borgwardt L, Larsen PN, et al. Nuclear imaging methods for the prediction of postoperative morbidity and mortality in patients undergoing localized, liver-directed treatments: a systematic review. EJNMMI Res 2020;10:101.
16. Chapelle T, Op de Beeck B, Driessen A, et al. Estimation of the future remnant liver function is a better tool to predict post-hepatectomy liver failure than platelet-based liver scores. Eur J Surg Oncol 2017;43:2277-84.
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. Gupta M, Choudhury PS, Singh S, et al. Liver Functional Volumetry by Tc-99m Mebrofenin Hepatobiliary Scintigraphy before Major Liver Resection: A Game Changer. Indian J Nucl Med 2018;33:277-83.
19. Olthof PB, Coelen RJS, Bennink RJ, et al. (99m)Tc-mebrofenin hepatobiliary scintigraphy predicts liver failure following major liver resection for perihilar cholangiocarcinoma. HPB (Oxford) 2017;19:850-8.
20. Serenari M, Bonatti C, Zanoni L, et al. The role of hepatobiliary scintigraphy combined with spect/ct in predicting severity of liver failure before major hepatectomy: a single-center pilot study. Updates Surg 2021;73:197-208.

21. Rassam F, Olthof PB, Richardson H, et al. Practical guidelines for the use of technetium-99m mebrofenin hepatobiliary scintigraphy in the quantitative assessment of liver function. Nucl Med Commun 2019;40:297-307.
22. Guiu B, Chevallier P, Denys A, et al. Simultaneous trans-hepatic portal and hepatic vein embolization before major hepatectomy: the liver venous deprivation technique. Eur Radiol 2016;26:4259-67.
23. Ekman M, Fjälling M, Friman S, et al. Liver uptake function measured by IODIDA clearance rate in liver transplant patients and healthy volunteers. Nucl Med Commun 1996;17:235-42.
24. 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.
25. Bellver Oliver M, Escrig-Sos J, Rotellar Sastre F, et al. Outcome quality standards for surgery of colorectal liver metastasis. Langenbecks Arch Surg 2020;405:745-56.
26. 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.
27. Rahbari NN, Garden OJ, Padbury R, et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). HPB (Oxford) 2011;13:528-35.
28. 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.
29. Filmann N, Walter D, Schadde E, et al. Mortality after liver surgery in Germany. Br J Surg 2019;106:1523-9.
30. 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.
31. Morris-Stiff G, Marangoni G, Hakeem A, et al. Redefining major hepatic resection for colorectal liver metastases: Analysis of 1111 liver resections. Int J Surg 2016;25:172-7.
32. Adam R, Laurent A, Azoulay D, et al. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg 2000;232:777-85.
33. Baumgartner R, Gilg S, Björnsson B, et al. Impact of post-hepatectomy liver failure on morbidity and short- and long-term survival after major hepatectomy. BJS Open 2022;6:zrac097.
34. Dorcaratto D, Mazzinari G, Fernandez M, et al. Impact of Postoperative Complications on Survival and Recurrence After Resection of Colorectal Liver Metastases: Systematic Review and Meta-analysis. Ann Surg 2019;270:1018-27.
35. 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.
36. Ribeiro HS, Costa WL Jr, Diniz AL, et al. Extended preoperative chemotherapy, extent of liver resection and blood transfusion are predictive factors of liver failure following resection of colorectal liver metastasis. Eur J Surg Oncol 2013;39:380-5.

Cite this article as: Cusumano C, Deshayes E, Guiu B, De Meeus G, Carrère S, Bouillin A, Ilonca D, Éberlé MC, Guillemard S, Fersing C, Sgarbura O, Quénet F. Prevention of post-hepatectomy liver failure after major resection of colorectal liver metastases: is hepato-biliary scintigraphy the optimal tool? Ann Transl Med 2023;11(5):202. doi: 10.21037/atm-22-3665