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Assessment of Liver Function Using ^{99m}Tc-Mebrofenin Hepatobiliary Scintigraphy in ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy)

Kasia P. Cieslak[a] Pim B. Olthof[a] Krijn P. van Lienden[b]
Marc G. Besselink[a] Olivier R.C. Busch[a] Thomas M. van Gulik[a]
Roelof J. Bennink[c]

Departments of [a]Surgery, [b]Radiology and [c]Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands

Key Words
^{99m}Tc-mebrofenin hepatobiliary scintigraphy · Monitoring of liver function · Postoperative liver failure · ALPPS (associating liver partition and portal vein ligation for staged hepatectomy)

Abstract
ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) is a new surgical technique for patients in whom conventional treatment is not feasible due to insufficient future remnant liver (FRL). During the first stage of ALPPS, accelerated hypertrophy of the FRL is induced by ligation of the portal vein and in situ split of the liver. In the second stage, the deportalized liver is removed when the FRL volume has reached ≥25% of total liver volume. However, FRL volume does not necessarily reflect FRL function. ^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS) with SPECT-CT is a quantitative test enabling regional assessment of parenchymal uptake function using a validated cut-off value for the prediction of postoperative liver failure (2.7%/min/m^2). This paper describes the changes in FRL function and FRL volume in a 79-year-old patient diagnosed with metachronous colonic liver metastases who underwent ALPPS. We have observed a substantial difference between the increase in FRL volume and FRL function suggesting that HBS with SPECT-CT enables monitoring of the FRL function and could be a useful tool in the timing of resection in the second stage of the ALPPS procedure.

Kasia P. Cieslak, MD
Department of Surgery, Academic Medical Center
University of Amsterdam, IWO 1-A1-113.1
NL–1100 DD Amsterdam (The Netherlands)
E-Mail k.p.cieslak@amc.uva.nl

Introduction

Pushing the boundaries of surgical options in the curative treatment of hepatic malignancies has recently led to the development of a new surgical technique for patients in whom a conventional major liver resection (≥3 liver segments) is not feasible. The technique, known as ALPPS (associating liver partition and portal vein ligation for staged hepatectomy), is a two-stage procedure encompassing portal vein ligation and in situ split of the liver parenchyma during the first phase and completion of the resection by removal of the deportalized liver after an interval of 1–2 weeks in the second phase (fig. 1) [1]. ALPPS is indicated in patients in whom insufficient volume of remnant liver is anticipated carrying a high risk of postoperative liver failure. This technique induces an accelerated hypertrophy response of the future remnant liver (FRL) following contralateral ligation of the portal vein, while transection of the parenchyma allows the deportalized liver to contribute to liver function until the second stage.

However, since the introduction of ALPPS, there has been an ongoing discussion regarding its safety [2], as the morbidity (i.e., Clavien-Dindo grade ≥IIIb) and 90-day mortality rates reported in the literature reach up to 59 and 29%, respectively [3]. One of the key issues in ALPPS is the timing of the second stage at the point sufficient hypertrophy response has been achieved. The reference standard in the assessment of the FRL is CT volumetry. This modality enables volumetric measurement of the total liver, FRL and tumor volumes. In patients with healthy liver parenchyma, FRL volume and function can be considered equal [4]. However, in the majority of cases, the quality of the liver remains uncertain and may be affected by longstanding chemotherapy or fibrosis.

^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS) with SPECT-CT is a quantitative liver function test measuring hepatic uptake of this liver-specific ^{99m}Tc-labeled iminodiacetic acid derivative. HBS has important advantages over CT volumetry and other quantitative function tests. Firstly, HBS is performed together with SPECT-CT allowing not only the measurement of the total uptake of mebrofenin in the whole liver, but also regional measurements in the liver segments, e.g. FRL [5]. Secondly, one single cutoff value of 2.7%/min/m^2 has been validated for both patients with compromised and with noncompromised liver parenchyma [6]. Since the validation of the cutoff value for the prediction of postoperative liver failure, HBS has become part of standard patient care at our center for patients who require major liver resection. HBS has also proven useful in the assessment of the hypertrophy response of the FRL after preoperative portal vein embolization and selective internal radiation therapy [5, 7].

As accurate assessment of the FRL function rather than its volume is crucial in performing the ALPPS procedure, HBS could play a prominent role in monitoring FRL function after the first stage of ALPPS, giving guidance in the timing of the second stage. We herein report the sequential changes in FRL function measured using HBS in a patient who underwent ALPPS procedure.

Case Report

A 79-year-old female patient was referred to our Surgical Department with metachronous colonic liver metastases. Laparoscopic sigmoid resection had previously been performed for a pT4aN2M0 tumor. The patient was diagnosed with 3 lesions suspicious of metastases in segments 4A, 7 and 8, and she was scheduled for metastasectomy of the aforementioned lesions. However, at examination, additional lesions in segments 3, 5 and 6 were found necessitating extended right hemihepatectomy (i.e. resection of segments 4–8) with concomitant metastasectomy of the lesion in segment 3. This procedure was not considered feasible at the time of examination as the FRL volume was 19.6%, which was below the volumetric cutoff value for safe resection (25% of total liver volume). Furthermore, the FRL uptake function of segments 1, 2 and 3 was only 1.5%/min/m^2, which is also below the cut-off value for safe resection (2.7%/min/m^2; table 1). Therefore, it was decided to apply the ALPPS procedure, and the first stage was carried out in order to induce hypertrophy of segments 2 and 3. The study has been approved by the institutional review board, and the need for written informed consent was waived.

Imaging

CT imaging with CT volumetry and HBS were performed before and after each stage of the ALPPS. CT volumetric measurements were performed as initially described by Heymsfield et al. [8]. HBS was performed after a 4-hour fast, as food consumption stimulates hepatic function and bile flow, which might influence test results. The patient was put in a supine position on the imaging table and a large FOV SPECT-CT camera (Symbia T16; Siemens) was positioned over the liver and heart region. The SPECT-CT camera was equipped with low-energy high-resolution collimators. After intravenous administration of 200 MBq (5.41 mCi) freshly prepared ^{99m}Tc-mebrofenin (Bridatec; GE-Amersham Health), dynamic acquisition was obtained (36 frames of 10 s/frame, 128 × 128 matrix), which was used for the calculation of the hepatic mebrofenin uptake rate. Subsequently, a fast SPECT acquisition was performed (60 projections of 8 s/projection, 256 × 256 matrix), centered on the peak of the hepatic time-activity curve, which was used for the 3-dimensional assessment of liver function and the calculation of functional liver volume. Immediately after SPECT, a low-dose non-contrast-enhanced CT scan was obtained for attenuation correction and anatomical mapping. In order to evaluate biliary excretion, a second dynamic acquisition (15 frames of 60 s/frame, 128 × 128 matrix) was obtained. Data were processed on a Hermes workstation (Hermes Medical Solutions, Sweden). The HBS parameters related to mebrofenin uptake in the total liver and FRL were calculated as described before [5, 9]. A cut-off value of 2.7%/min/m^2 was used to discriminate the normal from decreased FRL uptake rate as was validated in a previous study [6].

Results

Figure 2a shows the CT image after the first stage of the ALPPS procedure. On postoperative day (POD) 3, the FRL volume had increased from 19.6 to 26.2% of the total liver volume, while the FRL function had increased from 1.5 to 2.0%/min/m^2. The FRL volume was measured again on POD 6 showing a further increase in volume up to 26.5% (table 1). On POD 8, the FRL function had increased above the cutoff value to 2.9%/min/m^2 (fig. 3). Upon this result, the second stage of the procedure was conducted on POD 8 (fig. 2b).

In this patient, the functional and volumetric increase in the FRL after 1 week was comparable to volumetric and functional measurements performed on POD 90 in a historic cohort of patients who underwent major liver resection at our institute [10].

Microscopic examination of the pathology specimen confirmed the metastases (R0 resection). The postoperative course was complicated by ascites due to thrombosis of the left hepatic vein, which resolved after anticoagulation therapy. The patient could leave the hospital in good condition after 13 days.

Discussion

Insufficient FRL is one of the major limitations in curative treatment of liver malignancies. ALPPS induces fast and advanced hypertrophy of the FRL thereby allowing more extensive resections. Nearly all of the patients reported after ALPPS showed sufficient volume hypertrophy after the first stage of the procedure and went on to the second stage [3]. However the morbidity and mortality rates after ALPPS are high when compared to liver resection after preoperative portal vein embolization or in the setting of a conventional two-stage liver resection with an interval of 4–6 weeks. The timing of the second stage of the procedure is largely determined by the degree of the hypertrophy response. In this paper, we demonstrate a marked increase in the FRL function measured with HBS in a patient who underwent both stages of the procedure, showing that only 8 days after transection of the liver parenchyma, the mebrofenin uptake rate of the FRL had nearly doubled and was comparable with the average functional increase documented 90 days after regular major liver resection [10].

Furthermore, we were able to show a substantial difference between the increase in FRL volume and function. Just 3 days after the first stage of the resection, the FRL volume had increased from 19.6 to 26.2% indicating that the patient was ready to undergo the next step of the operation as the cutoff value for safe resection is approximately 25%. However, the FRL function at that time point was 2.0%/min/m^2, which is below the validated cutoff value for safe resection (2.7%/min/m^2). Five days later, the FRL function had sufficiently increased in order to proceed with the next step of resection. Hence, early after the first stage of ALPPS, the volume of the FRL might overestimate the function.

This paper describes measurements performed in 1 patient undergoing the full course of ALPPS. However, in previous studies, we have shown differences in the volumetric and functional assessment of the FRL, and we were able to establish a cutoff value irrespective of liver parenchymal quality for the effective prevention of postoperative liver failure [6]. Our previous experiences with HBS in risk assessment of patients considered for extended liver resections corroborate the value of HBS in the setting of ALPPS.

In conclusion, HBS with SPECT-CT is a quantitative test enabling monitoring of FRL function in patients undergoing ALPPS procedure. HBS is a useful tool in the timing of the second stage of ALPPS and may contribute to the improvement of the procedure-related morbidity and mortality rates.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that there are no conflicts of interest regarding the publication of this article. None of the authors has received funding related to this subject from the following organizations: National Institutes of Health; Wellcome Trust; Howard Hughes Medical Institute and other(s).

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Kasia P. Cieslak and Pim B. Olthof contributed equally to this work.

Table 1. Scintigraphic and volumetric measurements of the FRL in a patient who underwent ALPSS

Event	Total liver function, %/min	FRL function, %/min/m²	Total liver volume, cm³	FRL volume, cm³	FRL volume, % of total liver volume
Preoperative assessment	12.2	1.5	1,204	236	19.6
First stage of ALPPS					
POD 3	13.3	2.0	1,462	383	26.2
POD 8/POD 6	11.9	2.9	1,554	412	26.5
Second stage of ALPPS					
POD 20	6.25	3.4		759	63.0[a]

[a] Expressed as percentage of the pre-preoperative total liver volume.

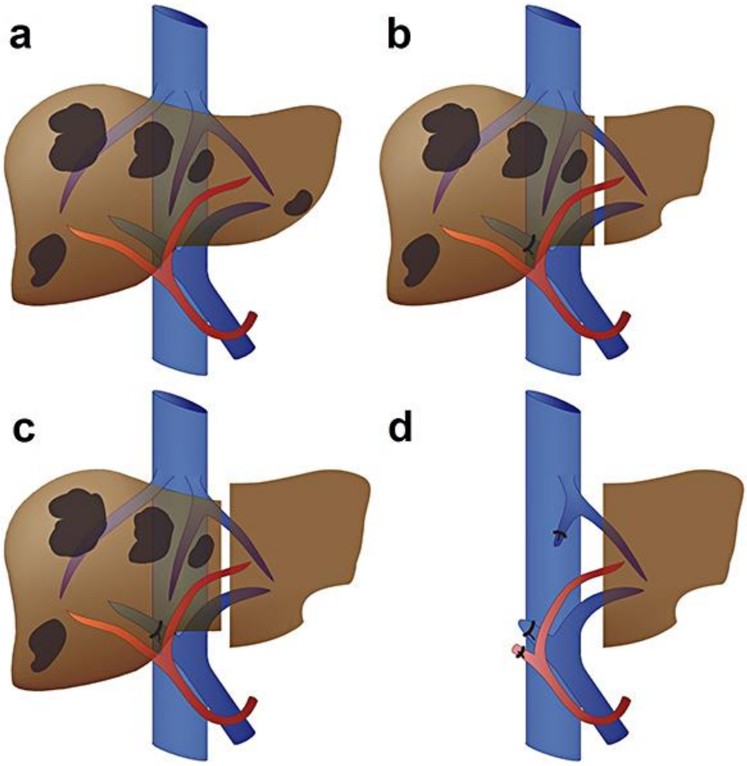

Fig. 1. Schematic overview of the ALPPS procedure. **a** Baseline situation with colorectal liver metastases in both hemilivers. **b** Excision of the metastases in the FRL, ligation of right portal vein and in situ partition of the liver. **c** Hypertrophy response of the FRL following liver partition. **d** Situation after the second stage of the procedure in which the deportalized liver has been removed.

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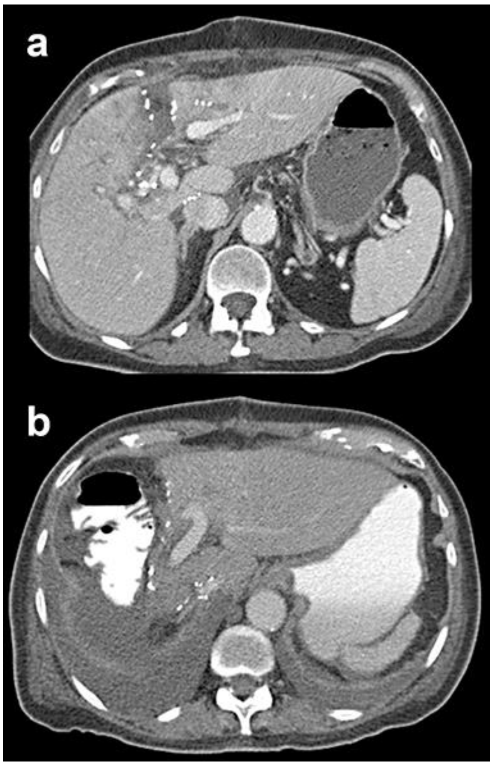

Fig. 2. **a** CT image after the first stage of the ALPPS procedure showing the in situ transection of the liver according to the planned extended right hemihepatectomy. The right portal vein has been ligated while the right hepatic artery and vein together with the bile system were preserved. **b** After an interval of 8 days, the resection was completed by removal of segments 4, 5, 6, 7 and 8, leaving segments 1, 2 and 3 as the liver remnant.

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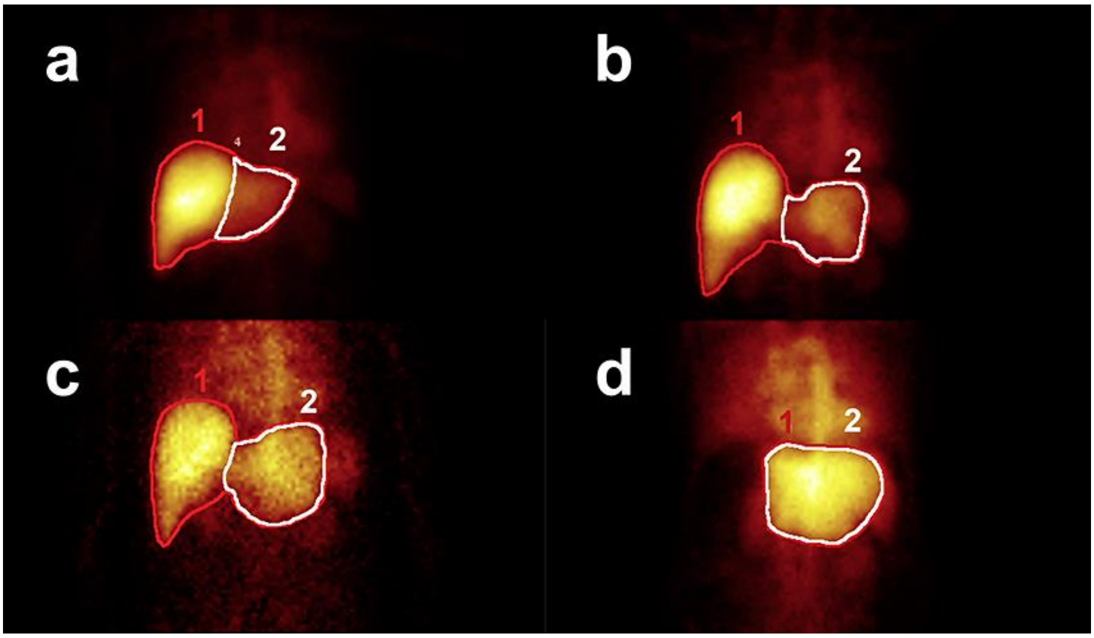

Fig. 3. Summed dynamic HBS with regions of interest (ROIs) drawn around the total liver (red line) and the FRL (segments 1, 2 and 3, white line). Another ROI around the mediastinum (not shown) serves as blood pool. From these ROIs, blood pool corrected time-activity curves can be generated. The uptake rate is subsequently corrected for the patient's metabolic requirements by dividing the uptake rate by the body surface area of the patient. **a** Baseline situation before the surgical intervention. After the first stage of ALPPS, the FLR uptake rate had increased on POD 3 (**b**) and 8 (**c**), owing to the hypertrophy response following the in situ liver transection and ligation of the right portal vein. **d** After the second stage with completion of the right extended hemihepatectomy, the uptake rate of the FRL had further increased on POD 20.