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ORIGINAL ARTICLE

Optimized separation of left and right liver lobe in dynamic ^{99m}Tc-mebrofenin hepatobiliary scintigraphy using a hybrid SPECT-CT scanner

Dominik Geisel · Lutz Lüdemann · Bernhard Gebauer · Vera Fröling · Vikas Prasad · Uwe Heimann · Martin Stockmann · Maciej Malinowski · Bernd Hamm · Winfried Brenner · Timm Denecke

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Abstract
Objective To correctly display the left and right liver lobe separately on dynamic projection scintigraphy, it is essential to adjust the collimator to the angle of the plane between the two liver lobes. We propose an optimized protocol for separating left and right liver lobe in ^{99m}Tc-mebrofenin hepatobiliary scintigraphy in a hybrid SPECT-CT device. The protocol uses the inherent attenuation correction low-dose CT (AC-CT) for individually adjusting gamma camera head angulation. The results of this protocol are compared with hypothetical results based on previous MRI, fixed angle, and traditional frontal projection.
Methods The absolute and relative degrees of overlapping volume between left and right liver lobe parenchyma for frontal projection, 45° right anterior oblique (RAO) projection, RAO angulation based on previously acquired MRI, and RAO based on the AC-CT were measured in 14 patients who underwent ^{99m}Tc-mebrofenin hepatobiliary scintigraphy.
Results Relative degree of overlap was 31.3 ± 15.2 % for frontal projection, 8.2 ± 6.5 % for 45° RAO, 5.5 ± 3.5 % for RAO based on previous MRI, and 3.6 ± 2.5 % for RAO based on AC-CT. The relative overlap of RAO projections based on previous MRI was significantly lower than for frontal projection ($p < 0.05$). Use of the angle from the prior AC-CT, however, resulted in an even lower degree of overlap ($p < 0.05$).
Conclusions Performing ^{99m}Tc-mebrofenin hepatobiliary scintigraphy using RAO detector alignment with an angle derived from a prior CT obtained in the SPECT-CT scanner can significantly reduce the degree of overlap between right and left liver lobe. If SPECT-CT is not available, previous CT or MRI or a fixed angle of 45° may be used.

Keywords MRI · SPECT · CT · Liver function · Mebrofenin scintigraphy

D. Geisel (✉) · B. Gebauer · V. Fröling · U. Heimann · B. Hamm · T. Denecke
Klinik für Radiologie, Campus Virchow-Klinikum, Charité, Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
e-mail: dominik.geisel@charite.de

L. Lüdemann
Department of Medical Physics, Essen University Hospital, Hufelandstraße 55, 45147 Essen, Germany

V. Prasad · U. Heimann · W. Brenner · T. Denecke
Klinik für Nuklearmedizin, Campus Virchow-Klinikum, Charité, Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany

M. Stockmann · M. Malinowski
Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Campus Virchow-Klinikum, Charité, Universitätsmedizin Berlin, Augustenburger Platz 1, 13353, Berlin, Germany

Introduction

The advent of new treatment options has led to an increasing need for assessing regional liver function and a rising demand for image-based regional liver function tests. The increasing popularity of imaging for this purpose is attributable to the development of new techniques in radiology and nuclear medicine with higher spatial and temporal resolution and the availability of new contrast agents. Sophisticated liver function tests are needed because more advanced surgical techniques such as extended liver resection require a reliable prognosis of postoperative residual liver function or because liver diseases such as primary biliary cirrhosis or primary sclerosing cholangitis that may affect the liver inhomogeneously may be difficult to diagnose with established tests [1–7].

Scintigraphic methods—mostly using ^{99m}Tc-iminodiacetate analogues (IDA) as tracers—are currently the only imaging-based liver function tests for assessing liver uptake and biliary excretion of such tracers that are used in clinical practice [8–10]. Dynamic ^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS) can be used to measure total liver function and to estimate the function of the residual liver volume after resection [5, 11]. Dynamic HBS has been shown to visualize the increase in future remnant liver function after preoperative portal vein embolization, to predict postoperative remnant liver function, and to correlate with the indicyanine green clearance test [4, 5, 11–13].

HBS was originally performed with a single-head gamma camera in a frontal projection [8, 14, 15]. Dual-head gamma cameras allow the acquisition of both anterior and posterior projections, with the advantage that posteriorly emitted photons also contribute to the quantitative dynamic analysis [12]. This, in theory, is more accurate for assessment of the right liver lobe, of which large parts are located dorsally in the body and are underrepresented in an anterior projection due to attenuation. The left liver lobe, on the other hand, is underrepresented on posterior projections due to the highly attenuating vertebrae behind the left lateral segments. This strongly argues against a combined anterior and posterior acquisition. With devices of the latest generation, 4D-SPECT and inherent CT scanning is possible with rapid SPECT acquisitions and SPECT-CT devices for attenuation correction (AC-CT) as promising approaches to improve regional function analysis of the liver by means of HBS [4]. However, as SPECT acquisition still provides inadequate temporal resolution for reliably displaying the early slope of liver perfusion and uptake, and quantification of the time-activity curve remains a problem with the SPECT technique, it is necessary to use a combination of SPECT and CT with intermittent planar acquisitions. Therefore, 4D-SPECT alone is still not the method of choice for quantitative assessment of regional liver function [4].

The HBS technique is typically used for separate assessment of right and left lobe liver function for planning extended liver resection. It is a planar dynamic acquisition in frontal projection, which is considered sufficient for selectively generating activity curves [8, 14, 15]. However, in a frontal view, the separation plane between right (segments 5–8) and left liver lobe (segments 1–4) or between the left lateral sector (segments 2 and 3) and segment 4, which is the resection line in right trisectionectomy, is usually not aligned perpendicular to the collimator. Therefore, acquisition in a strictly anterior–posterior orientation of the detector should result in a significant degree of overlap with the middle part of the liver representing information from both right and left liver lobes (Fig. 1).

We therefore propose an optimized protocol for separating left and right liver lobes in ^{99m}Tc-mebrofenin hepatobiliary scintigraphy by angulating the gamma camera individually based on the AC-CT acquired in a one-stop examination in a hybrid SPECT-CT scanner. This protocol is compared to the hypothetical degree of overlap resulting from the use of other angulations based on previous MRI, fixed 45° RAO, and traditional frontal projection.

Materials and methods

In this retrospective analysis, we included patients who underwent ^{99m}Tc-mebrofenin HBS according to the standard examination protocol of our department (see below) to separately assess left and right liver function between July 2010 and December 2013. Exclusion criteria were

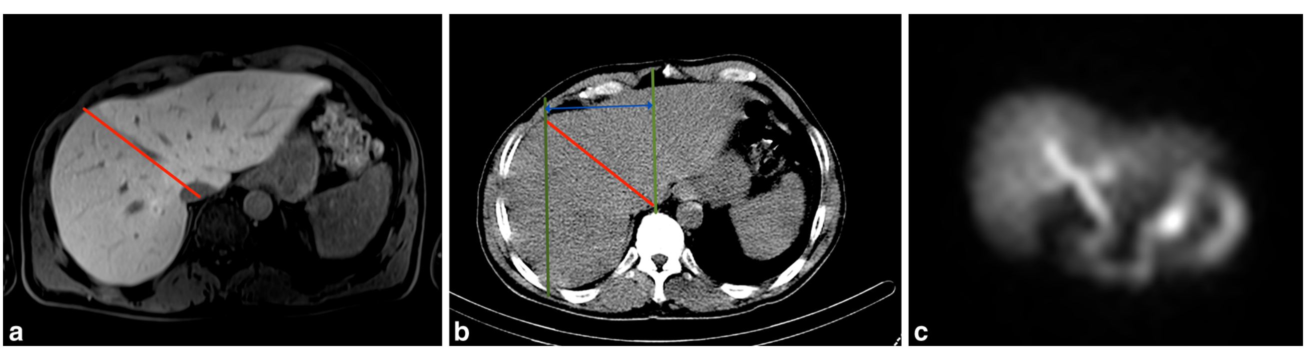

Fig. 1 50-year-old patient with colorectal liver metastasis. First image (**a**) shows Gd-EOB-enhanced MRI; the separation line between left and right liver lobe is added in the image (*red line*). Next image (**b**) shows CT scan obtained before scintigraphy; the separation line (*red*) is virtually identical. *Green lines* encircle the large area of overlap resulting when frontal projection is used; *blue line* represents the measured absolute overlap. Final image (**c**) is a representative scintigram obtained with angulated detector

age under 18 years and mental impairment. An MRI examination performed no more than 2 weeks before HBS was required for enrolment. The study complied with the Declaration of Helsinki. The study protocol was approved by the institutional review board, patients agreed in oral and written form to a possible retrospective analysis.

MRI

Gd-EOB-DTPA-enhanced MRI was performed no earlier than 2 weeks before hepatobiliary scintigraphy. MRI was acquired at 1.5 T using phased-array body coils. The imaging protocols included standard T1- and T2-weighted sequences and postcontrast T1-weighted sequences after intravenous administration of gadoxetic acid (0.025 mmol/kg body weight).

^{99m}Tc-Mebrofenin hepatobiliary scintigraphy/SPECT

All examinations were performed on a hybrid SPECT-CT scanner with a 6-slice multidetector CT component (Symbia, Siemens Healthcare, Erlangen, Germany). First, an unenhanced upper abdominal low-dose CT scan (130 kV, 36 mAs, 5 mm slices, B41s kernel) was acquired for attenuation correction.

Immediately after acquisition, the liver position in *z* axis and the angle of the plane between left and right liver lobe (landmarks: gall bladder bed, inferior vena cava, middle hepatic vein) were determined on the CT images by an experienced radiologist and nuclear medicine specialist. A line was drawn to best represent the main orientation of this plane giving the angulation to the *x*- and *y*-axes. This information was used for adjustment of the table position to cover the entire liver and the lower mediastinum including the heart and the ROA rotation angle of the gamma camera head.

Within the same examination and without moving the patient, the dynamic planar scintigraphy was started with intravenous bolus injection of 85 MBq ^{99m}Tc-mebrofenin followed by a 30 mL saline flush. A dynamic series was acquired with the liver and heart in the field of view [collimator HR all purpose; matrix 128 × 128; acquisition time, 10 s per frame for the first 10 min and 60 s per frame for the following 50 min (bile excretion sequence)].

Using only one collimator in a RAO-angled position for planar dynamic scintigraphy, falsification of count rates from the left and right liver lobe could result due to different attenuation of photons from liver tissue of the left and the right liver lobe given the distances of each liver part and the varying consistence of interposing structures (e.g. liver parenchyma, abdominal wall, ribs, air). To make sure that despite these effects a representative count rate can be acquired using the proposed technique, we performed in an initial patient with different functional capacity of the own right and the left liver lobe (auxiliary liver transplantation), a planar angle adjusted (25°) RAO-scan (acquisition time 60 min) and a SPECT/CT (LEHR collimators; FOV, 540 × 400 mm; matrix, 128 × 128; 120 frames; 3° steps; 15 s/frame) immediately after the dynamic acquisition (already hepatic plateau phase). The total measured counts in the right and left lobe in the

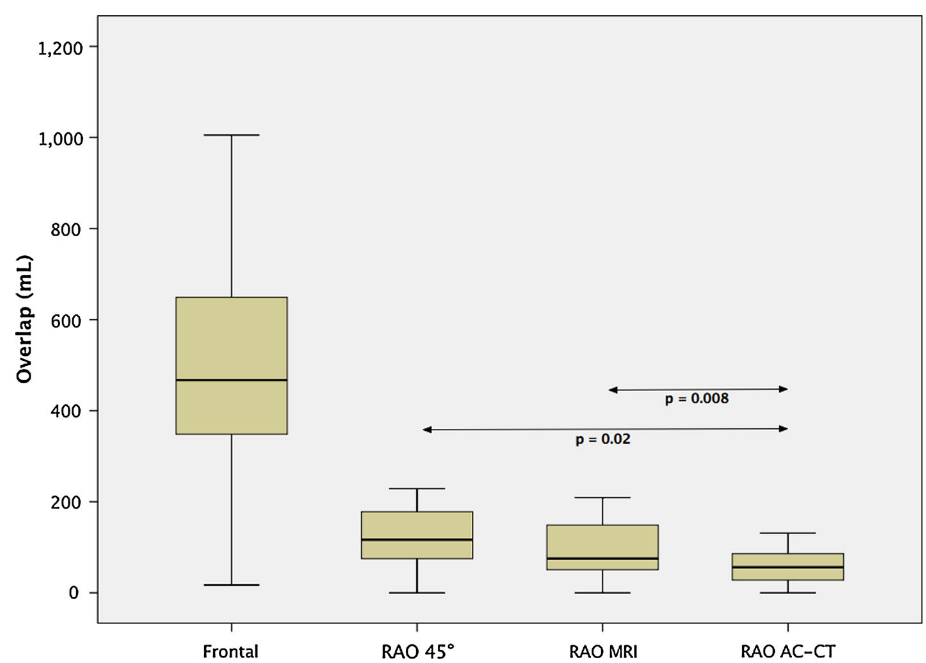

Fig. 2 Average degree of overlap in milliliter (mL) for frontal projection, fixed 45° RAO projection, RAO angle derived from previous MRI and RAO angle derived from AC-CT

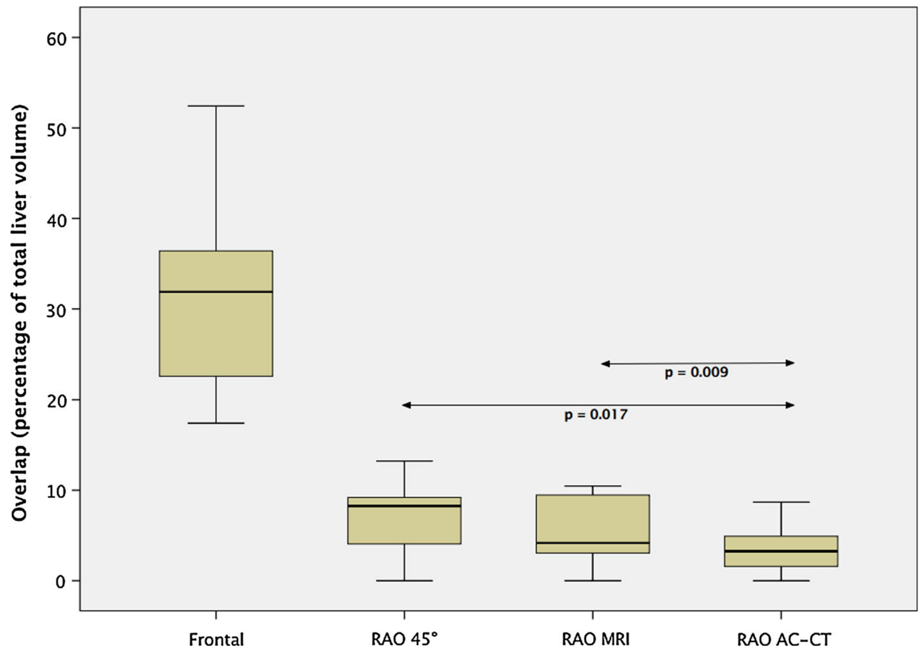

Fig. 3 Average degree of overlap expressed as percentage of total liver volume for frontal projection, fixed 45° RAO projection, RAO angle derived from previous MRI and RAO angle derived from AC-CT

attenuation corrected SPECT/CT were compared to the relative activity of the dynamic scan with RAO orientation; the proportion of right and left lobe activity happened to be equal (RLL 40.8 and 40.6 %, respectively).

Measurement of rotation angle and overlap

MRI and AC-CT images were evaluated by an experienced radiologist and nuclear medicine specialist using a dedicated 3D-viewing and postprocessing tool (OsiriX version 5.8, Pixmeo SARL, Bernex, Switzerland).

To generate the hypothetical RAO rotation angle on the basis of MRI, the MRI sequence best suited to visualize liver vein anatomy was individually selected, usually T1-weighted images in the hepatobiliary plateau phase after Gd-EOB-DTPA administration. The RAO angle was determined according to the measurement in the AC-CT as described above.

Total liver volume and all four determined degrees of overlapping volume were measured on the AC-CT scan.

To measure the overlap, the anatomical interface separating the right and left liver lobe was marked with a line individually selected in each plane using the anatomic landmarks (gallbladder, middle hepatic vein, and inferior vena cava) as proposed by Couinaud [16]. In the next step, two parallel lines with the individual rotation angle were added, one marking the rightmost portion of the overlap between liver lobes on all slices and intersecting with the separation line on the anterior liver surface and one marking the leftmost plane intersecting with the separation line on the posterior liver surface. The liver volume between these two lines, propagated on all slices, was defined as absolute overlapping volume.

First, the RAO angle, which was used for the actual rotation of the detector for the dynamic acquisition determined in the AC-CT scan, was used and the resulting overlap was measured. Next, the following three hypothetical overlap values were measured: (a) by transferring the RAO angle from the previous MRI, (b) using a fixed angle of 45° RAO, and (c) using a projection parallel to the horizontal reference line (frontal or true anterior–posterior projection).

Relative overlap was calculated as a percentage of total liver volume.

Statistical analysis

Statistical analysis was performed using PASW Statistics 21 (IBM, Armonk, NY, USA). The t test for paired values was applied to compare overlap at different angles. A p value of <0.05 was considered statistically significant. All quantitative data are expressed as mean ± standard deviation, unless otherwise indicated.

Results

Patient characteristics

A total of 14 patients (7 women, 7 men) were included in our study during the period from July 2010 to December 2013. They had a mean age of 60.3 ± 11.5 years (range

45–82). The indications for separate functional assessment of the right and left lobe using hepatobiliary scintigraphy were auxiliary liver transplantation in three patients and planned extended liver resection after portal vein embolization in eleven patients. Reasons for resection were colorectal liver metastases in two patients and cholangiocarcinoma in nine patients. Total serum bilirubin at the time of PVE was 1.52 ± 1.34 mg/dL (range 0.4–4.1, normal value <1.2 mg/dL). Four patients had Child–Pugh class A, one patient had Child–Pugh class B.

AC-CT

Gall bladder bed, inferior vena cava and main trunk of the middle hepatic vein were identifiable in all cases.

Absolute overlap

The average separation angle of right and left liver lobe in SPECT-CT was 47.1° ± 10.6°. The average absolute overlap was 536.7 ± 319.6 mL for frontal projection, 138.9 ± 116.7 mL for a fixed RAO angle of 45°, 89.7 ± 57.4 mL for RAO based on previous MRI, and 58.2 ± 39.8 mL for RAO based on inherent AC-CT. The absolute overlap for either MRI, AC-CT, or the 45° approach was significantly lower than for frontal projection ($p < 0.001$). Using AC-CT resulted in a significantly lower absolute overlap than using the fixed angle of 45° ($p = 0.02$) or RAO from MRI ($p = 0.008$) (Fig. 2).

Relative degree of overlap

The average liver volume was 1633.1 ± 326.5 mL. The relative overlap in relation to the total liver volume was 31.3 ± 15.2 % for frontal projection, 8.2 ± 6.5 % for fixed RAO of 45°, 5.5 ± 3.5 % for RAO based on previous MRI, and 3.6 ± 2.5 % for RAO based on inherent AC-CT. The relative overlap for each MRI, AC-CT, and the 45° approach was significantly lower than for frontal projection ($p < 0.001$). Using AC-CT resulted in a significantly lower relative overlap than using the fixed 45° angle ($p = 0.017$) or MRI ($p = 0.009$) (Fig. 3).

Discussion

Because of the unique potential of ^{99m}Tc-mebrofenin this drug seems to be well suited for imaging assessment and quantification of regional liver function in general and for separation of left and right lobe liver function in particular [8–10, 12–15, 17].

This, however, is possible only if the future liver remnant can be separated from the rest of the liver on the emission scan. Because 4D-SPECT still lacks temporal resolution to adequately measure the initial peak in tracer uptake, the planar scintigram has to be adjusted to individual needs. In our study population, the clinical task was to assess liver function of the left and right lobe separately and therefore, we had to develop a protocol which displays the two liver lobes side by side without overlap. With the introduction of hybrid SPECT/CT systems including diagnostic CT components, it has become straightforward to acquire a CT scan with sufficiently exact delineation of the anatomic landmarks necessary to delineate the anatomical plane between the left and right liver lobe as described by Couinaud and to determine an optimal rotation angle for the RAO position of the gamma camera head in a single examination without having to reposition the patient. This also avoids possible effects of volume shifts due to tumor or regeneration and atrophy after portal vein embolization, which may occur when older CT or MR images are used to determine the RAO angle.

With this background, we present an optimized protocol for separating left and right liver lobe in ^{99m}Tc-mebrofenin hepatobiliary scintigraphy by angulating the gamma camera using individually adjusted rotation angles and compare four different approaches to achieving this goal.

In earlier studies, investigators used anterior–posterior alignment of the detector to determine the function of the right and left liver lobe or of the future remnant liver [5, 11, 18, 19]. The anatomic position of the liver results in a distinct degree of overlap between right and left liver segments. Our investigation shows that the degree of overlap can be significantly reduced by angulating the detector to the right using either a fixed angle or an angle determined either on the basis of prior imaging or AC-CT on the SPECT/CT table. Both the absolute and relative amount of overlapping liver volume for MRI, CT, and use of a fixed 45° angle were significantly lower than for true anterior–posterior projection. This can easily be explained by the separation line practically never being oriented in anterior–posterior direction but rotated to the right with an average of about 47° in our study population. When the angle from the prior CT was used, this resulted in a significantly lower overlap than a fixed 45° angle or the angle derived from prior MRI. This can be explained by a possible difference in patient positioning on the scanner table, a different respiratory position, and changes in liver anatomy, for example because of left lobular hyperplasia following portal vein embolization.

^{99m}Tc-mebrofenin HBS is a relatively simple technique that can be applied in every nuclear medicine department with a gamma camera [10]. Our results suggest that, for separation of left and right liver lobe function, a rotating gamma camera should be used. If previous MR images are available, they can be used to determine the rotation angle.

Our study focused on the use of previous MR images as these were available for all patients. If MR images are not available, CT images may be used. Ideally, a low-dose CT scan should be acquired with the patient in the final position for HBS. This CT scan can be used to determine the rotation angle using the separation line between right and left liver lobe "on site", but has also several other advantages. First, the CT can be used to determine the optimal field of view, eliminating the risk that superior or inferior parts of the liver lie outside the detector area. CT images can also be used for liver volumetry as an additional outcome parameter of portal vein embolization. Furthermore, additional pathology that may affect the interpretation of HBS may be detected: bilioma after portal vein embolization and severe cholestasis are two examples.

Our results are most probably also transferrable to the other clinically used agent for functional liver scintigraphy—^{99m}Tc-labeled galactosylneoglycoalbumin (GSA) [20], whose distribution and kinetics in the liver can be detected using the same approach. GSA binds to asialoglycoprotein receptors—which is only present on hepatocytes—is taken up by receptor-mediated endocytosis and then degraded in lysosomes. Dynamic ^{99m}Tc-GSA scintigraphy is used for quantitative measurement of liver function as reflected by receptor concentration, although this requires a complex kinetic model [21, 22].

There are several limitations of our study. First, the number of patients analyzed was small, which can be explained by the fact that only a few patients currently undergo ^{99m}Tc-mebrofenin hepatobiliary scintigraphy. Second, the actual effect on outcome parameters derived from HBS such as mebrofenin uptake rate or hepatic extraction fraction has not been determined as this would have required multiple administrations of a radioactive tracer.

In conclusion, we propose the use of an optimized protocol with right anterior oblique alignment of the detector for ^{99m}Tc-mebrofenin hepatobiliary scintigraphy using an angle derived from a prior AC-CT in the SPECT-CT, as this can significantly reduce the degree of overlap between right and left liver lobe. If SPECT-CT is not available, CT or MRI performed just prior to HBS may be used.

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