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CLINICAL PRACTICE GUIDELINE

Joint EANM/SNMMI/IHPBA procedure guideline for [^{99m}Tc]Tc-mebrofenin hepatobiliary scintigraphy SPECT/CT in the quantitative assessment of the future liver remnant function

Pieter J.W. Arntz[1,2], Christophe M. Deroose[3], Charles Marcus[4], Christian Sturesson[5], Fabrizio Panaro[6], Joris Erdmann[1,2], Nevena Manevska[7], Renee Moadel[8], Lioe-Fee de Geus-Oei[9,10,11] & Roel J. Bennink[2,12]

[1]Department of Surgery, Amsterdam UMC, University of Amsterdam, [2]Cancer Center Amsterdam, the Netherlands, [3]Nuclear Medicine, University Hospitals Leuven, Nuclear Medicine and Molecular Imaging, Department of Imaging and Pathology, KU Leuven, Leuven, Belgium, [4]Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Emory University School of Medicine, Atlanta, GA, USA, [5]Division of Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden, [6]Department of Surgery, Division of HBP Surgery & Transplantation, Saint Eloi Hospital, Montpellier University Hospital, School of Medicine, 34000, Montpellier, France, [7]Institute of Pathophysiology and Nuclear Medicine, Acad Isak S. Tadzer, Skopje, Macedonia, [8]Division of Neuroradiology, Department of Radiology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, USA, [9]Department of Radiology, Section of Nuclear Medicine, Leiden University Medical Center, Leiden, [10]Biomedical Photonic Imaging Group, University of Twente, Enschede, [11]Department of Radiation Science and Technology, Delft University of Technology, Delft, and [12]Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands

Abstract

Purpose: The aim of this joint EANM/SNMMI/IHPBA procedure guideline is to provide general information and specific recommendations and considerations on the use of [^{99m}Tc]Tc-mebrofenin hepatobiliary scintigraphy (HBS) in the quantitative assessment and risk analysis before surgical intervention, selective internal radiation therapy (SIRT) or before and after liver regenerative procedures. Although the gold standard to estimate future liver remnant (FLR) function remains volumetry, the increasing interest in HBS and the continuous request for implementation in major liver centers worldwide, demands standardization.

Methods: This guideline concentrates on the endorsement of a standardized protocol for HBS elaborates on the clinical indications and implications, considerations, clinical appliance, cut-off values, interactions, acquisition, post-processing analysis and interpretation. Referral to the practical guidelines for additional post-processing manual instructions is provided.

Conclusion: The increasing interest of major liver centers worldwide in HBS requires guidance for implementation. Standardization facilitates applicability of HBS and promotes global implementation. Inclusion of HBS in standard care is not meant as substitute for volumetry, but rather to complement risk evaluation by identifying suspected and unsuspected high-risk patients prone to develop post-hepatectomy liver failure (PHLF) and post-SIRT liver failure.

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Correspondence

Pieter J.W. Arntz, Department of Surgery, Amsterdam UMC, University of Amsterdam, the Netherlands.
E-mail: p.j.arntz@amsterdamumc.nl

Background

Liver resection is a widely applied procedure and serves as the best option for cure intervention in primary and secondary liver malignancies. With a mortality rate below 5%, major liver resection (≥3 segments) according to the Brisbane classification, is an established safe procedure.[1,2] Depending on the parenchymal status and factors related to liver function, complications with resection limits arise when the FLR volume (FLRV) subsides

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below 30%.[3] An increase in both mortality (4–16%) and the risk of PHLF is seen when extensive resection results in a critically small FLR.[4–7] Severe postoperative complications and intensive care admission are observed in the vast majority of PHLF affected patients.[3] In the event of secondary PHLF, abdominal sepsis, portal vein and arterial thrombosis are found to be mainly at cause. For primary PHLF, severe blood loss (>2000 mL) and the absence of FLR assessment were identified as independent risk factors.[8] In order to avoid this life-threatening complication, an emphasis is made on the importance of preoperative assessment of the FLR to evaluate the risk of PHLF in patients scheduled for major liver resection.

Diagnostic standards mainly rely on computed tomography (CT)-volumetry in the determination of the FLR.[9,10] Volumetry substitutes well in healthy liver parenchyma and under the assumption that function is homogeneously distributed throughout the liver. Adversely, in patients with diseased liver parenchyma (e.g., steatosis, cirrhosis, cholestasis, chemotherapy induced damage) volume ceases to correlate well with function.[11] As a result, the actual liver function is either over- or underestimated leading to an inaccurate determination of the FLR function (FLRF).[12–15] To circumvent the incorrect substitution of volume for function, several quantitative function-based methods have been developed.[16,17]

Quantitative assessment by HBS integrates single photon emission computed tomography (SPECT) and CT imaging for the anatomical mapping of variations in regional function.[18] Although not supported by evidence from randomized trials, preoperative assessment carried out by HBS appears to be more reliable to estimate risk of post-SIRT liver failure, PHLF and liver failure-related mortalities after liver resection than assessment by CT volumetry.[12,16,19–26] Conversely, when comparing volumetric and functional cut-off values, conflicting interpretations may arise between adequate FLRV and FLRF values and result in misinterpretation of the FLR, leading to an unwarranted exclusion of a resection that is deemed safe based on HBS findings.[27,28] Therefore, in addition to volumetry, implementation of HBS is advised in the preoperative assessment for liver resection.[29,30] HBS is an increasingly applied clinical diagnostic measurement in the preoperative risk analysis of patients with an indication to undergo major liver resection.

Clinical indications and implications

Patients scheduled for major liver resection (≥3) according to the Brisbane classification,[31] with a serum bilirubin level <50 µmol/L (2.92 mg/dL) may benefit from HBS, especially when indications for an inhomogeneous distribution of liver function are present. Serum bilirubin levels require careful monitoring as hepatic uptake of [^{99m}Tc] Tc-mebrofenin in the presence of high bilirubin falsely reflects decreased hepatocyte function. The pretest high likelihood of a false low FLRF warrants postponing the acquisition until bilirubin levels decrease under conditions of reversible hyperbilirubinemia (e.g. after biliary drainage). The volumetric threshold for healthy liver parenchyma has roughly been set on an FLR of 25% of the total liver volume, considering clinical parameters are favorable. An FLRV of at least 40% is preferred in high-risk patients with diseased liver parenchyma to ensure proper postoperative liver function.[32] Misestimates of FLRV occur more frequently in high-risk patients, as function is more heterogeneously distributed in compromised livers. In these patients, rigid cut-off values for volume may oust patients from curative resection. Instead, FLRF values above cut-off still suggest safe curative resection, without increased risk of PHLF. Therefore, an additional diagnostic angle of approach is required. The advantage of HBS provides a universal cut-off value which can be applied in both healthy and compromised livers. The current clinical cut-off to pursue safe surgical resection resides at the initial value of 2.7%/min/m^2 while considerate variations in the clinical setting are observed. Additionally a cut-off value without normalization for body surface area (BSA) of 8.5%/min was instated for patients with suspected perihilar cholangiocarcinoma.[21] However, insufficient function contra-indicates resection and points to limited survival. Attention for quality of life in end stage disease is an increasingly important aspect of medicine and urges appropriate palliative care. It is recommended that no other nuclear medicine examination is performed in the 48 h for technetium and 24 h for fluorodeoxyglucose-positron emission tomography before HBS that could be misperceived as activity in the liver. The only absolute contraindication for HBS is limited to history of severe anaphylactic reaction to [^{99m}Tc]Tc-mebrofenin, however this is extremely rare.[33]

Currently used tools to evaluate liver function for SIRT include blood tests, clinical evaluation and prognostic models (i.e. Child-Pugh, MELD). Pre-SIRT assessment by HBS may improve risk evaluation and radionuclide treatment planning. SIRT is an evolving therapeutic modality, characterized by selective intra-arterial radioembolization with ^{90}Yttrium- or ^{166}Holmium microspheres. The technique predominantly targets tumorous tissue, however, inevitable radiation damage to the non-tumorous liver tissue caused by SIRT may decrease liver function of the considered healthy parenchyma. The additional deterioration of healthy liver tissue further decreases liver function and increases risk for post-SIRT liver failure. Moreover, SIRT-eligible patients frequently present with parenchymal liver disease and thus portray regional variation in the distribution of liver function, further jeopardizing functional liver capacity. Although limited, preliminary studies report on the superiority of predicting liver dysfunction with HBS over liver volumetry in monitoring functional reserve after SIRT in patients with hepatocellular carcinoma.[24,34,35]

Patients with a FLRF below the cut-off value of 2.7%/min/m^2 are more at risk of developing complications related to PHLF.[11,24] Dependent on the extent of insufficiency of the FLRF, several regenerative procedures to preoperatively increase the FLR are proposed to decrease risk of PHLF.[11,24,36] In the vast

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majority of expert hepatobiliary surgery centers portal vein embolization (PVE) is considered the standard of care for increasing FLR before major resections.[37] Structured application of preoperative PVE is suggested to contribute a major role in the decrease of liver failure and mortality rates.[21,25] However careful consideration of patients at risk for poor outcome is necessary to prevent insufficient post-PVE hypertrophy. Augmentation induced by portal and hepatic vein embolization (PVE/HVE) or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is recommended when initial FLRF values subside 1.7%/min/m^2 and estimates following PVE are predicted to induce insufficient FLR hypertrophy to ensure an adequate reserve capacity for safe resection.[38,39] Fig. 1 shows a flowchart of endorsed use of HBS.

Considerations

The following considerations have led to the inclusion of HBS in the preoperative risk analysis of patients with an indication for major liver resection, in addition to volumetry, clinical grading systems and TNM staging.

1. Volumetric assessment alone fails to identify patients with insufficient regional liver function, as volumetric measurements are incapable of discriminating between the parenchymal status of diseased and healthy livers. Extensive surgery pushes the boundaries of safe resections and requires a precise determination of the remaining functional liver capacity. Initially HBS will determine a global overview in liver function. Combined with the proposed resection margins, the FLRF value provides additional information in determining sufficient capacity of the FLR to support normal liver and regenerative function to recover from surgery without increased risk for PHLF.
2. The Indocyanine green clearance test and the LiMAx 13C-methacetin breath test provide quantitative information on liver function. Still these methods only reflect global liver function, offering no information on regional variations in functional distribution portrayed in patients with compromised liver parenchyma.[18] Performing HBS with [^{99m}Tc]Tc-galactosyl human serum albumin (Tc-GSA) is widely applied in South-East Asia. However, the fact that it is not approved for clinical use in most Western countries and its limited availability renders [^{99m}Tc]Tc-GSA unsuitable for global application [^{99m}Tc]Tc-mebrofenin is widespread available and approved for global clinical use.
3. Pre-SIRT risk-evaluation by HBS in recommended, since patients eligible for SIRT frequently present with underlying liver disease (e.g. cirrhosis, chemotherapy-associated liver injury) and consequentially more pronounced variations in the distribution of liver function. Additionally, after SIRT the susceptibility to liver insufficiency is temporarily increased by the decrease in liver function. The proposed segments for SIRT can be assessed by ability of HBS to perform measurement of regional liver function to predict the risk of post SIRT liver failure before the intervention. To anticipate high-risk predictions, SIRT can be performed in two sessions to allows the regeneration of individual segments in between. The function measurement of healthy parenchyma can be used to refine normal tissue complication probability models for SIRT, absorbed dosage could be correlated to the decrease in liver function and allows the prediction of post-SIRT total liver function (TLF).
4. Distinction between low- and high-risk patients following HBS will identify patients prone to develop PHLF and liver failure related complications. HBS can be used as a predictor to select patients for PVE/HVE, ALPPS or to refrain from FLR augmentation completely.[39]
5. Evaluation of PVE, PVE/HVE and ALPPS is complemented by HBS as a result of the strong redistribution of liver function that has been induced by embolization of the contralateral liver. Although ALPPS conveys a strong hypertrophic response, the relatively high rate of PHLF following resection is thought to be explained by the volumetric hypertrophy that exceeds the functional increase in reaching their target value. The lag of actual liver function is thereby missed in volumetry-only based assessment; as not all additional liver volume harbors equal liver function. In contrast, an underestimation of function by volume-only assessment has been found in PVE patients. Consequently, surgery can potentially be scheduled more timely as result of the discrepancy between volume and function after PVE or ALPPS.

Additional aspects currently under investigation should also be noticed.

6. Further distinction within tumor groups will provide specification in risk factors of HBS. For instance biliary excretion may provide additional information in the risk analysis in patients with possible post-hepatic obstruction (e.g. central or extrahepatic cholangiocarcinoma).
7. Two trials (HYPER-LIV01 & DRAGON1) are currently ongoing where PVE alone is compared with simultaneous PVE/HVE. The double vein embolization method is postulated to lead to increased hypertrophy and resectability. The disparity between the volumetric increase and functional increase that is seen after PVE and ALPPS will be investigated for simultaneous double vein embolization.

Cut-off values

The derivation of the initial and current FLRF cut-off value of 2.7%/min/m^2 is based on limited data from a small mixed cohort of 55 patients with predominantly biliary tumors.[11] Additionally, the HBS cut-off value is derived from a general population of patients preceding liver resection and therefore set at the higher end.[19] HBS accounts for the presence of underlying liver disease, thereby instating 2.7%/min/m^2 as a universal cut-off value

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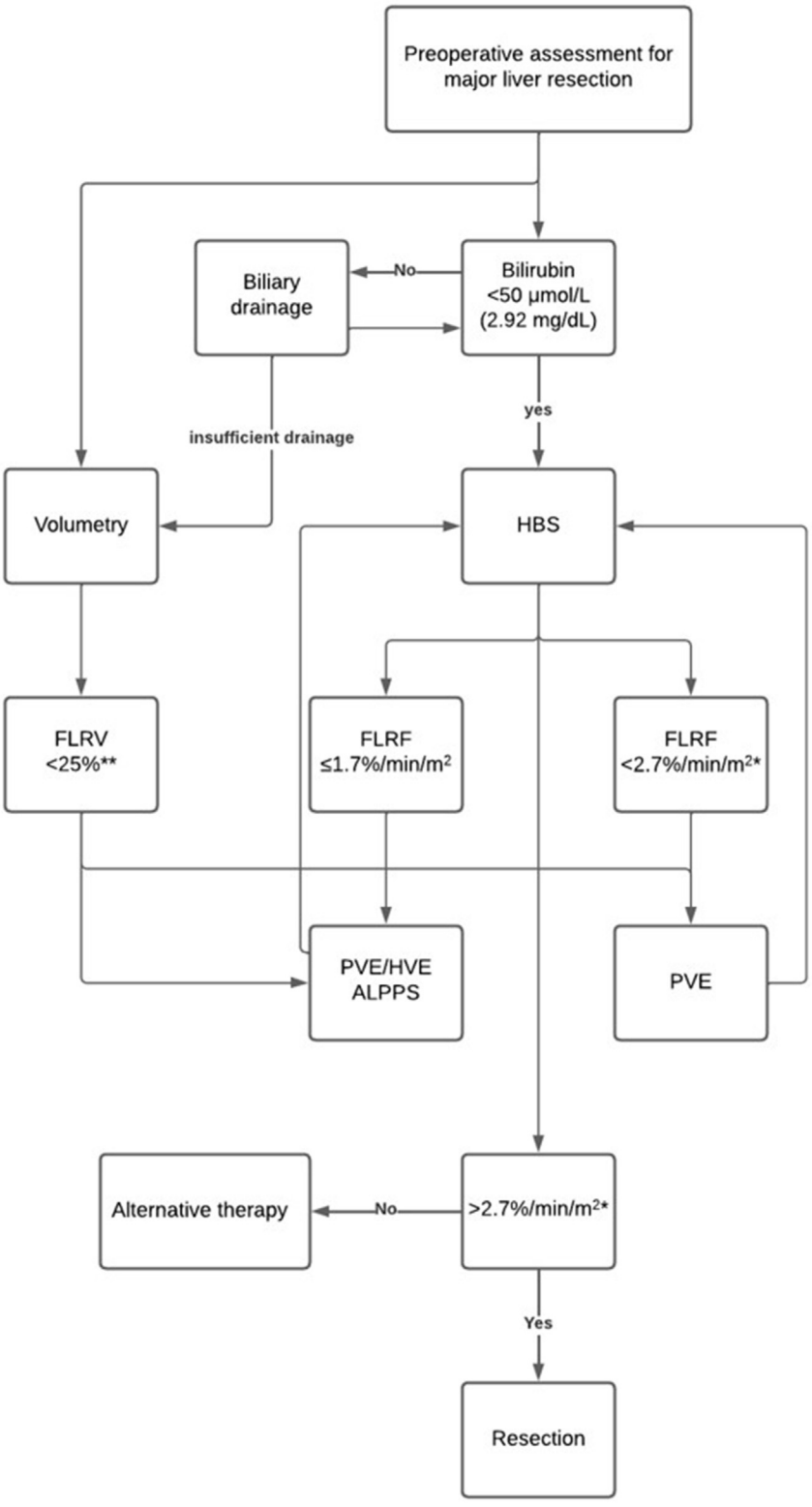

Figure 1 The clinical indication flow chart for HBS, considering the maximum serum bilirubin levels, the cut-off values and suggested regenerative procedure to achieve sufficient FLRF for safe resection. * In patients suspected of perihilar cholangiocarcinoma a cut-off value of 8.5%/min is kept. ** The volumetric threshold for healthy liver parenchyma is roughly on 25%. For diseased liver parenchyma, this is 40%. HBS:

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despite the differences in parenchymal quality. Despite the fact that the cut-off is based on a small mixed cohort, a significant decrease in the occurrence of PHLF has been achieved.[25] The cause of PHLF is multifactorial, stressing the importance of additional patient, disease and surgical related predictive factors in the risk analysis.[8,40] Initially the cut-off value should be apprehended, then again, liver function is multifactorial and the fact that HBS merely monitors the uptake and excretion of bilirubin, variation in cut-off values in the clinical setting are anticipated.[41,42] Several studies have reported a redefinition or validation of initial cut-off value either based on the "50-50 criteria" or the comprehensive "ISGLS criteria".[14,19,43–46] Dinant *et al.* proposed an additional cut-off value of 8.5%/min for patients suspected of perihilar cholangiocarcinoma.[21] In this case normalization for BSA attained no additional benefit in the prediction for PHLF. In the initial cohort only the normalized to BSA cut-off value was included in the prediction for PHLF hampering the discussion concerning the additional benefit of normalization.[11] Altogether, further specification of the cut-off values and determining the added benefit of normalization in distinct tumor types and in patients with underlying parenchymal disease is essential. Tumor and patient specific validation offers previously labelled unresectable patients a more personalized preoperative prediction of PHLF for resection without increasing morbidity and mortality. An increase in function of 1%/min/m^2 (IQR, 0.60–1.56) after PVE is reported in a mixed cohort of primary and secondary liver tumors. A cut-off value of $\geq$1.7%/min/m^2 was identified for patients who would meet a sufficient FLRF 3 weeks after PVE (area under the curve (AUC) = 0.820).[39] FLRF and TLF values should be evaluated to estimate PVE success rates. This may prevent unnecessary procedures that lead to insufficient induction of hypertrophy for safe resection.[39]

Procedure request

The uniformity of the procedure facilitates the request following the clinical indication. Patient distinction will occur during the interpretation process, depending on the tumor location and the thereby proposed resection (e.g. left or right (extended) hepatectomy with or without segment 1, 4a and 4 b). The request encompasses all for HBS clinically necessary information. This includes patient history regarding previous interventions encompassing the following: ablation, segmentectomy, SIRT, regenerative procedures and chemo- and bland embolization; past or planned neoadjuvant chemotherapeutic agent and number of administered cycles; parenchymal liver diseases; planned treatment; planned resection of segments; tumor type, both primary or secondary; parenchymal diseases; relevant laboratory values (ASAT, ALAT, GGT, bilirubin, alkaline phosphatase, albumin, PT, INR and PTT); and potential interacting medication.

Protocol

Patient preparation and precautions

Patient preparation is essential for consistency and reproducibility. The pharmacokinetic condition of the liver should be as uniform as possible since uptake of [^{99m}Tc]Tc-mebrofenin is affected by blood flow. Therefore acquisition after a minimum period of 4 h of fasting is essential to perform measurements in the presumable resting state of the hepatocytes.[47] Conversely, prolonged fasting exceeding 24 h must be prevented as biliary kinetics are altered significantly.[48] Diabetic patients are preferably scanned early in the morning.

Radiopharmaceutical ([^{99m}Tc]Tc-mebrofenin)

The administered radiopharmaceutical of interest is [^{99m}Tc]Tc-mebrofenin (2,4,6 trimethyl-3-bromoiminodiacetic acid). This iminodiacetic acid (IDA) agent is a lidocaine analogue with lipophilic properties and is taken up by hepatocytes and eliminated through the biliary tract. It allows non-invasive examination of the hepatobiliary system. Of all IDA analogues [^{99m}Tc]Tc-mebrofenin exhibits the highest hepatic uptake with minimal urinary excretion and strong resistance to displacement by elevated serum bilirubin levels.[49] The almost exclusive uptake and excretion of [^{99m}Tc]Tc-mebrofenin by the liver eliminates extrahepatic interference, characterizing it as most suitable radiopharmaceutical for the evaluation of liver function. There is a significant underestimation of mebrofenin scintigraphic liver clearance with increasing labeling-to-administration time. If liver function assessment is the purpose of a hepatobiliary study [^{99m}Tc]Tc-mebrofenin should be administered as close to the time of radiopharmaceutical preparation as possible, preferably within 1 h.[50] For the evaluation of liver function, the only cut-off values that are validated are those obtained with [^{99m}Tc]Tc-mebrofenin. Therefore, measurement of the hepatic uptake using all alternative radiolabeled IDA agents is strongly discouraged.

[^{99m}Tc]Tc-mebrofenin interactions

Hepatic uptake of [^{99m}Tc]Tc-mebrofenin is impaired in case of elevated serum bilirubin levels (>50 μmol/L) as a result of competitive uptake. Both molecules mainly follow the organic anion transporting polypeptides (OATP)1B1 and OATP1B3-mediated uptake, and predominantly multi resistant protein (MRP)2 excretion into the bile (Fig. 2).[21,41,51,52] It is hypothesized that bilirubin pharmacokinetics alter in cholestatic patients as a result of the predominant transportation of conjugated bile salts by sodium taurocholate co-transporting polypeptide. Under

hepatobiliary scintigraphy; FLRV: future liver remnant volume; PVE/HVE: portal and hepatic vein embolization; ALPPS: associating liver partition and portal vein ligation for staged hepatectomy.

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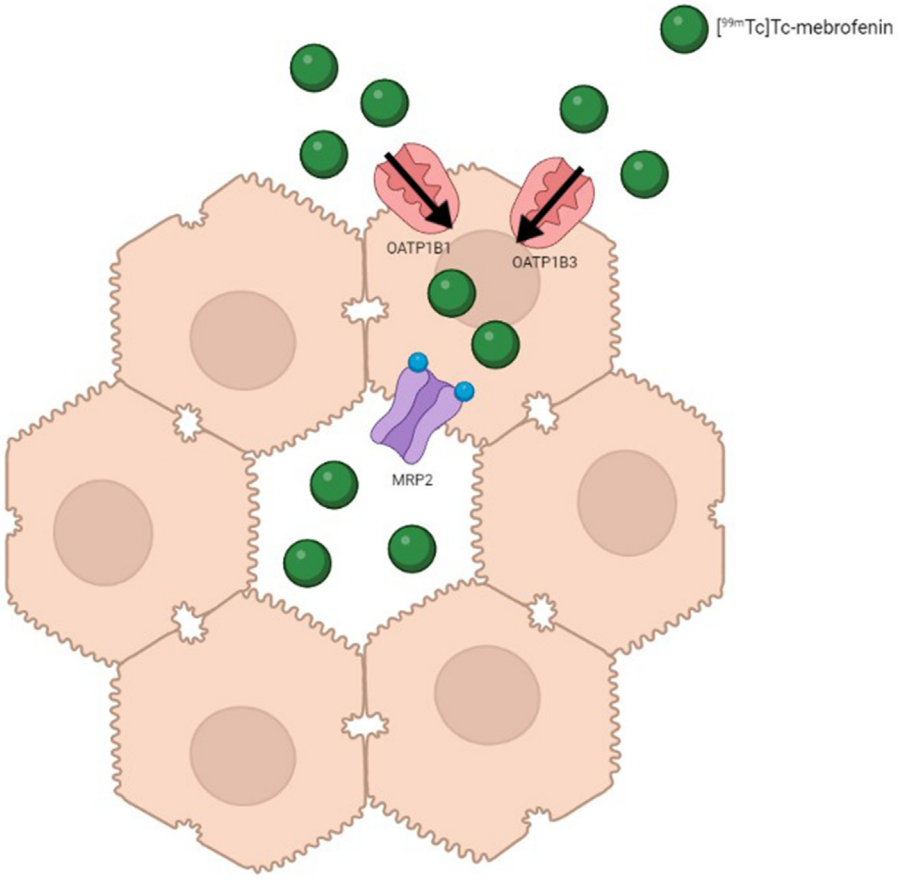

Figure 2 Predominant hepatic uptake (OATP1B1, OATP1B3) from the space of Disse and biliary excretion (MRP2) of [^{99m}Tc]Tc-mebrofenin into the biliary tract. OATP: Organic anion transporting polypeptides; MRP: Multi resistant protein

these circumstances these bile salts are redirected into the sinusoidal blood and further downstream taken up by hepatocytes for bile excretion called hepatocyte hopping.[52,53] In addition, OATP membrane transporters responsible for bilirubin uptake are downregulated under cholestatic conditions.[54] Whether the measured [^{99m}Tc]Tc-mebrofenin uptake rate (MUR) under these circumstances is an accurate representation of the actual hepatocyte function or an underestimation is subject of debate and needs further investigation.

Also severe hypoalbuminemia affects hepatic uptake of [^{99m}Tc]Tc-mebrofenin and consequentially increases renal excretion [^{99m}Tc]Tc-mebrofenin binds to albumin when transported though the blood, dissociates in the perisinusoidal space of Disse and is taken up into the hepatocytes (Fig. 3). When extremely low serum albumin levels are present, less [^{99m}Tc]Tc-mebrofenin enters the liver. Additionally, the affinity of [^{99m}Tc]Tc-mebrofenin to albumin relative to bilirubin is substantially lower leading to stronger competition between the substances.[55]

Lastly, several drug classes interact with OATP and MRP hepatocyte transporters, which potentially alter [^{99m}Tc]Tc-mebrofenin uptake and excretion kinetics.[56] Abstinence of OATPs inhibitory agents (e.g. immunosuppressors, rifampicin-antibiotics, antivirals) and MRP inhibitory agents (e.g. antivirals, cytostatic and antipsychotic agents) before HBS acquisition is instructed.[57,58]

Positioning

The patient is in supine position during the entire procedure. The patient is positioned on a dual-head SPECT/CT camera with the detectors in anterior-posterior position and the cardiac mediastinum and the liver in the field of view (FOV). The heart, liver and biliary tract up to the choledochus all are required to be in the FOV. An intravenous line, preferably with a 3-way tap is inserted in a vein of the preferred arm. The arm should be comfortably positioned, but out of the FOV to prevent interference. The arm is slightly elevated at 25°–30° and rests in place for the first dynamic acquisition to maintain continuous venous flow. For SPECT/CT, the arms should be comfortably positioned above the head. If necessary, the FOV can be modified before t = 150 s due to the lag time between the radiopharmaceutical injection and the hepatic uptake phase measurement window.

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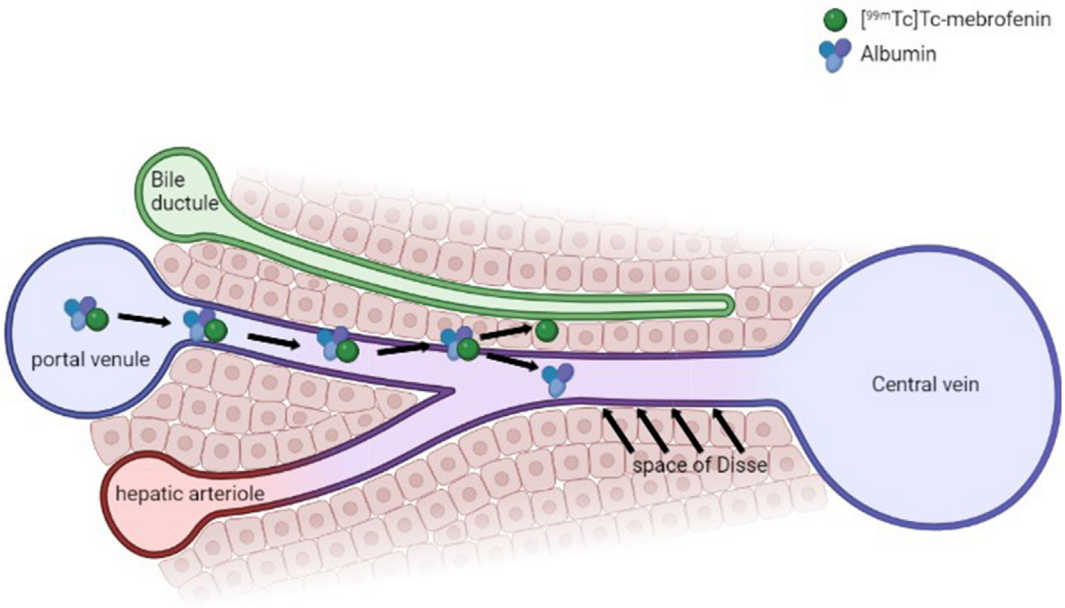

Figure 3 [^{99m}Tc]Tc-mebrofenin bound to albumin when transported though the blood dissociates in the perisinusoidal space of Disse and is taken up into the hepatocytes.

Acquisition

During the entire acquisition, no breath holds are performed. Two dynamic acquisitions are performed for measurement of the hepatic uptake phase and the biliary excretion phase. After the first dynamic acquisition, when the accumulation of the tracer has peaked, a fast SPECT/CT of the liver is performed. A correct way of positioning ensures continuous reproducibility of the process. Furthermore, the detectors need to be positioned before injection, so optimal positioning to include liver and heart is warranted.

Hepatic uptake (phase 1)

A dual head gamma camera is equipped with low-energy high resolution collimators. The energy window is set symmetrical around 140 KeV. The dynamic acquisition starts with the hepatic uptake phase and is initiated directly after the intravenous bolus injection of the radiopharmaceutical (200 MBq; 5.41 mCi). Here the extraction of tracer from the blood and the subsequent accumulation of the tracer in hepatocytes is monitored. The acquisition parameter settings are as followed: 38 frames of 10s/frame in matrix size 128 × 128, no zoom. This results in 2 spare (expendable) frames at start (the Ekman formula requires 36 frames of 10 s) to ensure that the correct frame showing appearance of activity within the abdominal aorta can be selected as the first frame for quantification.

SPECT/CT acquisition (phase 2)

In between the dynamic phases, a fast multiple angle 360° acquisition is performed to map the three-dimensional distribution of the radiopharmaceutical in the state of peak hepatic uptake. The recommended acquisition parameters are as followed: 60 frames (30 per head) of 8 s/frame in matrix size 256 × 256, zoom 1.0. For anatomical mapping fusion of SPECT with CT imaging, an additional low-dose non contrast CT scan is performed. In centers equipped with IV contrast on SPECT/CT, using IV contrast could be considered, allowing better anatomical delineation on the CT.

Biliary excretion phase (phase 3)

The dynamic acquisition continues with the biliary excretion phase. It is performed in the same patient position and immediately succeeds the SPECT/CT acquisition. The acquisition parameter settings are as followed: 20 frames of 60 s/frame in matrix size 128 × 128, no zoom.

Post-processing

Signal attenuation correction

Differences in signal intensity are detected when the anterior and posterior datasets are compared, caused by the anterior location of the left liver lobes (S2-3) relative to the cameras and the decrease in signal strength over distance (so called attenuation). To correct for the differences, a geometric mean (G_{mean}) of the combined datasets is calculated with the given formula for a more accurate estimation of the actual signal intensity.

$$G_{mean} = \sqrt{anterior \times posterior}$$

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Masking

Ideally post-processing is conducted in the state of peak hepatic uptake of the tracer. In case of rapid uptake and excretion of the tracer the SPECT acquisition will extend into the excretion phase, portraying biliary accumulation of the tracer. Biliary activity, either intrahepatic or extrahepatic, distorts the SPECT signal and impedes calculation of the TLF (Fig. 4). Biliary activity does not infer hepatic uptake and requires masking. The extrahepatic biliary ducts are defined as extrahepatic activity and reduced to a zero activity voxel count, whereas intrahepatic biliary activity is substituted with the average signal intensity of the surrounding parenchyma.

Processing of dynamic planar images to determine TLF

The first image in the hepatic uptake phase where radiopharmaceutical inflow in the aorta is detected, determines the universal starting point to ensure that all post-processing is done in similar timespan (Fig. 5). Imaging prior to the starting point is discarded. To clarify, when starting with post-processing of the

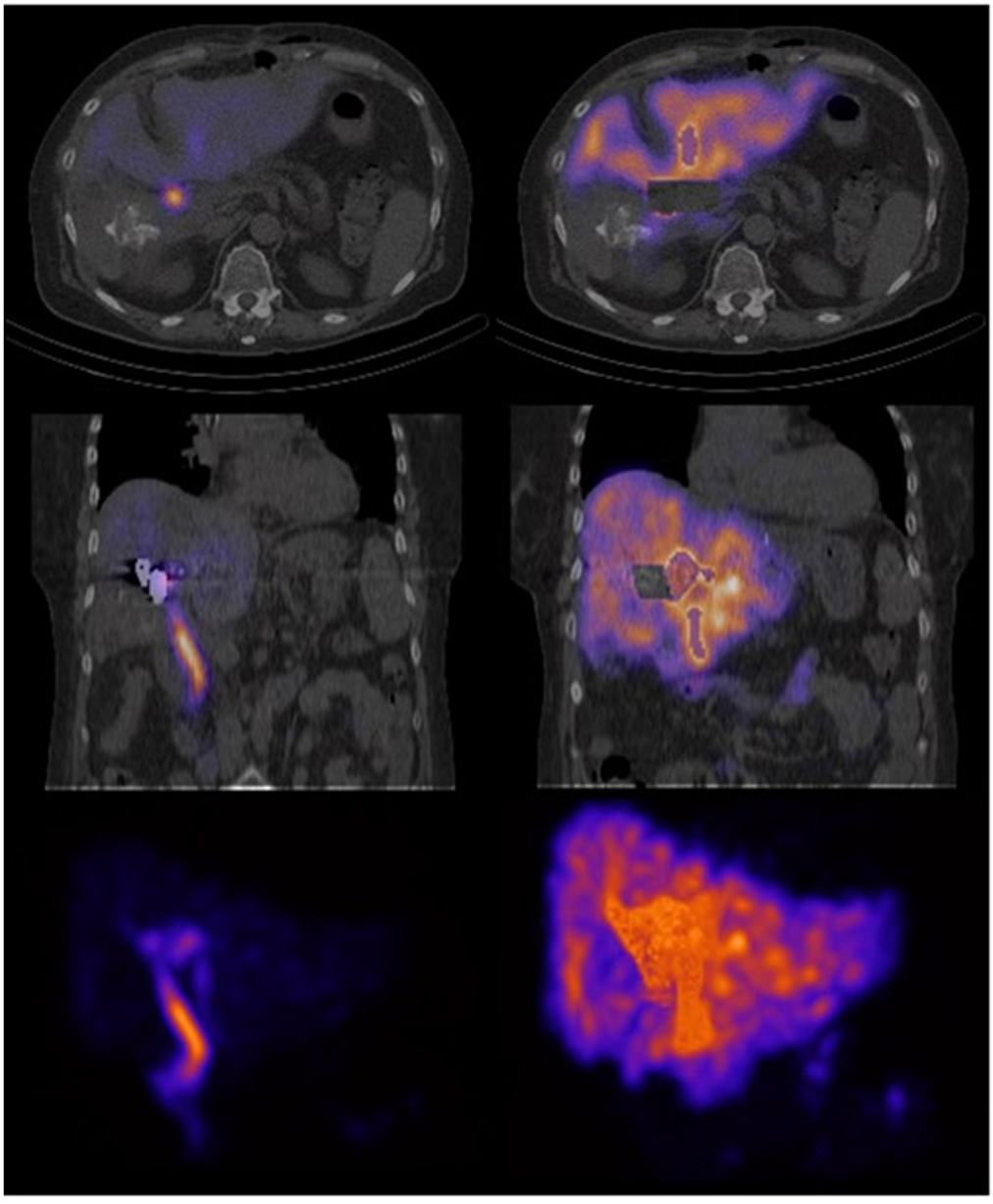

Figure 4 Result of masking the intra- and extrahepatic tracer activity in the SPECT/CT workflow. From top to bottom; the transversal and coronal plane and the 3D SPECT view. The left images represent the unmasked state with high extrahepatic tracer activity. The right images represent the masked state

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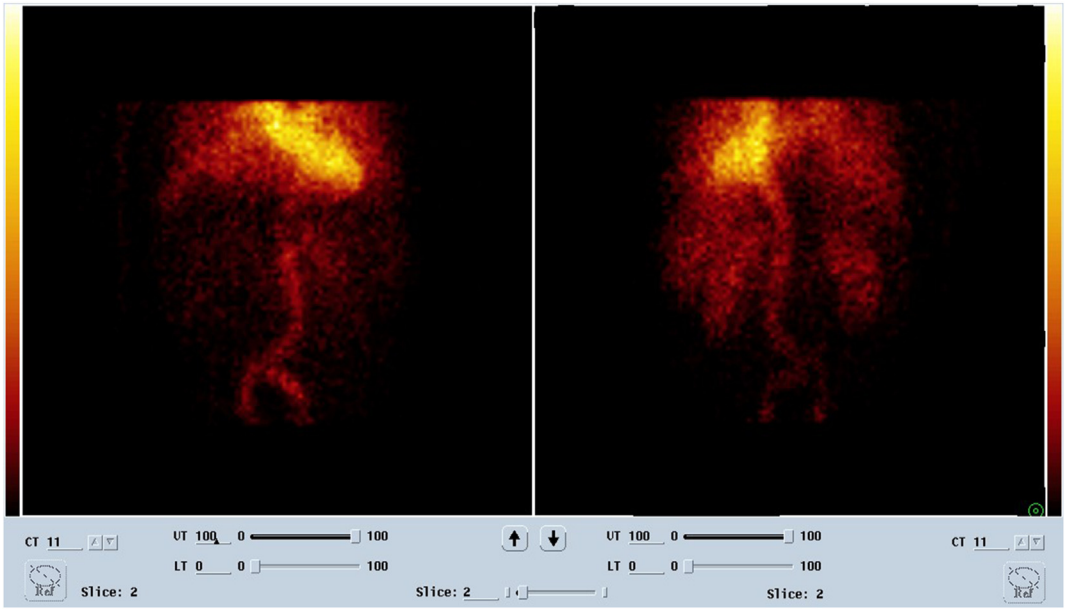

Figure 5 Anterior and posterior view of the universal starting point. The first image with tracer inflow into the aorta calibrates this point

dynamic planar images in the workflow, the selected files for post processing must be included: SPECT imaging (phase 2), low-dose CT for the demarcation of the resection margins and the corrected hepatic uptake phase (phase 1) in anterior and posterior view. The first step of post-processing comprises the selection of the region of interest (ROI) to determine the total and specific activity within the FOV. Delineation of the left ventricle demarcating strictly around the high signal intensity borders on the first image defines the first ROI, the blood pool (Fig. 6). The liver can be delineated semiautomatically, depending on the software package and forms the second ROI. Position the blood pool and liver regions with caution to prevent overlapping of the ROIs and incorrect summation of hepatic and cardiac activity. The last ROI is drawn automatically, enclosing the full FOV to define the total body activity. The time–activity curves of the ROIs are individually plotted. The [^{99m}Tc]Tc-mebrofenin hepatic uptake rate is derived from the differential gradient of the liver signal activity curve. Once all ROIs are defined, the TLF (%/min) is automatically calculated based on the Ekman formula on dynamic scans.[59] The TLF as well as the FLRF normalized to BSA (%/min/m^2) to account for individual metabolic rate is calculated based on the Mosteller formula.[60]

Processing of SPECT/CT to determine regional liver function and FLRF

The determined ROI of the liver in the hepatic uptake phase must be translated to SPECT to derive the functional share of the FLR. Delineation of the volume of interest generates the 3D functional distribution. To conduct surgical planning on the SPECT/CT fusion and determine FLRF values, the demarcation

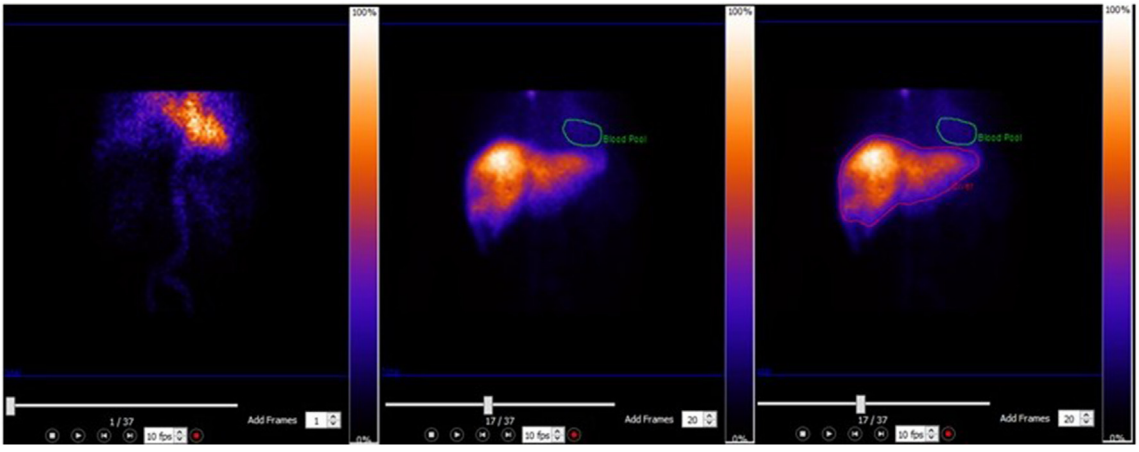

Figure 6 Delineation of the ROIs. The blood pool is demarcated in green, the liver in red

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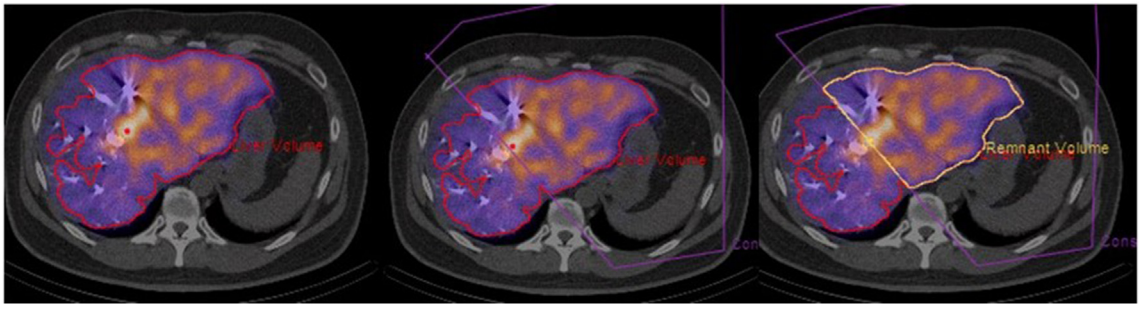

Figure 7 Demarcation of the volume of interest of the total liver and the drawn constraints to determine the FLRF of segments

of resections margins translates the ratio of sum of voxel counts from the functional share to the TLF. Delineation of the resection margins demarcates the FLR and should be done so according to the Couinaud classification (Fig. 7).[61] The FLRF can be computed by multiplying the count fraction of the FLR compared to the total liver times the FLR.

Biliary excretion rate

The biliary excretion is monitored in the second dynamic phase and is used to calculate the biliary excretion rate. The biliary excretion rate is calculated from the difference in count ratio in a representative peripheral liver ROI on the first and last frame and expressed in %/min using the following formula.

$$\frac{\frac{ROI\ frame_{20}}{ROI\ frame_{1}}}{20}100\%$$

Excretion rates below 0.5%/min in a patient with a reasonably good hepatic uptake rate can be indicative for obstruction and requires further diagnostic assessment. In patients with a very low hepatic uptake rate, excretion cannot be adequately assessed.

Reporting

The interpretation of the HBS scans are preferably reported by a nuclear medicine physician and radiologist with an expertise in HBS documentation. The report should always include a fusion of the SPECT/CT images as anatomical mapping for the display of regional variations in functional distribution is of interest for the hepatobiliary surgeon. The report should always include a summary of the procedure, commencing with a description of the first phase (liver perfusion) and an indication of the quality of the hepatic uptake of the radiopharmaceutical (second phase). This should be followed by an evaluation of the third phase: the excretion into the biliary tract, the intestinal outflow and the clearance. The variables that should be documented represent the TLF (%/min), the FLRF (%/min/m^2) with the corresponding segments and the bile excretion of these segments (%/min). Relevant results from previous scans should be included, including the numerical values of the previous examination to determine an increase or decrease in liver function.

Software

To process scintigraphic and SPECT/CT acquisitions, a variety of software programs are available on the market, which have been validated for the calculations of the MUR and are capable of determining total and regional liver function using formulas for liver clearance according to Ekman *et al.*[62] The dynamic SPECT and CT acquisitions can be shown and analyzed using the software's integrated workflow. Hepatic uptake is based on G_{mean}, and automatically derived from the anterior and posterior dynamic data sets. Within the same procedure, the SPECT and CT images are combined and visualized.

Hardware

A dual-headed SPECT/CT gamma camera equipped with a low-energy, high-resolution parallel-hole collimator is endorsed. The energy window is positioned on the photon peak of ^{99m}Tc (140 keV) at 15% or 20%. The CT component can be used as either an optimized diagnostic CT scan or for attenuation correction and anatomical localization. Use of a low milliampere-seconds setting (low-dose CT) is advised to reduce the radiation dosage to the patient if the CT scan is directed for attenuation correction and anatomical localization. Operators should be aware of the characteristics particular to their scanner as well as the range of settings that are consistent with achieving the required image quality and reference dosage values.

Literature perspectives

The initial study by De Graaf *et al.*[11] assessed the accuracy of HBS to predict PHLF in a population of high-risk patients requiring major hepatectomy. The correlation between the preoperatively predicted FLRF and the actual postoperative remnant liver function measured within 3 days was strong (Pearson r = 0.83, $P < 0.0001$). In addition, the relationship between FLRV and FLRF in healthy and compromised parenchyma was performed. This revealed the poor substitution of FLRV for FLRF in compromised liver parenchyma. Namely, FLRV showed a strong correlation with FLRF in healthy parenchyma (Pearson $r = 0.72$, $P < 0.0001$) and showed moderate correlation in compromised parenchyma (Pearson $r = 0.61$, $P < 0.0003$). The ROC analysis

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determined sensitivity (89%) and specificity (87%) for the FLRF cut-off value of 2.69%/min/m^2 to identify patients prone to develop PHLF. Patients with a value above this threshold had a 2.4% risk (negative predictive value = 97.7%, negative likelihood ratio = 0.12).

A follow-up study was performed by Dinant *et al.*[19] to compare the FLRF measured by HBS with the FLRV measured by CT-volumetry. The AUC values representing the predictive value for liver failure of FLRF were 0.90 (95% CI, 0.80–1.00) vs. 0.65 (95% CI, 0.37–93) for FLRV. The predictive value for liver failure-related mortality were 0.88 (0.75–1.00) for FLRF vs. 0.61 (0.21–1.00) for FLRV.

A consecutive study by Olthof *et al.*,[12] the increase in FLRV with the increase in FLRF was compared in 60 patients that underwent ALPPS evaluated by CT-volumetry and HBS. When comparing the parameters of liver volume with function, the AUC representing the predictive value of FLRF were 0.60 (95% CI, 0.30–0.90) for liver failure, 0.63 (0.49–0.78) for major morbidity, and 0.74 (0.50–0.98) for mortality in comparison with the AUC representing the predictive value of FLRV% was 0.51 (95% CI, 0.26–0.76) for liver failure, 0.54 (95% CI, 0.38–0.70) for major morbidity and 0.72 (0.45–0.99) for mortality.[39]

Qualifications and responsibilities of personnel

Physicians

HBS diagnostics is an interdisciplinary field at the intersection of HPB surgery, general-, interventional radiology and nuclear medicine. A close collaboration between these fields and a mutual understanding of both radiological and surgical aspects will lead to a more personalized and targeted treatment. Surgeons will determine the resection margins of the patient. Subsequently the nuclear medicine physician delineates the according segments and calculates the remnant liver function and provides an estimation on the preoperative risk for PHLF based on the FLRF. Regenerative procedures will be recommended when the segments show a function below the cut-off rate. Evaluation of these regenerative procedures will also be based on HBS to see if the gain in function has been sufficient. Physicians will work in the same workflow containing SPECT/CT imaging and the surgeon and nuclear medicine physician together settle on a surgical plan. Please refer to the practical guideline for supplementary information on the HBS methodology.[63]

Technologists

Nuclear medicine technologists need specific training to be qualified for the acquisition of HBS. The acquisition protocol is uniform and is carried out in the same manner for all patients. Nuclear medicine technologists bear responsibility for the entire image acquisition process. This includes preparing the patients, both physically and mentally since the process lasts approximately 45 min. Sustaining comfort for and correct positioning of the patient is essential to provide qualitative scan results.

The general condition and state of quality of the hardware installation must be checked and monitored regularly. Also, the technologist is involved in the patient scheduling, the ordering and/or preparing the radiopharmaceutical, proper intravenous injection and correct protocol execution, including the reconstruction and image processing. NM examinations should be executed by qualified registered/certified Nuclear Medicine Technologists.

Please refer to: Performance Responsibility and Guidelines for Nuclear Medicine Technologists 3.1 and http://www.eanm.org/content-eanm/uploads/2016/11/EANM_2017_TC_Benchmark.pdf for further details.

Physicists and IT personnel

All included personnel should be included in the multidisciplinary approach. Quality control of the equipment, which falls under specified responsibility of the technical support group (which may include technologists) or the medical physicist for both the nuclear medicine and the interventional radiology department must be maintained.

Equipment specifications, quality control and radiation safety in imaging

Gamma camera quality control must follow national rules or the manufacturer's instructions. For further guidance on routine quality control procedures for gamma cameras, refer to the SNMMI Guideline for General Imaging and the EANM guideline on routine quality control for nuclear medicine instrumentation. The radioactive concentration should be determined by measuring the activity of the radiopharmaceutical containing vial in a calibrated ionization chamber. Labelling efficiency should be >95%. The manufacturer's instructions for assessment of radiochemical purity (e.g. by thin-layer chromatography) and local laws should be followed. The administration must comply with local applicable guidelines and recommendations and has to be administered by the rapid injection as a bolus via the intravenous route, preferably via an indwelling catheter. Vials, syringes, injection needles and gloves used for injection are stored in lead-shielded containers until safe radioactive levels are attained. Side effects or incidents should be reported in accordance with applicable laws. Post-processing of data to obtain the hepatic uptake rate and future remnant liver function aimed at referring to published normal values and cut-off values should be performed according to the guidelines and with a validated application.

Conclusion

HBS is increasingly applied in the preoperative risk assessment for major liver resection and provides evaluation of both global

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and regional liver function. Standardization plays a vital role in enhancing the practicality of HBS and to encourage the widespread adoption on a global scale. The implementation of HBS into standard clinical practice is not intended to replace volumetry, but rather to complement the risk assessment by identifying both expected and unexpected high-risk patients who are susceptible to developing PHLF and SIRT liver failure. Moreover, HBS assists in the selection of regenerative procedures and outcome evaluation. Further comparison and validation of cut-off values in distinct tumor types necessitates evaluation of larger patient groups and centralization of data. Despite the fact that the use of HBS is associated with a decreased risk of PHLF, surgeons should be aware that patients are at risk of being withheld a potentially feasible resection based on borderline-insufficient function. This should be weighed in the context of potential oncological benefit and other clinical parameters in a tumor board.

Liability statement

This guideline summarizes the views of the EANM Oncology and Theranostics Committee, the SNMMI and IHPBA. It reflects recommendations for which the EANM/SNMMI/IHPBA cannot be held responsible. The recommendations should be taken into context of good practice of the different disciplines (mainly Nuclear Medicine and Hepatobiliary Surgery) and do not substitute for national and international legal or regulatory provisions.

Compliance with ethical standards

- This study received no funding.
- All authors declare no conflict of interest.
- Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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Declaration of competing interests

None to declare.

Supplementary information

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology, and practical application of nuclear medicine. The European Association of Nuclear Medicine (EANM) is a professional non-profit medical association that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985. SNMMI and EANM members include physicians, radiologists, technologists, and scientists specializing in the research and practice of nuclear medicine.

The International Hepato Pancreato-Biliary Association (IHPBA) is a world renowned non-profit organization founded in 1978, dedicated to alleviating global human suffering caused by hepatopancreaticobiliary illnesses through promoting understanding of the causes, investigation and treatment of disorders of the liver, pancreas and biliary tree. Also the interchange of clinical and scientific knowledge among surgeons and members of related disciplines working in this field is encouraged.

The SNMMI and EANM periodically define new guidelines for nuclear medicine practice to help advance the science of nuclear medicine and improve the quality of service to patients throughout the world. Existing practice guidelines are reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated. Each practice guideline, representing a joint policy statement by the SNMMI/EANM, has undergone a thorough consensus process in which existing evidence has been subjected to extensive review. The SNMMI and EANM recognize that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice guideline by those entities not providing these services is not authorized.

These guidelines represent an educational tool designed to assist practitioners in providing appropriate care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons, and those set forth below, both the SNMMI and the EANM caution against the use of these guidelines in litigation in which the clinical decisions of a practitioner may be called into question.

The officers and the committees of the IHPBA are committed to providing useful tools and communications to the member organization with a view to providing improved standards and training of hepato-pancreato-biliary surgeons.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the physician or medical physicist in light of all the circumstances presented. Thus, there is no implication that an approach differing from the guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, advances in knowledge or technology subsequent to publication of the guidelines, local regulatory requirement, or reimbursement frameworks. The practice of medicine includes both the art and the science of the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment.

Therefore, it should be recognized that adherence to these guidelines will not guarantee a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

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Members of the EANM Oncology Committee (Christophe Deroose, Nevena Manevska and Lioe-Fee de Geus-Oei) and the SNMMI representatives (Renee Moadel and Charles Marcus) invited the IHPBA Research Committee (represented by Fabrizio Panaro, Christian Sturesson and Joris Erdmann) and a senior and junior expert (Roel Bennink, Pieter Arntz) to take part in developing this guideline.

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