New Perspectives in the Assessment of Future Remnant Liver

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Abstract

In order to achieve microscopic radical resection margins and thus better survival, surgical treatment of hepatic tumors has become more aggressive in the last decades, resulting in an increased rate of complex and extended liver resections. Postoperative outcomes mainly depend on the size and quality of the future remnant liver (FRL). Liver resection, when performed in the absence of sufficient FRL, inevitably leads to postresection liver failure. The current gold standard in the preoperative assessment of the FRL is computed tomography volumetry. In addition to the volume of the liver remnant after resection, postoperative function of the liver remnant is directly related to the quality of liver parenchyma. The latter is mainly influenced by underlying diseases such as cirrhosis and steatosis, which are often inaccurately defined until microscopic examination after the resection. Postresection liver failure remains a point of major concern that calls for accurate methods of preoperative FRL assessment. A wide spectrum of tests has become available in the past years, attesting to the fact that the ideal method-

ology has yet to be defined. The aim of this review is to discuss the current modalities available and new perspectives in the assessment of FRL in patients scheduled for major liver resection.

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Introduction

Surgical resection remains the only potentially curative treatment option for patients diagnosed with primary or metastatic hepatic tumors. In order to achieve microscopically radical resection margins and thus better survival, surgical treatment has become more aggressive in the last decade, resulting in an increased rate of complex and extended liver resections being performed in specialized centers. This development has largely been made possible by thorough workup of candidates for major liver resection as well as new surgical techniques and improvements in the management of intraoperative and postoperative complications. Major liver resections are now established procedures in liver surgery with an acceptable procedure-related mortality. At the same time, the number of patients qualifying for liver resection has increased as the limits of liver resection have been pushed

further with new modalities to manipulate liver volume and tumor such as portal vein embolization (PVE) and neoadjuvant chemotherapy.

Postoperative outcomes mainly depend on the size and quality of the future remnant liver (FRL). Liver resection, when performed in the absence of sufficient FRL, inevitably leads to postresection liver failure, a severe and potentially life-threatening complication. The incidence of postoperative liver failure as reported in the literature ranges from 0.7 to 9.1% [1]. The management of postresection liver failure is mostly supportive and liver failure-related mortality remains as high as 80% [1]. In addition to the volume of the liver remnant after resection, postoperative function of the liver remnant is directly related to the quality of the liver parenchyma, which in turn is mainly dictated by underlying diseases such as cirrhosis and steatosis [2, 3].

Despite advances in the surgical and perioperative fields, postresection liver failure remains a point of major concern calling for accurate methods to assess function of the FRL in the workup of candidates for major resection. A wide spectrum of tests to assess FRL has become available in the past years, attesting to the fact that the ideal methodology has yet to be defined. The aim of this review is to discuss the current modalities available and address new perspectives in assessment of the FRL in patients scheduled for major liver resection.

Volumetric Measurement Techniques: The Gold Standard and Novel Methods

The current gold standard in the preoperative assessment of FRL volume is computed tomography (CT) volumetry, as initially described by Heymsfield et al. [4]. With this technique, FRL volume can be calculated by manually tracing the liver contour in each sectional image and summing up the volume of all slices. The three-dimensional reconstruction is then used to calculate the nontumorous liver volume, tumor volume, and FRL volume.

In most centers, an FRL volume of 25% is accepted as sufficient in patients without underlying parenchymal disease [5]. In patients with a compromised liver, an FRL volume of at least 40% is considered acceptable [6]. Insufficient FRL volume is associated with poor postoperative outcome as the frequency of major complications increases, including an increased occurrence of postresection liver failure and prolonged hospital stay [5, 7]. CT volumetry can be used as a tool in preoperative selection of patients for resection. When FRL volume is insuffi-

cient, applying CT to monitor the volumetric increase on FRL after PVE is considered an important prognosticator of postoperative liver function [8]. The main advantage of CT volumetry is its noninvasive character, and since CT is frequently used as part of the clinical follow-up, volumetric calculation can be carried out using the same CT imaging series.

Nevertheless, preoperative assessment of liver function based on CT volumetry alone does have important limitations. Firstly, the manual tracing of the liver contour is a time-consuming process. Secondly, tumor characteristics, such as small tumor size, multiple lesions, and liver characteristics (e.g. small or large liver due to compromised liver parenchyma) make CT volumetry an error-sensitive imaging technique [6, 9]. An important note to the latter is the discrepancy between CT volumetry, liver function, and postoperative outcome [10]. FRL volume does not reflect the function of the FRL, which might be impaired by underlying parenchymal disease or hepatic comorbidity such as fibrosis, cirrhosis, or steatosis. It is important to identify patients with a compromised liver in order to interpret the volumetry results correctly [11]. This has become even more important since many patients are now presented for resection after extensive induction or neoadjuvant chemotherapy, whereby liver parenchyma can be injured by postchemotherapy steatosis or veno-occlusive disease [12]. In the absence of preoperative biopsies, parenchymal damage or disease is often elusive until after the resection specimen has been examined. Thirdly, the selection criteria for resection based on volumetric data are to be considered arbitrary as the minimal FRL volumes proposed in literature vary widely (10–40%), are based on different grades of hepatic disease, and have been established by different measuring methods [13]. Finally, CT volumetry can be used to monitor FRL volume after PVE. However, as mentioned earlier, volume is not necessarily representative of FRL function. Recently, a discrepancy between the volumetric and functional changes after PVE has been described where FRL functional increase exceeded the volumetric increase [11].

Although CT volumetry is the current gold standard in the assessment of the FRL, its role should be reconsidered due to the limitations mentioned above. In order to better predict postoperative outcome, CT volumetry should be at least complemented with a regional liver function test.

In order to overcome some of the shortcomings of the traditional CT volumetric assessment, adjustments have been made to personalize this method. Urata et al. [14] introduced a novel method of total liver volume estima-

tion based on the finding that, in adults without chronic liver disease, liver volume correlates linearly with body size and weight. As this method was based on findings among an Asian population, it did not find application in Western countries. Vauthey et al. [15] introduced a modified method of total liver volume estimation based on Western patient characteristics: estimated total liver volume (eTLV; in ml) = $-794.41 + 1,267.28 \times \text{body surface area}$. The validity of this formula in estimation of total liver volume has been demonstrated several times [16–18]. The ratio of FRL volume measured by CT volumetry and eTLV is called the standardized FRL volume and represents the percentage of liver that will remain after resection. The standardized FRL volume is described as an accurate method in predicting postoperative outcome in patients with healthy liver parenchyma who undergo extended resection. The frequency of complications increases when standardized FRL volume is <20% of the eTLV [19]. According to Ribero et al. [20], the thresholds for safe hepatic resections using standardized FRL volume should be set to 20% in patients with normal livers, 30% in patients with chemotherapy-related liver injury, and 40% in case of chronic liver disease. PVE should be considered in patients who do not meet these criteria [20].

This method, however, has limitations, namely that it may not be reliable in patients who undergo repeated hepatectomies or in patients with a borderline FRL volume/eTLV ratio. Alternatively, Truant et al. [21] introduced another formula, consisting of the ratio of FRL volume measured by CT volumetry and body weight (FRLV-BWR). The concept originates from assessment of potential donors in living-donor liver transplantation surgery, where the minimum graft volume is estimated as 0.8% of the recipient's weight, although, in emergency cases, a graft volume of 0.6% of the recipient's weight is accepted [22–25]. Truant et al. [21] found that patients with an FRL volume of <0.5% of their body weight are at risk for postresection liver failure and ensuing mortality. They concluded that the FRLV-BWR method is more reliable as a predictor of postoperative course in noncirrhotic patients than traditional CT volumetry [25].

Both standardized volumetry and FRLV-BWR were compared in a small retrospective study including 68 patients, which revealed an equal ability of both methods to predict postoperative outcome after major resection [26]. Despite these promising results, the main limitation of CT volumetry methods is the fact that volumetric estimation of FRL does not take into account the quality of the liver tissue and therefore is not reliable as a predictor of function in patients with compromised livers.

A novel parameter in the evaluation of the degree of hypertrophy after PVE, kinetic growth factor, was recently proposed by Shindoh et al. [27]. Kinetic growth factor is the percentage point difference between the volume before and after PVE at the first post-PVE evaluation divided by the number of weeks. According to the authors, the kinetic growth factor is a more accurate predictor of postoperative outcome after resection in patients with colorectal metastasis compared to the standardized FRL volume.

Liver Function Tests

Although it is difficult to define liver function, it can be described as a spectrum of processes performed by the liver. Those processes can be divided in four categories: uptake, synthesis, biotransformation, and excretion [28, 29]. Liver function tests can be divided in conventional laboratory blood assays and quantitative tests. Both are discussed in the following sections.

Laboratory Blood Assays and Clinical Scoring Systems

Conventional liver function tests are frequently used in clinical practice. 'Liver function tests' refer mostly to the set of laboratory blood assays of liver-related biochemical substances. None of these measured substances, however, truly represents liver function as they measure products or by-products of the above mentioned processes instead of the processes themselves. This is exemplified by the frequently performed test to assess serum albumin, which is synthesized exclusively by hepatocytes and subsequently excreted into the blood. Despite its unique production site, albumin serum levels can be influenced by other processes in the body such as systemic inflammation, the nephrotic syndrome, malnutrition, or protein-losing enteropathy.

Nevertheless, conventional liver function tests are frequently used for different clinical purposes, including categorization schemes based on laboratory findings such as the Model for End-Stage Liver Disease (MELD) and Child-Pugh-Turcotte (CPT) scoring systems. MELD uses the International Normalized Ratio in combination with serum bilirubin and serum creatinine values to predict survival in patients with chronic liver disease. The CPT score is also widely used and includes serum bilirubin level, albumin level, and prothrombin time together with the presence or absence of encephalopathy and ascites. CPT categorizes patients into three groups and has been used in the selection of patients with hepatocellular carcinoma

and cirrhosis for resection or transplantation. However, both scoring systems are not able to identify patients at risk for postoperative liver failure, and as such they are not suitable as a diagnostic tool in the preoperative setting [30–33].

Quantitative Liver Function Tests

Other tools used in the assessment of FRL are quantitative liver function tests, which are based on the capacity of the liver to clear a systematically administered agent that is mostly or exclusively cleared by the liver. Quantitative liver function tests are distinctive for their noninvasive character. Furthermore, as these tests address one of the liver's true processes, they provide more reliable information in the setting of preoperative liver function assessment, especially in patients with unknown underlying liver disease.

Worldwide, the indocyanine green (ICG) clearance test is the most commonly used quantitative liver function test in clinical practice, especially in liver surgery. Once introduced as a modality for the measurement of blood flow, it is now mainly used for the assessment of liver function [34]. ICG is a highly plasma protein-bound, water-soluble anionic organic tricarbocyanine dye. It was first introduced by Caesar et al. [35] in 1961. After intravenous injection it is taken up by organic anion transporting polypeptides (OATPs) and Na⁺-taurocholate co-transporting polypeptide, which are abundantly located in the basolateral membrane of hepatocytes [36]. Subsequently, ICG is removed from the blood exclusively by the liver and excreted into the bile without intrahepatic biotransformation [37]. ATP-dependent, export pump multidrug resistance-associated protein 2 (MRP2) is responsible for the biliary excretion of ICG [38, 39]. This test reflects the capacity of the liver to take up and excrete organic anions such as bilirubin.

With respect to the protocol, 0.5 mg · kg⁻¹ of ICG is administered intravenously after an overnight fast. Clearance of the agent is measured by serum sampling or pulse dye densitometry using a transcutaneous optical sensor. The ICG clearance test is performed after an overnight fast as food consumption stimulates hepatic function and increases portal venous inflow and bile flow, and may thus influence the test results. The results can be expressed as the plasma disappearance rate, ICG elimination rate constant, or the percentage of retained ICG 15 min after administration (ICG-R15), of which ICG-R15 is most commonly used. Although several studies have found an additional value of the ICG test in predicting safe liver resection, there is no consensus on the safety

limit, as this varies from 14 to 20% ICG-R15 [40–42]. ICG-R15 was also proposed as a component of an algorithm together with bilirubin and ascites for the prediction of the safety of liver resection, especially in patients with chronic liver disease [43–45]. The authors report zero or close to zero mortality after resection when using the proposed decision tree. The preoperative ICG elimination rate constant is also described as a valuable parameter in evaluating liver functional reserve [46].

Despite its widespread use, the use of ICG as liver function test has several limiting factors as well. The uptake of ICG can be impaired in the presence of hyperbilirubinemia since the uptake is facilitated by common hepatic transporters. Furthermore, the ICG clearance test depends on overall liver blood flow, which means that the test is less reliable in patients with non-flow-depending hepatic diseases such as intrahepatic shunting or sinusoidal capillarization [44]. In order to avoid these shortcomings, interpretation of the ICG test should be done with caution. Moreover, the ICG test provides information on total liver function while segmental differences in liver function might exist, which can be of great significance, especially in the setting of major liver resection.

Scintigraphic Liver Function Tests

^{99m}Tc-labeled diethylenetriaminepentaacetic acid galactosyl human serum albumin (GSA) scintigraphy and hepatobiliary scintigraphy (HBS) with ^{99m}Tc-labeled iminodiacetic acid (IDA) derivatives are the most widely used radiopharmaceuticals for scintigraphic liver function tests. Although both methods are based on different principles, both provide quantitative and visual information on total and regional hepatic function. ^{99m}Tc-GSA scintigraphy and ^{99m}Tc-mebrofenin HBS are discussed in this section.

^{99m}Tc-GSA Scintigraphy

The asialoglycoprotein receptor is specific for asialoglycoproteins, which are formed after the removal of sialic acid from endogenous glycoproteins by sialidases. Asialoglycoproteins bind to asialoglycoprotein receptors on the hepatocyte sinusoidal surface and are subsequently taken up by receptor-mediated endocytosis and delivered to lysosomes for degradation. Chronic liver disease is associated with a decrease in the amount of asialoglycoprotein receptors [31] and accumulation of plasma asialoglycoproteins [31, 47, 48]. The ^{99m}Tc-labeled asialoglycoprotein analog, ^{99m}Tc-GSA, was clinically intro-

duced as a new scintigraphy agent for imaging of the human hepatic receptor [49, 50]. ^{99m}Tc -GSA is commercially available in an instant labelling kit in Japan [49]. The liver is the only uptake site for ^{99m}Tc -GSA, which makes it an ideal agent for liver function assessment. Furthermore, the uptake of ^{99m}Tc -GSA is not affected by high bilirubin serum levels, making ^{99m}Tc -GSA scintigraphy applicable in cholestatic patients [51].

^{99m}Tc -GSA is intravenously injected, after which a gamma camera is positioned over the heart and the liver. Regions of interest (ROIs) are generated enabling the calculation of the hepatic uptake and blood clearance of the agent. Multiple other parameters can be calculated using different kinetic models [52–55]. Due to the complexity of these models they are not widely used in clinical practice, leaving the hepatic uptake and blood clearance ratios as the most commonly used parameters. Both can be determined from planar dynamic ^{99m}Tc -GSA scintigraphy.

The clinical usefulness of planar dynamic ^{99m}Tc -GSA scintigraphy in liver surgery has frequently been described. Many studies have shown ^{99m}Tc -GSA scintigraphy to be a reliable method for preoperative prediction of postoperative outcome after liver resection, including major complications [56–59]. Prediction of postoperative complications based on the hepatic uptake ratio has been proposed several times, although postresection liver failure has also been observed in patients with relatively normal uptake of ^{99m}Tc -GSA, probably because planar dynamic ^{99m}Tc -GSA does not provide information on regional liver function [56, 58, 59].

Although hepatic uptake and blood clearance ratios of ^{99m}Tc -GSA have been used for the last 20 years, results can be influenced by scatter effects, body movements, and interoperator and interinstitutional differences [57, 60]. A novel parameter was introduced in order to overcome these shortcomings, i.e. the index of convexity – a parameter that is generated from the shape of the liver time-activity curve. Miki et al. [61] demonstrated that this parameter correlated well with conventional liver tests and was superior to the standard parameters in differentiating healthy and cirrhotic livers.

Another new kinetic model of ^{99m}Tc -GSA scintigraphy is the uptake index. The uptake index was developed to show the speed of receptor-mediated endocytosis of ^{99m}Tc -GSA. The uptake index is the ratio of the rate of transport of ^{99m}Tc -GSA through the hepatic cell membrane from the total plasma ^{99m}Tc -GSA at any given time. As this model correlates with traditional serological tests, the authors of this method expect this model to gain popularity in the field of liver function assessment [62].

In order to improve the assessment of regional liver function and to measure the functional liver volume, ^{99m}Tc -GSA scintigraphy was combined with static single photon emission computed tomography – CT (SPECT-CT). The great advantage of ^{99m}Tc -GSA SPECT-CT is the ability to distinguish functional liver tissue from non-functional liver tissue [63]. This is especially important in patients with advanced liver disease in whom liver volume does not correspond to the amount of functional hepatocytes, e.g. patients with advanced fibrosis who maintain at least the initial liver volume over a longer period of time while the amount of functional hepatocytes is decreased. Nowadays, ^{99m}Tc -GSA scintigraphy can be performed with dynamic SPECT-CT to allow a three-dimensional measurement of ^{99m}Tc -GSA uptake. The liver uptake ratio and liver uptake density can be calculated from dynamic SPECT-CT acquisitions. Dynamic SPECT-CT has proven valuable in the preoperative prediction of postoperative outcome after liver surgery [63]. The liver uptake ratio of the FRL has been shown to correlate well with postoperative liver function parameters and is considered a useful tool in the preoperative assessment [64]. Furthermore, functional liver volume can be correctly estimated with ^{99m}Tc -GSA SPECT-CT [65].

The applicability of ^{99m}Tc -GSA SPECT-CT in monitoring FRL after PVE has been evaluated several times. In cirrhotic and noncirrhotic patients, the increase in FRL function after PVE was more pronounced compared to the volumetric increase measured with CT volumetry [66, 67]. Currently, changes in the FRL after PVE are monitored by CT volumetry, implying that GSA could be of additional value in the management of patients who undergo PVE because of insufficient FRL.

Another field where ^{99m}Tc -GSA SPECT-CT could possibly find use is the monitoring of liver regeneration after hepatic resection. Several studies have reported a more advanced increase in liver function versus increase in volume [68–70], although the available studies do not deliver clear evidence for this statement due to methodological and analytical errors, leaving this question to be answered in the future. Moreover, the ^{99m}Tc -GSA uptake may underestimate hepatic regeneration in the later stages of liver regeneration, as shown by de Graaf et al. [71] in a rat model.

Recently, there has been increased interest in combining the validated ability of GSA in targeting asialoglycoprotein receptors with positron emission tomography (PET) because of its excellent imaging resolution and quantification possibilities. For this purpose, GSA needs to be labeled with gallium-68 (^{68}Ga). From the PET im-

ages, ROIs of the heart and the liver are generated followed by generation of time-activity curves and corresponding parameters (time to reach 90% of the peak value and the time in which the heart curve drops to 50% of the peak value). The GSA labeling techniques, metabolic stability, and imaging properties of ^{68}Ga -GSA were investigated and compared to standard $^{99\text{m}}\text{Tc}$ -GSA in a rat model, showing promising results for the future use of ^{68}Ga -GSA PET in the assessment of liver function [72].

HBS with IDA Derivatives

$^{99\text{m}}\text{Tc}$ -IDA agents were introduced in 1976 by Loberg et al. [73]. These lidocaine analogs are transported to the liver bound to albumin and dissociate from albumin in the space of Disse. Hereafter the compounds are taken up by hepatocytes by a process similar to the uptake of unconjugated bilirubin. Unlike unconjugated bilirubin, however, $^{99\text{m}}\text{Tc}$ -IDA agents do not undergo any biotransformation after hepatic uptake and are directly excreted into the biliary system in the same manner as other substances, such as conjugated bilirubin, hormones, and drugs. Hepatic uptake represents one of the main hepatic processes [74, 75].

$^{99\text{m}}\text{Tc}$ -mebrofenin is the most liver-specific $^{99\text{m}}\text{Tc}$ -IDA derivative [36, 76]. The uptake of mebrofenin is facilitated by OATPB1 and OATPB3 transporters [36]. Hepatic uptake of IDA agents via OATPs can be influenced by high serum bilirubin levels, as the same transporters are involved in the uptake of organic anions like bilirubin. Of all the available IDA agents, $^{99\text{m}}\text{Tc}$ -mebrofenin shows the lowest displacement by bilirubin in case of hyperbilirubinemia. The excretion of mebrofenin is most likely facilitated by MRP2 [76, 77]. The uptake, excretion, and lack of hepatic biotransformation of the IDA agents are similar to ICG. These properties make IDA agents suitable for imaging of the hepatobiliary system and for its use in diagnosis of different biliary diseases [73, 74, 78]. The application of IDA agents for the assessment of liver function was proposed in 1994 and has been elaborated for risk assessment of patients considered for major liver resection [79]. The high hepatic uptake, low displacement by bilirubin, and low urinary excretion make mebrofenin the most suitable IDA agent for hepatic function assessment.

Technically, camera-based measurement of the relative hepatic uptake rate was adapted from Ekman et al. [80]. After intravenous injection of freshly prepared $^{99\text{m}}\text{Tc}$ -mebrofenin, dynamic scintigraphy is performed with a gamma camera. As with $^{99\text{m}}\text{Tc}$ -GSA scintigraphy, the uptake of $^{99\text{m}}\text{Tc}$ -mebrofenin is calculated by deter-

mining ROIs around the heart and liver and the total field of view [81, 82]. Based on the ROIs, three time-activity curves can be generated. Using these parameters it is possible to calculate the hepatic mebrofenin uptake ratio. Subsequently, the uptake ratio is divided by the body surface area and expressed as $\%/\text{min}/\text{m}^2$ in order to compensate for differences in individual metabolic requirements, much like the standardized volumetry method introduced by Vauthey et al. [15] to individualize CT volumetric assessment of FRL. This technique makes it possible to generate other ROIs, e.g. the FRL, which allows functional assessment of the FRL [83].

The use of $^{99\text{m}}\text{Tc}$ -mebrofenin HBS for preoperative assessment of liver function in patients undergoing liver surgery was first described by Erdogan et al. [81]. The hepatic uptake of mebrofenin can be calculated in the same way as for ICG. The mebrofenin uptake rate strongly correlates with the ICG clearance test [81]. Preoperatively measured FRL function with $^{99\text{m}}\text{Tc}$ -mebrofenin HBS has been proven to correlate with postoperative FLR function on postoperative day 1 [82]. Furthermore, in patients without parenchymal disease undergoing partial liver resection, preoperative measurement of $^{99\text{m}}\text{Tc}$ -mebrofenin uptake by the FRL was more accurate in predicting postoperative liver insufficiency and liver insufficiency-related mortality than preoperative measurement of FRL volume [10]. Dinant et al. [10] described that postoperative liver failure occurs in 56% of patients with a hepatic $^{99\text{m}}\text{Tc}$ -mebrofenin FRL uptake $<2.5\%/\text{min}/\text{m}^2$ compared to 3% in patients with uptake $>3\%/\text{min}/\text{m}^2$. In surgical populations with and without compromised liver parenchyma the cutoff value was validated at $2.69\%/\text{min}/\text{m}^2$, making HBS more valuable in predicting postoperative liver failure compared to CT volumetry [84]. One single cutoff value for patients with compromised or noncompromised livers makes $^{99\text{m}}\text{Tc}$ -mebrofenin HBS an even more attractive liver function test in clinical practice, as underlying liver disease often is unknown or poorly defined until resection has taken place. Liver biopsies are not taken routinely as the distribution of compromised parenchyma in the liver is not homogeneous, leading to sampling errors, and because of the risk of biopsy-related complications [85–87].

The planar dynamic technique was developed in the era of single-head gamma cameras. Using this technique in anterior view, the function of right liver segments is underestimated due to attenuation. With the wide availability of dual-head gamma cameras, it is now possible to perform dual-head dynamic acquisition and subsequent calculation of a geometrical mean hepatic uptake. How-

Fig. 1. 67-year-old male patient with severe hepatic fibrosis and mild hepatosteosis. Coronal (left), sagittal (middle), and transverse (right) slices of F18-fluoromethylcholine (FCH) PET (**a**) fused with low-dose CT [128] (**b**) show increased FCH uptake in a large well-differentiated hepatocellular carcinoma (FDG PET/CT showed no tumor uptake – data not shown). The patient was considered for an extended right hemihepatectomy. FRL volume was calculated to be 47% of functional tissue (liver – tumor volume). ^{99m}Tc -mebrofenin scintigraphy showed a normal hepatic mebrofenin uptake rate of 14.4%/min (data not shown). On ^{99m}Tc -mebrofenin SPECT (**c**) and CT fusion (**d**) images, FRL function was only 1.9%/min/ m^2 , which is considered to be too low.

ever, the two-dimensional planar images lack the ability to assess detailed liver function on a segmental level. Therefore, a three-dimensional SPECT-CT has been devised to provide additional adequate anatomical information. As described by de Graaf et al. [88], the combination of the dynamic HBS with SPECT-CT delivers visible and quantitative information regarding segmental liver function and therefore constitutes an accurate measure of FRL function. Figure 1 illustrates one of the

possible applications of ^{99m}Tc -mebrofenin HBS with SPECT-CT.

^{99m}Tc -mebrofenin HBS with SPECT-CT is gaining applicability in patients undergoing PVE. Recent reports have indicated that the increase in FRL function is more pronounced than the increase in FRL volume [88]. This finding suggests that the time interval between PVE and liver resection should not be determined by volumetric parameters alone. Another possible application of HBS in

this group of patients is the selection of candidates for PVE as a prediction of liver failure on the basis of function of the FRL, which can be done more accurately by HBS.

Monitoring regeneration of liver function after resection is another potential application of HBS. As Bennink et al. [82] already described, volumetric regeneration after partial liver resection does not correlate with functional regeneration measured with HBS, while the latter did correlate with ICG clearance.

¹³C-Methacetin Breath Test (LiMAx)

There is a broad spectrum of ¹³C-breath tests available. The principle of the ¹³C-methacetin breath (LiMAx) test is based on the activity of the cytochrome P450 1A2 (CYP1A2) system, an enzyme system expressed in the liver. The activity of this enzyme system has been proven to be reduced in patients with severe chronic liver disease regardless of cholestasis [89]. CYP1A2 is distributed through the whole functional unit of the liver [90] and is not affected by drugs or genetic variation [91]. ¹³C-methacetin, the agent used to measure the activity of CYP1A2, is exclusively metabolized by CYP1A2 [92]. ¹³C-methacetin is instantly metabolized into paracetamol and ¹³CO₂, after which ¹³CO₂ is expired via the lungs. This causes alternations in the normal ¹³CO₂/¹²CO₂ ratio in the patient's breath [93]. In this manner, the ¹³C-methacetin breath test provides quantitative information on hepatic function.

After a minimum of 6 h of fasting, the baseline ¹³CO₂/¹²CO₂ ratio is measured. Subsequently, 2 mg/kg body weight of ¹³C-labeled methacetin is intravenously administered to the patient. Changes in the ¹³CO₂/¹²CO₂ ratio are analyzed by a modified, nondispersive, isotope-selective infrared spectroscopy-based device during 60 min after injection of the agent. The expired air is collected using a specially designed face mask. The results are expressed as µg/kg/h [94].

The LiMAx test is a noninvasive and easy-to-perform test which makes it an attractive option in clinical practice. The cutoff value of a normal LiMAx readout is set at 311–575 µg/kg/h [94]. While LiMAx assesses total liver functional capacity, the test can be used to measure the FRL function by combining it with CT volumetric analysis of the FRL [94]. The authors assumed that the percentage of liver function attributed to the FRL equals the percentage of FRL volume; however, this method does not take into account regional differences in liver function. On the other hand, preoperative FRL LiMAx values correlated with

the LiMAx values measured on the first postoperative day. The LiMAx value on postoperative day 1 has also been described as a predictor of postresection liver failure and liver failure-related mortality. The same research group proposed a decision tree based on the LiMAx results that is supposed to help the surgeon decide between resection and alternative or additional therapies such as PVE, neo-adjuvant treatment, or palliative therapy [95]. The value of this algorithm and the proposed cutoff values await further clinical assessment in a prospective setting.

The LiMAx test was also proposed as a tool in the monitoring of functional recovery after hepatic resection. Test readouts have shown that functional recovery of the liver remnant is completed significantly faster compared to volumetric recovery. With this knowledge the authors suggested tailored management of patients with sufficient recovery [96]. Because this test is based on the activity of an enzyme system, it is uncertain whether the readouts are influenced by the resection. In order to validate LiMAx in this setting, the expression of the enzymes should be investigated. The LiMAx test has not been explored yet in patients undergoing PVE.

The major limitation of the ¹³C-breath tests is the assumption that the contribution of FRL to total liver function is equal to the proportion of FRL to total liver volume. As already mentioned, hepatic function is not uniformly distributed throughout the liver, which makes this assumption less probable. Furthermore, the test results can potentially be affected by several factors, including hemodialysis, smoking, nutrition, and visceral hemodynamics [95]. Also, members of the CYP1A family are considerably downregulated in hepatocellular carcinomas [97].

Assessment of Liver Function Using Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) is a well-established liver imaging technique. MRI provides accurate anatomical information and has recently been introduced as a potential technique for preoperative assessment of liver function [98–100]. The use of contrast-enhanced MRI (CE-MRI) with gadolinium-based contrast agents allows more accurate depiction of benign or malignant liver lesions than CT [101]. CE-MRI is already part of the standard preoperative workup in patients scheduled for major liver resection in various centers around the world.

Gd-EOB-DTPA is a liver-specific contrast agent. Approximately 50% of the circulating agent is excreted by hepatocytes. The excretion of the remaining 50% is managed by the kidneys. The uptake of Gd-EOB-DTPA from the liver sinusoids is facilitated by OATPs and Na⁺-taurocholate cotransporting polypeptide [102–106], while MRP2 excretes Gd-EOB-DTPA into the biliary system [107, 108]. Excretion occurs without prior biotransformation. The pharmacokinetic properties of Gd-EOB-DTPA, including the uptake and excretion transporter proteins, are similar to those of mebrofenin as used in ^{99m}Tc-HBS, suggesting that this technique is of potential use in the assessment of liver function.

The concept of using CE-MRI with Gd-EOB-DTPA in the evaluation of liver function was first introduced in 1993 [103]. Subsequently, several studies were published showing correlation between MRI with Gd-EOB-DTPA and liver function in animal models [109–114]. Recently, data on the assessment of liver function using MRI with Gd-EOB-DTPA in humans have been published, all of them confirming the possibility of liver function assessment using MRI [115–122].

In a preliminary study, Saito et al. [100] retrospectively reviewed data of 28 patients who had undergone several quantitative liver function tests as well as a standard 5-phase CE-MRI with Gd-EOB-DTPA during workup for liver resection. They compared the intracellular contrast agent uptake rate and extracellular volume with the results of ICG and GSA tests and found statistically significant correlations between the uptake rate and the reference tests. These data indicate that Gd-EOB-DTPA CE-MRI, even in its simplest form, may already be of use for estimation of liver function. Future studies should target the additional value of dynamic CE-MRI. This would allow a more thorough analysis of the time versus signal intensity curve as more data are acquired during and after administration of the contrast agent.

Functional imaging with MRI-Gd-EOB-DTPA facilitates assessment of total and regional liver function in a similar way as scintigraphic modalities [122]. The latter, however, require additional CT imaging examinations in order to reach sufficient resolution, which forms an additional burden for the patient. Since MRI does not use ionizing radiation, the patient burden is lower. Furthermore, CT imaging used in combination with scintigraphic methods is usually insufficient for diagnostic purposes, while MR imaging provides high-quality information that can be used in the preoperative workup of the patient. MRI allows the segmental assessment of steatosis and can be used to assess fibrosis, making it a potential

one-stop-shop modality for both liver anatomy as well as function [123–126]. Another advantage is that Gd-EOB-DTPA uptake is reliable in patients with and without compromised liver parenchyma [115, 119, 120]. Hence, although the use of MRI with Gd-EOB-DTPA for liver function assessment is still under investigation, so far the evidence has shown promising results and offers the attractive prospect of combining diagnostic and functional imaging in one procedure.

Discussion

Improvement of short- and long-term survival after extensive liver surgery has been the main focus of liver surgeons over the last two decades. Modern surgical techniques have not only contributed to a reduction in procedure-related morbidity and mortality but have also led to undertaking more extensive hepatic resections in specialized centers. In parallel with these developments, postoperative liver failure has remained the most feared complication as the treatment options are very limited and the outcome is often lethal. Accurate preoperative assessment of FRL is essential in order to foresee postoperative liver dysfunction and to install alternative strategies such as resection after PVE or two-stage resection.

The current gold standard, CT volumetry, uses volumetric parameters in the prediction of postresection outcome. However, FRL volume does not necessarily correlate with FRL function, especially in patients with compromised liver parenchyma. Three quantitative liver function tests, i.e. ^{99m}Tc-GSA, ^{99m}Tc-mebrofenin HBS, and the LiMax test, have shown a discrepancy in functional versus volumetric increase after PVE. From this we can assume that the judgment of FRL should not be based on volumetric parameters only, as previously advocated by our group [127]. Furthermore, routine preoperative liver biopsy is considered controversial due to possible complications and a high probability of sampling errors. Given the fact that the quality of FRL parenchyma remains unknown until the resection specimen has been examined, additional quantitative liver function tests are advised in the preoperative selection of patients for major resection or for timing of resection after preoperative PVE. The exception obviously is the patient with FRL volume that greatly exceeds the minimum volume and in whom no parenchymal disease is anticipated.

The ICG clearance test was the first introduced quantitative liver test. Even though it found wide applicability in liver surgery, it is reliable for preoperative assessment

of liver function only in a select patient population (with cirrhosis), which makes the ICG clearance test less universally applicable. With this knowledge, hepatobiliary surgeons should focus on newer methods that are able to overcome the shortcomings of the older methods.

As mentioned above, underlying parenchymal disease is one of two major challenges in the assessment of hepatic function, making most of the available tests less suitable in the overall patient population. ^{99m}Tc -GSA, ^{99m}Tc -mebrofenin scintigraphy, and possibly the LiMAx test provide solutions for this problem. Both ^{99m}Tc -GSA and ^{99m}Tc -mebrofenin have been validated as preoperative liver function tests and correlated with postresection outcomes in several clinical studies involving patients with normal livers as well as patients with parenchymal liver diseases.

The second major limitation of most quantitative liver function tests, such as the ICG clearance and LiMAx tests, is the lack of accurate measurement of regional liver function, i.e. the function of specifically the FRL. ^{99m}Tc -GSA and ^{99m}Tc -mebrofenin HBS can be performed together with CT-SPECT, which offers the possibility to concomitantly obtain anatomical as well as functional information of on the FRL. The information is crucial in the setting of hepatic surgery. The choice of the scintigraphic method for the preoperative assessment of FRL function depends on the facilities available. Although both tests are based on different principles, both offer the possibility of measuring FRL function in normal and compromised liver parenchyma and are able to measure FRL function apart from total liver function. The only drawback of ^{99m}Tc -GSA is that it is not available in Western countries, whereas ^{99m}Tc -mebrofenin is inexpensive and freely available throughout the world. Both the gamma camera and

SPECT-CT possibilities are usually available in centers treating patients with hepatic disease, rendering implementation of the scintigraphic techniques less demanding.

Future opportunities in preoperative liver function assessment possibly lie in the field of MRI. The absence of radiation burden and the multipurpose character of MR could potentially replace current quantitative liver function tests and CT volumetry while reducing costs. The similarity between the kinetics of scintigraphic agents and contrast agents used with MRI encourages further investigation of functional MRI. Notwithstanding the outlook on new modalities, the current quantitative liver function tests offer a chance to reduce postoperative liver failure and should therefore be implemented in the regular preoperative workup of patients considered for major liver resection.

In conclusion, liver function involves a spectrum of metabolic functions and there is no test that can measure all functions at the same time. Laboratory blood assays and clinical scoring systems are unreliable in predicting postresection outcomes. Quantitative liver function tests mostly provide information on global liver function. Scintigraphic methods such as ^{99m}Tc -GSA and ^{99m}Tc -mebrofenin HBS in combination with SPECT allow for regional assessment of specifically the FRL. MRI using Gd-EOB-DTPA has potential as a combined diagnostic and functional imaging technique in patients considered for liver resection.

Disclosure Statement

The authors declare that there is no conflict of interests regarding the publication of this article.

References

- 1 van den Broek MA, Olde Damink SW, Dejong CH, Lang H, Malago M, Jalan R, Saner FH: Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. *Liver Int* 2008;28:767–780.
- 2 Cucchetti A, Cescon M, Ercolani G, Di Gioia P, Peri E, Pinna AD: Safety of hepatic resection in overweight and obese patients with cirrhosis. *Br J Surg* 2011;98:1147–1154.
- 3 Vetelainen R, van VA, Gouma DJ, van Gulik TM: Steatosis as a risk factor in liver surgery. *Ann Surg* 2007;245:20–30.
- 4 Heymsfield SB, Fulenwider T, Nordlinger B, Barlow R, Sones P, Kutner M: Accurate measurement of liver, kidney, and spleen volume and mass by computerized axial tomography. *Ann Intern Med* 1979;90:185–187.
- 5 Shoup M, Gonen M, D'Angelica M, Jarnagin WR, DeMatteo RP, Schwartz LH, Tuorto S, Blumgart LH, Fong Y: Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg* 2003;7:325–330.
- 6 Kubota K, Makuuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K, Harihara Y, Takayama T: Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 1997;26:1176–1181.
- 7 Shirabe K, Shimada M, Gion T, Hasegawa H, Takenaka K, Utsunomiya T, Sugimachi K: Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. *J Am Coll Surg* 1999;188:304–309.
- 8 Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN: Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. *Br J Surg* 2007;94:1386–1394.
- 9 Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, Hicks M, Alsfasser G, Lauwers G, Hawkins IF, Caridi J: Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 2000;127:512–519.

- 10 Dinant S, de Graaf W, Verwer BJ, Bennink RJ, van Lienden KP, Gouma DJ, van Vliet AK, van Gulik TM: Risk assessment of posthepatectomy liver failure using hepatobiliary scintigraphy and CT volumetry. *J Nucl Med* 2007; 48:685–692.
- 11 de Graaf W, van Lienden KP, van den Esschert JW, Bennink RJ, van Gulik TM: Increase in future remnant liver function after preoperative portal vein embolization. *Br J Surg* 2011;98:825–834.
- 12 Marsman HA, van der Pool AE, Verheij J, Padmos J, Ten Kate FJ, Dwarkasing RS, van Gulik TM, Ijzermans JN, Verhoef C: Hepatic steatosis assessment with CT or MRI in patients with colorectal liver metastases after neoadjuvant chemotherapy. *J Surg Oncol* 2011;104:10–16.
- 13 Clavien PA, Emond J, Vauthey JN, Belghiti J, Chari RS, Strasberg SM: Protection of the liver during hepatic surgery. *J Gastrointest Surg* 2004;8:313–327.
- 14 Urata K, Kawasaki S, Matsunami H, Hashikura Y, Ikegami T, Ishizone S, Momose Y, Komiyama A, Makuuchi M: Calculation of child and adult standard liver volume for liver transplantation. *Hepatology* 1995;21:1317–1321.
- 15 Vauthey JN, Abdalla EK, Doherty DA, Gertsch P, Fenstermacher MJ, Loyer EM, Lerut J, Materne R, Wang X, Encarnacion A, Herron D, Mathey C, Ferrari C, Charnsangavej C, Do KA, Denys A: Body surface area and body weight predict total liver volume in Western adults. *Liver Transpl* 2002;8:233–240.
- 16 DeLand FH, North WA: Relationship between liver size and body size. *Radiology* 1968;91:1195–1198.
- 17 Johnson TN, Tucker GT, Tanner MS, Rostami-Hodjegan A: Changes in liver volume from birth to adulthood: a meta-analysis. *Liver Transpl* 2005;11:1481–1493.
- 18 Heinemann A, Wischhusen F, Puschel K, Rogiers X: Standard liver volume in the Caucasian population. *Liver Transpl Surg* 1999;5: 366–368.
- 19 Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN: Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. *Arch Surg* 2002;137:675–680.
- 20 Ribero D, Chun YS, Vauthey JN: Standardized liver volumetry for portal vein embolization. *Semin Intervent Radiol* 2008;25:104–109.
- 21 Truant S, Oberlin O, Sergeant G, Lebuffe G, Gambiez L, Ernst O, Pruvot FR: Remnant liver volume to body weight ratio $> \text{or} = 0.5\%$: a new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. *J Am Coll Surg* 2007;204:22–33.
- 22 Lo CM, Fan ST, Liu CL, Lo RJ, Lau GK, Wei WI, Li JH, Ng IO, Wong J: Extending the limit on the size of adult recipient in living donor liver transplantation using extended right lobe graft. *Transplantation* 1997;63:1524–1528.
- 23 Marcos A, Fisher RA, Ham JM, Shiffman ML, Sanyal AJ, Luketic VA, Sterling RK, Fulcher AS, Posner MP: Liver regeneration and function in donor and recipient after right lobe adult to adult living donor liver transplantation. *Transplantation* 2000;69:1375–1379.
- 24 Ito T, Kiuchi T, Yamamoto H, Oike F, Ogura Y, Fujimoto Y, Hirohashi K, Tanaka AK: Changes in portal venous pressure in the early phase after living donor liver transplantation: pathogenesis and clinical implications. *Transplantation* 2003;75:1313–1317.
- 25 Lo CM, Fan ST, Chan JK, Wei W, Lo RJ, Lai CL: Minimum graft volume for successful adult-to-adult living donor liver transplantation for fulminant hepatic failure. *Transplantation* 1996;62:696–698.
- 26 Chun YS, Ribero D, Abdalla EK, Madoff DC, Mortenson MM, Wei SH, Vauthey JN: Comparison of two methods of future liver remnant volume measurement. *J Gastrointest Surg* 2008;12:123–128.
- 27 Shindoh J, Truty MJ, Aloia TA, Curley SA, Zimmiti G, Huang SY, Mahvash A, Gupta S, Wallace MJ, Vauthey JN: Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. *J Am Coll Surg* 2013;216:201–209.
- 28 Hoekstra LT, de GW, Nibourg GA, Heger M, Bennink RJ, Stieger B, van Gulik TM: Physiological and biochemical basis of clinical liver function tests: a review. *Ann Surg* 2013;257: 27–36.
- 29 van Gulik TM: Assessment of liver function: what are we measuring? *HPB (Oxford)* 2013; 15:325–326.
- 30 Nagashima I, Takada T, Okinaga K, Nagawa H: A scoring system for the assessment of the risk of mortality after partial hepatectomy in patients with chronic liver dysfunction. *J Hepatobiliary Pancreat Surg* 2005;12:44–48.
- 31 Garcea G, Ong SL, Maddern GJ: Predicting liver failure following major hepatectomy. *Dig Liver Dis* 2009;41:798–806.
- 32 Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC: Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 2006;243:373–379.
- 33 Kamath PS, Kim WR: The Model for End-Stage Liver Disease (MELD). *Hepatology* 2007;45:797–805.
- 34 Clavien PA, Emond J, Vauthey JN, Belghiti J, Chari RS, Strasberg SM: Protection of the liver during hepatic surgery. *J Gastrointest Surg* 2004;8:313–327.
- 35 Caesar J, Shaldon S, Chiandussi L, Guevara L, Sherlock S: The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin Sci* 1961;21:43–57.
- 36 de Graaf W, Hausler S, Heger M, van Ginhoven TM, van CG, Bennink RJ, Kullak-Ublick GA, Hesselmann R, van Gulik TM, Stieger B: Transporters involved in the hepatic uptake of (99m)Tc-mebrofenin and indocyanine green. *J Hepatol* 2011;54:738–745.
- 37 Paumgartner G: The handling of indocyanine green by the liver. *Schweiz Med Wochenschr* 1975;105:1–30.
- 38 Huang L, Vore M: Multidrug resistance p-glycoprotein 2 is essential for the biliary excretion of indocyanine green. *Drug Metab Dispos* 2001;29:634–637.
- 39 Hendrikse NH, Kuipers F, Meijer C, Havinga R, Bijleveld CM, van der Graaf WT, Vaalburg W, de Vries EG: In vivo imaging of hepatobiliary transport function mediated by multidrug resistance associated protein and P-glycoprotein. *Cancer Chemother Pharmacol* 2004;54:131–138.
- 40 Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J: Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. *Br J Surg* 1997;84: 1255–1259.
- 41 Fan ST, Lai EC, Lo CM, Ng IO, Wong J: Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Arch Surg* 1995;130:198–203.
- 42 Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J: Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg* 2004;240:698–708.
- 43 Torzilli G, Makuuchi M, Inoue K, Takayama T, Sakamoto Y, Sugawara Y, Kubota K, Zucchi A: No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. *Arch Surg* 1999;134: 984–992.
- 44 Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M: Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. *J Hepatobiliary Pancreat Surg* 2005;12: 16–22.
- 45 Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, Takayama T, Makuuchi M: One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg* 2003; 138:1198–1206.
- 46 Ohwada S, Kawate S, Hamada K, Yamada T, Sunose Y, Tsutsumi H, Tago K, Okabe T: Perioperative real-time monitoring of indocyanine green clearance by pulse spectrophotometry predicts remnant liver functional reserve in resection of hepatocellular carcinoma. *Br J Surg* 2006;93:339–346.
- 47 Suzuki Y, Kohno Y, Takeda Y, Hiraki Y: Evaluation of liver function parameters by Tc-99m-GSA using multivariate analysis: a study of 47 clinical cases. *Acta Med Okayama* 1999; 53:225–232.
- 48 Sawamura T, Kawasato S, Shiozaki Y, Sameshima Y, Nakada H, Tashiro Y: Decrease of a hepatic binding protein specific for asialoglycoproteins with accumulation of serum asialoglycoproteins in galactosamine-treated rats. *Gastroenterology* 1981;81:527–533.

- 49 Kokudo N, Vera DR, Makuuchi M: Clinical application of TcGSA. *Nucl Med Biol* 2003; 30:845–849.
- 50 Kwon AH, Ha-Kawa SK, Uetsuji S, Kamiyama Y, Tanaka Y: Use of technetium 99m diethylenetriamine-pentaacetic acid-galactosyl-human serum albumin liver scintigraphy in the evaluation of preoperative and postoperative hepatic functional reserve for hepatectomy. *Surgery* 1995;117:429–434.
- 51 Mimura T, Hamazaki K, Sakai H, Tanaka N, Mimura H: Evaluation of hepatic functional reserve in rats with obstructive jaundice by asialoglycoprotein receptor. *Hepatogastroenterology* 2001;48:777–782.
- 52 Vera DR, Stadalnik RC, Trudeau WL, Scheibe PO, Krohn KA: Measurement of receptor concentration and forward-binding rate constant via radiopharmacokinetic modeling of technetium-99m-galactosyl-neoglycoalbumin. *J Nucl Med* 1991;32:1169–1176.
- 53 Miki K, Kubota K, Kokudo N, Inoue Y, Bandai Y, Makuuchi M: Asialoglycoprotein receptor and hepatic blood flow using technetium-99m-DTPA-galactosyl human serum albumin. *J Nucl Med* 1997;38:1798–1807.
- 54 Miki K, Kubota K, Inoue Y, Vera DR, Makuuchi M: Receptor measurements via Tc-GSA kinetic modeling are proportional to functional hepatocellular mass. *J Nucl Med* 2001; 42:733–737.
- 55 Ha-Kawa SK, Tanaka Y: A quantitative model of technetium-99m-DTPA-galactosyl-HSA for the assessment of hepatic blood flow and hepatic binding receptor. *J Nucl Med* 1991;32: 2233–2240.
- 56 Nanashima A, Yamaguchi H, Shibasaki S, Morino S, Ide N, Takeshita H, Sawai T, Nakagoe T, Nagayasu T, Ogawa Y: Relationship between indocyanine green test and technetium-99m galactosyl serum albumin scintigraphy in patients scheduled for hepatectomy: clinical evaluation and patient outcome. *Hepatol Res* 2004;28:184–190.
- 57 Kokudo N, Vera DR, Tada K, Koizumi M, Seki M, Matsubara T, Ohta H, Yamaguchi T, Takahashi T, Nakajima T, Muto T: Predictors of successful hepatic resection: prognostic usefulness of hepatic asialoglycoprotein receptor analysis. *World J Surg* 2002;26:1342–1347.
- 58 Kim YK, Nakano H, Yamaguchi M, Kumada K, Takeuchi S, Kitamura N, Takahashi H, Hasebe S, Midorikawa T, Sanada Y: Prediction of postoperative decompensated liver function by technetium-99m galactosyl-human serum albumin liver scintigraphy in patients with hepatocellular carcinoma complicating chronic liver disease. *Br J Surg* 1997;84: 793–796.
- 59 Takeuchi S, Nakano H, Kim YK, Kumada K, Nagasaki H, Sasaki J, Sanada Y, Baek Y, Hasebe S, Midorikawa T, Yoshizawa Y, Yamaguchi M: Predicting survival and post-operative complications with Tc-GSA liver scintigraphy in hepatocellular carcinoma. *Hepatogastroenterology* 1999;46:1855–1861.
- 60 Koizumi M, Yamada Y, Nomura E, Takiguchi T, Kokudo N: An easy and reproducible semi-automatic method for the evaluation of ^{99m}Tc-galactosyl human serum albumin. *Ann Nucl Med* 1997;11:345–348.
- 61 Miki K, Matsui Y, Teruya M, Kaminishi M, Kokudo N: Index of convexity: a novel liver function index using Tc-GSA scintigraphy. *World J Gastroenterol* 2013;19:92–96.
- 62 Du S, Mao Y, Tong J, Li F, Che L, Li S, Yang H, Ba J, Hu N, Xing H, Lu X, Sang X, Zhang X, Wang X, Zhong S: A novel liver function evaluation system using radiopharmacokinetic modeling of technetium-99m-DTPA-galactosyl human serum albumin. *Nucl Med Commun* 2013;34:893–899.
- 63 Satoh K, Yamamoto Y, Nishiyama Y, Wakabayashi H, Ohkawa M: ^{99m}Tc-GSA liver dynamic SPECT for the preoperative assessment of hepatectomy. *Ann Nucl Med* 2003; 17:61–67.
- 64 Iimuro Y, Kashiwagi T, Yamanaka J, Hirano T, Saito S, Sugimoto T, Watanabe S, Kuroda N, Okada T, Asano Y, Uyama N, Fujimoto J: Preoperative estimation of asialoglycoprotein receptor expression in the remnant liver from CT/^{99m}Tc-GSA SPECT fusion images correlates well with postoperative liver function parameters. *J Hepatobiliary Pancreat Sci* 2010;17:673–681.
- 65 Beppu T, Hayashi H, Okabe H, Masuda T, Mima K, Otao R, Chikamoto A, Doi K, Ishiko T, Takamori H, Yoshida M, Shiraishi S, Yamashita Y, Baba H: Liver functional volumetry for portal vein embolization using a newly developed ^{99m}Tc-galactosyl human serum albumin scintigraphy SPECT-computed tomography fusion system. *J Gastroenterol* 2011;46:938–943.
- 66 Hirai I, Kimura W, Fuse A, Suto K, Urayama M: Evaluation of preoperative portal embolization for safe hepatectomy, with special reference to assessment of nonembolized lobe function with ^{99m}Tc-GSA SPECT scintigraphy. *Surgery* 2003;133:495–506.
- 67 Nishiyama Y, Yamamoto Y, Hino I, Satoh K, Wakabayashi H, Ohkawa M: ^{99m}Tc galactosyl human serum albumin liver dynamic SPET for pre-operative assessment of hepatectomy in relation to percutaneous transhepatic portal embolization. *Nucl Med Commun* 2003; 24:809–817.
- 68 Kwon AH, Matsui Y, Ha-Kawa SK, Kamiyama Y: Functional hepatic volume measured by technetium-99m-galactosyl-human serum albumin liver scintigraphy: comparison between hepatocyte volume and liver volume by computed tomography. *Am J Gastroenterol* 2001;96:541–546.
- 69 Kwon AH, Matsui Y, Kaibori M, Kamiyama Y: Functional hepatic regeneration following hepatectomy using galactosyl-human serum albumin liver scintigraphy. *Transplant Proc* 2004;36:2257–2260.
- 70 Tanaka A, Shinohara H, Hatano E, Sato S, Kanazawa A, Yamaoka Y, Torizuka T, Konishi J, Tamaki N: Perioperative changes in hepatic function as assessed by asialoglycoprotein receptor indices by technetium 99m galactosyl human serum albumin. *Hepatogastroenterology* 1999;46:369–375.
- 71 de Graaf W, Bennink RJ, Heger M, Maas A, de BK, van Gulik TM: Quantitative assessment of hepatic function during liver regeneration in a standardized rat model. *J Nucl Med* 2011;52:294–302.
- 72 Haubner R, Vera DR, Farshchi-Heydari S, Helbok A, Rangger C, Putzer D, Virgolini JJ: Development of ⁶⁸Ga-labelled DTPA galactosyl human serum albumin for liver function imaging. *Eur J Nucl Med Mol Imaging* 2013; 40:1245–1255.
- 73 Loberg MD, Cooper M, Harvey E, Callery P, Faith W: Development of new radiopharmaceuticals based on N-substitution of iminodiacetic acid. *J Nucl Med* 1976;17:633–638.
- 74 Krishnamurthy S, Krishnamurthy GT: Technetium-99m-iminodiacetic acid organic anions: review of biokinetics and clinical application in hepatology. *Hepatology* 1989;9: 139–153.
- 75 Krishnamurthy GT, Krishnamurthy S: Cholescintigraphic measurement of liver function: how is it different from other methods? *Eur J Nucl Med Mol Imaging* 2006;33:1103–1106.
- 76 Ghibellini G, Leslie EM, Pollack GM, Brouwer KL: Use of tc-99m mebrofenin as a clinical probe to assess altered hepatobiliary transport: integration of in vitro, pharmacokinetic modeling, and simulation studies. *Pharm Res* 2008;25:1851–1860.
- 77 Hendrikse NH, Kuipers F, Meijer C, Havinga R, Bijleveld CM, van der Graaf WT, Vaalburg W, de Vries EG: In vivo imaging of hepatobiliary transport function mediated by multidrug resistance associated protein and P-glycoprotein. *Cancer Chemother Pharmacol* 2004;54:131–138.
- 78 Trauner M, Meier PJ, Boyer JL: Molecular pathogenesis of cholestasis. *N Engl J Med* 1998;339:1217–1227.
- 79 Heyman S: Hepatobiliary scintigraphy as a liver function test. *J Nucl Med* 1994;35:436–437.
- 80 Ekman M, Fjalling M, Friman S, Carlson S, Volkman R: Liver uptake function measured by IODIDA clearance rate in liver transplant patients and healthy volunteers. *Nucl Med Commun* 1996;17:235–242.
- 81 Erdogan D, Heijnen BH, Bennink RJ, Kok M, Dinant S, Straatsburg IH, Gouma DJ, van Gulik TM: Preoperative assessment of liver function: a comparison of ^{99m}Tc-mebrofenin scintigraphy with indocyanine green clearance test. *Liver Int* 2004;24:117–123.
- 82 Bennink RJ, Dinant S, Erdogan D, Heijnen BH, Straatsburg IH, van Vliet AK, van Gulik TM: Preoperative assessment of postoperative remnant liver function using hepatobiliary scintigraphy. *J Nucl Med* 2004;45:965–971.

- 83 de Graaf W, Bennink RJ, Vetelainen R, van Gulik TM: Nuclear imaging techniques for the assessment of hepatic function in liver surgery and transplantation. *J Nucl Med* 2010;51:742–752.
- 84 de Graaf W, van Lienden KP, Dinant S, Roelofs JJ, Busch OR, Gouma DJ, Bennink RJ, van Gulik TM: Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. *J Gastrointest Surg* 2010;14:369–378.
- 85 McGill DB, Rakela J, Zinsmeister AR, Ott BJ: A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology* 1990;99:1396–1400.
- 86 Ratzliff V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T: Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005;128:1898–1906.
- 87 Lindor KD, Bru C, Jorgensen RA, Rakela J, Bordas JM, Gross JB, Rodes J, McGill DB, Reading CC, James EM, Charboneau JW, Ludwig J, Batts KP, Zinsmeister AR: The role of ultrasonography and automatic-needle biopsy in outpatient percutaneous liver biopsy. *Hepatology* 1996;23:1079–1083.
- 88 de Graaf W, van Lienden KP, van Gulik TM, Bennink RJ: (99m)Tc-mebrofenin hepatobiliary scintigraphy with SPECT for the assessment of hepatic function and liver functional volume before partial hepatectomy. *J Nucl Med* 2010;51:229–236.
- 89 George J, Murray M, Byth K, Farrell GC: Differential alterations of cytochrome P450 proteins in livers from patients with severe chronic liver disease. *Hepatology* 1995;21:120–128.
- 90 Palmer CN, Coates PJ, Davies SE, Shephard EA, Phillips IR: Localization of cytochrome P-450 gene expression in normal and diseased human liver by in situ hybridization of wax-embedded archival material. *Hepatology* 1992;16:682–687.
- 91 Jiang Z, Dragin N, Jorge-Nebert LF, Martin MV, Guengerich FP, Aklilu E, Ingelman-Sundberg M, Hammons GJ, Lyn-Cook BD, Kadlubar FF, Saldana SN, Sorter M, Vinks AA, Nassr N, von RO, Jin L, Nebert DW: Search for an association between the human CYP1A2 genotype and CYP1A2 metabolic phenotype. *Pharmacogenet Genomics* 2006;16:359–367.
- 92 Guengerich FP, Krauser JA, Johnson WW: Rate-limiting steps in oxidations catalyzed by rabbit cytochrome P450 1A2. *Biochemistry* 2004;43:10775–10788.
- 93 Schoeller DA, Schneider JF, Solomons NW, Watkins JB, Klein PD: Clinical diagnosis with the stable isotope ^{13}C in CO_2 breath tests: methodology and fundamental considerations. *J Lab Clin Med* 1977;90:412–421.
- 94 Stockmann M, Lock JF, Riecke B, Heyne K, Martus P, Fricke M, Lehmann S, Niehues SM, Schwabe M, Lemke AJ, Neuhaus P: Prediction of postoperative outcome after hepatectomy with a new bedside test for maximal liver function capacity. *Ann Surg* 2009;250:119–125.
- 95 Stockmann M, Lock JF, Malinowski M, Niehues SM, Seehofer D, Neuhaus P: The LiMAX test: a new liver function test for predicting postoperative outcome in liver surgery. *HPB (Oxford)* 2010;12:139–146.
- 96 Lock JF, Malinowski M, Seehofer D, Hoppe S, Rohl RI, Niehues SM, Neuhaus P, Stockmann M: Function and volume recovery after partial hepatectomy: influence of preoperative liver function, residual liver volume, and obesity. *Langenbecks Arch Surg* 2012;397:1297–1304.
- 97 McKinnon RA, Hall PD, Quattrochi LC, Tukey RH, McManus ME: Localization of CYP1A1 and CYP1A2 messenger RNA in normal human liver and in hepatocellular carcinoma by in situ hybridization. *Hepatology* 1991;14:848–856.
- 98 Nilsson H, Nordell A, Vargas R, Douglas L, Jonas E, Blomqvist L: Assessment of hepatic extraction fraction and input relative blood flow using dynamic hepatocyte-specific contrast-enhanced MRI. *J Magn Reson Imaging* 2009;29:1323–1331.
- 99 Sourbron S, Sommer WH, Reiser MF, Zech CJ: Combined quantification of liver perfusion and function with dynamic gadoteric acid-enhanced MR imaging. *Radiology* 2012;263:874–883.
- 100 Saito K, Ledsam J, Sourbron S, Hashimoto T, Araki Y, Akata S, Tokuyue K: Measuring hepatic functional reserve using low temporal resolution Gd-EOB-DTPA dynamic contrast-enhanced MRI: a preliminary study comparing galactosyl human serum albumin scintigraphy with indocyanine green retention. *Eur Radiol* 2014;24:112–119.
- 101 Niekel MC, Bipat S, Stoker J: Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 2010;257:674–684.
- 102 Clement O, Muhler A, Vexler V, Berthezene Y, Brasch RC: Gadolinium-ethoxybenzyl-DTPA, a new liver-specific magnetic resonance contrast agent. Kinetic and enhancement patterns in normal and cholestatic rats. *Invest Radiol* 1992;27:612–619.
- 103 Schuhmann-Giampieri G: Liver contrast media for magnetic resonance imaging. Interrelations between pharmacokinetics and imaging. *Invest Radiol* 1993;28:753–761.
- 104 Schuhmann-Giampieri G, Schmitt-Willich H, Press WR, Negishi C, Weinmann HJ, Speck U: Preclinical evaluation of Gd-EOB-DTPA as a contrast agent in MR imaging of the hepatobiliary system. *Radiology* 1992;183:59–64.
- 105 Leonhardt M, Keiser M, Oswald S, Kuhn J, Jia J, Grube M, Kroemer HK, Siegmund W, Weitschies W: Hepatic uptake of the magnetic resonance imaging contrast agent Gd-EOB-DTPA: role of human organic anion transporters. *Drug Metab Dispos* 2010;38:1024–1028.
- 106 van Montfort JE, Stieger B, Meijer DK, Weinmann HJ, Meier PJ, Fattinger KE: Hepatic uptake of the magnetic resonance imaging contrast agent gadoterate by the organic anion transporting polypeptide Oatp1. *J Pharmacol Exp Ther* 1999;290:153–157.
- 107 Schuhmann-Giampieri G, Schmitt-Willich H, Frenzel T, Schitt-Willich H: Biliary excretion and pharmacokinetics of a gadolinium chelate used as a liver-specific contrast agent for magnetic resonance imaging in the rat. *J Pharm Sci* 1993;82:799–803.
- 108 Pascolo L, Petrovic S, Cupelli F, Bruschi CV, Anelli PL, Lorusso V, Visigalli M, Uggeri F, Tiribelli C: Abc protein transport of MRI contrast agents in canalicular rat liver plasma vesicles and yeast vacuoles. *Biochem Biophys Res Commun* 2001;282:60–66.
- 109 Schmitz SA, Muhler A, Wagner S, Wolf KJ: Functional hepatobiliary imaging with gadolinium-EOB-DTPA. A comparison of magnetic resonance imaging and ^{153}Gd -gadolinium-EOB-DTPA scintigraphy in rats. *Invest Radiol* 1996;31:154–160.
- 110 Kim T, Murakami T, Hasuike Y, Gotoh M, Kato N, Takahashi M, Miyazawa T, Narumi Y, Monden M, Nakamura H: Experimental hepatic dysfunction: evaluation by MRI with Gd-EOB-DTPA. *J Magn Reson Imaging* 1997;7:683–688.
- 111 Shimizu J, Dono K, Gotoh M, Hasuike Y, Kim T, Murakami T, Sakon M, Umeshita K, Nagano H, Nakamori S, Kato N, Miyazawa T, Nakamura H, Monden M: Evaluation of regional liver function by gadolinium-EOB-DTPA-enhanced MR imaging. *Dig Dis Sci* 1999;44:1330–1337.
- 112 Ryeom HK, Kim SH, Kim JY, Kim HJ, Lee JM, Chang YM, Kim YS, Kang DS: Quantitative evaluation of liver function with MRI using Gd-EOB-DTPA. *Korean J Radiol* 2004;5:231–239.
- 113 Tsuda N, Okada M, Murakami T: Potential of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) for differential diagnosis of nonalcoholic steatohepatitis and fatty liver in rats using magnetic resonance imaging. *Invest Radiol* 2007;42:242–247.
- 114 Tsuda N, Okada M, Murakami T: New proposal for the staging of nonalcoholic steatohepatitis: evaluation of liver fibrosis on Gd-EOB-DTPA-enhanced MRI. *Eur J Radiol* 2010;73:137–142.
- 115 Nilsson H, Blomqvist L, Douglas L, Nordell A, Janczewska I, Naslund E, Jonas E: Gd-EOB-DTPA-enhanced MRI for the assessment of liver function and volume in liver cirrhosis. *Br J Radiol* 2013;86:20120653.

- 116 Tschirch FT, Struwe A, Petrowsky H, Kalkes I, Marincek B, Weishaupt D: Contrast-enhanced MR cholangiography with Gd-EOB-DTPA in patients with liver cirrhosis: visualization of the biliary ducts in comparison with patients with normal liver parenchyma. *Eur Radiol* 2008;18:1577–1586.
- 117 Motosugi U, Ichikawa T, Sou H, Sano K, Tominaga L, Kitamura T, Araki T: Liver parenchymal enhancement of hepatocyte-phase images in Gd-EOB-DTPA-enhanced MR imaging: which biological markers of the liver function affect the enhancement? *J Magn Reson Imaging* 2009;30:1042–1046.
- 118 Takao H, Akai H, Tajima T, Kiryu S, Watanabe Y, Imamura H, Akahane M, Yoshioka N, Kokudo N, Ohtomo K: MR imaging of the biliary tract with Gd-EOB-DTPA: effect of liver function on signal intensity. *Eur J Radiol* 2011;77:325–329.
- 119 Tajima T, Takao H, Akai H, Kiryu S, Imamura H, Watanabe Y, Shibahara J, Kokudo N, Akahane M, Ohtomo K: Relationship between liver function and liver signal intensity in hepatobiliary phase of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging. *J Comput Assist Tomogr* 2010;34:362–366.
- 120 Katsube T, Okada M, Kumano S, Hori M, Imaoka I, Ishii K, Kudo M, Kitagaki H, Murakami T: Estimation of liver function using T1 mapping on Gd-EOB-DTPA-enhanced magnetic resonance imaging. *Invest Radiol* 2011;46:277–283.
- 121 Nishie A, Ushijima Y, Tajima T, Asayama Y, Ishigami K, Kakihara D, Nakayama T, Takayama Y, Okamoto D, Abe K, Obara M, Yoshimitsu K, Honda H: Quantitative analysis of liver function using superparamagnetic iron oxide- and Gd-EOB-DTPA-enhanced MRI: comparison with technetium-99m galactosyl serum albumin scintigraphy. *Eur J Radiol* 2012;81:1100–1104.
- 122 Nilsson H, Blomqvist L, Douglas L, Nordell A, Jonas E: Assessment of liver function in primary biliary cirrhosis using Gd-EOB-DTPA-enhanced liver MRI. *HPB (Oxford)* 2010;12:567–576.
- 123 Reeder SB, Cruite I, Hamilton G, Sirlin CB: Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. *J Magn Reson Imaging* 2011;34:spcone.
- 124 van Werven JR, Marsman HA, Nederveen AJ, Smits NJ, Ten Kate FJ, van Gulik TM, Stoker J: Assessment of hepatic steatosis in patients undergoing liver resection: comparison of US, CT, T1-weighted dual-echo MR imaging, and point-resolved 1H MR spectroscopy. *Radiology* 2010;256:159–168.
- 125 Bohte AE, Garteiser P, De NA, Groot PF, Sinkus R, Stoker J, Nederveen AJ: MR elastography of the liver: defining thresholds for detecting viscoelastic changes. *Radiology* 2013;269:768–776.
- 126 Venkatesh SK, Yin M, Ehman RL: Magnetic resonance elastography of liver: technique, analysis, and clinical applications. *J Magn Reson Imaging* 2013;37:544–555.
- 127 Heger M, de Graaf W, Bennink RJ, Beuers U, van Gulik TM: A clinical perspective on the criteria for liver resection and the use of liver function tests. *World J Surg* 2010;34:868–869.
- 128 Bieze M, Klumpen HJ, Verheij J, Beuers U, Phoa SS, van Gulik TM, Bennink RJ: Diagnostic accuracy of (18) F-methylcholine positron emission tomography/computed tomography for intra- and extrahepatic hepatocellular carcinoma. *Hepatology* 2014;59:996–1006.