Preoperative Evaluation of Liver Function

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Introduction

Surgical treatment remains the only potentially curative treatment option for patients diagnosed with colorectal liver metastases. Hepatic resection has become more aggressive in the last decade, resulting in an increased rate of complex and extended resections being performed in specialized centers. This development has largely been made possible owing to thorough work-up of candidates for major hepatic resection, as well as new surgical techniques and improvements in the management of intraoperative and postoperative complications. Major hepatic resections are now established procedures in liver surgery, with an acceptable procedure-related mortality. At the same time, the number of patients qualifying for hepatic resection has increased as the limits of hepatic resection have been pushed further, with new modalities to manipulate liver volume and tumor using neoadjuvant chemotherapy, two-stage resection, portal vein embolization (PVE), and associated liver partition and portal vein ligation for staged hepatectomy (ALPPS).

Postoperative outcomes mainly depend on the size and quality of the future liver remnant (FLR). Hepatic resection, when performed in the absence of sufficient FLR, inevitably leads to post-resectional liver failure, a severe and potentially life-threatening complication. The incidence of postoperative liver failure as reported in literature, ranges from 0.7 to 9.1% [1]. Management of post-resectional liver failure is mostly supportive and liver-failure-related mortality remains as high as 80% [1]. Apart from the volume of liver remnant after resection, postoperative function of the liver remnant is directly related to the quality of liver parenchyma which is mainly dictated by underlying diseases such as fibrosis/cirrhosis and steatosis, as well as by chemotherapy-induced liver injury [2–4].

Assessment of liver function is therefore crucial in the preoperative work-up of patients who are exposed to extreme hepatic resection. A wide spectrum of tests to assess FLR has become

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available in the last few years, attesting to the fact that the ideal methodology has yet to be defined. The aim of this overview is to discuss the current modalities available, and new perspectives in assessment of the future remnant liver in patients scheduled for major hepatic resection.

Definition of Liver Function

The liver is responsible for a spectrum of functions including the uptake, synthesis, biotransformation, and excretion of various endogenous and foreign substances, in which transporters play an important role [5, 6]. The liver also provides an immunological function, as the reticuloendothelial capacity of the liver plays a role in phagocytosis and clearance of micro-organisms and endotoxins from the portal blood [7]. The secretion of bile is an important end-point of liver function, and the production of bile immediately ceases when perfusion of the liver is arrested. The complexity of liver function is best reflected by our inability to restore full liver function during liver failure, insofar as liver-assist devices and bioartificial livers have not proven to fully substitute all the components of liver function yet [8, 9]. In addition, there is no liver function test available that measures all components of liver function.

Passive Liver Function Tests

The term liver function tests refers 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.

Aminotransaminases

The aminotransaminase enzymes, aspartate transferase (AST) and alanine transferase (ALT), are exclusively intracellular enzymes, and their presence in plasma are therefore markers of liver injury [10]. Damaged hepatocyte cell membranes release their contents, including ALT and AST, into the extracellular space. The released enzymes enter the blood circulation, leading to an increase in plasma levels of ALT and AST that can be measured by routine clinical chemistry. Although a persisting release of these enzymes will ultimately result in the loss of liver functional capacity, they are not parameters of function per se. AST is predominantly present in cells of the liver, heart, skeletal muscles, and red blood cells. ALT is an enzyme primarily present in hepatocytes, and therefore a more specific indicator of liver damage than AST, as AST may also be elevated in diseases affecting other organs, making it an unspecific marker for hepatocellular damage.

Bilirubin

Plasma bilirubin concentration provides indirect information on the uptake, conjugation, and excretion function of the liver. Elevated plasma concentrations of bilirubin are specific markers for serious liver injury and therefore liver function loss. Importantly, bilirubin levels may also be influenced by non-hepatic factors such as an increased production as a result of e.g., hemolysis during sepsis [11]. Therefore, plasma bilirubin concentration is not a parameter of liver function per se. The plasma bilirubin concentration is often used in combination with other laboratory parameters of hepatocellular injury (e.g., AST, ALT, albumin levels) that constitute integral parts of clinical grading systems such as the Child–Pugh and MELD scores (see sections “Child–Pugh Score” and “MELD (Model for End-Stage Liver Disease) Score”, respectively).

Albumin and Coagulation Factor Synthesis

Albumin and proteins involved in secondary hemostasis and fibrinolysis, including vitamin K-dependent coagulation proteins (factors II, VII, IX, X, protein C, protein S, and protein Z),

as well as factor V, XIII, fibrinogen, antithrombin, α2-plasmin inhibitor, and plasminogen, are exclusively synthesized by the liver, and their plasma concentrations are therefore used as indirect indicators of liver synthesis function. Albumin, clotting factors, and coagulation parameters such as the international normalized ratio (INR) are measured by routine clinical chemistry. Albumin is also an important transport protein for fatty acids, bilirubin, and hormones [12]. In liver disease such as cirrhosis, there is a decrease in the synthesis of albumin and coagulation factors, resulting in an increase in prothrombin time (PT) and its derivative measures INR and prothrombin ratio, due to the reduced synthesis of coagulation factors.

Ammonia Elimination and Urea Production

One of the crucial metabolic functions of the liver is the conversion of ammonia into urea. In patients with an impaired liver function, the affected liver lacks the capacity to produce urea, which leads to hyperammonemia. At high concentrations, ammonia is a very potent neurotoxin that is known to induce astrocyte swelling in the brain, leading to hepatic encephalopathy [13]. Increased plasma ammonia levels are therefore indicative of severely compromised liver function, and most patients with hyperammonemia are not candidates for major liver resection. In the setting of post-resectional liver function, progressive increase in plasma ammonia is an ominous sign of remnant liver failure.

Hyaluronic Acid Clearance

Hyaluronic acid (HA) is composed of repeating disaccharide units of *N*-acetyl-D-glucosamine and D-glucuronate. HA is a glycosaminoglycan that is produced by connective tissue cells and synovial cells, and is taken up from the blood and metabolized primarily by the sinusoidal endothelial cells of the liver by HA receptor-mediated uptake and degradation [5, 6]. HA levels are low in normal liver tissue, but serum levels of HA increase in a variety of liver diseases, including liver fibrosis and cirrhosis [14–16]. Serum CD44, which is one of the cell surface receptors for HA, is also elevated in patients with chronic liver diseases, especially liver cirrhosis. However, CD44 is a cell surface adhesion molecule on numerous cells of non-hepatic origin. HA concentration in the blood may therefore not be considered a specific test for sinusoidal endothelial cell function.

Clinical Grading Systems

Child–Pugh Score

Clinical grading systems combine several biochemical parameters with clinical symptoms of insufficient liver function. The Child–Pugh score, a widely used clinical scoring system, includes total plasma bilirubin level, plasma albumin level, and PT, together with the presence or absence of encephalopathy and ascites. The scoring system is divided into class A, B, and C on the basis of a 1- and 2-year survival of 100% and 85%, 81% and 57%, and 45% and 35% respectively. The Child–Pugh scoring system is particularly useful in selecting patients with HCC and cirrhosis for resection or transplantation. In Western clinical practice, most class Child B and class Child C patients are candidates for transplantation, leaving class Child A patients eligible for resection. Patients with liver metastases usually have normal liver parenchyma and are typically classified as class Child A. In these patients, the Child–Pugh score has been shown to be quite variable, and may be unreliable for predicting the outcome of liver resections [17–19]. Therefore, additional clinical chemistry data (AST and ALT), blood clearance tests (such as the indocyanine green test and galactose elimination capacity test), and molecular imaging techniques (for example the ^{99m}Tc-galactosyl serum albumin scintigraphy and ^{99m}Tc-mebrofenin hepatobiliary scintigraphy) may be employed to complement the Child–Pugh score [19].

MELD (Model for End-Stage Liver Disease) Score

The MELD score was originally developed to predict short-term survival in patients undergoing transcutaneous intrahepatic portosystemic shunt procedures (TIPS), and was later validated as an accurate predictor of survival among patients with end-stage liver disease awaiting transplantation [20]. The MELD score incorporates the serum bilirubin and creatinine levels and the INR [21, 22]. Although the MELD score is related to the risk of liver failure after surgery [22], survival cannot be accurately predicted in 15–20% of patients [22], and it does not predict morbidity or mortality after elective liver resection [23]. It is unclear whether the predictive power of the MELD score is superior to the Child-Pugh score, although the MELD score is quickly replacing the Child–Pugh score [24].

Volumetric Measurements: the Gold Standard

Current gold standard in the preoperative assessment of future remnant liver volume (FLR volume) is managed by computed tomography (CT) volumetry as initially described by Heymsfield et al. [25]. With this technique, the FLR 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 non-tumorous liver volume, tumor volume, and FLR volume.

In most centers, a FLR volume of 20–30% is accepted as sufficient in patients without underlying parenchymal disease [26]. In patients with a compromised liver, a FLR volume of at least 40% is considered acceptable [27]. Insufficient FLR volume is associated with poor postoperative outcome as the frequency of major complications increases, including an increased occurrence of post-resectional liver failure and prolonged hospital stay [26, 28]. CT volumetry can be used as a tool in preoperative selection of patients for resection. When FLR volume is insufficient, CT volumetry is sequentially applied to monitor volume-increase of FLR after PVE or ALPPS, which is considered an important prognosticator of postoperative liver function [29]. The main advantage of CT volumetry is its non-invasive character; and because CT is frequently used as part of the diagnostic process, volumetric calculation can be carried out using the same CT imaging series.

However, preoperative assessment of liver function based on CT volumetry alone does come with important limitations. Firstly, tumor characteristics (e.g., 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 [27, 30]. An important note to the latter is the uncertain correlation of CT volumetry with liver function and postoperative outcome [31]. FLR volume does not reflect function of FLR which might be impaired by underlying parenchyma disease or hepatic comorbidity such as fibrosis, cirrhosis, or steatosis. It is important to identify patients with compromised liver in order to interpret the volumetry results correctly [32]. This has become even more important, since many patients are now presented for resection after extensive induction or neoadjuvant chemotherapy, in which liver parenchyma is injured by post-chemotherapy steatosis or veno-occlusive disease [33]. In the absence of preoperative biopsies, parenchymal damage or disease is often unknown until after the resection specimen is examined. Secondly, the selection criteria for resection based on volumetric data are to be considered arbitrary as the minimal FLR volumes proposed in literature vary widely (10–40%), are based on different grades of hepatic disease, and have been established by different measuring methods [34]. Finally, CT volumetry can be used to monitor FLR volume after PVE and ALPPS [35]; however, as mentioned earlier, volume is not necessarily representative of FLR function. We recently showed a discrepancy between the volumetric and functional changes after PVE, in as much as FLR functional increase exceeded the volumetric increase [32].

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

Standardized CT Volumetry

In order to overcome some of the shortcomings of the traditional CT-volumetric assessment, adjustments were made to personalize this method. Urata et al. introduced a novel method of total liver volume estimation based on the finding that in adults without chronic liver disease, liver volume correlates linearly with body size and weight [36]. As this method was based on findings among an Asian population, it did not find application in Western countries. Vauthey et al. have introduced a modified method of total liver volume estimation based on Western patient characteristics: estimated total liver volume (eTLV) [cc] = −794.41 + 1267.28 × BSA [37]. The validity of this formula in estimation of total liver volume has been demonstrated several times [38–40]. The ratio of FLR volume measured by CT volumetry and eTLV is called the standardised FLR volume, and represents the percentage of liver that will remain after resection. The standardized FLR volume is described as an accurate method in prediction of postoperative outcome in patients with healthy liver parenchyma who underwent extended resection. The frequency of complications was shown to have increased when standardized FLR volume was <20% of eTLV [39–41]. According to Ribero et al., the thresholds for safe hepatic resections using standardized FLR 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 [39, 40, 42]. However, this method also has limitations, namely it may not be reliable in patients who undergo repeated hepatectomies or in patients with a borderline FLR volume-eTLV ratio.

Body Weight Ratio

Truant et al. introduced a novel formula, consisting of the ratio of FLR volume measured by CT volumetry and body weight (FLRV-BWR) [43]. 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 [44–47]. Truant and associates found that patients with a FLR volume <0.5% of their body weight are at risk for post-resectional liver failure and ensuing mortality. They concluded that the FLRV-BWR method is more reliable as predictor of postoperative course in non-cirrhotic patients than traditional CT volumetry [47].

Standardized volumetry and FLRV-BWR were compared in a small retrospective study including 68 patients showing equal ability of both methods to predict postoperative outcome after major resection [48, 49]. Despite these promising results, the main limitation of CT-volumetric methods remains the fact that volumetric estimation of FLR 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.

Dynamic Quantitative Liver Tests

Other tools used in the assessment of FLR are the dynamic quantitative liver function tests. Quantitative liver function tests are based on the capacity of the liver to clear the administered agent that is mostly or exclusively cleared by the liver. Distinctive for quantitative liver function tests is their non-invasive character. Furthermore, as they 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. Several of the most common quantitative liver function tests are discussed below.

Indocyanine Green Clearance Test

The Indocyanine Green (ICG) clearance test is worldwide 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 protein-bound, water-soluble anionic organic tricarbocyanine dye. It was first introduced by Caesar et al. in 1961 [50]. After intravenous injection it is taken up by organic anion-transporting polypeptides (OATPs) and Na^+-taurocholate co-transporting polypeptides (NTCPs) [51]. Subsequently, ICG is removed from the blood exclusively by the liver and excreted into the bile without intrahepatic conjugation [52]. ATP-dependent, export pump multidrug-resistance associated protein 2 (MRP 2) is responsible for the excretion of ICG [53, 54]. This test reflects the capacity of the liver to excrete organic anions, such as bilirubin.

After an overnight fast, 0.5 mg/kg of ICG is administered intravenously. 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 bile flow, and may influence the test results. The results can be expressed as various parameters: 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 they vary from 14 to 20% ICG-R15 [55–57]. ICG-R15 has also been 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 [58–60]. The authors report non or close to non 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 [61].

Despite its widespread use, ICG has several limiting factors as well. The uptake of ICG can be impaired in the presence of hyperbilirubinemia, since the uptake is managed by similar transporters for both ICG and bilirubin. Furthermore, the ICG clearance test depends on overall liver blood flow, meaning that the test is less reliable in patients with non-flow-depending hepatic diseases, such as intrahepatic shunting or sinusoidal capillarization [58]. 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.

Galactose Elimination Capacity (GEC) Test

The galactose elimination test determines the metabolic capacity of the liver. Galactose in free form enters hepatocytes from the blood [62] and is phosphorylated intracellularly to galactose-1-phosphate by galactokinase. Galactose-1-phosphate is then converted to glucose-1-phosphate by the action of four enzymes in the Leloir pathway [63, 64]. Galactose is administered intravenously, and the GEC is calculated from serial serum samples from 20 to 50 min postinjection, making the test somewhat time-consuming.

The GEC has shown prognostic significance in chronic liver disease [65, 66], such as fulminant hepatic failure [67], primary biliary cirrhosis [68–70], and chronic active hepatitis [66, 69, 71]. Abnormal clearance has also been frequently observed in patients with metastatic liver neoplasms [69]. A low GEC-value can predict postoperative complications and death, whereas a high GEC-value is associated with longer survival [66].

As is the case with most liver function tests, alterations in environmental conditions or liver metabolism will affect test outcomes. Galactose is an essential component of membrane glycoproteins and glycolipids. During liver regeneration, an increased membrane synthesis can lead to an augmented galactose demand [72]. Furthermore, galactose can be converted into glucose, which is used as an energy source during anaerobic respiration, especially during fasting [72]. As a result, altered galactose kinetics during, for example, liver regeneration and fasting [72, 73] may provide false-positive results with respect to liver function.

Lidocaine Clearance (MEGX) Test

Lidocaine is taken up by hepatocytes and metabolized into monoethylglycinexylidide (MEGX), the *N*-deethylated metabolite, by the cytochrome P450 3A pathway [74]. MEGX is subsequently converted to glycinexylidide (GX) in the liver through sequential oxidative *N*-dealkylation [75] and *N*-deethylation [76]. MEGX can be measured by high-performance liquid chromatography [77–79], gas–liquid chromatography [80], or by enzyme-linked immunosorbent assay [75] in blood samples before and 15 min after intravenous injection of lidocaine (1 mg/kg). Lidocaine has a relatively high extraction rate, as a result of which this liver function test is dependent on hepatic blood flow in addition to hepatic cytochrome P450 activity [75].

The clearance of lidocaine is reduced in chronic liver disease, with prolongation of its half-life, and MEGX levels decrease gradually with time when liver injury progresses [76, 81]. Decreased MEGX levels have been correlated with increased complication rates after liver resection [82], especially in patients with cirrhosis or hepatocellular carcinomas (HCCs) [82]. The MEGX test has been widely used in the liver transplantation setting, both for the evaluation of liver function in potential donors and for the prediction of survival after transplantation [75, 83, 84]. A hepatic resection can be performed safely with a MEGX-value of <25 ng/ml [82].

Two considerable disadvantages of the MEGX test have been reported, and therefore this method has been largely abandoned. Firstly, there are variations in cytochrome P450 activity in the general population, with the consequence that in (stable) liver patients a broad range of MEGX production levels have been found [74]. This is probably due to the complexity of the pharmaco- and enzyme kinetics associated with lidocaine and its metabolic end-products, which rely on intrahepatic blood flow, uptake of lidocaine, conversion of lidocaine to MEGX, MEGX export out of the cell, and conversion of MEGX to GX. Secondly, other medications interfere with the cytochrome P450 system [76, 85] and can influence MEGX kinetics and thus skew the interpretation of liver function. Moreover, as is the case with other blood clearance tests, the MEGX test only provides information about the global liver function.

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 derivates are the most common representatives of this group. Although the two 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 [17] and accumulation of plasma asialoglycoproteins [17, 86, 87]. The ^{99m}Tc-labeled asialoglycoprotein analog, ^{99m}Tc-GSA, was clinically introduced as a new scintigraphy agent for imaging of the human hepatic receptor [88, 89]. ^{99m}Tc-GSA is commercially available in an instant labelling kit in Japan [88]. 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 the ^{99m}Tc-GSA scintigraphy applicable even in cholestatic patients [90].

^{99m}Tc-GSA is intravenously injected, after which a gamma camera is positioned over the heart and the liver of the patient. 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 [91–94]. Due to the complexity of these suggested models, they are not widely used in clinical practice, leaving hepatic uptake and blood clearance ratio 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 hepatic 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 [95–98]. Prediction of postoperative complications based on hepatic uptake ratio has been proposed several times, although post-resectional liver failure has been observed also 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 [95, 97, 98].

Although hepatic uptake and blood clearance ratio of ^{99m}Tc-GSA have been used for the last 20 years, results can be influenced by scatter effects, body movements or inter-operator and inter-institutional differences [88, 97–99]. 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. demonstrated that this parameter correlated well with conventional liver tests and was superior to the standard parameters in differentiating healthy and cirrhotic livers [100].

Another new kinetic model of ^{99m}Tc-GSA scintigraphy is the uptake index. The uptake index has been developed to show the speed of receptor-mediated endocytosis of ^{99}Tc GSA. Uptake index is the ratio of the rate of transport of ^{99}Tc GSA through the hepatic cell membrane from the total plasma ^{99}Tc GSA, at any given time. As this model correlated with traditional serological tests, the authors of this method expect this model to gain popularity in the field of assessment of liver function [101].

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-proton 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 [102]. This is especially important in patients with advanced liver disease in whom the liver volume is not corresponding to the amount of functional hepatocytes, e.g., patients with advanced fibrosis who do maintain at least the initial liver volume over a longer period of time, whereas the amount of functional hepatocytes is decreased. Nowadays ^{99m}Tc-GSA scintigraphy can be performed with dynamic SPECT-CT, allowing a three-dimensional measurement of ^{99m}Tc-GSA uptake. Liver uptake ratio and liver uptake density can be calculated from dynamic SPECT-CT acquisitions. Dynamic SPECT-CT has proven valuable for the preoperative prediction op–postoperative outcome after liver surgery [102]. The liver uptake ratio of the FLR was shown to correlate well with postoperative liver function parameters, and is considered a useful tool in preoperative assessment [103]. Furthermore, functional

liver volume can be estimated correctly using ^{99m}Tc-GSA SPECT-CT [104].

The applicability of ^{99m}Tc-GSA SPECT-CT in monitoring FLR after PVE has been evaluated several times. In cirrhotic and non-cirrhotic patients, the increase of FLR function after PVE was found to be more pronounced compared to the volumetric increase measured with CT volumetry [105, 106]. Currently the changes in FLR after PVE are monitored by CT volumetry; this finding implies that GSA could be of additional value in the management of patients who underwent PVE because of insufficient FLR.

Another field where ^{99m}Tc-GSA SPECT-CT could possibly find its use is the monitoring of liver regeneration after hepatic resection. Several studies report a more advanced increase in liver function versus increase in volume [107–109], 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.

Recently, there has been an increasing interest in combining the validated ability of GSA in targeting the asialoglycoproteins receptor concentration with positron emission tomography (PET) because of its excellent imaging resolution and quantifying qualities. For this purpose GSA needs to be labelled with gallium-68 (^{68}Ga). From the PET images, ROIs of the heart and the liver are generated, followed by generation of time–activity curves and corresponding parameters (t50 and t90). The GSA labelling techniques, the metabolic stability, and the imaging properties of ^{68}Ga-GSA were investigated and compared to standard ^{99}Tc-GSA in an animal study showing promising results for the future use of ^{68}Ga-GSA PET in the assessment of liver function [110].

HBS with IDA Derivates

^{99m}Tc-IDA agents were introduced in 1976 by Loberg et al. [111] These lidocain analogs are transported to the liver bound to albumin, and dissociate from albumin in the hepatic space of Disse. Thereafter, they are taken up by the hepatocytes, a process similar to the uptake of unconjugated bilirubin. Unlike unconjugated bilirubin, ^{99m}Tc-IDA agents do not undergo any biotransformation after hepatic uptake, and are directly excreted into the bile canaliculi in the same manner as other substances such as conjugated bilirubin, hormones, and drugs. Hepatic uptake represents one of the main hepatic processes [112, 113].

^{99m}Tc-mebrofenin is the most hepatic specific ^{99m}Tc-IDA derivative [51, 114]. The uptake of mebrofenin is managed by OATPB1 and OATP1B3 [51]. 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 such as bilirubin. Of all available IDA agents, ^{99m}Tc-mebrofenin shows the lowest displacement by bilirubin in cases of hyperbilirubinaemia. The excretion of mebrofenin is most likely facilitated by MRP2 [53, 114]. The uptake, excretion, and lack of hepatic biotransformation of the IDA agents are similar to ICG. These properties make IDA agents suitable for the imaging of the hepatobiliary system and for its use in diagnosis of different biliary diseases [111, 112, 115]. The application of IDA agents for the assessment of liver function was first proposed in 1994, and has recently been elaborated by our group for risk assessment of patients considered for major liver resection [116]. The high hepatic uptake, low displacement by bilirubin and, furthermore, low urinary excretion make mebrofenin the most suitable IDA agent for hepatic function assessment.

Camera-based measurement of the relative hepatic uptake rate was developed by Ekman et al. [117]. After intravenous injection of freshly prepared ^{99m}Tc-mebrofenin, dynamic scintigraphy is performed with a gamma camera. Also here, the uptake of ^{99m}Tc-mebrofenin is calculated by determining ROIs around the heart, the liver, and the total field of view. 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 (BSA) and expressed

as %/min/m^2 in order to compensate for differences in individual metabolic requirements, similarly to the standardized volumetry method introduced by Vauthey et al. to individualize CT-volumetric assessment of FLR. This technique makes it possible to generate other ROIs, e.g., the FLR, which makes it possible to estimate specifically the function of the FLR [118].

The use of ^{99m}Tc-mebrofenin HBS for preoperative assessment of liver function in patients undergoing liver surgery was first described by Erdogan et al. The hepatic uptake of mebrofenin can be calculated in the same way as for ICG. The mebrofenin uptake rate strongly correlated with the ICG clearance test [119]. Preoperatively measured FLR function with ^{99m}Tc-mebrofenin HBS proved to correlate with postoperative FLR function on postoperative day 1 [120]. Furthermore, in patients without parenchymal disease undergoing partial liver resection, preoperative measurement of ^{99m}Tc-mebrofenin uptake by FLR was more accurate in prediction of postoperative liver insufficiency and liver insufficiency related mortality than was preoperative measurement of FLR volume [31]. Dinant et al. described a risk of postoperative liver failure of 56% in patients with a hepatic ^{99m}Tc-mebrofenin FLR uptake below 2.5%/min/m^2, compared to 3% in patients with uptake above 3%/min/m^2. In surgical populations with and without compromised liver parenchyma, the cut-off value was validated at 2.69/min/m^2, making HBS more valuable in predicting postoperative liver failure compared to CT volumetry [121]. One single cut-off value for patients with compromised or non-compromised livers makes ^{99m}Tc-mebrofenin HBS an even more suitable 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 [122–124]. This fact increases the value of ^{99m}Tc-mebrofenin HBS in daily practice.

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 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. However, 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 for additional adequate anatomical information. As described by De Graaf et al., combination of the dynamic HBS with SPECT-CT delivers visible and quantitative information with regard to segmental liver function, and therefore is an accurate measure of FLR function (Fig. 3.1) [125–127].

^{99m}Tc-mebrofenin HBS with SPECT-CT is gaining applicability in patients undergoing PVE. Recent reports have indicated that the increase in the FLR function is more pronounced than the increase in the FLR volume [125]. 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 prediction of liver failure on the basis of function of the FLR can be done more accurate by HBS.

Monitoring of regeneration of liver function after resection is another potential application of HBS. As Bennink et al. already described, volumetric regeneration after partial liver resection does not correlate with functional regeneration measured with HBS, while the latter has been shown to correlate with ICG clearance [120].

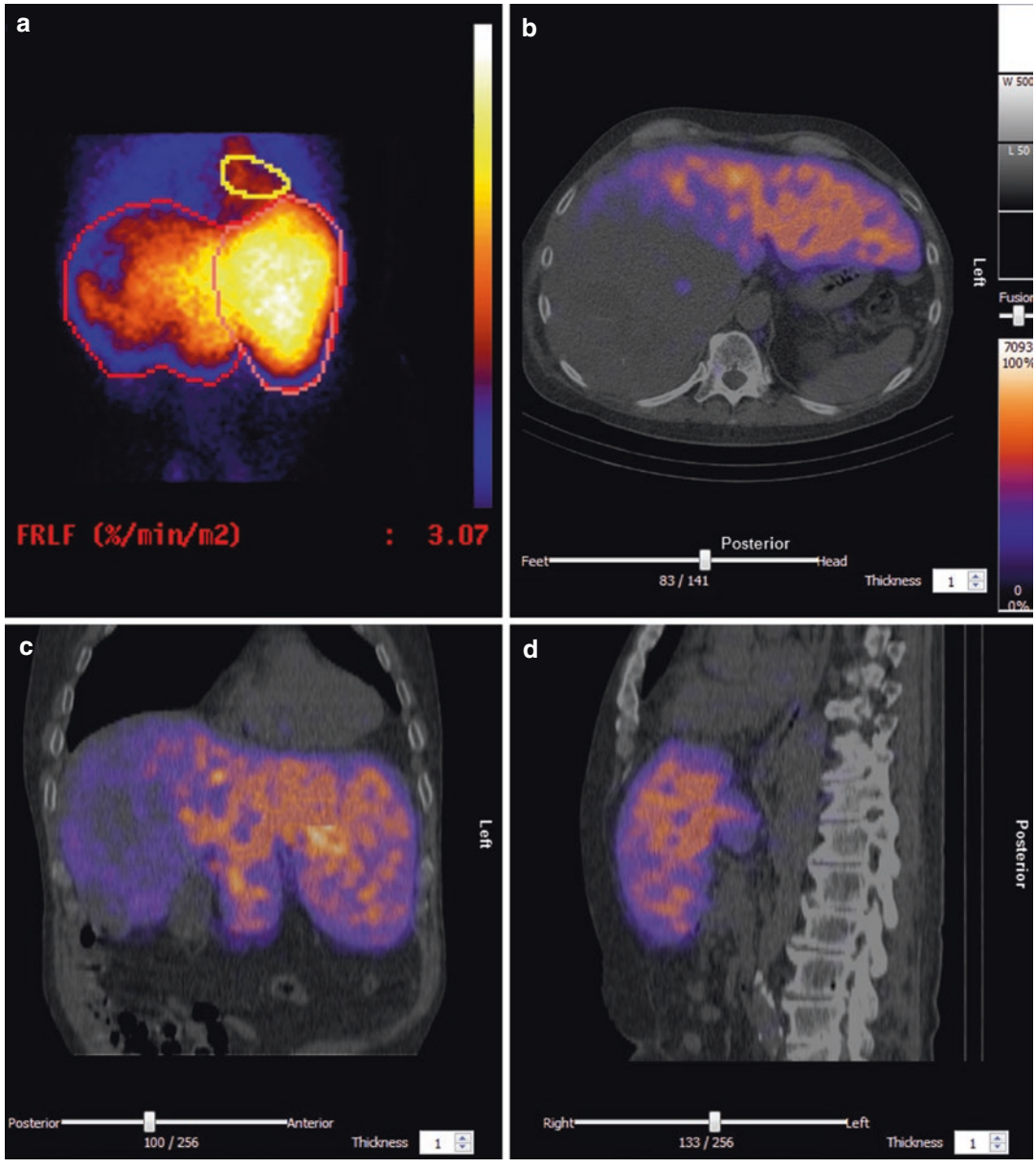

Fig. 3.1 Preoperative hepatobiliary scintigraphy in a 56-year-old male patient with a large resectable HCC in the right liver segments. Summed dynamic scintigraphy (**a**) showing hypertrophy and function of the left liver segments. The future remnant liver function was determined at 3.07%/min/m^2. Transverse (**b**), coronal (**c**) and sagittal (**d**) SPECT-lowdoseCT planes of the liver showing a large non-functional mass in the right liver and hypertrophy of left liver segments with sufficient function for safe right hemihepatectomy

Other Modalities for Assessment of Liver Function

Bioenergetic Tests

A key determinant of liver functional status and reserve is the energy state of the organ. The availability of adenosine triphosphate (ATP) is therefore critical for the maintenance of integrity and function of liver cells, particularly since the liver is the most metabolically active organ. When the ATP-generating ability of liver cells is compromised, as is the case in chronic parenchymal disease, the energy status of the liver decreases. This in turn leads to compensatory suppression of energy-consuming processes such as active ion transport and protein and nucleic acid synthesis [128]. The latter is important for liver cell proliferation, which is a key feature of liver regeneration. Assessment of the energy state of the liver therefore provides direct information on the liver functional reserve.

The liver functional reserve can be estimated by measurement of ketone bodies, which reflect the redox state in liver mitochondria (i.e., the site of ATP production) [129]. These are determined by the redox tolerance index (RTI), which is reflected in a 100-fold cumulative enhancement of ketone body ratio relative to glucose level (100 × AKBR/A glucose) [129]. Furthermore, it can be estimated by 31-phosphorus (^{31}P) magnetic resonance spectroscopy. The naturally abundant ^{31}P isotope constitutes an important element in molecules such as tri- and diphosphate nucleotides that play a central role biological energy metabolism [130, 131].

^{13}C-Methacetin Breath Test, LiMAx

There is a broad spectrum of ^{13}C-breath tests available. The principle of the ^{13}C-methacetin breath (LiMAx) test is based on the activity of cytochrome P450 1A2 (CYP1A2) system, an enzyme system that is exclusively expressed in the liver. The activity of this enzyme system proved to be reduced in patients with severe chronic liver disease, regardless of cholestasis [132]. CYP1A2 is distributed through the whole functional unit of the liver [133], and is not affected by drugs or genetic variation [133]. ^{13}C-methacetin, the agent used to measure the activity of CYP1A2, is exclusively metabolized by the CYP1A2 [134]. ^{13}C-methacetin is instantly metabolized into paracetamol and $^{13}CO_2$, after which $^{13}CO_2$ is excreted through the lungs. This causes alternations in the normal $^{13}CO_2/^{12}CO_2$ ratio in patients' breath [135]. In this manner, the ^{13}C-methacetin breath test provides quantitative information on hepatic function.

After a minimum of 6 h fast, the base line of $^{13}CO_2/^{12}CO_2$ ratio is measured. Subsequently, 2 mg/kg body weight (BW) 13C-labeled methacetin is intravenously administered to the patient. Changes in the $^{13}CO_2/^{12}CO_2$ ratio are analyzed by a modified, non-dispersive, isotope-selective infrared spectroscopy-based device during 60 min after injection of the agent. The expired air is collected using a specially designed facemask. The results are expressed as μg/kg/h [136].

The LiMAx test is a non-invasive and easy to perform test which makes it an attractive option in clinical practice. The cut-off value of normal LiMAx readout is set at 311–575 μg/kg/h [136]. While LiMax assesses total liver functional capacity, the test can be used to measure the FRL function by combining LiMAx test with CT-volumetric analysis of FLR [136]. The authors assume that the percentage of liver function attributed to the FLR equals the percentage of FLR volume; however, this method does not take into account regional differences in liver function. On the other hand, preoperative FLR LiMAx values correlated with the LiMAx values measured on the first postoperative day. LiMAx value on postoperative day 1 has also been described as a predictor of post-resectional liver failure and liver failure related mortality. The same research group proposed a decision tree based on the LiMAx results which is supposed to help the surgeon to decide between resection and alternative or additional therapies such as PVE, neoadjuvant treatment, and palliative therapy [137]. The value of this algorithm and the proposed cut-off values await further clinical assessment in a prospective setting.

The LiMAx test has also been proposed as a tool in the monitoring of functional recovery after hepatic resection. Test readouts showed that functional recovery of the liver remnant was completed significantly faster compared to volumetric recovery. With this knowledge, the authors suggested tailored management for patients with sufficient recovery [138]. Because this test is based on the activity of an enzyme system, it is uncertain, however, if the readouts are influenced by the resection. In order to validate LiMAx in this setting, the expression of the enzyme system should be investigated.

The LiMAx test has recently been explored in patients undergoing PVE [139]. In this study, the LiMax was used to visualize the changes in FRL function in the time between PVE and major liver resection, showing an increase in FLR function after PVE. Furthermore, they found that function of FLR post-resection was lower in comparison to the preoperatively calculated function, which they explain as loss of function due to intraoperative injury. The authors plead that an overestimation-margin of the FLR is needed preoperatively in order to compensate for this loss, which is an interesting point that could contribute to safety management in liver surgery, especially in patients who are scheduled for complex resections.

The major limitation of the ^{13}C-breath tests is the assumption that the contribution of FLR to total liver function is equal to the proportion of FLR to total liver volume. Malinowski et al. advocate in their study that the distribution of liver function does not change after PVE [139]. The FLR function measured with LiMax shortly after PVE did not differ from FLR function measured before PVE. Furthermore, they found that overestimation of FLR function preoperatively was not different between PVE and non-PVE patients. However, both arguments attest to the fact that the test is based on indirect measurement of liver function. Inhomogeneous distribution of liver function throughout the liver has been demonstrated using scintigraphic methods [105, 140, 141] and MRI as well [142].

Another difficulty in the application of the Limax test is that the test results are potentially affected by several factors such as hemodialysis, smoking, nutrition, and visceral hemodynamics [137]. Also, members of the CYP1A family are considerably downregulated in hepatocellular carcinomas, rendering the test less universal in use for the whole population of patients requiring liver resection [143].

The greatest advantage of the LiMax test is its non-invasive character. This permits a more intensive frequency of measurement of total liver function in the setting of prospective studies. Currently, little is known of the changes in total liver function in the course of the work-up before resection, e.g., neoadjuvant chemotherapy. Using Limax, a mild impairment of liver function has been shown [144]; however, this study should be repeated in a lager cohort of patients before any conclusions can be drawn.

Assessment of Liver Function Using Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) is well established as a liver imaging technique. MRI provides accurate anatomical information and has recently also been introduced as a potential technique for preoperative assessment of liver function [145–147]. The use of contrast-enhanced MRI (CE-MRI) with gadolinium-based contrast agents allows more accurate depiction of benign or malign liver lesions than with CT [148]. Contrast-enhanced MRI is already part of the standard preoperative work-up in patients scheduled for major liver resection in various centers over the world.

Gd-EOB-DTPA is a liver-specific contrast agent. Approximately 50% of the circulating agent is excreted by the hepatocytes. The excretion of the remaining 50% is managed by the kidneys. The uptake of Gd-EOB-DTPA from the liver sinusoids is managed by the OATPs and the NTCPs [149–153], while the MRP2 excrete Gd-EOB-DTPA into the bile canaliculi [154, 155]. 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 [151]. Subsequently, several studies have been published showing correlation between MR imaging with Gd-EOB-DTPA and liver function in an animal model [156–161]. Recently, data on 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 [162–169].

In a preliminary study, Saito et al. retrospectively reviewed data of 28 patients who had undergone several quantitative functional tests as well as a standard 5-phase CE-MRI with Gd-EOB-DTPA during work-up for liver resection [147]. 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 contrast enhanced 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 [169]. 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 irradiation, 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 work-up of the patient. Given that MRI now allows the segmental assessment of steatosis and can be used to assess fibrosis, this makes it a potential one-stop-shop modality for both liver anatomy and function [170–173]. Another advantage is that Gd-EOB-DTPA uptake is reliable in patients with and without compromised liver parenchyma [162, 166, 167]. Hence, although the use of MRI with Gd-EOB-DTPA for liver function assessment is still under investigation, the evidence up to now shows promising results, and offers the attractive prospect of combining diagnostic and functional imaging in one procedure.

Discussion

Improvement of short-term and long-term survival after extensive liver surgery has been the main focus of liver surgeons during the last two decades. Modern surgical techniques have not only contributed to the reduction of procedure-related morbidity and mortality, but have also led to undertaking more extensive and even extreme 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 outcome often turns out to be lethal. Accurate preoperative assessment of FLR is essential in order to foresee postoperative liver dysfunction and to install alternative strategies, such as resection after portal vein embolization or two-stage resection.

In patients with liver-specific diseases, accurate assessment of liver function is critical for the selection of treatment options. Treatment of HCC in cirrhotic patients, i.e., by liver resection or transplantation, is determined by the severity of underlying liver disease. In cirrhosis, fibrosis is accompanied by a reduction of functional hepatocytes that is characterized by fibrous tissue septa that separate hepatocyte nodules, leading to altered resistance to blood flow in the liver and portal hypertension [174, 175]. The most commonly used liver function tests in cirrhotic patients include plasma aminotransferases, bilirubin clearance, albumin levels, PT, HA uptake, the Child–Pugh classification, and the ICG test.

Liver steatosis and steatohepatitis are associated with an increased risk of partial liver resection of intrahepatic tumors, especially after

neo-adjuvant chemotherapy, or in living donor liver transplantation [3]. When CT volumetry is used as a prognostic tool for surgical outcome, a functional overestimation can be made in patients with steatosis. The accumulation of triacylglycerols in hepatocytes leads to hepatocyte enlargement in combination with steatosis-induced perfusion defects; i.e., phenomena that distort the actual liver function when deduced from CT scans. Increases in liver fat infiltration reduce liver blood flow and hepatic microcirculation, which in turn affect the extent to which molecules such as ICG can reach hepatocytes. ICG clearance and ^{99m}Tc-mebrofenin HBS therefore possess the potential to assess hepatic function in steatotic livers, because of the combination of impaired parenchymal perfusion and liver dysfunction [176].

Prolonged cholestasis produces hepatocellular injury and fibrosis. The uptake of ^{99m}Tc-mebrofenin and ICG is impaired under these conditions, due to competitive uptake of bilirubin and ICG/mebrofenin by the same cellular transporter systems. Although this impaired uptake still reflects the uptake function of the liver at that specific time, it does not represent the function of the liver after surgery once the biliairy obstruction is resolved. Preoperative assessment of liver function using the ICG clearance test or ^{99m}Tc-mebrofenin HBS therefore requires complete biliary drainage in patients, with concomitant obstruction of (part of) the biliary tree, as seen in hilar cholangiocarcinoma. Alternatively, when percutaneous transhepatic biliary drainage has been performed, ICG or mebrofenin excretion can be measured directly in the drained bile.

The current gold standard, CT volumetry, uses volumetric parameters in the prediction of post-resectional outcome. However, FLR volume does not necessarily correlate with FLR function, especially in patients with a 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 judgement of FLR should not be based on volumetric parameters only. 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 FLR 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 FLR volume that greatly exceeds the minimum volume and in whom no parenchymal disease is anticipated.

The ICG clearance test was the first quantitative liver test to be introduced. Even though it has 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 have brought solutions for this problem. Both ^{99m}Tc-GSA and ^{99m}Tc-mebrofenin have been validated as preoperative liver function tests and correlated with post-resectional 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 test and the LiMAx test, is the lack of accurate measurement of regional liver function, i.e., function of specifically the FRL. ^{99m}Tc-GSA and ^{99m}Tc-mebrofenin HBS can be performed together with a single proton emission computed tomography CT (SPECT-CT), which offers the possibility to obtain at the same time anatomical as well as functional information of the FLR. The information is crucial in the setting of hepatic surgery. The choice which of the scintigraphic methods is to be preferred for the preoperative assessment of FLR function depends on the

facilities available. Although the two tests are based on different principles, both offer the possibility of measuring FLR function in both normal and compromised liver parenchyma, and are able to measure FLR 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 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 multi-purpose character of MRI potentially replace current quantitative liver function tests and CT volumetry, reducing costs at the same time. 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 therefore should be implemented in the regular preoperative work-up of patients considered for major liver resection.

Because of the complexity of liver function, one single test cannot represent overall liver function and accurately predict operative risk in any given patient considered for major liver resection [177, 178]. We still rely on the combination of clinical parameters and quantitative liver function tests to estimate liver functional reserve and to decide whether we can perform a safe resection in any patient presented to us. Scoring methods need to be developed in which clinical parameters, CT volumetric criteria, and the results of dynamic quantitative liver function tests guide our decision-making in patients requiring major liver resection [59]. Objective functional criteria are necessary to define patients at increased risk. Until appropriate scoring methods and objective functional criteria have become available, multiple tests measuring different components of liver function should be combined for the optimal assessment of liver function.

In conclusion, liver function involves a spectrum of metabolic functions, and there is not one test that can measure all functions at the same time. Laboratory blood assays and clinical scoring systems are unreliable in predicting postresectional 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 permit regional assessment of specifically, the FLR. MRI using Gd-EOB-DTPA has potential as a combined diagnostic and functional imaging technique in patients considered for liver resection. The ideal method for evaluation of liver function and surgical risk in patients considered for extreme liver resection should combine clinical parameters, volumetric data, and the results of dynamic quantitative liver function tests.

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