Hepatology Research

Hepatology Research 2015; **45**: 10–19 doi: 10.1111/hepr.12325

Review Article

Recent advances in estimating hepatic functional reserve in patients with chronic liver damage

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Preoperative estimation of liver functional reserve is important in liver surgery to prevent postoperative liver failure. Although the hepatic functional reserve of patients with chronic liver disease is generally evaluated by measuring indocyanine green dye retention at 15 min, no standard method of estimating regional liver function has been established to date. Several recently introduced imaging modalities, such as hepatobiliary scintigraphy and magnetic resonance imaging with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid, may be used to evaluate liver function. Here, we review recent advances in estimating hepatic functional reserve, mainly by radiological modalities, in patients with chronic liver damage.

Key words: fusion imaging, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid, regional hepatic functional reserve, scintigraphy with technetium-99*m* galactosyl human serum albumin

INTRODUCTION

THREE-DIMENSIONAL COMPUTED TOMOGRAPHY (CT), which is used to assess preoperative hepatic volume and details of liver anatomy, has become essential for liver surgeons.[1–3] In addition, assessing hepatic functional reserve is one of the most important issues in liver surgery, especially in patients with hepatocellular carcinoma and underlying chronic liver disease. Although no "reference standard" has yet been established, several studies have evaluated the clinical use of preoperative liver function tests, such as indocyanine green dye retention at 15 min (ICG-R15), which mainly measures hepatic blood flow or anion excretion; and volumetric assessments to estimate hepatic functional reserve before hepatectomy (Table 1).[4–9] Many of the complications of extended hepatic resection are thought to be because of the small functional volume of the remnant liver, rather than to the amount of liver resected.[10]

Evaluating regional liver functional reserve requires imaging of both the anatomical structure of the liver and the functional reserve. Hepatobiliary scintigraphy with technetium-99*m* (^{99m}Tc) iminodiacetic acid or ^{99m}Tc galactosyl human serum albumin (GSA) has been used to assess regional hepatic function.[6,11] GSA is a ligand specific to the asialoglycoprotein receptor present exclusively on the plasma membrane of hepatocytes. GSA is bound only by this receptor, thus providing valuable information about receptor population density as well as functioning hepatocyte mass.[12] However, hepatobiliary scintigraphy requires the use of radioactive isotopes, whereas magnetic resonance imaging (MRI) with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), namely, EOB-MRI, does not require additional equipment or any radioactive agents.

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid is an MRI contrast medium used to examine the hepatobiliary system. The lipophilic nature of Gd-EOB-DTPA enables its easy uptake by hepatocytes and its secretion into the biliary system without any change in its chemical structure.[13] Because of these characteristics, EOB-MRI is highly sensitive in detecting small hepatic nodules and has recently become one of the standard preoperative imaging modalities for patients with liver tumors.[14,15] Although several studies in experimental animal models have shown that

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Received 16 February 2014; revision 16 February 2014; accepted 5 March 2014.

Table 1 Quantitative liver function tests

Quantitative tests	Function tested
Non-isotopic methodology	
Antipyrine clearance	Microsomal function
Caffeine clearance	Microsomal function
Lidocaine and MEGX clearance	Microsomal function
Galactose elimination capacity	Cytosolic function
Albumin synthesis	Synthetic function
Urea synthesis	Synthetic function
Low-dose galactose clearance	Hepatic blood flow
Indocyanine green clearance	Hepatic blood flow, anion excretion
Sorbitol clearance	Hepatic blood flow
Isotopic methodology	
Aminopyrine breath test (^{13}C or ^{14}C-methyl)	Microsomal function
Methacetin breath test (^{13}C-methacetin)	Microsomal function
Hepatobiliary scintigraphy (^{99m}Tc-mebrofenin)	Hepatic perfusion, anion excretion
Hepatocyte mass scintigraphy (^{99m}Tc-GSA)	Functional hepatocyte mass

^{99m}Tc, technetium-99*m*; GSA, galactosyl human serum albumin; MEGX, monoethyl glycine xylidide.

EOB-MRI may be used to estimate liver function,[16–18] few studies to date have examined its ability to determine liver function in the clinical setting.[19–22]

Over the last decade, the number of elderly patients undergoing liver resection has increased. However, differences in hepatocyte function and regenerative ability between young and old liver remain unclear. A recent evaluation of liver regeneration after major hepatic resection found that mean longer term increases in liver volume were significantly greater in younger than in older patients, although the difference was not significant during the early postoperative period.[23]

Here, we review recent advances in methods used to estimate hepatic functional reserve in patients with chronic liver damage, focusing on ^{99m}Tc-GSA scintigraphy and EOB-MRI.

HEPATOBILIARY SCINTIGRAPHY

^{99m}Tc-GSA scintigraphy

THE ASIALOGLYCOPROTEIN RECEPTOR is present only in mammalian hepatocytes and 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. Patients with chronic liver diseases show a significant decrease in asialoglycoprotein receptors, together with the accumulation of asialoglycoproteins in plasma.[24–26] The synthetic asialoglycoprotein ^{99m}Tc-GSA was developed for clinical use to visualize and quantify binding to the asialoglycoprotein receptor.[27] The liver is the only site of ^{99m}Tc-GSA uptake, making this agent ideal for functional liver scintigraphy.[28]

Although many parameters can be calculated from kinetic models, they are highly complex and therefore not widely used in the context of liver surgery. The most frequently used parameters in planar dynamic ^{99m}Tc-GSA scintigraphy are hepatic uptake ratio and blood clearance ratio of ^{99m}Tc-GSA. Blood clearance ratio is calculated by dividing the radioactivity of a region of interest (ROI) in the heart 15 min after ^{99m}Tc-GSA injection by that at 3 min after injection. The hepatic uptake ratio is calculated by dividing the radioactivity of a liver ROI by the radioactivity of the liver plus heart ROI at 15 min after injection (LHL15).[28–30] These parameters obtained from planar ^{99m}Tc-GSA scintigraphy have proven valuable in assessing liver function in cirrhotic patients and have demonstrated a strong correlation with conventional liver function tests. Discrepancies between the results of indocyanine green (ICG) clearance tests and ^{99m}Tc-GSA scintigraphy have been observed in 9–20% of patients, with the histological severity of disease better reflected by ^{99m}Tc-GSA scintigraphy. Hepatic ^{99m}Tc-GSA uptake is not influenced by hyperbilirubinemia, and ^{99m}Tc-GSA scintigraphy can also be used in cholestatic patients.[31–33] In addition, preoperative planar dynamic ^{99m}Tc-GSA scintigraphy results have been tested for their ability to predict postoperative complications.[8,34–36]

Single-photon emission computerized tomography (SPECT) has been introduced to improve the assessment of segmental liver function and to measure functional liver volume.[32,37–39] In a study involving predominantly cirrhotic patients, preoperative functional volume on static ^{99m}Tc-GSA SPECT was found more suitable in predicting remnant liver function than CT volumetry.[32,39] This discrepancy may be a result of the ability of ^{99m}Tc-GSA SPECT to measure functional hepatocyte mass, in contrast to CT volumetry, which cannot distinguish between functional and non-functional liver tissue.[38]

Dynamic SPECT has been used to determine liver uptake ratio and liver uptake density, and has also proven valuable for the preoperative prediction of outcome after liver surgery.[38,40,41] Furthermore, functional liver volume can be estimated correctly using ^{99m}Tc-GSA SPECT/CT.[42]

Recently, a combined SPECT/CT system was developed with dual-head detectors and a 16-row multidetector row CT scanner. The two instruments were juxtaposed so that the CT table bearing the patients could be moved directly into the SPECT scanner for CT.[42]

^{99m}Tc-GSA scintigraphy in experimental surgical research

Technetium-99*m* GSA scintigraphy with SPECT was used to assess liver function and functional volume during liver regeneration in a rat model.[43] In normal rat livers, as well as in regenerating livers, a strong correlation was observed between functional and conventional liver volumes, indicating that ^{99m}Tc-GSA SPECT is useful in the non-invasive measurement of functional liver volume. In contrast, hepatic ^{99m}Tc-GSA uptake measured by dynamic scintigraphy apparently underestimated hepatic regeneration in comparison to liver volume.

Unlike ICG, ^{99m}Tc-GSA uptake is not directly inhibited by hyperbilirubinemia and therefore can be used to evaluate liver function during cholestasis. Using a rat model of obstructive jaundice, hepatic ^{99m}Tc-GSA uptake was found to decrease as the period of jaundice was prolonged, a finding likely because of a decrease in affinity of the asialoglycoprotein receptor for ^{99m}Tc-GSA.[33]

^{99m}Tc-GSA scintigraphy in clinical settings

Preoperative assessment of liver function

Preoperative planar dynamic ^{99m}Tc-GSA scintigraphy has been tested for its ability to predict postoperative complications.[8,34–36] Specific cut-off values for LHL15 (i.e. 0.90 and 0.875) have been shown to select patients at high risk for complications.[34,35] Other cut-off values include LHL15/preoperative liver volume of 0.76 and total asialoglycoprotein receptor concentration in the future remnant liver (FRL) of 0.05 mmol.[8,31,34] In patients with a discrepancy between ICG retention rate at 15 min (ICG-R15) and LHL15, ^{99m}Tc-GSA scintigraphy was better in predicting postoperative complications.[34] The finding of postoperative liver failure in patients with relatively normal liver function (LHL15, >0.875) was likely because of the ability of LHL15 to measure total preoperative liver function, not FRL function.

Static ^{99m}Tc-GSA SPECT was introduced to measure functional volume and to more accurately assess segmental liver function.[32,37–39] Whereas ^{99m}Tc-GSA SPECT measures of functional volume reflect functional hepatocyte mass, CT volumetry cannot distinguish between functional and non-functional liver tissue. This is of especial interest in cirrhotic patients, in whom advanced fibrosis is accompanied by a reduction of functional hepatocytes.[38,44] In a study of mostly cirrhotic patients, ^{99m}Tc-GSA SPECT measurements of preoperative functional volume were more suitable than CT volumetry for predicting remnant liver function.[32,39] Although the outline extraction method is regularly used to calculate functional hepatic volume, that method assumes that liver function is uniformly distributed throughout the tissue included within the cut-off value.[32,39,44–46] In many patients, especially those with tumor-bearing and compromised livers, however, liver function is not distributed homogeneously. Therefore, functional volume does not necessarily correlate with intrinsic liver function measured by dynamic planar ^{99m}Tc-GSA scintigraphy.[30,38]

Dynamic SPECT was developed to overcome this problem, showing advantages in assessing regional liver function. For example, liver functional volume, liver uptake ratio and liver uptake density were calculated in patients with different severities of parenchymal liver disease.[47] The ratio of liver uptake by the left and right liver lobes, as well as the ratio of liver uptake density, was altered as liver disease progressed, confirming that liver function is not distributed homogeneously in patients with compromised livers.

Postoperative liver regeneration

Postoperative liver regeneration is currently evaluated by CT volumetry. Differences have been observed, however, between postoperative functional recovery and volumetric liver regeneration. Functional recovery was reported more impaired after large resection than volumetric regeneration.[31] However, that study also showed that, 4 weeks after resection, the average LHL15 recovered to 95% of its preoperative level, whereas average volume recovered to approximately 70%, suggesting that functional recovery was greater than volumetric recovery. Other studies also showed that functional regeneration was more rapid than volumetric regeneration, as measured by CT volumetry, with both functional and volumetric liver regeneration delayed in patients with underlying liver disease.[39,46] Although ^{99m}Tc-GSA SPECT and CT volumetry were not compared directly, functional recovery was reported to be more rapid in patients with injured livers. Thus, while ^{99m}Tc-

GSA scintigraphy has been shown useful in assessing liver regeneration, current evidence makes it difficult to draw conclusions on the difference between functional and volumetric regeneration.

Technetium-99*m* GSA scintigraphy has also been used to preoperatively predict the rate of liver regeneration after partial hepatectomy in patients with liver fibrosis.[48] ^{99m}Tc-GSA scintigraphy results were found to correlate with the severity of liver fibrosis, and impaired liver regeneration has also been described in patients with an increased severity of liver fibrosis.[49]

Recently, impaired liver regeneration was reported in older patients (aged >65 years) who underwent major hepatic resection, such as hepatic segmentectomy or lobectomy.[23] Future studies are needed to evaluate age-related hepatic functional reserve in regenerative liver.

EOB-MRI

GADOLINIUM-ETHOXYBENZYL-DIETHYLENETRIAMINE PENTAACETIC ACID is a hepatocyte-specific contrast agent, up to 50% of which undergoes hepatobiliary excretion in normal liver. The hepatocyte uptake of Gd-EOB-DTPA occurs mainly via the organic anion transporter polypeptides OATP1B1 and B3, located at the sinusoidal membrane, whereas biliary excretion occurs via the multidrug resistance-associated protein MRP2 located at the canalicular membrane.[50] Gd-EOB-DTPA-enhanced MRI has advantages over other imaging modalities in the regional assessment of hepatic function because it offers both excellent delineation of hepatic anatomy and hepatocyte-specific function (Table 2).

Assessment of hepatic function in experimental surgical research

Several studies using experimental animal models have shown that EOB-MRI may be useful in estimating liver function.[16–18] In a rat ischemia–reperfusion model, the ischemic lobes were clearly visualized as a high-intensity area during the late phase of Gd-EOB-DTPA enhancement.[17] The signal intensity (SI) in ischemic lobes correlated significantly with the duration of vascular

Table 2 Summary of studies assessing hepatic function with Gd-EOB-DTPA-enhanced hepatic MRI

Study (first author)	Simplicity	Key confounder	Requirement of additional imaging sequence
Biliary enhancement			
Tamada[51]	+++	Biliary flow impairment	–
Takao[52]			
Tschirch[53]			
Wibmer[54]			
Smith[55]			
Parenchymal enhancement			
Direct SI measurement			
Motosugi[56]	+++	A number of technical factors affecting signal intensity	–
Watanabe[57]			
Yamada[58]			
Utsunomiya[22]			
Tamada[59]			
Nishie[21]			
Nakamura[60]			
Cho[61]			
MR relaxometry			
Katsube[62]	++	Hepatic blood flow	+
Katsube[63]			
DCE-MRI			
Chen[64]	+	Complex hepatic hemodynamics and date analysis	+
Nilsson[65]			
Nilsson[66]			

DCE, dynamic contrast-enhanced; Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; MR, magnetic resonance; MRI, magnetic resonance imaging; SI, signal intensity.

clamping, indicating that this imaging modality was able to quantify the extent of acute liver damage. Recently, EOB-MRI was found to be a promising non-invasive technique that could be used to evaluate the degree of chronic liver damage after administration of carbon tetrachloride to rabbits.[18]

Assessment of hepatic function in clinical settings

The time and degree of Gd-EOB-DTPA biliary enhancement was found to be affected by hepatic function.[51–55,67] For example, biliary enhancement was significantly delayed and weaker in patients with liver cirrhosis than in normal subjects.[51] Assessments of the relative SI of the bile duct normalized to that of muscle showed that the relative SI of the bile duct was significantly lower in patients with chronic liver disease than in patients with normal liver function.[52] In addition, the ICG-R15 was also a significant predictor of the relative SI of the bile duct.

In addition, hepatic function can be evaluated by hepatic parenchymal enhancement with Gd-EOB-DTPA. Patients with severe hepatic dysfunction often present with reduced hepatic parenchymal enhancement in EOB-MRI. Therefore, EOB-MRI can be used to measure the differential degree of hepatic parenchymal enhancement, with the results interpreted to assess hepatic function. To date, three different approaches have been described: direct measurement of hepatic parenchymal SI; measurement of T_1 or T_2* relaxation time changes on magnetic resonance (MR) relaxometry and dynamic contrast-enhanced MRI (DCE-MRI).

Direct measurement of hepatic parenchymal SI

Owing to its simplicity, direct measurement of hepatic parenchymal SI on Gd-EOB-DTPA-enhanced hepatic MRI is the approach most frequently used to assess hepatic function. Methods ranging from purely qualitative to more sophisticated quantitative methods, including visual assessment of hepatic enhancement, measurement of the signal to noise ratio (SNR) of the hepatic parenchyma in the hepatobiliary phase, and corrected measurement of hepatic parenchymal SI using internal tissue standards such as the spleen and skeletal muscles.[20,21,56–61,68,69]

Measurements of hepatic parenchymal SNR in the hepatobiliary phase of Gd-EOB-DTPA-enhanced liver MRI showed that hepatic parenchymal SI was significantly lower in patients with chronic liver disease than in those with normal liver function.[20] More recently, hepatic parenchymal enhancement corrected by muscle or spleen SI has been used to assess hepatic function.[21,56–61,69] For example, a corrected liver to muscle enhancement ratio in 100 patients who underwent liver biopsy or surgery found that the corrected liver enhancement ratio strongly predicted liver fibrotic stage.[56] In addition, a "contrast enhancement index", corresponding to the degree of hepatic parenchymal enhancement corrected by splenic SI, was found to strongly correlate with fibrotic stage.[57]

Although methods based on the direct measurement of hepatic parenchymal SI are simple, they also have several limitations, such as sampling errors and technical factors. Measuring SI at a single time point may not sufficiently reflect serial hepatic responses over time. However, this problem may be overcome by analyzing the area under the time–SI curve.[61]

MR relaxometry

Magnetic resonance relaxometry methods were developed to overcome some of the limitations associated with direct hepatic parenchymal SI measurements.[62,63] In this method, hepatic function is evaluated by measuring the ability of Gd-EOB-DTPA uptake to change T_1 or T_2* relaxation time. The post-contrast T_1 relaxation time of the liver was reported significantly longer, with lower rates of reduction in cirrhotic patients than in control individuals.[62] Because Gd-EOB-DTPA has the ability to shorten not only T_1 but also T_2* values, the effect of Gd-EOB-DTPA on T_2* relaxation time was also assessed.[63] In that study, the T_2* reduction rate was significantly lower in cirrhotic patients than in the control group.

The T_1 or T_2* relaxation times measured by MR relaxometry were found to correlate directly with Gd-EOB-DTPA concentration, suggesting that MR relaxometry may be more reliable and less subjective than the direct hepatic SI method in assessing hepatic function. Two MR relaxometry studies also presented segmental hepatic function maps.[62,63] Compared with the direct hepatic SI method, the MR relaxometry method required additional scan sequences and dedicated software to calculate relaxation times.[62,63] In addition, the uptake of ICG and Gd-EOB-DTPA into hepatocytes is influenced by both hepatocyte function and hepatic blood flow.[34]

DCE-MRI technique

Dynamic contrast-enhanced MRI of the liver is a relatively new approach to determine perfusion parameters

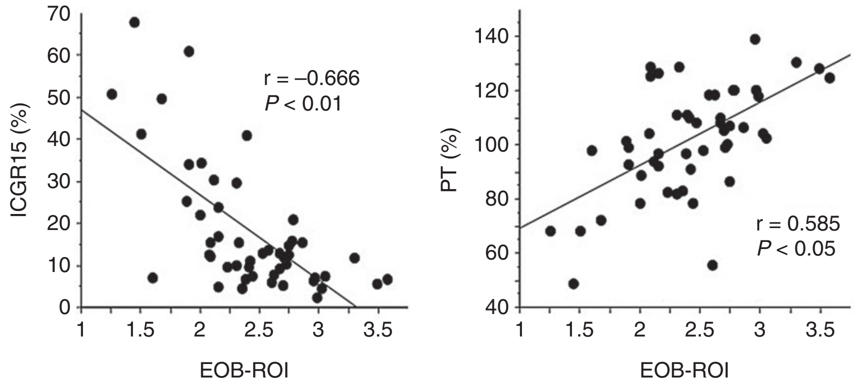

Figure 1 Correlations between signal intensity (SI) on gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid magnetic resonance imaging (EOB-MRI) and indocyanine green dye retention at 15 min (ICG-R15 = 70.3–21.5 × relative SI) (a) or prothrombin time (ICG-R15 = 38.5 + 25.9 × relative SI) (b). ROI, region of interest.

and quantify the microcirculatory status of the hepatic parenchyma.[70] DCE-MRI data consist of one T_1-weighted signal time curve for every voxel in the field of view. Using dedicated software, these data can be analyzed descriptively or quantitatively to determine the physiological state of the tissue.[65]

Studies have proposed using dynamic EOB-MRI to measure a time–intensity curve over the portal vein and hepatic parenchyma and to use a deconvolution method to compute a "hepatic extraction fraction" (HEF).[65,66] HEF represents the proportion of a tracer extracted by the liver from the system. HEF values were found to be significantly lower in patients with primary biliary cirrhosis than in normal subjects. These studies also provided hepatic function maps to depict the anatomic distribution of hepatic function. A more recent study adopting a dual-input single compartment model suggested that arterial blood flow was a good predictor of mild fibrosis.[64]

Among the advantages of the DCE-MRI method is that it evaluates serial hepatic uptake of Gd-EOB-DTPA according to both hepatic function and hepatic blood flow. However, DCE-MRI requires dedicated software and complex mathematical modeling. Moreover, the liver has a dual blood supply, with image acquisition affected by breathing motion, unlike the brain. In addition, DCE-MRI of the liver lacks uniformity in measurement and analysis methods, and the reproducibility of this method has not been determined.[70] Additional technical developments and validation studies are therefore required to overcome these challenges.

Correlation between liver function tests and the relative SI of EOB-MRI

Studies have assessed the correlation between the results of liver function tests and the relative SI of EOB-MRI or the receptor index (LHL15) of GSA imaging. For example, one study evaluating the correlation coefficient between relative SI and LHL15 showed better correlation coefficients between relative SI and measures of liver functional reserve, including ICG-R15 and prothrombin time (Fig. 1).[22] Modest correlations were also observed between relative SI and measures of liver fibrosis, including hyaluronic acid and type IV collagen. Relative SI also showed good correlation coefficients with serum albumin and total bilirubin concentrations. Taken together, these results indicate that EOB-MRI may be as accurate as ^{99m}Tc-GSA scintigraphy in estimating liver functional reserve in clinical practice.

Possible estimation of regional liver function by relative SI

Determining the extent of hepatic resection in a patient with a malignancy obstructing the major branch of the hepatic duct requires precise evaluation of the regional function of the remnant liver. Figure 2 shows a representative patient with hilar cholangiocarcinoma and obstruction of the major branch of the right hepatic duct. Both CT scan and intraoperative findings revealed atrophy of the right lobe owing to regional dysfunction of this hepatic lobe. Volumetric assessment was 62% for the left lobe and 38% for the right lobe. Examination of the relative SI in each Couinaud segment, except for the caudate lobe, showed that the mean relative SI was significantly lower for the right (S5, S6, S7, S8) than for the left (S2, S3, S4) lobe (2.4 ± 0.3 vs 3.1 ± 0.1, $P < 0.05$). Using a formula that converts relative SI to ICG-R15 (ICG-R15 = 70.3 – [21.5 × relative SI]) showed that the ICG-R15 values in the right and left lobes were 18.7% and 3.7%, respectively. Thus, the combination of ^{99m}Tc-GSA SPECT and CT fusion images may be useful in

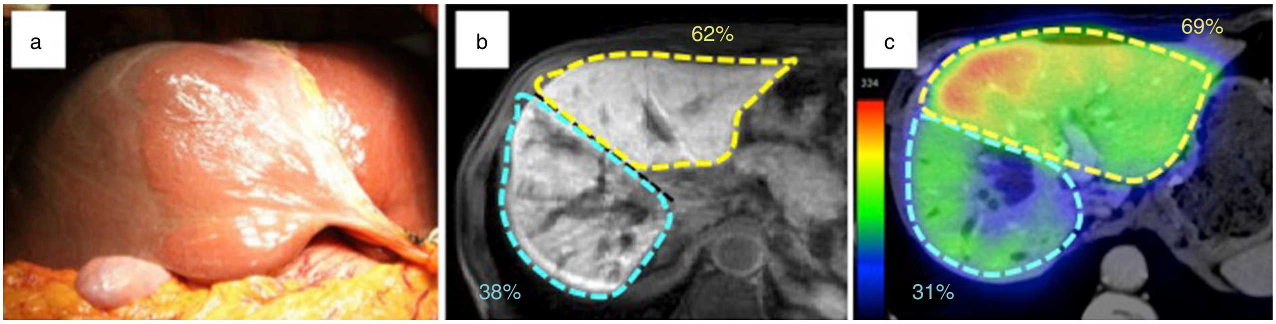

Figure 2 (a) Intraoperative view of the liver surface in a patient with hilar cholangiocarcinoma and (b) a gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid image indicating an atrophic change in the right hepatic lobe. Volumetric assessment of both lobes revealed 62% for the left and 38% for the right lobe. (c) Functional volume of each lobe from single-photon emission computerized tomography fusion images, showing that the left lobe had 69% and the right lobe 31% of the function of the entire liver.

estimating FRL function precisely in patients with jaundice owing to obstruction of a major bile duct.

Although this finding awaits confirmation in a large number of patients, a marked difference in the relative SI of the lobes suggests the ability of this imaging strategy to precisely estimate regional liver function reserve.

CONCLUSION

TECHNETIUM-99*M* GSA SCINTIGRAPHY and EOB-MRI are non-invasive, reliable techniques that may provide visual and quantitative information on both total and regional liver function. In particular, regional assessment of hepatic function mapped onto hepatic anatomy may be clinically more meaningful than conventional indicators of hepatic function in patients with locally varying hepatic parenchymal abnormalities. Although dynamic SPECT would be able to estimate functional liver volume, EOB-MRI cannot only improve the detection and characterization of small hepatic tumors, but also can be used to estimate regional liver functional reserve, without the need for exposure to radiation. However, the technique is still evolving and requires further development and validation to be standardized and accepted in routine clinical practice.

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