Editorial

Looking into the future (remnant liver)

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Introduction

The most common primary malignancy of the liver is hepatocellular carcinoma (HCC) (1). Approximately 80% of patients with HCC show chronic liver disease and cirrhosis. Chronic infection with hepatitis B or C virus, alcoholic liver disease and nonalcoholic steatohepatitis are the most frequent causes for developing liver cirrhosis (2). Other risk factors are hemochromatosis, primary biliary cirrhosis (PBC) and autoimmune hepatitis (3). Partial liver resection or liver transplantation remain the only potentially curative treatment options in patients with HCC. In recent years the indications for liver resection have been expanded due to improvements in surgical technique, perioperative care and chemotherapy regimens, leading to an increased number of patients that is now eligible for partial liver resection (4). This resulted in larger resections and consequently an increased risk of postresectional liver failure (PLF). PLF is the most important cause of death after partial liver resection (5,6). Between 0.7% and 9.1% of all patients undergoing partial liver resection develop this complication that is caused by insufficient remnant liver volume and function (5). Surgical treatment of patients with multifocal HCCs who do not meet the Milan criteria (one lesion smaller than 5 cm or a maximum of 3 lesions smaller than 3 cm in absence of vascular invasion and extrahepatic disease) is controversial, and in these cases transarterial chemoembolization is recommended (7). However, in patients with multifocal HCCs who do not meet the Milan criteria and complete resection of all tumours is not feasible, the combination of partial liver resection and radiofrequency ablation (RFA) can be considered, due to potential survival benefits especially in case of small tumours (8).

Liver volume

In most hepatobiliary units liver-specific preoperative risk assessment prior to major liver surgery comprises liver volumetry only. Automated and manual liver volumetry using CT or MRI is considered valid and accurate (9,10). In order to prevent PLF, about 25–30% of the total liver volume needs to be preserved in patients without background liver disease (11). Especially patients with liver cirrhosis have diminished liver function and in these patients the generally considered acceptable remnant liver volume is about 50%. However, the degree of liver cirrhosis is variable. Therefore tailored estimation of the amount of liver tissue that can be removed is essential.

Liver function

Liver volume does not necessary equal function as function is often heterogeneously distributed (12). Moreover, liver tumours (especially cholangiocarcinoma) can cause bile duct obstruction, cholestasis and can possibly compromise portal venous and arterial flow leading to atrophy and regionally diminished liver function. Also, interventions to increase resectability prior to or during partial hepatectomy [i.e., portal vein embolisation, associating liver partition

and portal vein ligation for staged hepatectomy (ALPPS) procedures and RFA] influence regional liver function.

Although prone to sampling error and disease dissemination, liver biopsy is still considered the most accurate way to evaluate the overall quality of the liver. According to a large multicenter study in 2,740 patients undergoing percutaneous liver biopsies, serious adverse events occur in 1% of patients most often due to haemorrhage (13).

Ultrasound and to a lesser extent CT evaluation of the liver, can give some clues on liver dysfunction. Surface nodularity, atrophy of the right hemiliver with synchronous hypertrophy of the caudate lobe and the left lateral section of the liver, next to heterogeneous echotexture and signs of portal hypertension (such as slow hepatopetal flow or hepatofugal flow, splenomegaly, portal vein enlargement, ascites and collateral formation), can all be observed and provide information on the severity of possible cirrhosis. Moreover, steatosis can easily be recognized. However all of the mentioned factors are descriptive characteristics and are insufficient to scale liver function adequately prior to partial liver resection.

Multiple global liver function tests and scoring systems have been proposed but to date a golden standard has not been clearly defined. Most widely used tests are static tests (i.e. serum values of liver enzymes) (14,15). Independently, none of these tests is able to predict mortality or PLF. The Child-Pugh classification, MELD score and AST-to-platelet-ratio index incorporate several laboratory tests with and without clinical features, but are unable to accurately identify patients at risk of developing PLF (6). Next to these static tests, dynamic tests can be performed and the most widespread quantitative liver function tests are the Indocyanine Green clearance test (ICG R15) and the aminopyrine breath test (14-17). Recently a methacetin breath test was developed (LiMAx test) which is currently considered one of the more accurate liver function tests (18). A future remnant liver LiMAx function per kg bodyweight of 100 µg per kilogram body weight per hour is thought to be sufficient to prevent PLF (18).

The combination of CT or MRI volumetry and global liver function analysis, is considered appropriate to assess patients prior to major liver resections. However, the downside is that regional functional differences in the liver cannot be evaluated by these imaging techniques and PLF still occurs. In patients needing a critical liver resection, focal differences in liver function can make the difference between an uneventful and a detrimental postoperative course. In other words, a remnant liver volume of 50% does not necessarily indicate a remnant liver function of 50%. In an era in which liver surgeons continuously seek the limits of resectability this is a potentially dangerous limitation of global liver function tests combined with CT or MRI volumetry.

Dynamic hepatocyte specific contrast enhanced mri using gadoxic acid

A promising and relatively new method to evaluate liver function is dynamic contrast enhanced T1-weighted MRI with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA, also known as gadoxic acid and Eovist in the US and Primovist in Europe). Gadoxic acid is a hepatocyte-specific contrast agent which is taken up by hepatocytes via the basolateral OATP1B1/B3 transport proteins and secreted into bile through MRP2 (19). MRI has the potential to evaluate the liver parenchyma at the level of a voxel and is therefore suitable to evaluate regional differences within the liver.

Gadoxic acid uptake by the hepatocytes can be estimated using static and dynamic MRI parameters. "Relative liver enhancement" (RLE) is the first and most widely used static parameter evaluating liver function. Through multiple Region-Of-Interest (ROI) signal intensity (SI) measurements on unenhanced and hepatobiliary phase scans, the relative liver enhancement can be determined as follows: $RLE = (SI_{enhanced} - SI_{unenhanced})/SI_{unenhanced}$ (20). The "contrast enhancement index" (CEI) compares the SI ratio (SIR) between the liver and para-spinal muscles on enhanced and unenhanced series using the following formula: $CEI = SIR_{enhanced} / SIR_{unenhanced}$ (21). Moreover, the "hepatic uptake index" (HUI) has been proposed as informative measure. The latter also takes volume into account and can therefore be used as a segmental and global liver function assessment tool using the following formula: $HUI = \text{Liver volume} \times [(SI_{liver}/SI_{spleen}) - 1]$ (22). The last static method to evaluate liver function using gadoxic acid MR imaging is "T1 mapping" that uses the linear relationship between T1 relaxation time and contrast agent concentration. However, the fact that gadoxic acid is present in more than one compartment (i.e., hepatocytes and bile ducts) seems to influence the relaxation times. Relaxometry has been proposed to overcome this limitation (23). In fact, none of the above mentioned methods found its way into daily clinical practice as none of these tests is considered the golden standard for liver function analysis.

Reporting in the *Journal of Hepatology*, Yoon *et al.* (24) elaborated on the pioneering work of Nilson and coworkers by using dynamic hepatocyte-specific contrast-enhanced (DHCE) MRI in the context of preoperative assessment of liver function in patients scheduled for partial hepatectomy (19,25). They describe that the impulse response function can be estimated by using the input function (which can be defined by measuring the SI over time in the hilar part of the portal vein), the response function (which can be measured as the enhancement of liver parenchyma in different regions over time) and deconvolutional analysis of the data obtained. The impulse response function can then be used to determine relevant parameters such as the "hepatic extraction fraction" (HEF). Moreover the "peak blood flow relative to the input function" ("input relative blood flow", irBF) and the "area under the curve" seem to be interesting parameters in the evaluation of global and segmental liver function. Semiquantative parameters such as "time to peak", "elimination half life" and "maximum enhancement" also provide information on liver function to some extent. Yoon *et al.* evaluated liver function and volume on a segmental level and observed clear differences between regions. These differences were more pronounced in patients with Child-Pugh B score than in patients classified as Child-Pugh A, indicating that liver function heterogeneity is increased in patients with parenchymal disease. As obesity and hepatic steatosis is becoming increasingly prevalent in the general population, background liver steatosis might also magnify heterogeneity of liver function. This factor could therefore be of interest for a wider range of liver tumours than HCC and cholangiocarcinoma alone. As the most common indication for partial liver resection is metastatic disease, future studies should also evaluate the influence of liver steatosis on liver function heterogeneity in this population.

Yoon *et al.* evaluated correlations between preoperative ICG and DHCE MRI parameters, postoperative ICG and DHCR MRI parameters, as well as predicted remnant DHCE MRI parameters and actual postoperative ICG R15 values. Predicted remnant HEFml was significantly correlated with ICG R15 at post-operative day 3 (POD3, r=–0.45), with possible influence of early regenerative events on ICG clearance accounting for the modest association. HEF% and HEFml were each related to ICG R15 values, both in the preoperative trajectory and on POD3 (correlation coefficient between –0.33 and –0.54). Overall, these modest correlations may be due to the lack of a golden standard to assess liver function, with ICG clearance providing an easy -yet far from ideal- measure.

The acquisition time to perform DHCE MRI and the physical condition (motion artifact, difficulty to perform adequate breath-holds) of the patients during the first 48 hours after surgery, make early evaluation of MRI based liver function challenging.

The preoperative entity 'estimated remnant HEFml' (HEF of the future remnant liver multiplied by the future remnant liver volume) and remnant HEF percentage, seem to be valuable parameters that might predict PLF better than currently employed global liver function assessment combined with liver volumetry. Large series combining DHCE MRI with volumetry are needed to define normal values and cut-off values to indicate patients at risk for PLF.

In the cohort studied by Yoon *et al.* a single patient developed PLF. This is remarkable since most of patients had moderate to severe background liver disease, and 19 out of 54 patients underwent resection of 4 or more liver segments. As the authors also state, this may be caused by alterations in peri-operative management based on ICG and DHCE MRI findings. The patient developing PLF had a HEF value of 0.17 and a HEFml of 135 mL, with both values in the lowest quartile of the study population. These values can be indicative for future studies establishing cut-off values for PLF.

Interestingly, Yoon *et al.* were able to shorten the scanning protocol from over 80 minutes (19,25) to 45 minutes; thereby increasing its clinical feasibility. However, future studies should focus on optimizing post-processing software to reduce time to evaluate all data. As liver centers increasingly use standard MRI in their preoperative work-up because of diagnostic benefits over CT, evaluation of the liver function using DHCE MRI could easily be incorporated in standard preoperative assessment once shortcomings, that are inherent to novel approaches, have been overcome.

Conclusions

As patients undergoing partial hepatectomy for primary malignancies of the liver (i.e., HCC and cholangiocarcinoma) often suffer from concomitant liver cirrhosis, impaired liver function or parenchymal dysfunction due to bile duct obstruction or atrophy, preoperative functional analysis of the liver is essential. To date a golden standard for global functional analysis is lacking. Scoring systems, laboratory values and breath tests all have at least one major drawback: they are unable to

detect regional differences within the liver which are present even in healthy patients. In an era where preoperative liver function changing interventions are frequently performed the differences are even more profound and of more interest. Evaluation of liver function using MR imaging and gadoxic acid is gaining more and more attention. Static methods such as RLA, CEI, TUI and T1 mapping already seem to provide additional useful information on global and regional liver function. The dynamic variant of gadoxic acid enhanced MR imaging provides even more relevant parameters such as irBF, HEF and HEFml. Combined with preoperative liver volumetry and calculation of the future remnant liver volume this might well be the way to assess patients with HCC or other tumours prior to potential critical liver resections. Current drawbacks of this method are the prolonged scanning time and the time-consuming evaluation of the DHCE MRI data. Moreover, large series are needed to define cut-off values for impending PLF before it can be implemented in standard clinical practice. The promising technique of DHCE MRI might become the golden standard for liver function assessment prior to liver surgery, and may proof to reduce the occurrence of PLF.

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Footnote

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