Commentary

Prediction of postoperative liver failure in patients diagnosed with hepatocellular carcinoma using ^{99m}Tc-GSA SPECT/CT

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Although relatively rare in the Western countries, hepatocellular carcinoma (HCC) is the third cause of death due to cancer in the world and its incidence increases each year (1,2). Complete excision remains the treatment of choice, whether by liver resection or liver transplantation. In patients considered for liver resection, assessment of the future remnant liver (FRL) is of utmost importance in order to prevent postoperative liver failure. Computed tomography (CT) volumetry is the most widely used method in the preoperative assessment of the FRL, but, although it is the gold standard, does not provide any information on the function of FRL and its role in the preoperative work-up for liver surgery is therefore questionable (3). The same accounts for the laboratory liver function tests as they merely offer an approximation of the liver's metabolic processes as an entire organ (i.e., uptake, synthesis, biotransformation and excretion) (4). Furthermore, it has been shown that there is only moderate correlation between FRL volume and FRL function in patients with hepatic comorbidity (3). Consequently, interest in imaging based quantitative liver function tests has increased. There are two main challenges in the preoperative assessment of function of the FRL: selective segmental measurement of FRL function independently of the quality of liver parenchyma and validation of a threshold value for safe resection.

^{99m}Tc-labeled diethylenetriaminepentaacetic acid galactosyl human serum albumin (GSA) scintigraphy is a frequently reported method of preoperative assessment of liver function, unfortunately until now, limited to the Asian market. The asialoglycoprotein receptor is specific for asialoglycoproteins and its decrease is associated with chronic liver disease (5). ^{99m}Tc-labeled GSA is used for clinical imaging of the receptor (6,7). ^{99m}Tc-GSA allows not only for measurement of total liver function but also enables segmental assessment of liver function (8-10), rendering ^{99m}Tc-GSA along with the hepatic ^{99m}Tc-mebrofenin uptake-rate scintigraphy used in the Western world, one of the most advanced techniques in the assessment of FRL to date (3,11,12). Many models using ^{99m}Tc-GSA have been proposed since the introduction of the test, all of them showing promising results. Unfortunately, most of the models have proven rather complex. The uptake index (UI) of ^{99m}Tc-GSA, i.e., a kinetic model of ^{99m}Tc-GSA to show the speed of asialoglycoprotein receptor-mediated endocytosis, is one of the last introduced parameters awaiting validation in clinical practice (13), which was recently published (14).

In their paper, Mao *et al*. evaluate the validity of the Zhong System for the assessment of hepatic function in patients before and after hepatectomy (14). This imaging system combines the assessment of liver function with ^{99m}Tc-GSA and the UI with 3-dimentional CT imaging, providing 3D functional imaging of the liver. Moreover, in this prospective study among patients with HCC Child-Pugh A/B and healthy volunteers, the authors establish the functional liver volume index (FLVI). FLVI is the ratio between the UI value measured in a patient and the median UI measured in the healthy population.

The authors describe a significant difference in UI values between patients with Child-Pugh A (score 5 and 6) and patients with Child-Pugh B (score 7, 8 and 9), suggesting that UI could be used as a universal parameter for accurate differentiation between the different grades of chronic liver disease. Furthermore, preoperative UI correlated well with preoperative clinical and biochemical parameters, as well as the ICG test, a widely used clearance test of plasma indocyanine green; i.e., patients with and without ascites, elevated bilirubin levels and/or prolonged ICG15 can be distinguished based on the UI value. However, one should mind the small sample size this analysis was based on (n=69).

Another key finding of Mao and colleagues was the excellent correlation of the preoperatively predicted UI value with the actual postoperative UI value in 33 patients who underwent preoperative and postoperative ^{99m}Tc-GSA measurements. The authors also described good correlation of the predicted UI values with the occurrence of postoperative ascites and elevated bilirubin levels.

In the same study, the authors propose a critical value that is able to accurately indicate patients at risk for developing liver insufficiency. However, the authors had to overcome the main limitation in their study of examining liver function in this particular, small patient population. The UI values measured in patients with Child-Pugh C liver disease ideally, should have been used to discriminate the critical value. However, as the authors describe in their article, it was difficult to recruit patients of this category. Consequently, Moa and colleagues considered the probability of having liver disease beyond Child-Pugh A or B as surrogate for suffering from liver failure. A critical UI of 0.73 and FLVI of 26% were defined as the lower threshold of the test indicating patients at high risk for liver failure.

Due to its lethal character, postoperative liver failure is one of the most feared complications after liver resection, especially in patients with cirrhosis. In order to validate the ability of ^{99m}Tc-GSA to predict postoperative liver failure, the authors performed a ROC analysis. The objective of this analysis was to define a cut-off value at which patients would be at risk for postoperative liver failure. Preoperative measurements of the patients who underwent surgery but no postoperative ^{99m}Tc-GSA (n=36) and postoperative measurements of the patients who did (n=33), were used for the analysis. For this purpose, the authors decided to define patients with Child-Pugh score 9 as patients at high risk for developing postoperative liver failure, because none of the included patients was diagnosed with Child-Pugh C (score ≥10) and because of ethical concerns regarding surgery in patients in whom postoperative Child-Pugh C was expected. Using ROC analysis the authors found a cut-off value for UI of 0.9 (FLVI =32%) with a corresponding sensitivity of 100% and specificity of 92%.

However, there are several concerns regarding the methodological design of the prediction model used in this study. Firstly, major liver surgery (≥3 segments) was performed in only 7 out of the 33 patients who had undergone both preoperative and postoperative ^{99m}Tc-GSA. Among the remaining patients, more than one segment was resected in 25 patients while 1 patient had undergone minor liver surgery only. Secondly, the validity of a model designed to predict liver failure should be evaluated by means of liver failure as the primary endpoint of the study. In this context, other primary hepatic or metastatic tumor types and patients with and without preoperative neoadjuvant chemotherapy should be taken into account. Ideally, consecutive patients should undergo preoperative ^{99m}Tc-GSA while the decision to resect or not, must be based on the regular gold standard applied at the same centre. Analysis of patients who develop postoperative liver failure or not will reveal the true cut-off values of the functional test.

The abovementioned study design was applied by de Graaf and colleagues in their paper on the estimation of the cut-off value for hepatic ^{99m}Tc-mebrofenin uptake-rate scintigraphy [^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS)] (3). The authors describe a heterogeneous cohort of 55 patients with compromised and non-compromised liver parenchyma and diagnosed with different hepatic lesions, all of whom underwent resection of at least 3 segments. Preoperative HBS was performed in all patients, although the results were not taken into account during the preoperative work-up. Nine of the 55 patients developed postoperative liver failure. From the analysis, a universal cut-off value was calculated whereupon the test was implemented in standard patient care for all patients scheduled to undergo major liver surgery, independently of the quality of the liver parenchyma and of the suspected diagnosis.

In conclusion, quantitative liver function tests as opposed to CT volumetric studies, provide the only means to accurately determine the functional capacity of the FRL. UI and FLVI threshold values measured using ^{99m}Tc-GSA, as the Zhong System, are interesting and promising but clinical application awaits further evaluation in controlled studies.

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