Strategies to improve outcome after partial liver resection

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Preoperative assessment of postoperative remnant liver function with hepatobiliary scintigraphy

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Abstract

Introduction. Hepatic resection is the therapy of choice for malignant and symptomatic benign hepatobiliary tumors. The concept of remnant liver volume (RLV) has been introduced and can be assessed with CT. However, inhomogeneous liver function distribution and a lack of correlation between morphologic hypertrophy and functional recovery fuelled the enthusiasm for functional imaging. The aim of the present study was to assess liver function reserve (LFR) and remnant liver function (RLF) before and after major liver surgery with hepatobiliary scintigraphy (HBS) and to compare scintigraphic results with volumetric CT data and ICG clearance test results. Furthermore, HBS was used to assess functional recovery of liver function and results were compared with volumetric data.

Methods. Fifteen patients with a partial liver resection were included. HBS was performed before, 1 day after and 3 mo after surgery. ICG clearance and CT were performed before and 3 mo after surgery. Liver function determined with HBS was compared to ICG and volumetric data.

Results. Liver function determination using HBS was highly reproducible. There was a strong positive association ($r = 0.84$) between LFR determined with HBS and ICG clearance. There was little or no association ($r = 0.27$) between CT volumetry and corresponding ICG clearance. There was a strong positive association ($r = 0.95$) between the RLF determined preoperatively on HBS and the actually measured value postoperatively. There was a weak positive association ($r = 0.61$) between functional liver regeneration and liver volume regeneration in 3 mo time after partial liver resection.

Conclusion. HBS offers a unique combination of functional liver uptake and excretion assessment with the ability to determine the preoperative LFR and to estimate the RLF preoperatively. Determination of the RLF instead of the RLV might clarify some of the discrepancies observed in the literature between RLV and clinical outcome in patients with a nonhomogeneous liver function. Finally, liver function regeneration can be monitored using HBS.
Introduction

Hepatic resection is the therapy of choice for malignant and symptomatic benign hepatobiliary tumors. Recent improvement in the safety of liver surgery has resulted in the performance of more extended hepatic resections. The improvement of results is largely due to better techniques and selection of patients.

The maximum extent of resection compatible with a safe postoperative outcome remains unknown, but it is generally believed that the risk for perioperative complications increases when the remnant liver volume is too small. Therefore, preoperative assessment of hepatic function and remnant liver volume (RLV) is advocated. Preoperative and remnant liver volumes can be accurately estimated with CT. However, most strategies evaluating preoperative hepatic function reserve and estimating the remnant liver volume rely on a homogeneous liver function. Unlike patients undergoing liver resection for metastatic cancer or benign liver conditions, patients with hepatocellular carcinoma (HCC) or obstructing tumors like cholangiocarcinoma may have underlying chronic liver disease or cholestasis with primary or secondary impaired total or segmental liver function.

Hepatobiliary scintigraphy (HBS) using $^{99m}$Tc-labeled iminodiacetic acid (IDA) analogues has been proposed as a liver function test. The liver uptake function can be measured by first pass hepatocyte extraction fraction or the IDA liver uptake rate. There is a good correlation between the preoperative $^{99m}$Tc-mebrofenin liver uptake rate and the ICG clearance test in patients scheduled for major liver surgery. As IDA-scintigraphy is commonly used for the evaluation of hepatobiliary function, hepatobiliary scintigraphy might be interesting for evaluation of both total and regional hepatocyte uptake function as well as excretory kinetics for risk assessment before major liver surgery.

Therefore, the aim of this study was to validate total and regional hepatobiliary scintigraphy as a tool to measure total and regional liver function before and after major liver surgery and to compare scintigraphic results with volumetric data and ICG clearance test results. Furthermore, the correlation of the immediate postoperative remnant liver function predicted on preoperative scintigraphy and measured 24 h after surgery with scintigraphy was assessed. Finally, the relation between liver function regeneration determined with HBS and volumetry was assessed.

Materials and methods

Subjects

55 patients, who were asked to participate in a trial assessing metabolic effects of major liver resection, and in whom partial liver resection for hepatobiliary tumors was considered, were screened in a period of 2 years. Eight patients refused to participate. In 8 patients concurrent volumetric data was not available. Sixteen patients had an irresectable tumor. Three patients had a severe perioperative complication (blood loss > 2 L), excluding them from further participation in the primary trial. Seven patients had severe perioperative complications (sepsis, $n = 4$: abdominal bleeding, $n = 1$ and lethal
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hepatic insufficiency, \( n = 2 \). We included 15 consecutive patients (7 men, 8 women, mean age 60.8 range 37-77 yrs) with a peroperative uncomplicated partial liver resection. There were no patients with biliary obstruction at the time of inclusion. 6 patients were treated for cholangiocarcinoma, 7 patients had a solitary metastasis of a colon carcinoma and 2 patients had a hepatocellular carcinoma without liver cirrhosis. 5 patients had a right hemihepatectomy, 4 patients had an extended right hemihepatectomy, 3 patients had a left hemihepatectomy and 3 patients had only 1 or 2 liver segments removed. All patients had an ICG clearance test one day before and 3 mo after surgery. Immediate postoperative ICG clearance was not performed. All patients had hepatic CT volumetry and HBS max. 2 wk before, and 3 mo after surgery. All patients had HBS 24 h after surgery. The volume of the resected liver was measured by immersing the specimen in water. The postoperative liver volume was calculated by subtracting the volume of the resection specimen from the preoperative measured CT liver-volume. All patients gave written informed consent to participate in the study, which was approved by the medical ethics committee of the Academic Medical Center of the University of Amsterdam.

**ICG clearance test**

On every occasion, bilateral intravenous lines were placed in the antecubital veins. After an overnight fast, 25 mg of ICG (Infracyanine; Laboratoires pharmaceutiques) was dissolved in 10 mL of 5% dextrose solution and injected rapidly into the antecubital vein. The clearance tests were performed after overnight fasting because food consumption stimulates hepatic function and bile flow. Blood samples were drawn at the contralateral side of injection before the administration of ICG (blank) and at 5, 10, 15 and 20 min after ICG injection. Plasma samples were read against the plasma blank at 805 nm by photospectrometry to determine the concentration of ICG. The theoretical maximum concentration at zero minutes was estimated by using the least squares method. Results were expressed as the percentage ICG cleared at 15 min (ICG-C15 value).

**CT volumetry**

CT volumetry was performed as described by Vauthey et al. Patients had a diagnostic CT abdomen with and without i.v. contrast before and 3 mo after surgery. All CT examinations were performed with a helical scanner (Philips). CT of the abdomen was performed to include the whole liver in one breath-hold, using a 5 mm collimation. Liver volumes were calculated by integrated software techniques that use density threshold seeding. With this technique, the levels of density desired for inclusion in the data set was selected. Regions that were of the selected density but should not be included in the data set - such as inferior vena cava, gall bladder, abdominal and chest wall muscles - were excluded. Liver volumes were calculated before and 3 mo after surgery. Liver volume recovery was calculated by subtraction of the measured volume after 3 mo and the immediate postoperative volume. A comparison was made between CT volumetry and ICG clearance as gold standard before and 3 mo after surgery. Finally, the relation between liver function regeneration determined with HBS and volumetry was assessed.
Scintigraphic assessment of remnant liver function

Scintigraphic Test Procedure

Patients underwent hepatobiliary scintigraphy using the radiopharmaceutical agent $^{99m}$Technetium ($^{99m}$Tc)-mebrofenin (Bridatec; Amersham Health). After intravenous administration of 85 MBq $^{99m}$Tc-mebrofenin, dynamic image acquisition was performed with a gamma camera (Diacam; Siemens Medical Systems) with the liver and heart in the field-of-view (FOV), using a 128 x 128 matrix. Dynamic acquisition was performed in 1 h at 10 sec per frame for 60 frames (liver uptake sequence) followed by 50 frames of 1 min (bile excretion sequence). Data was processed on a Hermes workstation (Nuclear Diagnostics). The liver uptake rate was calculated as described by Ekman et al. Regions of interest (ROI) were drawn around the liver, the heart and large vessels within the mediastinum (serving as blood pool) and around the total FOV (indicative of total activity). The liver ROI was drawn automatically on a threshold-based algorithm using 20% of the max. liver value on a summed image of the first 10 min of the acquisition as cut-off. Three different time-activity curves were generated, based on the liver, blood pool and total FOV. Liver uptake was calculated in %/min, based on these 3 parameters. Furthermore, ROI could be drawn around parts of the liver to calculate regional differences in $^{99m}$Tc-mebrofenin uptake. Calculations of hepatic $^{99m}$Tc-mebrofenin uptake were performed using scanned radioactivity values acquired between 150 and 350 sec after injection, to make sure that calculations were made during a phase of homogeneous distribution of the agent in the blood pool and before the rapid phase of hepatic excretion.

All studies were processed twice by the same operator to assess the reproducibility of the hepatic uptake calculations. A correlation was made between the scintigraphic liver uptake and the ICG clearance as gold standard before and 3 mo after surgery.

For calculating regional liver uptake of the future remnant liver on the preoperative HBS, the global liver ROI was manually divided into 2 parts. The remnant liver ROI was drawn upon guidance of the surgeon performing the hemihepatectomy. In this remnant liver ROI, the estimated RLF was calculated. Furthermore, the remnant liver ROI of the immediate postoperative HBS was copied on the preoperative HBS dataset to recalculate the RLF. Subsequently, a comparison was made between the preoperative estimated RLF and the actually measured immediate postoperative RLF. The functional hepatic recovery was calculated by subtraction of the measured scintigraphic liver function after 3 mo and the immediate postoperative liver function. Three mo after surgery, functional scintigraphic liver regeneration was compared to CT volumetric regeneration.

Statistical analysis

The relationship between ICG clearance, liver uptake of $^{99m}$Tc-mebrofenin and CT volumetry was tested using the standard Pearson correlation coefficient. All results are expressed as mean ± SEM values. All statistical tests were 2-tailed and differences were evaluated at the 5% level of significance.
Results

Patient volumetric and functional data are summarized in Table 1. A total of 45 HBS's were performed in 15 patients (Fig. 1). On every scintigraphy, the hepatic uptake rate of $^{99m}$Tc-mebrofenin was calculated twice, once on the day the scintigraphy was performed and once in batch after completion of the trial by the same operator. There was an excellent correlation ($r = 0.99, P < 0.001$) between both calculations (Fig. 2A). Altman-Blant statistics are shown in figure 3A. In 27 HBS's (preoperative and 3 mo after surgery) a corresponding ICG clearance was performed. There was a strong positive association ($r = 0.84, P < 0.001$) between the LFR determined with HBS and ICG clearance (Fig. 2B).

Upon guidance of the surgeon, a ROI was drawn on the preoperative HBS encompassing the future remnant liver (Fig. 4A and 5A). The scintigraphic remnant liver function (RLF) within this ROI was assessed and compared to the scintigraphic liver uptake 1 day after surgery (Fig. 4B and 5B). There was a strong positive association ($r = 0.95, n = 15, P < 0.001$) between these measurements (Fig. 2C). Altman-Blant statistics are shown in figure 3B. When the ROI of the remnant liver on the immediate postoperative HBS was copied on the baseline preoperative scintigraphy to calculate the RLF, the correlation ($r = 0.97, n = 15, P < 0.001$) was slightly better.

Liver volumes were assessed with CT preoperatively and 3 mo after surgery. In 27 CT volumetry assessments (preoperative and 3 months after surgery) a corresponding ICG clearance was performed. There was little or no association ($r = 0.27$) between the measured liver volume and function, determined with CT and ICG clearance, respectively.

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RLF_{HBS} = RLF determined on preoperative HBS, Vol_{pre} = Surgically resected volume, Vol_{rem} = Volume remnant liver

Table 1. Patient volumetric and functional data
Figure 1. Hepatobiliary scintigraphy

Preoperative HBS (pt. 13) in a patient with a proximal cholangiocarcinoma. Panel A shows reframed images of the dynamic acquisition. There is a homogeneous liver uptake with moderate cholestasis in the left side without functional repercussion. Panel B shows a summed image from 150 – 350 sec after intravenous injection of 80 MBq $^{99m}$Tc-mebrofenin. A ROI is drawn semi-automatically (threshold 20%) around the entire liver. A second ROI is drawn in the mediastinum (blood pool). Panel C shows a blood pool corrected liver-uptake time-activity curve. Liver uptake (d) is calculated as increase of specific (corrected for blood pool) $^{99m}$Tc-mebrofenin uptake (y-axis) per minute over a time period of 200 sec (x-axis).

Figure 2. Correlation plots

Scatter plots with linear regression line of HBS liver function calculation reproducibility (A), HBS and ICG clearance LFR assessment (B), HBS preoperative RLF assessment and postoperative RLF measurement (C), liver volume recovery and liver function recovery (D).
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Figure 3. Altman-Blant statistics of liver uptake function

Altman-Bland plot with the mean of the repeated liver uptake function calculation on HBS in 45 studies on the horizontal axis and the differences in the repeated calculations on the vertical axis (A). Altman-Bland plot with the mean of FLR determination on HBS before and after surgery in 15 studies on the horizontal axis and the differences in the repeated measurements on the vertical axis (B). Data are expressed as %/min hepatic 99mTc-mebrofenin uptake. The horizontal solid line indicates the mean difference between both calculations. The horizontal dashed line indicates the 95% limits of agreement (mean ± 1.96 SD).

Table 2. Liver recovery data

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HBS<sub>(post)</sub> = Assessment 1 day after surgery, HBS<sub>(3m)</sub> = Assessment 3 months after surgery, HBS<sub>(Rec)</sub> = Functional recovery determined with HBS, Vol<sub>(Rec)</sub> = Volume recovery determined with CT

Finally, functional liver regeneration was assessed with HBS and compared to volume regeneration assessed with CT volumetry (Table 2). There was a strong positive association ($r = 0.81$, $n = 10$, $P < 0.01$) between liver function assessed with HBS and ICG clearance 3 mo after surgery. There was a weak association ($r = 0.61$, $n = 15$, $P = 0.16$) between functional liver regeneration and liver volume regeneration in 3 mo time after partial liver resection (Fig. 2D). An example of HBS in a patient with a right-sided hemihepatectomy is shown in Figure 4. An example of HBS in a patient with a left-sided hemihepatectomy is shown in Figure 5.
Scintigraphic assessment of remnant liver function

**Figure 4.** Right-sided hemihepatectomy

Summed images from 150 – 350 sec after intravenous injection of 80 MBq $^{99m}$Tc-mebrofenin (pt. 3) preoperative (A), 1 d postoperatively after right-sided hemi-hepatectomy (B) and 3 mo postoperatively (C). Images are normalized to the preoperative HBS. On panel A, a ROI is drawn over the entire liver (black), the future remnant liver (white) and mediastinal blood pool (bl). The ROIs were copied on the HBS performed 1 day and 3 mo postoperative. The total liver function was 16.05 %/min and the RLF was estimated at 5.88 %/min on preoperative HBS. The measured RLF 1 day postoperative was 5.15 %/min. After 3 mo, the liver function recovered to 12.80 %/min with hypertrophy visible on HBS.

**Figure 5.** Left-sided hemihepatectomy

Summed images from 150 – 350 sec after intravenous injection of 80 MBq $^{99m}$Tc-mebrofenin (pt. 15) preoperative (A), 1 day postoperatively after left-sided hemi-hepatectomy (B) and 3 months postoperatively (C). Images are normalized to the preoperative HBS. On panel A, a ROI is drawn over the entire liver (black), the future remnant liver (white) and mediastinal blood pool (bl). The ROIs were copied on the HBS performed 1 day and 3 mo postoperative. The total liver function was 10.30 %/min and the RLF was estimated at 8.99 %/min on preoperative HBS. The measured RLF 1 day postoperative was 9.30 %/min. After 3 mo, the liver function recovered to 11.79 %/min with hypertrophy visible on HBS.

**Discussion**

Improvement in the safety of liver surgery has resulted in the performance of more extended hepatic resections $^{1,2}$. The improvement of results is largely due to better techniques resulting in reduction of blood loss. $^3$ However, better selection of patients and exclusion of high-risk patients seems to be another important contributory factor $^3$. Furthermore, preoperative (selective) portal vein embolization is used in patients with and without underlying liver disease to increase safety and tolerance of major hepatectomy with a small liver remnant $^4$. 

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Important parameters in risk assessment for major hepatectomy are the preoperative liver function reserve (LFR) and the remnant liver volume (RLV). Several methods of liver function assessment have been used, including liver biochemistry, Child classification and quantitative liver function tests. The ICG clearance test is regarded as the most accurate test for the evaluation of preoperative hepatic function reserve and in predicting postoperative mortality. However, test results reflect total liver function but cannot provide information on the distribution of liver function among liver segments.

Preoperative liver volume and RLV can be accurately assessed with CT. The combination of functional data with morphology is able to predict hepatic dysfunction in patients with normal liver parenchyma undergoing major liver resection. However, many patients undergoing partial hepatectomy for HCC have associated liver cirrhosis. Furthermore, patients with obstructing biliary tumors like cholangiocarcinoma may have cholestasis with secondary impaired total or segmental liver function. Therefore, $^{99m}$Tc-DTPA-galactosyl human serum albumin ($^{99m}$Tc-GSA) scintigraphy was previously tested and refined for hepatic function testing and risk assessment for safe partial hepatectomy. Major limitations are the availability of $^{99m}$Tc-GSA and the fact that $^{99m}$Tc-GSA is not excreted into the bile making it impossible to study liver uptake and excretory function within one test which can be useful in tumors or pathology with the possibility of obstruction.

HBS has been performed in liver transplant patients to assess the functional and morphological status of the graft, including structural complications like bile leakage or bile duct obstruction. The uptake mechanism of IDA-analoues by the hepatocyte is similar to those of other anorganic anions. Both ICG and IDA-analogue are excreted in the bile by hepatocytes by the ATP-dependent export pump multidrug-resistance associated protein 2 (MRP 2), without undergoing biotransformation during transit through the hepatocyte. The liver uptake function measured by Iodida clearance rate was described by Ekman et al. We adopted this technique but used $^{99m}$Tc-mebrofenin as radiopharmaceutical. $^{99m}$Tc-mebrofenin shows a high liver uptake and minimal urinary excretion and resists strongly the displacement by a high bilirubin level.

In our study, there was a strong positive association between the LFR measured with ICG and HBS, which confirmed earlier observations. Furthermore, the reproducibility of the liver function calculation based on HBS was high. However, it has to be stressed that reproducibility depends largely on the level of automatic and systematic ROI drawing, which is subject to a learning curve. Therefore, only one operator performed calculations in this phase of the trial program.

It can be argued that diseased regions are difficult to localize on planar registration and differences in volumes of liver ROIs might influence the findings. Therefore, SPECT techniques offer potential advantages in localization. However, quantitative or semiquantitative analysis in SPECT has limitations of its own and implementation of attenuation and scatter correction should be considered. Furthermore, the LFR determined with planar dynamic HBS correlates well with ICG clearance and the RLF assessed preoperatively correlated well with the postoperative measured value. Therefore, we feel confident to use planar HBS for the assessment of LFR and RLF. The asymmetric liver shape can produce over or underestimation of uptake on planar anterior dynamic scintigraphy. Despite the fact that this did not significantly affect our data in this study, dual-head dynamic
Scintigraphic assessment of remnant liver function

acquisition with geometric mean value calculation could improve the reliability of RLF and
this will be evaluated in the future.

It has been shown that CT is able to assess liver volumes with accuracy \(^6\). However, the
question remains whether volume and function can be related in any given situation. When a
small tumor has to be resected in a homogeneous and normal functioning liver, volume and
function can be related \(^{19}\). For these patients, restricted surgery is needed and the significance
of remnant liver function determination is questionable \(^4\). For multiple resectable or large
tumors, liver function distribution is not homogeneous. Furthermore, patients with HCC
frequently present with associated underlying disease like cirrhosis and cholestasis induced
by obstructing biliary tumors can affect total or segmental liver function. In these patients
it is possible that morphologic volumetry will not reflect functional volumetry, which might
explain the reported lack of association between the volume of the remaining liver and the
postoperative course \(^4,^{19}\).

When assessing functional recovery of the liver after hemihepatectomy, our results show
that there is only a weak association between functional liver regeneration and liver volume
regeneration in 3 mo time after partial liver resection. This emphasizes the importance of
functional imaging and might play an important role in patients subject to preoperative liver
function enhancement techniques such as portal embolization \(^{30}\).

Finally, HBS offers the ability to assess both liver uptake and excretory function. Besides
preoperative assessment of functional consequences of possible cholestasis, postoperative
assessment of remnant liver function can be combined with biliary function and bile
leak assessment. This combination of investigations is not possible with laboratory (ICG),
morphological (CT) or other scintigraphic techniques \(^{23,31,32}\).

Conclusion

Hepatobiliary scintigraphy offers a unique combination of functional liver uptake and
excretion assessment with the ability to determine the preoperative LFR and to estimate the
RLF preoperatively. Determination of the RLF instead of the RLV might clarify some of the
discrepancies observed in the literature between RLV and clinical outcome in patients with
a nonhomogeneous liver function. Finally, it has been shown that liver function regeneration
can be monitored using HBS.

References


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