Case report

Usefulness of measuring hepatic functional volume using Technetium-99m galactosyl serum albumin scintigraphy in bile duct carcinoma: Report of two cases

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Running title: Functional liver volume before hepatectomy

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Abstract

We report the usefulness of measuring functional liver volume in 2 patients undergoing hepatectomy. Case 1 involved a 47-year-old man with hepatitis B virus infection. Indocyanine green test retention rate at 15 min (ICGR15) was 14%. Liver uptake ratio (LHL15) by technetium-99m galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy was 0.91. The patient displayed hilar bile duct carcinoma necessitating right hepatectomy. After preoperative portal vein embolization (PVE), future remnant liver volume became 54% and functional volume by ^{99m}Tc-GSA became 79%. Although the permitted resected liver volume was lower than liver volume, scheduled hepatectomy was performed following the results of functional liver volume. Case 2 involved a 75-year-old man with diabetes. ICGR15 was 27.4% and LHL15 was 0.87. The patient displayed bile duct carcinoma located in the upper bile duct with biliary obstruction in the right lateral sector. The right hepatectomy was scheduled. After PVE, future remnant volume became 68% and functional volume became 88%. Although ICGR15 was worse as 31%, planned hepatectomy was performed due to the results of functional volume. In the liver with biliary obstruction or portal embolization, functional liver volume is decreased more than morphological volume. Measurement of functional volume provides useful information for deciding operative indication.

Key words: Bile duct carcinoma• Technetium-99m galactosyl human serum albumin liver scintigraphy• Functional liver volume• Biliary obstruction• Portal vein embolization

Introduction

Incidence of postoperative hepatic failure in hilar bile duct carcinoma has markedly decreased in recent years following the introduction of adequate preoperative evaluation of hepatic function and estimation of resected liver volume, induction of preoperative portal vein embolization (PVE) and improvements in perioperative management.[1] Child-Pugh classification or indocyanine green (ICG) test is classically used to define the indications for radical operations.[2] Furthermore, Makuuchi's criterion applying ICG retention rate at 15 min (ICGR15) for operative procedures has been often applied in Japan, and is suitable for hepatectomy in primary or metastatic liver tumors.[3] However, in cases involving hepatectomy for bile duct carcinomas, limitations apply to this criterion because of increased total bilirubin levels or poor ICG results due to biliary obstruction. Regardless of PVE and preoperative biliary drainage, total bilirubin level and result of ICG testing are unimproved and the operation must be delayed for a long time in some patients until improvement of such liver functions is seen.[4] Liver scintigraphy has been used to evaluate functional liver reserve and evaluation of the separated liver area is possible using this method.[5] Liver volume represents another piece of useful information to define operative indications, and is usually measured by computed tomography.[2-4, 6-8] In cases of PVE, both morphological liver volume and functional liver volume may change before and after embolization. Asialoglyco-protein receptors on hepatocytes reflect functional liver cells.[9, 10] Using scintigraphy, functional hepatic volume in the separated lobe of the liver can also be measured by applying single-photon emission computed tomography (SPECT).[10-16] As a result, technetium-99m galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy provides information about both liver function and the volume of active liver, and should be useful in selecting the most appropriate hepatectomy. We also hypothesize that functional volume shifts from the injured liver by biliary obstruction or PVE to counterparts much more than morphological liver volume. We reported two bile duct carcinoma patients in whom measurement of functional liver volume was considered useful in deciding operative indications.

METHODS

Evaluation of liver functions for hepatectomy

Child-Pugh classification is basically evaluated and only patients with Child-Pugh A are selected for major hepatectomy. In our hospital, the permitted volume of liver to be resected is determined preoperatively based on ICGR15 using Takasaki's formula. A dose of 0.5 mg ICG/kg body weight was injected intravenously and ICGR15 was measured using a photopiece applied to the fingertip (Sumitomo Electric, Tokyo, Japan) without blood sampling. [15] Estimated resected liver volume, excluding tumor volume, is measured by CT volumetry. [4, 8] Essentially, the planned hepatectomy is performed where permitted resected volume of the liver is greater than estimated resected volume of the liver. In cases where permitted resected volume is less than estimated volume, preoperative PVE is selected according to our criterion. [16] Preoperative PVE was performed in 10 of 20 hilar bile duct carcinoma (HBDC) patients. Liver uptake ratio at 15 min (LHL15) by ^{99m}Tc-GSA scintigraphy and serum hyaluronic acid level were also examined preoperatively, along with ICGR15 and other functional liver parameters. [17, 19] Based on previous studies, LHL15 >0.87 was an indication for major hepatectomy. When dissociation between ICGR15 and LHL15 was observed, preference was given to the results of LHL15.

Volumetric measurement by CT and ^{99m}Tc-GSA liver scintigraphy

Morphological volume was measured using contrast CT. [2-4, 6-8] Serial transverse scans at 0.7-cm intervals were downloaded onto a personal computer. Using NIH Image software (Scion Co., Frederick, ML, USA), actual areas without tumors and large vessels in each liver slice were traced and measured. Hepatic volume of each hemi-liver was then measured by summation of areas in each slice. All patients received 3 mg (185 MBq) of ^{99m}Tc-GSA (Nihon Medi-Physics, Nishinomiya, Japan) as a bolus dose into the antecubital vein. Images were obtained with a large field-of-view gamma camera (Picker PRISM-2000; Picker Prism International, Cleveland, OH) equipped with a high resolution, parallel-hole collimator centered on the liver and precordium. Sequential abdominal digital images (128 × 128 matrix) were acquired to an on-line nuclear data processor (Odyssey Series; Picker Prism International) at 30 s/frame for the first 16 min after injection. SPECT images were acquired after the dynamic study. [10, 14-16, 18, 19] Each set of projection data was obtained in a 128 × 128 matrix, and 120 projections (3°/step, 15 s/projection) were acquired. A Butterworth filter was used as the pre-reconstruction filter, and final reconstruction was performed with a Ramp filter. Attenuation correction was performed using Chang's procedure and a value of 0.09 cm^{-1} was used as the effective attenuation correction coefficient. [14, 18] Transaxial SPECT images were reconstructed using 3.9-mm slice thickness (Fig. 1). The border between right and left hemi-livers was manually determined through the gallbladder bed and inferior vena cava. A cut-off level was set at 40% of maximum counts of the liver, as this level yielded the closest results to actual volume from a phantom study in the radiology department at our institute (unpublished data).

Technique of portal vein embolization and evaluation

The approach to the right portal vein was direct catheterization of percutaneous transhepatic puncture. [16] Substances used for embolization comprised a mixture of 0.6 g of gelatin pieces (Spongel; Astellas Pharma, Tokyo, Japan) and 5 ml lipiodol (Schering, Berlin, Germany) in Case 1 and 1 g of 5% ethanolamine oleate iopamiodole (Oldamin; Takeda Pharma, Osaka, Japan) in Case 2. Permanent embolization materials were not used. Embolization was completed when the entire right portal vein was completely occluded. At 14 days after PVE, hepatic volumes of the unembolized liver and embolized liver (liver to be resected) were reassessed by CT volumetry, and liver function was also reassessed by ^{99m}Tc-GSA scintigraphy. Surgical resection of the liver was performed at 21 days after PVE.

Case reports

Case 1

A 47-year-old man presented with mental disorder and chronic hepatitis B virus infection. He reported abdominal discomfort and liver dysfunction was apparent. Intraductal papillary growing-type hilar bile duct carcinoma was identified spreading to the right liver (Fig. 2). Extended right hepatectomy with resection of the caudate lobe and extrahepatic bile duct was therefore planned. Hepatitis B virus antigen was positive, but hepatitis C antibody was negative. Total bilirubin level was slightly increased at 1.3 mg/dl, although parameters of liver function were almost stable. Serum hyaluronic acid level was 70 ng/ml. Liver damage was grade A and ICGR15 and K value were 14% and 0.124, respectively. LHL15 by ^{99m}Tc-GSA liver scintigraphy was 0.91. Table 1 shows liver volume and functional liver volume in the right and left liver, respectively. Liver volumes between CT volumetry and GSA volumetry were almost identical. Permitted resected liver volume by Takasaki's formula was 54% in case of chronic injured liver. According to Makuuchi's criterion, left hepatectomy was a limit of hepatic resection due to the results of ICGR15. Estimated resected volume was beyond the permitted volume and PVE in the right liver was therefore performed. After preoperative PVE, embolized liver volume became atrophic and functional liver volume in the embolized liver was still decreased in comparison with liver volume by CT volumetry (Table 2; Fig. 3A-D). Future remnant liver volume was increased at 54% and functional liver volume was more increased, at 79%. While waiting for hepatectomy, obstructive jaundice progressed and total bilirubin level reached 11.5 mg/dl. Percutaneous transhepatic biliary drainage was performed and jaundice improved. However, ICGR15 worsened slightly to 18%. Permitted resected liver volume at this point was 46%, at the borderline on CT volumetry. However, as LHL15 improved to 0.97 and functional volume was still lower than permitted volume, scheduled hepatectomy was performed on day 38 after PVE. Although massive ascites was observed and total bilirubin level had increased by day 10 to 6.5mg/dl, these values gradually improved. Pneumothorax and related pyothorax occurred on day 35 and second operation was performed. Remnant liver volume increased by 20% compared to that at day 14 after PVE and the patient was eventually discharged in healthy condition on day 85.

Case 2

A 75-year-old man with diabetes presented with abdominal discomfort in the upper abdomen and liver dysfunction was identified at the clinic. The patient displayed bile duct carcinoma located in the upper and middle bile duct with biliary obstruction and narrowing of the portal vein in the right lateral sector (Fig. 4). The right liver was markedly atrophic and right hepatectomy was planned. Hepatitis B virus antigen was positive. Total bilirubin level was increased to 1.6 mg/dl. Serum hyaluronic acid level was 96 ng/ml. Liver damage was grade A and ICGR15 and K value were 27% and 0.083, respectively. LHL15 by ^{99m}Tc-GSA liver scintigraphy was 0.87. Table 3 shows liver volume and functional liver volume in the right and left liver, respectively. Liver volumes by GSA volumetry (i.e., functional volume) were markedly lower in the right liver and higher in the left liver compared with volume by CT volumetry. Permitted resected liver volume by Takasaki’s formula was 49% in case of chronic liver injury. Based on Makuuchi’s criterion, subsegmental resection was a limit of hepatic resection due to the results of ICGR15. Based on CT volumetry, estimated resected volume was beyond the permitted volume, whereas GSA volumetry allowed right hepatectomy. PVE in the right liver was eventually performed to reduce operative risk as much as possible at this point. After PVE, functional liver volume in the embolized liver was markedly decreased compared with liver volume on CT volumetry (Fig. 5A-D). Future remnant liver volume reached 68% and functional volume became 88% (Table 4). Although ICGR15 worsened to 31.4% after embolization, the planned hepatectomy was performed based on functional volume. Scheduled right hepatectomy with resection of extrahepatic bile duct and right caudate lobe was performed on day 21 after PVE. Remnant liver volume at day 24 after hepatectomy was increased by 14% compared to that on day 14 after PVE. Maximum total bilirubin level was 2.6 mg/dl. The patient did not have any complications and was discharged on day 25 after hepatectomy.

Discussion

As a relatively new reliable test to assess hepatic functional reserve, ^{99m}Tc-GSA scintigraphy has been used in patients with liver disease.[18, 19] This test shows live hepatic cells. We have previously reported the clinical significance of ^{99m}Tc-GSA scintigraphy in patients with various hepatic backgrounds who underwent hepatic resection.[17, 20] The result of ^{99m}Tc-GSA scintigraphy is often dissociated from the results of ICG testing in patients with chronic hepatitis and vascular shunt or icteric liver.[17, 21] In such situations, ^{99m}Tc-GSA scintigraphy is more reliable for the evaluation of liver function than ICG testing. Functional liver volume in ^{99m}Tc-GSA scintigraphy changes more dynamically than morphological volume after PVE.[20] Atrophic or damaged areas of liver by biliary obstruction due to tumor invasion or PVE may contribute to a result of poor liver function for the whole liver. Evaluation by other useful functional tests or examination of separated liver functions in injured and healthy liver (i.e., future remnant liver) is thus necessary. ICG concentration in drained bile juice was analyzed in separated parts of liver by Uesaka et al.[22] and Nagino et al.[23] However, preoperative biliary drainage is not always possible in HBDC patients and this method thus cannot be performed routinely. Application of ^{99m}Tc-GSA scintigraphy seems likely to address the limitations of these liver function tests, as this test can evaluate separated liver functions in any situation of background liver function. Although the reliability of ^{99m}Tc-GSA scintigraphy compared to ICGR15 or other liver function has not yet been clarified, this test appears promising.

In hepatic resection of HBDC, preoperative adequate assessment of liver functional reserve is quite necessary, as the risk of postoperative morbidity and mortality is still high regardless of improvements in perioperative management, including induction of PVE.[1] In the present cases, serum bilirubin levels increased with biliary tumor stenosis. In Case 1, biliary obstruction progressed during waiting for surgery and ICGR15 worsened after PVE. If the ICG test alone had been applied to decide operative indications, timing of hepatectomy would have been further delayed. In Case 2, total bilirubin level was already at a mildly high level and results of ICGR15 were not good. Furthermore, ICGR15 worsened after PVE. This case would not generally have been considered a suitable candidate for hemihepatectomy based only on the results of the ICG test. In HBDC patients, ICG clearance test cannot be applied in cases with increased bilirubin levels. [4] Furthermore, intrahepatic blood flow in the embolized liver is decreased after PVE, so ICG clearance may be delayed in the whole liver. Nagino et al. applied the index of (*ICG K-value (disappearance rate)* $\times$ *future remnant volume (%) of the liver).*[1] This index >0.05 is a criterion for major hepatectomy in the Nagoya series, which has the highest number of hepatectomies for HBDC in the world. By applying this criterion, the indications for hemi-hepatectomy were a borderline and these criteria would be more reliable than Makuuchi's criterion [3] or Takasaki's formula [14] in cases of HBDC.

In tests of ^{99m}Tc-GSA scintigraphy, both LHL15 [24, 25] and heart activity at 15 min by heart activity at 3 min (HH15) [25], or maximal removal rate (Rmax) [18], are reliable as non-invasive methods for evaluating hepatic functional reserve without blood sampling. Since 1996, our department has used ^{99m}Tc-GSA scintigraphy preoperatively in combination with ICGR15 and conventional liver function tests in patients with liver diseases including HBDC. [17]. In our previous analysis, approximately 16 of 201 patients with liver diseases (8%) showed marked differences between ICGR15 and LHL15 on ^{99m}Tc-GSA scintigraphy, including 5 HBDC patients. [17] In the present series, LHL15 provided a much better reflection of clinical outcomes after hepatectomy than ICGR15. Since completing this study, we have preferred to apply LHL15 to decide operative indications for hepatectomy in case of discrepancies between both liver functions, and decisions in the present cases were performed based on this reason. Eventually, the present cases overcame the major hepatectomy despite the poor ICG results mentioned above.

Measurement of functional hepatic volume in separate regions of the liver by ^{99m}Tc-GSA scintigraphy has recently become available and we have reported preliminary comparisons with morphological liver volume. [9-11] Although the morphological and functional liver volumes were significantly correlated [20], both volumes were not identical basically. Furthermore, as described above, both volumes may be dissociated in the situation of injured livers such as a patient undergoing PVE or with biliary obstruction. To the best of our knowledge, the usefulness or evaluation of ^{99m}Tc-GSA scintigraphy has not been fully examined in HBDC patients with biliary obstruction or PVE. [26] The present report showed differences of functional hepatic volume in injured liver by biliary stenosis and changes in functional hepatic volume after PVE, which were more significant than those in morphological liver volume on CT. We believe that functional shift may occur from the injured liver to the healthy liver following biliary tumor occlusion or PVE. In such cases, the indications for major hepatectomy might be suitable to decide markedly reduced functional volume. The functional mass detected by asialoglycoprotein receptor might be decreased by hepatic injury, which cannot be detected by enhanced CT. Measuring functional liver volume by ^{99m}Tc-GSA scintigraphy is useful to accurately evaluate the future remnant liver in comparison with evaluation by CT.

In the present cases, we hypothesized that changes in embolized lobe after PVE would be dramatic due to cell damage secondary to reduction of blood supply. Hypertrophy of the unembolized left liver as assessed by ^{99m}Tc-GSA scintigraphy did not differ substantially from that as assessed by CT volumetry, contrary to results in the embolized liver. Sugai *et al.* [12] also reported that functional volume in the unembolized liver did not significantly increase, but that the increase in liver uptake density was marked. Although functional shift in the unembolized liver could not have been prominently visible even by ^{99m}Tc-GSA scintigraphy, we speculate that the potential for regeneration in the remnant liver after hepatectomy might be accumulated.

Furthermore, the safety of major hepatectomy following PVE [27, 28] might be confirmed, since the embolized right liver lost much more hepatic function after PVE.

Several reports have shown that a lower level of ^{99m}Tc-GSA clearance is associated with post-hepatectomy complications. [10, 22, 25, 29, 30] Functional hepatic volume would be useful for predicting post-hepatectomy complications. In the present study, Case 1 required long-term hospitalization due to complications, but jaundice recovered after 1 week. Case 2 showed no complications of note. A good result on 99mTc-GSA scintigraphy thus seems to indicate the safety of major hepatectomy.

In conclusion, we have demonstrated the usefulness of LHL15 by ^{99m}Tc-GSA scintigraphy as a preoperative functional liver reserve in 2 cases of HBDC. Furthermore, functional volume as estimated by ^{99m}Tc-GSA is apparently decreased in the liver with biliary stenosis or embolization following PVE compared with that estimated by CT volumetry.

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FIGURE LEGENDS

Fig. 1 Transaxial SPECT images for calculating functional volume in the right and left liver. A line indicates a border between right and left liver.

Fig. 2. Enhanced CT for Case 1. Arrow shows intraductal tumor in the hilar bile duct.

Fig. 3. Measurement of hepatic volume in each lobe of the liver in Case 1 by **A)** CT and **B)** ^{99m}Tc-GSA scintigraphy. **C)** CT finding on day 14 after PVE. **D)** Results of ^{99m}Tc-GSA scintigraphy on day 14 after PVE. An encircled area and arrows indicate an embolized right liver. A line indicates a border between right and left liver.

Fig. 4. Enhanced CT for Case 2. **A)** Coronary view. Thin arrow, bile duct tumor; dotted arrow, left hepatic duct; black arrowhead, right anterior hepatic duct; and white arrowhead, right posterior hepatic duct. **B)** CT angiography. Arrow shows portal vein in the right posterior sector.

Fig. 5. Measurement of hepatic volume in each lobe of the liver in Case 2 by **A)** CT and **B)** ^{99m}Tc-GSA scintigraphy. **C)** CT findings on day 14 after PVE. **D)** Results of ^{99m}Tc-GSA scintigraphy on day 14 after PVE. An encircled area and arrows indicate an embolized right liver. A line indicates a border between right and left liver.

Table 1 Morphological and functional liver volume in each hemi-liver

	Right liver volume	Left liver volume
CT volumetry	591 cm3 (59%)	291 cm3 (41%)
^{99m}Tc-GSA liver scintigraphy	517 cm3 (60%)	325 cm3 (40%)

Parenthesis is a rate of the whole liver volume.

Table 2 Changes of morphological and functional liver volume before and after the right portal vein embolization in each hemi-liver

	Right liver	Changes of volume	Left liver	Changes of volume
CT volumetry	591 → 469 cm^3 (59 → 46%)	-122cm3 (-13%)	291 → 552 cm^3 (41 → 54%)	+261cm3 (+13%)
^{99m}Tc-GSA volumetry	517 → 137 cm^3 (58 → 21%)	-380cm3 (-27%)	325 → 515 cm^3 (42 → 79%)	+190cm3 (+27%)

Parenthesis is a rate of the whole liver volume.

Table 3 Morphological and functional liver volume in each hemi-liver

	Right liver	Left liver
CT volumetry	400 cm^3 (50%)	394 cm^3 (50%)
^{99m}Tc-GSA volumetry	131 cm^3 (18%)	596 cm^3 (82%)

Parenthesis is a rate of the whole liver volume.

Table 4 Changes of morphological and functional liver volume before and after the right portal vein embolization in each hemi-liver

	Right liver	Changes of volume	Left liver	Changes of volume
CT volumetry	400 → 332 cm^3 (50 → 32%)	-68cm^3 (-18%)	394 → 722 cm^3 (50 → 68%)	+328cm^3 (+18%)
^{99m}Tc-GSA volumetry	131 → 62 cm^3 (18 → 11%)	-69cm^3 (-6%)	596 → 663 cm^3 (82 → 88%)	+67cm^3 (+6%)

Parenthesis is a rate of the whole liver volume.

Figure1

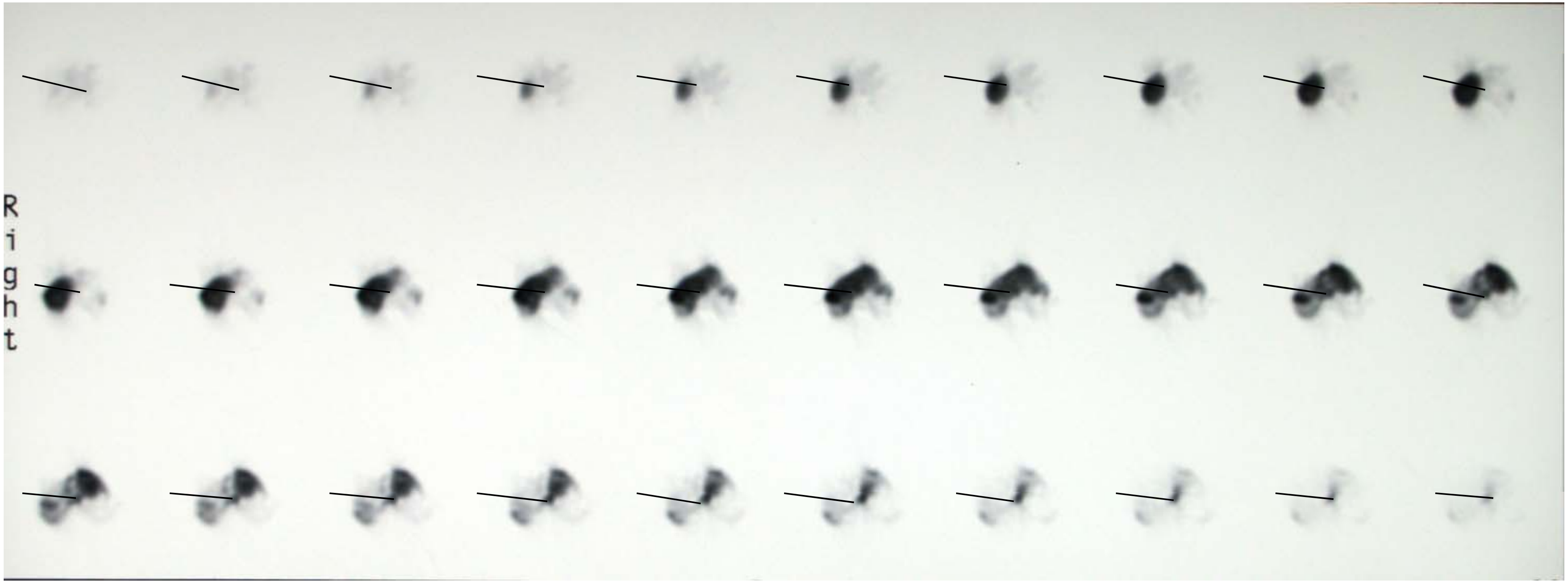

Figure 2

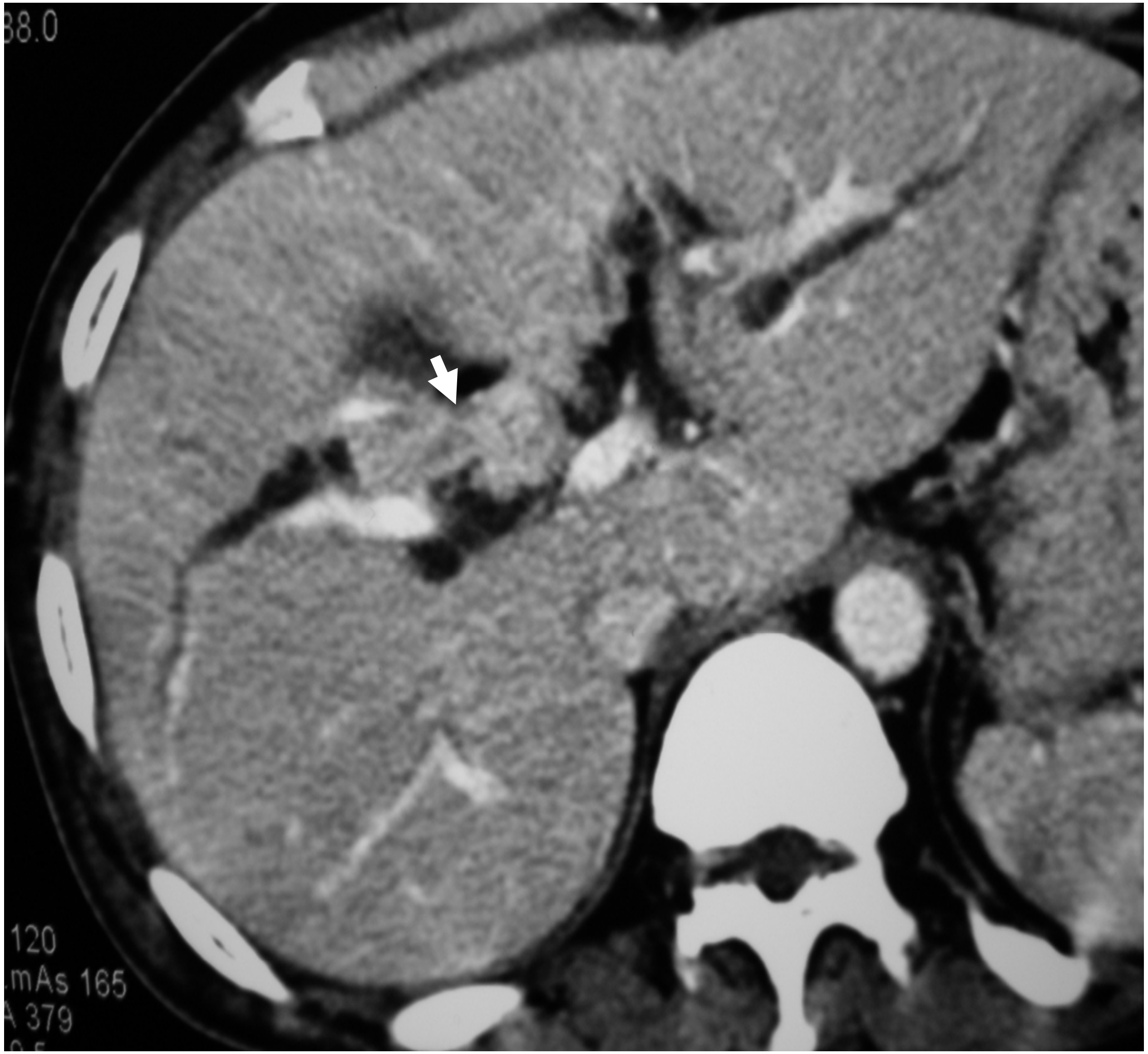

Figure 3

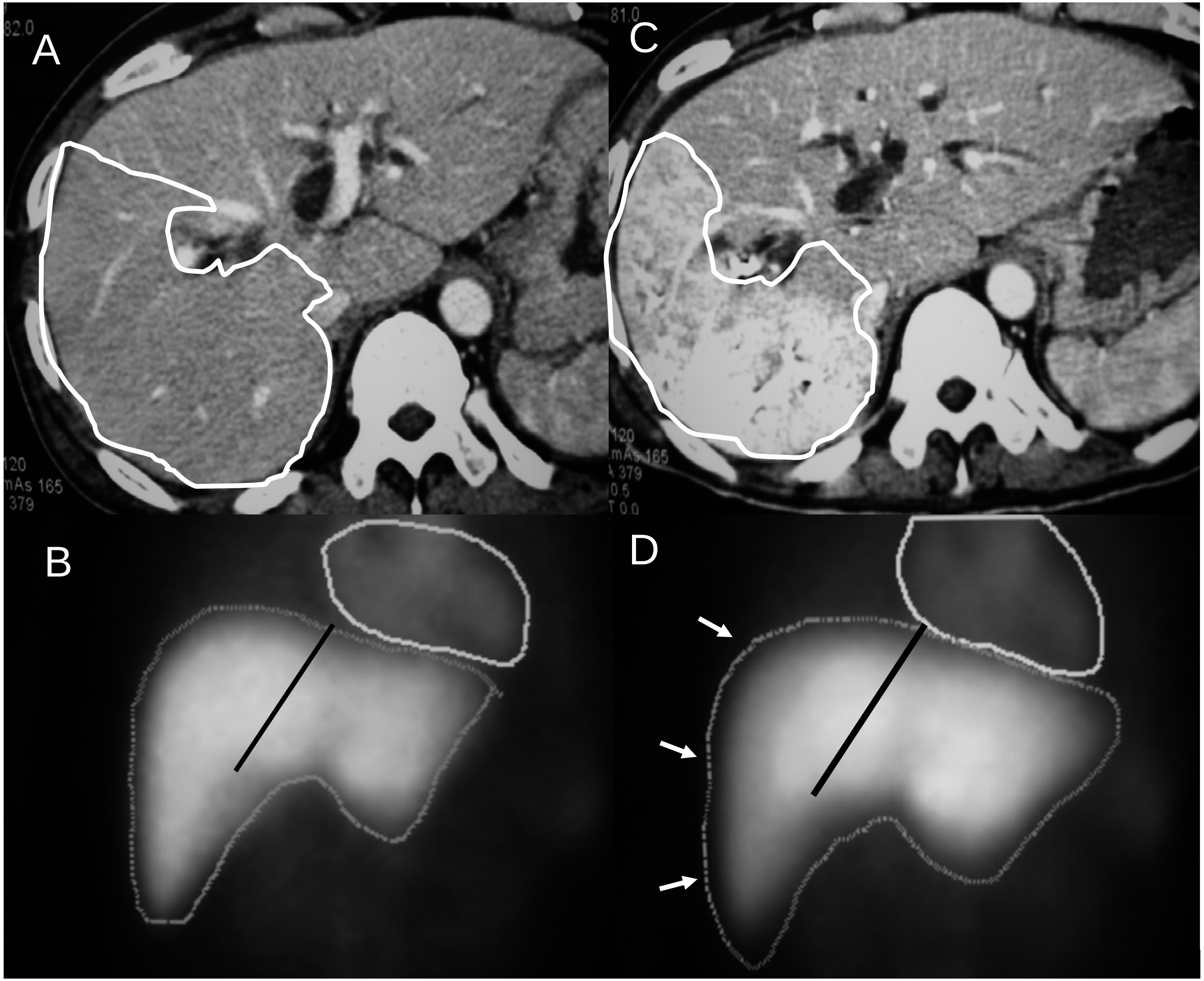

Figure 4

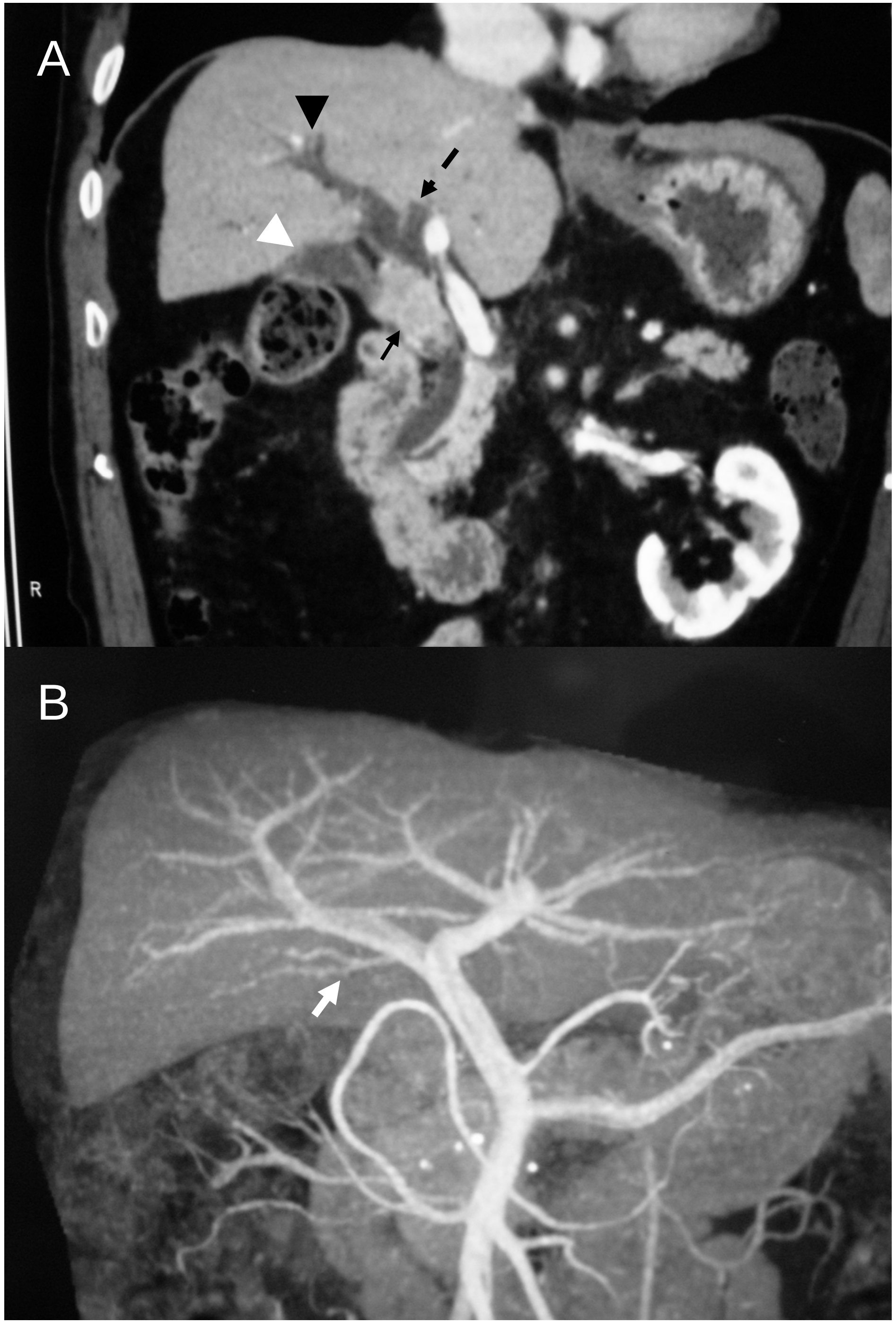

Figure 5