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RETROSPECTIVE STUDY

Hepatic clearance measured with ^{99m}Tc-GSA single-photon emission computed tomography to estimate liver fibrosis

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Abstract

AIM: To evaluate the clinical utility of hepatic clearance (HC) measured with technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) single-photon emission computed tomography (SPECT) to estimate the degree of liver fibrosis.

METHODS: Seventy-eight consecutive patients who underwent initial hepatectomy due to hepatocellular carcinoma were enrolled in this study. Indocyanine green clearance (ICG R15), quantitative indices estimated by ^{99m}Tc-GSA [the receptor index (LHL15 and HH15) and HC *via* SPECT analysis], and conventional liver function tests were performed before hepatectomy. Correlations among the quantitative indices for liver functional reserve, conventional liver function tests, and the degree of liver fibrosis were evaluated.

RESULTS: The degree of liver fibrosis was correlated with ICG R15, HH15, LHL15, and HC. HC showed the best correlation with conventional liver function tests. According to multivariate analysis, HC and LHL15 were significant independent predictors of severe fibrosis. HC was the most valuable index for predicting severe fibrosis.

CONCLUSION: HC measured with ^{99m}Tc-GSA SPECT is a reliable index for assessing liver fibrosis before hepatectomy.

Key words: Fibrosis; Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin; Single-photon emission computed tomography; Hepatic clearance; Liver resection

Core tip: This retrospective study evaluated the clinical utility of hepatic clearance measured with technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) single-photon emission computed tomography for estimating the degree of liver fibrosis. We demonstrated that ^{99m}Tc-GSA hepatic clearance showed strong correlations with the degree of liver fibrosis and conventional liver function tests. It is a reliable index for assessing severe liver fibrosis. We believe that this quantitative index can yield a more accurate estimation of liver fibrosis compared with currently used measures before hepatectomy for hepatobiliary surgeons.

Taniguchi M, Okizaki A, Watanabe K, Imai K, Uchida K, Einama T, Shuke N, Miyokawa N, Furukawa H. Hepatic clearance measured with ^{99m}Tc-GSA single-photon emission computed tomography to estimate liver fibrosis. *World J Gastroenterol* 2014; 20(44): 16714-16720 Available from: URL: http://www.wjgnet.

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INTRODUCTION

Liver fibrosis is a negative predictive factor for postoperative hepatic failure[1-3]. Cirrhosis is a well-known risk factor for postoperative hepatic failure[1,3,4]. Moreover, morbidity and mortality are high for patients with severe liver fibrosis undergoing liver resection[2,5,6]. Therefore, the accurate preoperative estimation of the extent of hepatic fibrosis is essential for successful liver surgery. Although many liver fibrosis indicators have been proposed for preoperative evaluation[7-10], the best indicator for evaluating liver fibrosis has not yet been established.

Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy reflects the liver functional reserve and is reported to correlate with several hepatic function tests[11,12]. However, few available analyses can determine the degree of liver fibrosis. Single-photon emission computed tomography (SPECT) analysis in ^{99m}Tc-GSA liver scintigraphy, which can evaluate GSA accumulation in the liver, was also developed to investigate liver function[13]. These analyses calculate hepatic clearance (HC) with the outline extraction method, using a program based on a radiopharmacokinetic model, as described by Shuke *et al*[14,15].

In this study, we investigate the contribution of HC measured with ^{99m}Tc-GSA SPECT to assess liver fibrosis.

MATERIALS AND METHODS

Patients

Between January 2011 and March 2014, 78 consecutive patients who underwent an initial hepatectomy due to hepatocellular carcinoma were enrolled in this study. The surgery was performed within 1 wk after ^{99m}Tc-GSA liver scintigraphy examination, and conventional tests were performed. All procedures were performed after informed consent was received from the patients and after approval from the Ethics Committee of Asahikawa Medical University Hospital was obtained. This study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

^{99m}Tc-GSA liver scintigraphy and the receptor index

^{99m}Tc-GSA liver scintigraphy was scheduled for the patients on the day before their hepatectomy. ^{99m}Tc-GSA was supplied by Nihon Medi-Physics (Nishinomiya, Japan). After the intravenous injection of 185 MBq ^{99m}Tc-GSA, dynamic imaging was performed with the patient in the supine position. LHL15 was calculated by dividing the radioactivity of the region of interest (ROI) of the liver by the radioactivity of the ROI of the liver and the heart 15 min after injection. HH15 was calculated by dividing the radioactivity of the ROI of the heart 15 min after injection by the radioactivity of the ROI of the heart 3 min after injection[16,17].

SPECT analysis in ^{99m}Tc-GSA liver scintigraphy

Dynamic SPECT was performed using a dual-head gamma camera system equipped with low-energy, general-purpose collimators and a dedicated data processing unit (Millennium VG, GE, Tokyo, Japan). The in-plane spatial resolution of this system was 14 mm full width at half-maximum. After fasting overnight, the patient was placed in a supine position to ensure that the liver and lower part of the heart were within the detectors' field of view. ^{99m}Tc-GSA (185 MBq) was injected intravenously as a bolus. After it was confirmed that the entire liver was covered by the detector's view, dynamic SPECT data acquisition was started 1 min after injection and continued for 20 rotations in a 180° continuous rotation mode with an acquisition time of 1 min per rotation. In each rotation, the data from 60 projections were recorded in a 64 × 64 matrix (pixel size = 68.84 mm × 8.84 mm). SPECT images were reconstructed with a filtered back-projection method using a ramp filter after preprocessing with a Butterworth filter (cutoff frequency = 0.40 cycle per centimeter; order of 8) to obtain 8.84-mm-thick transaxial SPECT images. HC was determined from the SPECT data and was calculated with the outline extraction method using a program based on a radio pharmacokinetic model, as described by Shuke *et al*[14,15].

Conventional liver function tests

The serum albumin (Alb), total bilirubin (T-bil), and cholinesterase (Ch-E) levels; prothrombin time international normalized ratio (PT-INR); and platelet count (Plt) were measured in the peripheral blood before hepatectomy. The indocyanine green (ICG) test was conducted preoperatively, and the ICG clearance (ICG R15) was calculated using standard methods. The model for end-stage liver disease (MELD) score[18] and the Child-Turcotte-Pugh (CTP) score[19] were used as indices of liver dysfunctions.

Histopathological features of liver specimens

Liver fibrosis was diagnosed using surgical specimens, which were resected at a distance from the tumors. The degree of hepatic fibrosis was assessed and graded 0-6 according to the Ishak classification for chronic hepatitis[20]: 0: no fibrosis; 1: fibrous expansion of some portal areas, with or without short fibrous septa; 2: fibrous expansion of most portal areas, with or without short fibrous septa; 3: fibrous expansion of most portal areas with occasional portal-to-portal bridging; 4: fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central); 5: marked bridging (portal to portal and/or portal to central) with occasional nodules; and 6, cirrhosis, probable or definite. Scores of 0, 1, 2, and 3 were considered to reflect nonsevere fibrosis. Scores of 4, 5, and 6 were recorded as severe fibrosis. Tumor size, tumor number, and tumor vascular invasion (portal vein, hepatic artery, and hepatic vein) were evaluated using surgical specimens.

Table 1 Patient characteristics

Variables	*n* = 78
Age (yr)	66.7 ± 10.3
Gender (male/female)	63/15
HBs-Ag (+/-)	26/52
HCV-Ab (+/-)	21/57
Alcohol abuse (+/-)	10/68
NASH (+/-)	14/64
Diabetes mellitus (+/-)	25/73
Hyperlipidemia (+/-)	18/60
Platelets (× 10^4/mm^3)	16.6 ± 7.0
Prothrombin time (INR)	1.05 ± 0.11
Albumin (g/dL)	4.0 ± 0.6
Total bilirubin (mg/dL)	0.8 ± 0.3
Cholinesterase (U/L)	248 ± 70
Tumor size (cm)	49.6 ± 36.9
Tumor number	1.2 ± 0.5
Tumor vascular invasion (+/-)	21/57
Ishak classification 0/1/2/3/4/5/6	14/11/8/18/4/13/10
MELD score	5.3 ± 1.3
CTP score	5.2 ± 0.2
ICG R15 (%)	11.6 ± 6.0

HBs-Ag: Hepatitis B surface antigen; HCV-Ab: Hepatitis C virus antibody; NASH: Nonalcoholic steatohepatitis; MELD score: Model for end-stage liver disease score; CTP score: Child-Turcotte-Pugh score; ICG R15: Indocyanine green dye retention at 15 min.

Statistical analysis

The data are expressed as the mean ± SD unless otherwise stated. The data were analyzed using the Mann-Whitney *U* test, Pearson's correlation coefficient, and linear regression. These statistical analyses were performed using SPSS 11.0 for Windows (SPSS, Chicago, IL, United States). The receiver operating characteristic (ROC) curve for calculating the area under the ROC curve (AUC) and interactive dot diagrams were created using MedCalc (software, 12.7.4; Ostend, Belgium).

RESULTS

Patient characteristics

The clinical characteristics of all participating patients are listed in Table 1. The mean age of the 78 patients was 66.7 ± 10.3 years, and there were 63 men. Of the 78 patients, 71 had chronic liver disease (chronic hepatitis B, n = 26; chronic hepatitis C, n = 21; non-alcoholic steatohepatitis, n = 14; and alcoholic hepatitis, n = 10). The remaining patients were diagnosed with normal livers. Concerning the degree of hepatic fibrosis, 10 patients were graded 6, 13 were graded 5, 4 were graded 4, 18 were graded 3, 8 were graded 2, 11 were graded 1, and 14 were graded 0. The mean ICG R15 was 11.6 ± 6.0.

Correlations between the degree of liver fibrosis and quantitative indices of liver functional reserve

Table 2 shows the correlations between the degree of liver fibrosis and preoperative liver function parameters. The degree of liver fibrosis was positively linearly correlated with ICG R15 and HH15 and negatively linearly correlated with HC.

Table 2 Correlations between the degree of liver fibrosis and quantitative indices for liver functional reserve

	r	*P* value
ICG R15	0.330	0.003
HH15	0.272	0.016
LHL15	-0.198	0.083
HC	-0.598	< 0.00001

The degree of liver fibrosis was correlated with ICG R15, HH15, and HC. ICG R15: Indocyanine green dye retention at 15 min; HC: Hepatic clearance.

Correlations between quantitative indices for liver functional reserve and conventional liver function tests

As Table 3 shows, we evaluated the correlations between the preoperative parameters for liver function and conventional liver function tests. LHL15 was correlated with platelet count (r = 0.235, P = 0.038) and albumin level (r = 0.263, P = 0.020), and HH15 was correlated with total bilirubin level (r = 0.289, P = 0.010) and cholinesterase level (r = -0.263, P = 0.020). HC was correlated with all conventional liver function tests after liver resection: platelet count (r = 0.348, P = 0.002), prothrombin time (r = -0.287, P = 0.011), albumin level (r = 0.233, P = 0.040), total bilirubin level (r = -0.345, P = 0.002), and cholinesterase level (r = -0.419, P = 0.0001).

Univariate and multivariate stepwise regression analysis of various factors affecting liver fibrosis

Univariate analysis showed that platelet count (P < 0.001), prothrombin time (P = 0.032), total bilirubin level (P = 0.001), tumor size (P = 0.042), MELD score (P = 0.009), ICG R15 (P = 0.019), LHL15 (P = 0.042), HH15 (P = 0.0004), and HC (P < 0.0001) were significant predictors of severe cirrhosis. When we entered platelet count, prothrombin time, total bilirubin level, tumor size, MELD score, ICG R15, LHL15, HH15, and HC into a multivariate logistic regression model to identify variables with independent predictive value for severe fibrosis, we found that HC and LHL15 were the significant independent predictors (Table 4).

ROC curve and interactive dot diagrams of HC and LHL15 for the diagnosis of severe fibrosis

In Figure 1, we present the ROC curves for each of the 2 variables, HC and LHL15, that were identified as the significant independent predictors of severe fibrosis. The AUC of the ROC curves for HC and LHL15 were 0.826 and 0.641, respectively. There was a significant difference between the two values (P = 0.0146). Based on the analysis employing interactive dot diagrams, the cutoff values for predicting severe cirrhosis with the highest sensitivity and specificity were 298 (sensitivity, 77.8%; specificity, 84.3%) for HC and 0.926 (sensitivity, 74.1%; specificity, 60.8%) for LHL15.

Table 3 Correlations between quantitative indices for liver functional reserve and conventional liver function tests

	ICG R15		LHL 15		HH 15		HC	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Platelets (× 10^4/mm^3)	-0.160	0.161	0.235	0.038	-0.185	0.105	0.348	0.002
Prothrombin time (INR)	0.082	0.473	-0.122	0.289	-0.016	0.888	-0.287	0.011
Albumin (g/dL)	-0.044	0.703	0.263	0.020	-0.123	0.285	0.233	0.040
Total bilirubin (mg/dL)	0.204	0.073	-0.217	0.057	0.289	0.010	-0.345	0.002
Cholinesterase (U/L)	-0.113	0.324	0.221	0.052	-0.263	0.020	0.419	0.0001

LHL15 was correlated with platelet count and albumin level. HH15 was correlated with total bilirubin level and cholinesterase level. HC was correlated with all conventional liver function tests. ICG R15: Indocyanine green dye retention at 15 min; HC: Hepatic clearance.

Table 4 Univariate and multivariate analyses of variables predictive of severe fibrosis

Variable	Severe fibrosis		*P* value	
	Yes (*n* = 27)	No (*n* = 51)	Univariate analysis	Multivariate analysis
Gender (male/female)	23/4	Nov-40	0.474	
Age (yr)	66.5 ± 10.0	66.8 ± 10.5	0.950	
HBs-Ag (+/-)	10/17	16/35	0.616	
HCV-Ab (+/-)	10/17	11/40	0.145	
Alcohol abuse (+/-)	2/25	8/43	0.301	
NASH (+/-)	4/23	10/41	0.602	
Platelets (× 10^4/mm^3)	12.7 ± 3.9	18.7 ± 7.4	< 0.001	0.096
Prothrombin time (INR)	1.09 ± 0.12	1.03 ± 0.10	0.032	0.223
Albumin (g/dL)	4.0 ± 0.6	4.1 ± 0.6	0.388	
Total bilirubin (mg/dL)	0.9 ± 0.3	0.7 ± 0.3	0.001	0.354
Cholinesterase (U/L)	234 ± 75	255 ± 68	0.229	
Tumor size (cm)	3.5 ± 1.6	5.7 ± 4.2	0.042	0.137
Tumor number	1.1 ± 0.4	1.2 ± 0.6	0.543	
Tumor vascular invasion (+/-)	5/22	16/35	0.226	
MELD score	5.8 ± 1.1	5.1 ± 1.2	0.009	
CTP score	5.3 ± 0.6	5.2 ± 0.4	0.685	
ICG R15 (%)	14.3 ± 6.1	10.2 ± 5.5	0.019	0.183
LHL 15	0.901 ± 0.044	0.935 ± 0.024	0.042	0.041
HH 15	0.648 ± 0.068	0.556 ± 0.067	0.004	0.053
HC	263.3 ± 90.4	381.1 ± 96.7	< 0.001	0.030

Platelet count, prothrombin time, total bilirubin level, tumor size, MELD score, ICG R15, LHL15, HH15, and HC were significant predictors of severe cirrhosis in the univariate analysis. In the multivariate analysis, HC and LHL15 were the significant independent predictors. HBs-Ag: Hepatitis B surface antigen; HCV-Ab: Hepatitis C virus antibody; NASH: Nonalcoholic steatohepatitis; MELD score: Model for end-stage liver disease score; CTP score: Child-Turcotte-Pugh score; ICG R15: Indocyanine green dye retention at 15 min; HC: Hepatic clearance.

DISCUSSION

In the current study, we demonstrated correlations between the degree of liver fibrosis and ICG R15, HH15, LHL15, and HC. Among these indicators, HC showed the best correlation with conventional liver function tests. HC was the most valuable index for predicting severe cirrhosis. An HC of 298 could be used to predict severe cirrhosis.

The degree of liver fibrosis is a negative predictor of liver regeneration and the restoration of liver function after liver resection[9]. Therefore, estimating the liver functional reserve, which is a reflection of liver fibrosis, is important. Several laboratory variables, such as prothrombin time and cholinesterase, have prognostic value in chronic liver disease[21]. In addition, the Alb level, T-bil level, and prothrombin time are the most useful routine laboratory tests for establishing a prognosis for hepatitis patients[22]. However, none of these laboratory variables reflects liver fibrosis directly. As a result, these variables cannot be used as indices for determining the extent of liver resection for patients with liver tumors. In contrast, several studies have evaluated the liver functional reserve before hepatectomy[23-25]. In particular, the indocyanine green (ICG) clearance test has been widely used to evaluate liver functional reserve[25,26] for liver resection. However, it does not provide quantitative parameters. Moreover, there are occasional discrepancies between the ICG clearance values and histologic findings in the liver because of the imbalance of portal inflow or portasystemic shunts. Such discrepancies make direct assessments of the extent of liver fibrosis difficult. Therefore, a new method to estimate the liver functional reserve that accurately reflects the degree of fibrosis is required.

The asialoglycoprotein receptor (ASGPR) is localized on hepatocytes and is involved in the clearance of glycoproteins containing terminal galactose residues from the circulation[27,28]. The expression of this receptor decreases according to the number of functional hepatocytes. Therefore, liver scintigraphy with ^{99m}Tc-GSA,

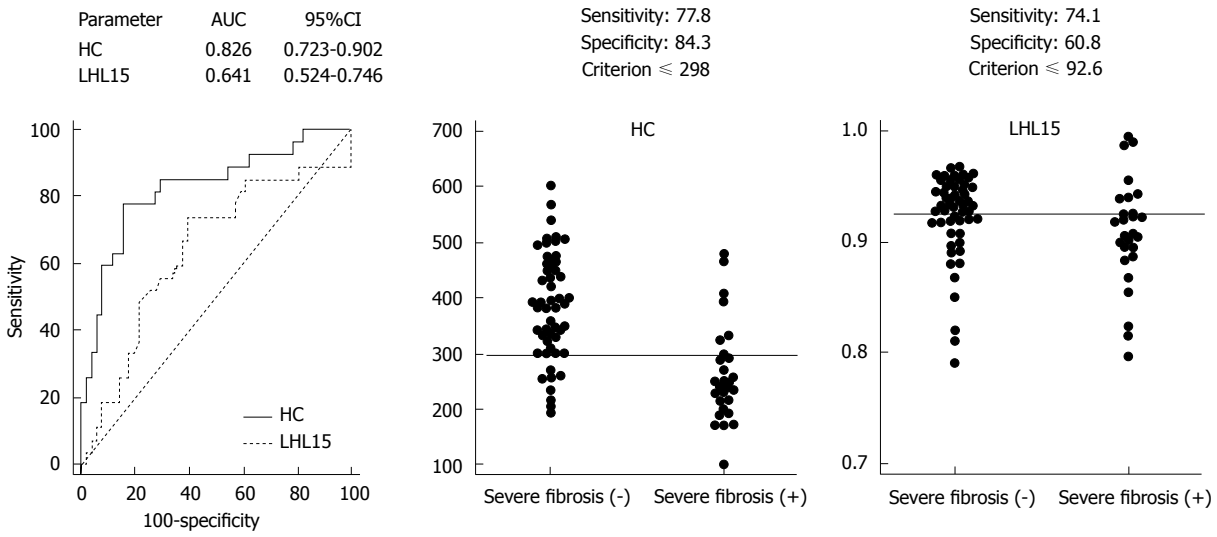

Figure 1 Receiver operating characteristic curve and interactive dot diagrams of hepatic clearance and LHL15 for the diagnosis of severe fibrosis. A: ROC analysis for HC and LHL15. There was a significant difference between the two values (P = 0.0146); B: Interactive dot diagrams showing HC predicts severe cirrhosis. The cutoff value for predicting severe cirrhosis with the highest sensitivity and specificity was 298 (sensitivity, 77.8%; specificity, 84.3%) for HC. The horizontal line indicates the cutoff point with the best separation between the 2 groups (severe fibrosis+, severe fibrosis-); C: Interactive dot diagrams showing LHL15 predicts severe cirrhosis. The cutoff value for predicting severe cirrhosis with the highest sensitivity and specificity was 0.926 (sensitivity, 74.1%; specificity, 60.8%) for LHL15. The horizontal line indicates the cutoff point with the best separation between the 2 groups (severe fibrosis+, severe fibrosis-). AUC: Area under the ROC curve; ROC: Receiver operating characteristic; HC: Hepatic clearance.

an analog of asialoglycoprotein, enables the quantitative evaluation of liver functional reserve. SPECT analysis in ^{99m}Tc-GSA liver scintigraphy, which allows the evaluation of GSA accumulation in the liver, was also developed to investigate liver function[13]. ^{99m}Tc-GSA HC, which is determined based on SPECT data, demonstrates the precise distribution of ASGPR in the liver, thereby providing an accurate calculation of liver functional reserve[29]. In this study, ^{99m}Tc-GSA HC showed a correlation with conventional liver function tests and the extent of liver fibrosis that was better than that of LHL15 or HH15. LHL15 and HH15, which are hepatic uptake and blood clearance ratios in ^{99m}Tc-GSA liver scintigraphy, are the simplest and most commonly used variables. However, they may be insufficient for accurately estimating the degree of liver fibrosis because these indices are calculated from planar scintigraphic images, which do not correctly reflect hepatocyte volume. In contrast, ^{99m}Tc-GSA HC measured by SPECT analysis contains volumetric information and may correctly estimate the hepatocyte volume, thus reflecting the degree of liver fibrosis.

In liver surgery, the risk of perioperative complications is generally believed to increase when the remnant liver volume (RLV) is excessively small[30]. Therefore, reports have advocated preoperatively assessing RLV with CT volumetry[31]. However, CT volumetry can never reflect the function of the remnant liver, especially in patients with parenchymal disease[30,32], such as chronic hepatitis or cirrhosis. Additionally, several reports concerning ^{99m}Tc-GSA SPECT findings have indicated that regional function is not necessarily uniform throughout the liver[33,34], suggesting that an accurate estimation of regional liver function is more important for predicting postoperative liver functional reserve. In this study, ^{99m}Tc-GSA HC strongly reflected the degree of liver fibrosis. Therefore, we believe that using the combined ^{99m}Tc-GSA HC and CT volumetric measurements of the remnant liver can evaluate remnant liver functional reserve after hepatectomy[35]. Further studies are needed to test this hypothesis.

In conclusion, we demonstrated that HC measured with ^{99m}Tc-GSA SPECT showed correlations with the degree of liver fibrosis and conventional liver function tests. ^{99m}Tc-GSA HC was the most valuable index for predicting severe fibrosis. It could yield a more accurate estimation of liver fibrosis compared with currently used measures before hepatectomy for hepatobiliary surgeons.

COMMENTS

Background

Liver fibrosis is a negative predictive factor for postoperative hepatic failure. Therefore, the accurate preoperative estimation of the extent of hepatic fibrosis is essential for successful liver surgery. Although many liver fibrosis indicators have been proposed for preoperative evaluation, the best indicator for evaluating liver fibrosis has not yet been established.

Research frontiers

Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy reflects the liver functional reserve and is reported to correlate with several hepatic function tests. In addition, single-photon emission computed tomography analysis in ^{99m}Tc-GSA liver scintigraphy, which can evaluate GSA accumulation in the liver, was also developed to investigate liver function.

Innovations and breakthroughs

Hepatic clearance which was measured with ^{99m}Tc-GSA single-photon emission computed tomography (SPECT) is a reliable index for assessing liver fibrosis.

Applications

Hepatic clearance which was measured with ^{99m}Tc-GSA SPECT could yield a

more accurate estimation of liver fibrosis compared with currently used measures before hepatectomy for hepatobiliary surgeons.

Terminology

^{99m}Tc-GSA liver scintigraphy: Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin liver scintigraphy. SPECT analysis: Single-photon emission computed tomography analysis.

Peer review

The manuscript evaluates the utility of ^{99m}Tc-GSA SPECT to reliably predict the degree of liver fibrosis in patients for liver resection is planned. Comparisons are made to particularly state that hepatic clearance is superior to other measurements (LHL15 and HH15), other techniques (ICGR15), and clinical parameters of liver function when predicting fibrosis. The study has relevance and is interesting in its concept; however some conclusions are made that need to be justified by more rigorous data analysis.

REFERENCES

1 **Wu CC**, Ho WL, Yeh DC, Huang CR, Liu TJ, P'eng FK. Hepatic resection of hepatocellular carcinoma in cirrhotic livers: is it unjustified in impaired liver function? *Surgery* 1996; **120**: 34-39 [PMID: 8693420 DOI: 10.1016/S0039-6060(96)80238-8]

2 **Farges O**, Malassagne B, Flejou JF, Balzan S, Sauvanet A, Belghiti J. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. *Ann Surg* 1999; **229**: 210-215 [PMID: 10024102 DOI: 10.1097/00000658-199902000-00008]

3 **Nagasue N**, Yukaya H, Ogawa Y, Kohno H, Nakamura T. Human liver regeneration after major hepatic resection. A study of normal liver and livers with chronic hepatitis and cirrhosis. *Ann Surg* 1987; **206**: 30-39 [PMID: 3038039 DOI: 10.1097/00000658-198707000-00005]

4 **Yamanaka N**, Okamoto E, Kuwata K, Tanaka N. A multiple regression equation for prediction of posthepatectomy liver failure. *Ann Surg* 1984; **200**: 658-663 [PMID: 6486915 DOI: 10.1097/00000658-198411000-00018]

5 **Tsao JI**, Loftus JP, Nagorney DM, Adson MA, Ilstrup DM. Trends in morbidity and mortality of hepatic resection for malignancy. A matched comparative analysis. *Ann Surg* 1994; **220**: 199-205 [PMID: 8053742 DOI: 10.1097/00000658-199408000-00012]

6 **Midorikawa Y**, Kubota K, Takayama T, Toyoda H, Ijichi M, Torzilli G, Mori M, Makuuchi M. A comparative study of postoperative complications after hepatectomy in patients with and without chronic liver disease. *Surgery* 1999; **126**: 484-491 [PMID: 10486600 DOI: 10.1016/S0039-6060(99)70089-9]

7 **Mizuguchi T**, Katsuramaki T, Nobuoka T, Kawamoto M, Oshima H, Kawasaki H, Kikuchi H, Shibata C, Hirata K. Serum hyaluronate level for predicting subclinical liver dysfunction after hepatectomy. *World J Surg* 2004; **28**: 971-976 [PMID: 15573250 DOI: 10.1007/s00268-004-7389-1]

8 **Saito K**, Ledsam J, Sourbron S, Hashimoto T, Araki Y, Akata S, Tokuuye K. Measuring hepatic functional reserve using low temporal resolution Gd-EOB-DTPA dynamic contrast-enhanced MRI: a preliminary study comparing galactosyl human serum albumin scintigraphy with indocyanine green retention. *Eur Radiol* 2014; **24**: 112-119 [PMID: 23949726 DOI: 10.1007/s00330-013-2983-y]

9 **Miyazaki S**, Takasaki K, Yamamoto M, Tsugita M, Otsubo T. Liver regeneration and restoration of liver function after partial hepatectomy: the relation of fibrosis of the liver parenchyma. *Hepatogastroenterology* 1999; **46**: 2919-2924 [PMID: 10576373]

10 **Shimada M**, Matsumata T, Adachi E, Itasaka H, Watiyama S, Sugimachi K. Estimation of degree of liver cirrhosis using a fibrosis score; a multivariate analysis of clinical parameters and resected specimens. *Hepatogastroenterology* 1994; **41**: 177-180 [PMID: 8056410]

11 **Kwon AH**, Ha-Kawa SK, Uetsuji S, Inoue T, Matsui Y, Kamiyama Y. Preoperative determination of the surgical procedure for hepatectomy using technetium-99m-galactosyl human serum albumin (99mTc-GSA) liver scintigraphy. *Hepatology* 1997; **25**: 426-429 [PMID: 9021958 DOI: 10.1002/hep.510250228]

12 **Fujioka H**, Kawashita Y, Kamohara Y, Yamashita A, Mizoe A, Yamaguchi J, Azuma T, Furui J, Kanematsu T. Utility of technetium-99m-labeled-galactosyl human serum albumin scintigraphy for estimating the hepatic functional reserve. *J Clin Gastroenterol* 1999; **28**: 329-333 [PMID: 10372930 DOI: 10.1097/00004836-199906000-00009]

13 **Imaeda T**, Kanematsu M, Asada S, Seki M, Doi H, Saji S. Utility of Tc-99m GSA SPECT imaging in estimation of functional volume of liver segments in health and liver diseases. *Clin Nucl Med* 1995; **20**: 322-328 [PMID: 7788989 DOI: 10.1097/00003072-199504000-00008]

14 **Shuke N**, Aburano T, Okizaki A, Zhao C, Nakajima K, Yokoyama K, Kinuya S, Watanabe N, Michigishi T, Tonami N. Estimation of fractional liver uptake and blood retention of 99mTc-DTPA-galactosyl human serum albumin: an application of a simple graphical method to dynamic SPECT. *Nucl Med Commun* 2003; **24**: 503-511 [PMID: 12717066 DOI: 10.1097/01.mnh.0000071243.54690.fd]

15 **Shuke N**, Okizaki A, Kino S, Sato J, Ishikawa Y, Zhao C, Kinuya S, Watanabe N, Yokoyama K, Aburano T. Functional mapping of regional liver asialoglycoprotein receptor amount from single blood sample and SPECT. *J Nucl Med* 2003; **44**: 475-482 [PMID: 12621017]

16 **Kudo M**, Todo A, Ikekubo K, Hino M. Receptor index via hepatic asialoglycoprotein receptor imaging: correlation with chronic hepatocellular damage. *Am J Gastroenterol* 1992; **87**: 865-870 [PMID: 1615940]

17 **Kira T**, Tomiguchi S, Takahashi M, Yoshimatsu S, Sagara K, Kurano R. Correlation of 99mTc-GSA hepatic scintigraphy with liver biopsies in patients with chronic active hepatitis type C. *Radiat Med* 1999; **17**: 125-130 [PMID: 10399780]

18 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

19 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1800600817]

20 **Ishak K**, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995; **22**: 696-699 [PMID: 7560864 DOI: 10.1016/0168-8278(95)80226-6]

21 **Christensen E**, Schlichting P, Andersen PK, Fauerholdt L, Schou G, Pedersen BV, Juhl E, Poulsen H, Tygstrup N. Updating prognosis and therapeutic effect evaluation in cirrhosis with Cox's multiple regression model for time-dependent variables. *Scand J Gastroenterol* 1986; **21**: 163-174 [PMID: 3520795 DOI: 10.3109/00365528609034642]

22 **Orrego H**, Israel Y, Blake JE, Medline A. Assessment of prognostic factors in alcoholic liver disease: toward a global quantitative expression of severity. *Hepatology* 1983; **3**: 896-905 [PMID: 6629318 DOI: 10.1002/hep.1840030602]

23 **Kubota K**, Makuuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K, Harihara Y, Takayama T. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 1997; **26**: 1176-1181 [PMID: 9362359 DOI: 10.1053/jhep.1997.v26.pm0009362359]

24 **Yamanaka N**, Okamoto E, Oriyama T, Fujimoto J, Furukawa K, Kawamura E, Tanaka T, Tomoda F. A prediction scoring system to select the surgical treatment of liver cancer. Further refinement based on 10 years of use. *Ann Surg* 1994; **219**: 342-346 [PMID: 8161258 DOI: 10.1097/00000658-199404000-00003]

25 **Makuuchi M**, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, Kawasaki S. Surgery for small liver cancers. *Semin Surg Oncol* 1993; **9**: 298-304 [PMID: 8210909 DOI: 10.1002/ssu.2980090404]

26 **Miyagawa S**, Makuuchi M, Kawasaki S, Kakazu T. Criteria for safe hepatic resection. *Am J Surg* 1995; **169**: 589-594 [PMID: 7771622 DOI: 10.1016/S0002-9610(99)80227-X]

27 **Ashwell G**, Morell AG. The role of surface carbohydrates in the hepatic recognition and transport of circulating glycoproteins. *Adv Enzymol Relat Areas Mol Biol* 1974; **41**: 99-128 [PMID: 4609051]

28 **Morell AG**, Gregoriadis G, Scheinberg IH, Hickman J, Ashwell G. The role of sialic acid in determining the survival of glycoproteins in the circulation. *J Biol Chem* 1971; **246**: 1461-1467 [PMID: 5545089]

29 **Iida T**, Isaji S, Yagi S, Hori T, Taniguchi K, Ohsawa I, Mizuno S, Usui M, Sakurai H, Yamagiwa K, Yamakado K, Uemoto S. Assessment of liver graft function and regeneration by galactosyl-human serum albumin (99mTc-GSA) liver scintigraphy in adult living-donor liver transplantation. *Clin Transplant* 2009; **23**: 271-277 [PMID: 19191810 DOI: 10.1111/j.1399-0012.2008.00933.x]

30 **Yigitler C**, Farges O, Kianmanesh R, Regimbeau JM, Abdalla EK, Belghiti J. The small remnant liver after major liver resection: how common and how relevant? *Liver Transpl* 2003; **9**: S18-S25 [PMID: 12942474 DOI: 10.1053/jlts.2003.50194]

31 **Fan ST**. Methods and related drawbacks in the estimation of surgical risks in cirrhotic patients undergoing hepatectomy. *Hepatogastroenterology* 2002; **49**: 17-20 [PMID: 11941945]

32 **Farges O**, Belghiti J, Kianmanesh R, Regimbeau JM, Santoro R, Vilgrain V, Denys A, Sauvanet A. Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg* 2003; **237**: 208-217 [PMID: 12560779 DOI: 10.1097/01.SLA.0000048447.16651.7B]

33 **Akaki S**, Okumura Y, Sasai N, Sato S, Tsunoda M, Kuroda M, Kanazawa S, Hiraki Y. Hepatectomy simulation discrepancy between radionuclide receptor imaging and CT volumetry: influence of decreased unilateral portal venous flow. *Ann Nucl Med* 2003; **17**: 23-29 [PMID: 12691127]

34 **Iimuro Y**, Kashiwagi T, Yamanaka J, Hirano T, Saito S, Sugimoto T, Watanabe S, Kuroda N, Okada T, Asano Y, Uyama N, Fujimoto J. Preoperative estimation of asialoglycoprotein receptor expression in the remnant liver from CT/99mTc-GSA SPECT fusion images correlates well with postoperative liver function parameters. *J Hepatobiliary Pancreat Sci* 2010; **17**: 673-681 [PMID: 20703846 DOI: 10.1007/s00534-010-0264-6]

35 **Uchida K**, Taniguchi M, Shimamura T, Suzuki T, Yamashita K, Ota M, Kamiyama T, Matsushita M, Furukawa H, Todo S. Three-dimensional computed tomography scan analysis of hepatic vasculatures in the donor liver for living donor liver transplantation. *Liver Transpl* 2010; **16**: 1062-1068 [PMID: 20818744 DOI: 10.1002/lt.22109]

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