Significance of the preoperative regional maximal removal rate of technetium-99m-galactosyl human serum albumin in the future remnant liver: a sequential study of regional maximal removal rate of technetium-99m-galactosyl human serum albumin in the whole liver

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Background The relationship between posthepatectomy complications and liver functional parameters was preliminary reported in a pilot study. The present study sequentially evaluated the clinical significance of maximal removal rate of technetium-99m-galactosyl human serum albumin (GSAR_{max}) in the future remnant liver (rGSAR_{max}) in patients to predict posthepatectomy complications.

Methods Between 2010 and August 2017, GSAR_{max}, rGSAR_{max}, their difference (Dif), and the rGSAR_{max} to GSAR_{max} ratio were examined in 247 additional patients who underwent hepatectomy for liver and biliary diseases. Hepatectomy-related postoperative complications (i.e. long-term ascites, intra-abdominal infection, and hepatic failure) occurred in 73 (29.6%) patients.

Results The median and mean preoperative GSAR_{max} values were 0.477 and 0.498 ± 0.166 mg/min, respectively; rGSAR_{max} values were 0.341 and 0.366 ± 0.145 mg/min, respectively; Dif values were 0.105 and 0.132 ± 0.111 mg/min, respectively; and the rGSAR_{max} to GSAR_{max} ratio values were 0.774 and 0.746 ± 0.177, respectively. Among these, the GSAR_{max} and rGSAR_{max} values were significantly correlated with the liver functional parameters ICGR15, LHL15, HH15, prothrombin activity, serum hyaluronic acid level, and platelet count (all $P < 0.01$). The rGSAR_{max} values

were significantly lower in patients with long-term ascites ($P < 0.05$), and the predictive cutoff values of rGSAR_{max} were 0.290 mg/min; however, the multivariate logistic regression analysis showed that rGSAR_{max} was not independently related to long-term ascites.

Conclusion When accompanied by other functional liver reserve parameters, rGSAR_{max} seemed to be an alternative liver functional parameter related to ascites. *Nucl Med Commun* 40:145–152 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Keywords: GSAR_{max} in the remnant liver, hepatic failure, liver resection, postoperative complications, predictive functional parameter, regional maximal removal rate of ^{99m}Tc-GSA liver scintigraphy

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Introduction

Operative morbidity and mortality in patients with several underlying hepatobiliary diseases who undergo hepatic resection have decreased markedly in recent years owing to advances in operative procedures and perioperative management [1]. In patients with injured livers, such as cirrhosis, and in those who undergo major hepatectomy, the operative risk is still a concern and must be carefully evaluated preoperatively [2,3]. Hepatectomy-related complications such as hepatic failure, long-term ascites, and intra-abdominal infection are still troublesome issues after hepatectomy, as they lead to prolonged hospitalization and potentially life-threatening outcomes [4].

As well as the indocyanine green (ICG) test and other useful liver functional tests [5–8], technetium-99m-galactosyl human serum albumin (GSA) liver scintigraphy has been used to evaluate regional liver function [9]. As well as the parameters LHL15 and HH15 from GSA liver scintigraphy, Ha-Kawa *et al.* [10,11], using multicompartmental analysis, found that the maximal removal rate of GSA (GSAR_{max}) is a useful general index for evaluating the functional reserve capacity of the liver. Several researchers have reported the preoperative decision making in the surgical procedure for hepatectomy using GSAR_{max} [12,13]. Kwon *et al.* [12] and Kaibori *et al.* [14] showed the significance of measuring the GSAR_{max} as the

best parameter of this scintigraphy to determine the indication for hepatectomy or to predict postoperative complications or mortality. Our preliminary study showed a significant relationship between $GSAR_{max}$ in the entire liver and other liver functional parameters or postoperative long-term ascites in 200 patients [15]. However, the significance of this parameter with respect to ascites on multivariate analysis has not been fully evaluated, and the serum hyaluronic acid (HA) level and platelet count were still independent predictors [15]. On the contrary, Kwon and colleagues recommended the $GSAR_{max}$ of the remnant liver ($rGSAR_{max}$) as the most powerful parameter to evaluate remnant liver function after hepatectomy [16,17]. The advantage of this parameter is that it allows the evaluation of future remnant liver function in any part separated from the entire liver or resected liver. In addition, it allows the evaluation of postoperative short-term outcomes, as noted in previous reports [16]. Therefore, we hypothesized that decreased liver function in the remnant liver as measured by $rGSAR_{max}$ would be a more sensitive predictor of postoperative morbidity than $GSAR_{max}$ in the whole liver, which was examined in the preliminary study. Furthermore, additional parameters were newly evaluated by comparing $GSAR_{max}$ of the whole liver and $rGSAR_{max}$.

In the present study, $rGSAR_{max}$ was sequentially examined, and the relationships between $rGSAR_{max}$, the difference between $GSAR_{max}$ and $rGSAR_{max}$ (Diff), and the $rGSAR_{max}$ to $GSAR_{max}$ ratio with clinicopathological characteristics, conventional functional liver reserve, surgical record parameters, and posthepatectomy complications of 247 patients in addition to the patients in the preliminary setting were evaluated to clarify their clinical significance with respect to future remnant liver function.

Participants and methods

Patients

The participants were 247 patients with various liver diseases who underwent hepatectomy, more than in the preliminary study, in the Division of Hepato-Biliary-Pancreas Surgery, Department of Surgery of the University of Miyazaki Faculty of Medicine, between 2010 and August 2017. They included 175 men and 72 women with a mean $\pm$ SD age of 68 ± 10 years (range: 24–86 years). The liver diseases warranting hepatic resection included hepatocellular carcinomas in 163 patients, intrahepatic cholangiocarcinomas in 19 patients, metastatic liver carcinomas in 42 patients, gallbladder carcinomas in 10 patients, bile duct carcinomas in four patients, invasion of renal carcinoma in one patient, and other benign liver diseases in eight patients. The background liver diseases included chronic viral liver diseases in 112 patients, cirrhosis in 59 patients, obstructive jaundice in six patients, normal liver in 48 patients, and others in 22 patients.

In our hospital, the volume of liver to be resected is estimated before surgery on the basis of the results of the indocyanine green retention rate at 15 min (ICG R15), using Takasaki's formula [18]. The liver volume,

excluding any tumor volume (cm^3), is measured by computed tomography volumetry [19], and we have also examined ^{99m}Tc -GSA scintigraphy to evaluate some parameters or functional hepatic volumetry [13]. In this cohort, the following procedures were performed: partial resection in 107 patients, subsegmentectomy in 44 patients, segmentectomy in 47 patients, central bisegmentectomy in two patients, lobectomy in 42 patients, and extended lobectomy in nine patients. Postoperative hepatectomy-related complications occurred in 73 (29.6%) patients and included persistent ascites (defined as massive ascites unresponsive to diuretics for >2 weeks) in 24 patients, intra-abdominal infection or abscess formation in 18 patients, bile leakage in 20 patients, and hepatic failure (defined by total bilirubin >5 mg/dl on postoperative day 7 or postoperative death without other cause) in 38 patients. The definition of complications in the present study was the same as in the preliminary setting. Death during the hospital stay was observed in one patient, because of hepatic failure. Laparoscopic resection, the combined resection of other organs and main hepatic vasculature, was excluded in this analysis. The study design was approved by the Ethics Review Board of our university (#2017-0248; approval date 17 January 2018), and informed consent for data collection was obtained by the opt-out method at our website and information board at the outpatient clinic between October and December 2017.

Evaluated parameters

Clinical data, conventional liver function data, and surgical data were analyzed. ICG was injected intravenously at a dose of 0.5 mg/kg body weight, and the 15-min retention rate (ICGR15) was measured by blood sampling at 5, 10, and 15 min after injection.

The protocol of ^{99m}Tc -GSA scintigraphy before operation was similar to that in the preliminary study. After fasting for more than 8 h, each patient was administered 185 MBq of ^{99m}Tc -GSA (Nihon MediPhysics, Nishinomiya, Japan) as a bolus injection into an antecubital vein [19]. Images were acquired with a large field of view using a dual-head gamma camera and computer system (E-CAM; Siemens, Philadelphia, Pennsylvania, USA) equipped with a low-medium-energy collimator centered over the liver and precordium. Dynamic images were taken immediately after the bolus injection of ^{99m}Tc -GSA at 30 s/frame for 40 min. After acquiring serial images, single-photon emission computed tomography (SPECT) images of the liver were acquired in 40 steps over 360° of rotation at a rate of 10 s/view. Data were collected digitally (128×128 matrix) in a dedicated computer system (E-soft; Siemens). SPECT image reconstruction was performed with an ordered subset expectation maximization method. The clearance index of ^{99m}Tc -GSA (HH15) and the hepatic uptake ratio of ^{99m}Tc -GSA (i.e. LHL15, the count ratio of the liver to the sum of the heart and liver 15 min after injection of ^{99m}Tc -GSA) were calculated after injection of ^{99m}Tc -GSA [10,19]. The values usually calculated were the ratio of

Fig. 1

Compartmental scheme for the distribution of intravenously injected ^{99m}Tc -GSA. A, maximal removal rate (R_{max}); ^{99m}Tc -GSA, technetium-99m-galactosyl human serum albumin. Modified from: Ha-Kawa, Tanaka [10]. $GSA \cdot R_{max}$ means the maximum rate of removal of the ligand per min from the hepatic vascular space to the receptors in the sinusoidal membrane of hepatocytes.

LHL15 and HH15, $GSAR_{max}$, $rGSAR_{max}$, the difference between $GSAR_{max}$ and $rGSAR_{max}$ (Dif), and the $rGSAR_{max}$ to $GSAR_{max}$ ratio. $GSAR_{max}$ was calculated using specific analysis software (Fit AS, version 1.20) developed by Dr S.K. Ha-Kawa in Kansai Medical School (Hirakata, Japan). The method uses a five-compartment model (extrahepatic blood, intrahepatic blood, receptor, interstitial, and urine). $GSAR_{max}$ means the maximum rate of removal of the ligand per min from the hepatic vascular space to the receptors in the sinusoidal membrane of hepatocytes [10] (Fig. 1). $GSAR_{max}$ in the predicted remnant liver ($rGSAR_{max}$) was calculated using analysis software developed by Dr N. Shuke in Asahikawa Medical College (Asahikawa, Japan). By defining the cutoff value as 40% of the maximum counts in the liver, the liver edge was delineated in the reconstructed image of the SPECT. Then, $rGSAR_{max}$ in the predicted remnant liver was calculated according to the planned surgical procedure. Kwon *et al.* [12,13] found that the $rGSAR_{max}$ in the whole liver for safe hepatectomy was established at over 0.15 mg/min. The lowest normal $GSAR_{max}$ value at our institute was set at 0.65 ± 0.12 mg/min.

Peripheral blood samples for serum HA level assays were collected from every patient in stable condition early in the morning during hospitalization. Blood samples were centrifuged at 3000 rpm for 15 min, and serum was stored at -80°C . HA was assayed using the sandwich protein-binding assay (SRL Inc., Tokyo, Japan); the normal serum HA level determined by the laboratory of SRL Inc. is less than 50 ng/ml [19].

The conventional liver functional parameters, including total bilirubin level, prothrombin activity (%), and platelet count, were examined. Parameters from the surgical records, including blood loss, blood transfusion, and operative and transection times under hepatic inflow occlusion, were examined. Postoperative liver functional parameters measured within day 7 were total bilirubin level, aspartate aminotransferase level, alanine aminotransferase level, prothrombin activity, platelet count, and C-reactive protein level.

Statistical analysis

Correlations between continuous data were evaluated by Pearson's correlation analysis, and correlation coefficients (r) were calculated. Continuous data are expressed as mean $\pm$ SD. Data were compared between groups using one-way analysis of variance and examined with the Mann-Whitney U -test. The optimal predictive cutoff value for posthepatectomy complications was determined for each parameter by receiver operating characteristic curve analysis. Comparisons of categorical data were performed with the χ^2 -test. Logistic regression analysis was performed to determine the predictive values of risk factors. Potential predictors were identified using a significance level of P less than 0.05 on univariate analysis, and the identified factors were then entered into a logistic regression multivariate analysis. A two-tailed P value less than 0.05 was considered significant. The Statistical Package for the Social Sciences, version 18.0 software (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses.

Table 1 Correlation of GSAR_{max}, rGSAR_{max}, and related parameters with patient demographics, preoperative liver functional parameters, and surgical records in patients with and without posthepatectomy complications

	GSAR _{max}	rGSAR _{max}	Difference	Ratio
Age (years)	−0.359**	−0.319**	−0.120	0.100
ICGR15 (%)	−0.402**	−0.298**	−0.211**	0.080
LHL15	0.625**	0.435**	0.366**	−0.200**
HH15	−0.611**	−0.462**	−0.309**	0.107
Total bilirubin (mg/dl)	0.024	−0.008	0.046	−0.013
Platelet count (/mm ³)	0.405**	0.259**	0.268**	−0.119
Prothrombin activity (%)	0.200**	0.218**	0.014	0.036
Hyaluronic acid (ng/ml)	−0.362**	−0.233**	−0.245**	0.167*
Operating time (minutes)	0.012	−0.214**	0.297**	−0.341**
Transection time (minutes)	−0.039	−0.152*	0.144*	−0.227**
Blood loss (ml)	0.015	−0.119	0.179**	−0.201**
Blood transfusion (ml)	0.010	−0.081	0.121	−0.138*
Hospital stay (days)	−0.008	−0.071	0.081	−0.095
Postoperative parameters ^a				
Total bilirubin (mg/dl)	0.159*	0.000	0.239**	−0.186**
Aspartate aminotransferase (U/l)	0.053	−0.083	0.188**	−0.221**
Alanine aminotransferase (U/l)	0.077	−0.037	0.164*	−0.189**
Prothrombin activity (%)	0.032	0.203**	−0.218**	0.260**
Platelet count (/mm ³)	0.047	0.119	−0.085	0.138*
C-reactive protein (mg/dl)	0.141*	0.192**	−0.042	0.062

^aThe maximum or minimum within day 7 after hepatectomy.*0.01 > *P* < 0.05.***P* < 0.01.

Results

Relationships between parameters of the regional maximal removal rate of technetium-99m-galactosyl human serum albumin and associated parameters and posthepatectomy complications

In the present results, GSAR_{max} ranged between 0.171 and 1.019 mg/min (first quartile 0.382 and third quartile 0.620 mg/min). The median and mean values of GSAR_{max} were 0.477 and 0.498 ± 0.166 mg/min, respectively. For rGSAR_{max}, the range was between 0.114 and 0.866 mg/min (first quartile 0.261 and third quartile 0.451 mg/min). The median and mean values of rGSAR_{max} were 0.341 and 0.366 ± 0.145 mg/min, respectively. Dif ranged between −0.037 and 0.691 mg/min (first quartile 0.054 and third quartile 0.185 mg/min). The median and mean values of Dif were 0.105 and 0.132 ± 0.111 mg/min, respectively. The rGSAR_{max} to GSAR_{max} ratio ranged between 0.196 and 1.216 (first quartile 0.650 and third quartile 0.869). The median and mean values of the rGSAR_{max} to GSAR_{max} ratio were 0.774 and 0.746 ± 0.177, respectively. Table 1 shows correlations of these parameters related to GSAR_{max} and rGSAR_{max} with 19 continuous variables (preoperative parameters, surgical record parameters, and postoperative liver parameters within day 7). For rGSAR_{max}, univariate analysis identified seven preoperative parameters (all *P* < 0.01), including age, ICGR15, LHL15, HH15, platelet count, prothrombin activity, and serum HA level, and surgical record parameter, operating time. Preoperative rGSAR_{max} was mostly correlated with some surgical record parameters such as operating time and

transection time (Table 1, all *P* < 0.05) and was not significantly correlated with the duration of hospital stay. Among the preoperative parameters of GSA liver scintigraphy, rGSAR_{max} was the most significantly correlated with the postoperative prothrombin activity level and the C-reactive protein level (Table 1, all *P* < 0.05); no correlations with postoperative liver dysfunction were observed. Alternatively, Dif and the rGSAR_{max} to GSAR_{max} ratio showed correlations with surgical record parameters such as operation time, transection time, and bleeding. In addition, there were also correlations with postoperative total bilirubin, aspartate aminotransferase, and prothrombin activity (Table 1, all *P* < 0.05). There was a significant correlation with postoperative hepatic dysfunction, unlike rGSAR_{max}.

Table 2 shows the comparisons between the parameters relating to GSAR_{max} and rGSAR_{max} and preoperative clinical features, surgical parameters, and postoperative complications. Univariate analysis showed that male patients had significantly higher GSAR_{max} values (*P* < 0.05), but there was no significant difference in rGSAR_{max}. The rGSAR_{max} data were the most significantly different in background liver with cirrhosis (*P* < 0.05). There were no significant differences in the extent of hepatectomy and surgical devices. Preoperative rGSAR_{max} was significantly lower in patients with than without hepatectomy-related complications, hepatic failure and long-term ascites (all *P* < 0.05); otherwise, no significant differences in complications were observed. On the contrary, the rGSAR_{max} to GSAR_{max} ratio was significantly lower in patients with hepatic failure than in those without (*P* < 0.05), with no significant differences in GSAR_{max} and Dif between patients with and without postoperative complications.

Analysis of factors associated with posthepatectomy long-term ascites

Continuous and categorical parameters associated with postoperative long-term ascites were analyzed by univariate analysis (Table 3). LHL15, HH15, rGSAR_{max}, serum HA level, and platelet count were significantly different between patients with and without long-term ascites (all *P* < 0.05). The prevalence of liver cirrhosis was significantly higher in patients with long-term ascites (*P* < 0.05). Patients with long-term ascites showed significantly lower C-reactive protein levels after hepatectomy (*P* < 0.05). The prevalence of other hepatectomy-related complications and duration of hospital stay were significantly higher in patients with long-term ascites (both *P* < 0.05). The predictive cutoff values for posthepatectomy long-term ascites of each of the continuous parameters were calculated by receiver operating characteristic curve analyses (0.88 for LHL15, 0.60 for HH15, 132 ng/ml for HA, 12.5/mm³ for platelet count, and 0.29 mg/min for rGSAR_{max}). The aforementioned five preoperative liver functional parameters were entered into the multivariate analysis to define a logistic regression model to identify parameters associated with posthepatectomy long-term ascites (Table 4). The multivariate analysis showed that a

Table 2 GSAR_{max}, rGSAR_{max}, and related parameters in clinical and operative features, and postoperative complications

	GSAR _{max}	rGSAR _{max}	Difference	Ratio
Sex				
Male (<i>n</i> = 175)	0.512 ± 0.166	0.374 ± 0.151	0.137 ± 0.109	0.739 ± 0.181
Female (<i>n</i> = 72)	0.464 ± 0.163 ¹	0.345 ± 0.128	0.119 ± 0.114	0.763 ± 0.166
Background liver				
Normal (<i>n</i> = 48)	0.531 ± 0.178	0.389 ± 0.163	0.142 ± 0.112	0.744 ± 0.191
Chronic viral hepatitis (<i>n</i> = 112)	0.500 ± 0.150	0.369 ± 0.140	0.131 ± 0.098	0.741 ± 0.168
Cirrhosis (<i>n</i> = 59)	0.410 ± 0.145 ²	0.313 ± 0.121 ³	0.096 ± 0.088	0.778 ± 0.167
Obstructive jaundice (<i>n</i> = 6)	0.705 ± 0.110	0.364 ± 0.177	0.342 ± 0.211	0.525 ± 0.237
Others (fatty/alcoholic/NASH/CASH) (<i>n</i> = 22)	0.594 ± 0.161	0.440 ± 0.149	0.154 ± 0.128	0.751 ± 0.169
Diseases				
Benign (<i>n</i> = 8)	0.588 ± 0.218	0.452 ± 0.174	0.136 ± 0.085	0.773 ± 0.104
Hepatocellular carcinoma (<i>n</i> = 163)	0.474 ± 0.155	0.356 ± 0.138	0.117 ± 0.095	0.759 ± 0.165
Cholangiocellular carcinoma (<i>n</i> = 19)	0.456 ± 0.160	0.296 ± 0.127	0.160 ± 0.137	0.683 ± 0.245
Colorectal liver metastasis (<i>n</i> = 42)	0.549 ± 0.178	0.403 ± 0.165	0.147 ± 0.115	0.738 ± 0.172
Gallbladder carcinoma (<i>n</i> = 10)	0.574 ± 0.137	0.424 ± 0.103	0.150 ± 0.128	0.764 ± 0.181
Bile duct carcinoma (<i>n</i> = 4)	0.739 ± 0.117	0.395 ± 0.220	0.344 ± 0.269	0.551 ± 0.300
Invasion of renal carcinoma (<i>n</i> = 1)	0.643	0.341	0.302	0.530
Extent of hepatectomy				
Partial resection (<i>n</i> = 107)	0.475 ± 0.164	0.379 ± 0.149	0.095 ± 0.086	0.806 ± 0.162
Subsegmentectomy (<i>n</i> = 40)	0.525 ± 0.163	0.408 ± 0.148	0.116 ± 0.084	0.782 ± 0.137
Segmentectomy (<i>n</i> = 47)	0.475 ± 0.140	0.330 ± 0.139	0.145 ± 0.091	0.694 ± 0.169
Central bisegmentectomy (<i>n</i> = 2)	0.510 ± 0.243	0.245 ± 0.117	0.266 ± 0.127	0.479 ± 0.000
Lobectomy (<i>n</i> = 42)	0.537 ± 0.176	0.341 ± 0.129	0.196 ± 0.149	0.659 ± 0.189
Extended lobectomy (<i>n</i> = 9)	0.590 ± 0.229	0.346 ± 0.161	0.244 ± 0.144	0.608 ± 0.164
Operative device ^a				
Ultrasonic coagulation (<i>n</i> = 194)	0.480 ± 0.161	0.358 ± 0.140	0.122 ± 0.095	0.753 ± 0.166
Ligasure sealing system (<i>n</i> = 45)	0.572 ± 0.170	0.395 ± 0.157	0.178 ± 0.152	0.709 ± 0.211
Biclamp (<i>n</i> = 6)	0.513 ± 0.201	0.441 ± 0.220	0.072 ± 0.098	0.850 ± 0.158
Use of soft coagulation				
No (<i>n</i> = 35)	0.572 ± 0.166	0.395 ± 0.160	0.177 ± 0.121	0.696 ± 0.182
Yes (<i>n</i> = 212)	0.486 ± 0.163	0.361 ± 0.143	0.125 ± 0.108	0.754 ± 0.175
Hepatectomy-related complications				
No (<i>n</i> = 174)	0.506 ± 0.165	0.380 ± 0.150	0.126 ± 0.108	0.759 ± 0.174
Yes (<i>n</i> = 73)	0.478 ± 0.168	0.331 ± 0.128 ^b	0.146 ± 0.118	0.714 ± 0.180 ^f
Hepatic failure				
No (<i>n</i> = 209)	0.501 ± 0.163	0.374 ± 0.146	0.127 ± 0.109	0.756 ± 0.174
Yes (<i>n</i> = 38)	0.479 ± 0.183	0.319 ± 0.134 ^c	0.160 ± 0.121	0.692 ± 0.186 ^d
Intra-abdominal infection				
No (<i>n</i> = 229)	0.500 ± 0.165	0.368 ± 0.144	0.131 ± 0.112	0.749 ± 0.177
Yes (<i>n</i> = 18)	0.475 ± 0.186	0.335 ± 0.165	0.140 ± 0.105	0.703 ± 0.178
Long-term ascites				
No (<i>n</i> = 223)	0.504 ± 0.167	0.371 ± 0.149	0.133 ± 0.112	0.745 ± 0.178
Yes (<i>n</i> = 24)	0.439 ± 0.143 ^g	0.320 ± 0.097 ^e	0.119 ± 0.103	0.754 ± 0.162
Bile leakage				
No (<i>n</i> = 227)	0.494 ± 0.168	0.365 ± 0.148	0.129 ± 0.108	0.749 ± 0.175
Yes (<i>n</i> = 20)	0.536 ± 0.137	0.373 ± 0.115	0.163 ± 0.143	0.715 ± 0.200

CASH, chemotherapy associated steatohepatitis, NASH, nonalcoholic steatohepatitis.

^aOne patient did not undergo hemostatic devices for transection.^b*P* = 0.017 versus no complication.^c*P* = 0.032 versus no complication.^d*P* = 0.042 versus no complication.^e*P* = 0.028 versus no complication.^f*P* = 0.068 versus no complication.^g*P* = 0.067 versus no complication.¹*P* = 0.04 versus male.²*P* < 0.01 versus others.³*P* = 0.005 versus others.

higher serum HA level and a lower platelet count were significant, independent factors associated with long-term ascites, with risk ratios of 1.005 and 0.816, respectively (*P* < 0.05). However, lower rGSAR_{max} was not significantly associated with long-term ascites on multivariate analysis, as in the preliminary study [20].

Discussion

Previous studies showed that various risk factors were associated with posthepatectomy complications [2–7,9,

20–25]. By considering the balance between curability of malignancy and surgical risks, the surgeon usually carefully decides on the indication for hepatectomy to avoid lethal outcomes. In cases of borderline liver dysfunction or a large volume of hepatectomy, more reliable predictive parameters are particularly needed before conducting hepatectomy. However, nobody has been able to achieve a distinct, comprehensive strategy for determining the extent of hepatectomy. In the preliminary study described above of a promising new parameter, the

Table 3 Comparison of patient demographics, preoperative liver functional parameters, surgical records, and outcomes in patients with and without posthepatectomy long-term ascites

	Ascites (–) (n = 223)	Ascites (+) (n = 24)	P value
Age (years)	68 ± 10	67 ± 10	0.659
Sex (male/female)	156/67	19/5	0.345
Background liver			
Normal/Ch/LC/J/others	46/103/48/4/22	2/9/11/2/0	0.011
Diseases			
Benign/HCC/CCC/mets/GBC/BDC/RCC	7/144/17/42/10/2/1	1/19/2/0/0/2/0	0.022
ICGR15 (%)	11.7 ± 7.7	16.6 ± 11.1	0.050
LHL15	0.91 ± 0.04	0.89 ± 0.04	< 0.01
HH15	0.59 ± 0.09	0.63 ± 0.08	0.019
GSAR _{max}	0.504 ± 0.167	0.439 ± 0.143	0.067
rGSAR _{max}	0.371 ± 0.149	0.320 ± 0.097	0.028
Difference between GSAR _{max} and rGSAR _{max}	0.133 ± 0.112	0.119 ± 0.103	0.532
Ratio (rGSAR _{max} /GSAR _{max} –rGSAR _{max})	0.745 ± 0.178	0.754 ± 0.162	0.811
Total bilirubin (mg/dl)	0.72 ± 0.34	0.88 ± 0.85	0.372
Platelet count (/mm ³)	18 ± 7	13 ± 7	< 0.01
Prothrombin activity (%)	92 ± 17	89 ± 14	0.422
Hyaluronic acid (ng/ml)	111 ± 117	258 ± 225	< 0.01
Operating time (min)	390 ± 144	468 ± 200	0.075
Extent of hepatectomy			
Partial/subseg/seg/central/lob/exlob	94/38/44/2/37/8	13/2/3/0/5/1	0.682
Hemostatic devices			
Ultrasonic/ligasure/biclamp	173/43/6	21/2/0	0.382
Hepatic transection time (min)	49 ± 46	57 ± 43	0.427
Blood loss (ml)	980 ± 1365	1848 ± 3705	0.266
Blood transfusion (ml)	330 ± 1016	1395 ± 4708	0.280
Postoperative parameters ^a			
Total bilirubin (mg/dl)	1.85 ± 1.40	1.64 ± 0.70	0.479
Aspartate aminotransferase (U/l)	443 ± 336	369 ± 351	0.317
Alanine aminotransferase (U/l)	386 ± 308	282 ± 248	0.121
Platelet count (/mm ³)	11.5 ± 6.2	10.2 ± 11.2	0.390
Prothrombin activity (%)	61 ± 11	62 ± 13	0.971
C-reactive protein (mg/dl)	10.09 ± 4.64	7.32 ± 4.82	< 0.01
Duration of hospital stay (days)	16.2 ± 14.8	36.7 ± 40.4	0.021
Hepatectomy-related other complications			
No/yes	174/49	11/13	< 0.01

Continuous data are presented as the mean ± SD.

BDC, bile duct carcinoma; CCC, cholangiocellular carcinoma; central, central bisegmentectomy; Ch, chronic hepatitis; exlob, extended lobectomy; GBC, gallbladder carcinoma; HCC, hepatocellular carcinoma; J, obstructive jaundice; LC, liver cirrhosis; lob, lobectomy; mets, liver metastasis; others, fatty, alcoholic, nonalcoholic steatohepatitis and chemotherapy associated steatohepatitis liver; partial, partial resection; RCC, invasion of renal carcinoma; seg, segmentectomy; ubseg, sub-segmentectomy.

^aThe maximum or minimum within day 5 after hepatectomy.

Table 4 Multivariate logistic regression analysis of preoperative liver functional parameters for long-term ascites after hepatectomy

	LHL15	HH15	rGSAR _{max}	HA	Platelet counts
P value	0.909	0.592	0.447	0.002	0.001
Risk ratio	1.011	0.975	0.151	1.005	0.816
95% CI (–)	0.843	0.890	0.001	1.002	0.721
95% CI (+)	1.211	1.069	19.769	1.007	0.923

CI, confidence interval; HA, hyaluronic acid; rGSAR_{max}, regional maximal removal rate of technetium-99m-galactosyl human serum albumin in the future remnant liver.

significance of the relationship between GSAR_{max} and posthepatectomy morbidity was not clarified [15]. In the present study, the focus was on rGSAR_{max} which represents the function of the future remnant liver, and additional related parameters, such as Dif and the rGSAR_{max} to GSAR_{max} ratio, different from the preliminary study, to examine their clinical significance in a larger series of patients than in the preliminary study. Some previous reports suggested that rGSAR_{max} was a more reliable liver functional parameter for predicting

postoperative morbidity or mortality [12–14], but this parameter has not yet been widely applied. Therefore, the clinical significance of rGSAR_{max} has not been fully clarified, except for Kwon's reports [12–14]. Thus, it is necessary to show its relationships to the type of morbidity in detail. Furthermore, rGSAR_{max} would be more likely to be associated with postoperative liver functional parameters than in the previous pilot study in this institute [13]. Therefore, in the present study, the relationships of several clinical, functional, and surgical parameters with posthepatectomy morbidity were examined in our clinical setting, as in the preliminary study [15]. By considering the importance of rGSAR_{max}, the decreased volume of the remnant liver was an important issue because the changes in GSAR_{max} might be affected by high-volume resection, such as a major hepatectomy [13,16,17], which should be related to posthepatectomy complications including hepatic failure. To reflect the changes of resected or remnant liver volume, the difference between GSAR_{max} and rGSAR_{max},

which might show the resected volume, and the rGSAR_{max} to GSAR_{max} ratio, which was also thought to indicate the remnant liver volume based on our hypothesis, were examined in the present study. Such modified parameters related to GSAR_{max} were examined in the present study.

Similar to previous reports [12,13,16], GSAR_{max} and rGSAR_{max} were significantly correlated with other conventional liver functional parameters on univariate analysis, and, therefore, these were thought to be useful as preoperative liver tests. Only preoperative total bilirubin was not correlated with rGSAR_{max} in the present study, and the total bilirubin level in this series was selected to be less than 1.2 mg/dl. Therefore, the range of this level was very limited in comparison with other parameters. The rGSAR_{max} was significantly lower in cirrhotic liver associated with decreased liver function.

With respect to intraoperative surgical record parameters, rGSAR_{max} and related parameters were significantly correlated with some parameters; in particular, Dif and the rGSAR_{max} to GSAR_{max} ratio showed a correlation with blood loss, as other liver functional parameters were correlated with blood loss or transfusion in previous reports [24]. In our hypothesis, Dif and the rGSAR_{max} to GSAR_{max} ratio were indicators of resected volume and remnant liver volume; therefore, these parameters were correlated with the extent of hepatectomy and blood loss or transfusion [24]. Because of the correlation with blood loss, preoperative Dif and the rGSAR_{max} to GSAR_{max} ratio were more closely correlated with postoperative liver functional parameters such as total bilirubin than rGSAR_{max} [23,24].

Useful preoperative parameters such as rGSAR_{max}, Dif, and the rGSAR_{max} to GSAR_{max} ratio used in this study were associated with posthepatectomy complications, as in previous studies [13,17], particularly with long-term ascites. Long-term ascites was affected by preoperative liver function, intraoperative surgical record parameters, and postoperative liver dysfunction, as in previous reports, which lead to a longer hospital stay or worse overall patient prognosis in malignant hepatic diseases [24]. There was a significant difference between the presence or absence of ascites in rGSAR_{max}, but not in Dif and the rGSAR_{max} to GSAR_{max} ratio, which were correlated with the extent of hepatectomy and blood loss. Long-term ascites might be more affected by hepatic reflux disorder owing to a decreased liver blood flow rate and functional residual liver volume than hepatic resection volume and blood loss [10,11,13].

In this study, multivariate analysis showed that the serum HA level and platelet count were significantly associated with an increased risk ratio compared with other parameters, and the risk ratio of rGSAR_{max} was the lowest. This result was different from report by Kwon *et al.* [13], and the degree of liver dysfunction in cirrhosis in their

study seemed to be worse than in the present study; there were only three patients with a low rGSAR_{max} (<0.15 mg/min) in the present study. On the contrary, Yachida *et al.* [7], reported a predictive cutoff value of serum HA concentration of 150 ng/ml for post-hepatectomy complications, and the value of 132 ng/ml in the present study was similar. The serum HA level reflects the function of hepatic sinusoids and is a sensitive marker of liver endothelial cell dysfunction after liver ischemia [18], which is increased in the presence of chronic liver injury. In cases with lower values of rGSAR_{max}, a higher risk ratio may be detected for rGSAR_{max} than for serum HA for postoperative long-term ascites. Kaibori *et al.* [14] reported that the HA/GSAR_{max} ratio can predict liver failure. Thus, the combination of HA and rGSAR_{max} may be a better predictor of post-hepatectomy outcomes.

The extent of hepatectomy was also a significant risk factor for posthepatectomy complications, despite the fact that the operative indication has recently been carefully determined by predictive parameters [8,19]. Therefore, it is necessary to use additional parameters to decide the criteria for surgery. In the present study, GSAR_{max} or rGSAR_{max} were not shown to be clinically useful. With respect to uncontrolled ascites in the case of major hepatectomy, associated parameters including rGSAR_{max} for hepatectomy-related complications should be evaluated. By restricting the extent of resection to major hepatectomy, suppressing the effect of resection range, it is possible that rGSAR_{max} could reflect post-operative liver function.

Conclusion

In patients who are scheduled for various hepatic resections, the clinical significance of GSAR_{max}, rGSAR_{max}, and related parameters calculated by ^{99m}Tc-GSA liver scintigraphy was examined based on our preliminary study of whole liver GSAR_{max} alone. Although the univariate analysis showed that a lower rGSAR_{max} was significantly associated with lower preoperative liver function and the presence of postoperative long-term ascites, on multivariate analysis, rGSAR_{max} and related parameters were not predictors. The independent significance and sensitivity of rGSAR_{max} and related parameters were not clarified, but rGSAR_{max} would be useful as a complementary parameter with other preoperative makers to predict postoperative long-term ascites.

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The authors declare that the present study was performed as a new clinical study and obtained different ethics committee approval from the previous study of whole liver GSAR_{max}.

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organizing the entire research as a supervisor who managed all clinical research in the Department of Surgery; Drs Y.T., K.Y., Y.F., M.H., N.I., T.H., M.I., and T.W., staff members of the liver surgery group, collected data for liver function and from surgical records; and Dr Y.M. and Prof. T.H., experts in nuclear medicine for GSA liver scintigraphy, measured GSAR_{max} and rGSAR_{max}.

Conflicts of interest

There are no conflicts of interest.

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