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Estimation of Post-therapeutic Liver Reserve Capacity Using 99mTc-GSA Scintigraphy Prior to Carbon-ion Radiotherapy for Liver Tumors

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Estimation of Post-therapeutic Liver Reserve Capacity Using ^{99m}Tc-GSA Scintigraphy Prior to Carbon-ion Radiotherapy for Liver Tumors

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Abbreviations: CIRT, carbon-ion radiotherapy; Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid; GSA-RL, GSA-Rmax of the estimated residual liver; GSA-Rmax, maximal removal rate of ^{99m}Tc -GSA; SPECT, single-photon emission computed tomography; ^{99m}Tc-GSA, ^{99m}Tc-galactosyl human serum albumin; VOI, volume of interest

Key results:

The median GSA-RL was 0.393 [range, 0.057–0.729] mg/min, GSA-Rmax after CIRT was 0.369 [range, 0.037–0.780] mg/min (P = .40).

The linear regression equation representing the relationship between the GSA-RL and GSA-Rmax after CIRT was y = 0.05 + 0.84x (R^2 = 0.67, P < .0001). There was a positive correlation between the estimated and actual post-treatment values as well as in the group with impaired liver reserve (R^2 = 0.62, P = .0005).

A summary statement: ^{99m}Tc-GSA scintigraphy can be used to accurately estimate liver reserve capacity after carbon-ion radiotherapy in patients with liver tumors regardless of disease severity.

Abstract

Background: There is currently no established imaging method for assessing liver reserve capacity prior to carbon-ion radiotherapy (CIRT) for liver tumors. In order to perform safe CIRT, it is essential to estimate the post-therapeutic residual reserve capacity of the liver.

Purpose: To evaluate the ability of pre-treatment ^{99m}Tc-GSA scintigraphy to accurately estimate the residual liver reserve capacity in patients treated with CIRT for liver tumors.

Materials and Methods: This retrospective study evaluated 50 patients who were performed CIRT for liver tumors between December 2018 and September 2020 and underwent ^{99m}Tc-GSA scintigraphy before and 3 months after CIRT, Gd-EOB-DTPA-enhanced MRI within 1 month before CIRT were evaluated. The maximal removal rate of ^{99m}Tc-GSA (GSA-Rmax) was analyzed for the evaluation of pre-treatment liver reserve capacity. Then, the GSA-Rmax of the estimated residual liver (GSA-RL) was calculated using liver SPECT images fused with the Gd-EOB-DTPA-enhanced MRI. GSA-RL before CIRT and GSA-Rmax at 3 months after CIRT were compared using non-parametric Wilcoxon signed-rank test and linear regression analysis.

Results: Overall, 50 patients were included (mean age ± standard deviation, 73 years ± 11; range, 29–89 years, 35 men). The median GSA-RL was 0.393 [range, 0.057–0.729] mg/min, the median GSA-Rmax after CIRT was 0.369 [range, 0.037–0.780] mg/min ($P = .40$). The linear regression equation representing the relationship between the GSA-RL and GSA-Rmax after CIRT was $y = 0.05 + 0.84x$ ($R^2 = 0.67$, $P < .0001$). There was a positive correlation between the estimated and actual post-treatment values for all patients, as well as in the group with impaired liver reserve capacity ($y = - 0.02 + 1.09x$ ($R^2 = 0.62$, $P = .0005$)).

Conclusions: ^{99m}Tc-GSA scintigraphy has potential clinical utility for estimating the residual liver reserve capacity in patients undergoing carbon-ion radiotherapy for liver tumors.

Clinical Trial registration: UMIN000038328, https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000043545

Key Words

^{99m}Tc-GSA Scintigraphy; Carbon-ion Radiotherapy; GSA-Rmax; GSA-RL; Liver Tumor

Introduction

Primary liver cancer was the sixth most common type of cancer and the fourth most common cause of death worldwide in 2015, with the highest incidence of cases and deaths observed in East Asia [1]. Standard treatment strategies for localized hepatocellular carcinoma are surgical resection, radiofrequency ablation (RFA), and transcatheter arterial chemoembolization (TACE) [2-4]. Metastatic liver tumors are significantly more common than primary liver cancer and are difficult to cure despite various treatment approaches [5, 6] . Although surgical resection is the current standard treatment for metastatic liver tumors, other treatments such as proton beam radiotherapy, immunotherapy have been applied for hepatocellular carcinoma and metastatic liver tumor [7-11]. However, treatment options are updated year by year, the selection policy for newly developed treatments have not yet been established. Carbon-ion radiotherapy (CIRT) is another therapeutic option for primary and metastatic liver tumor. CIRT delivers high doses to the target tumors while sparing normal liver tissue, which allows reducing toxicity to normal tissues [12, 13]. In addition, CIRT has biological advantages because of high linear energy transfer radiation compared to proton beam and X-ray [12-14]. CIRT has showed efficacy and safety for the treatment of primary and metastatic liver tumors, even in cases that are considered difficult to manage surgically [7, 12, 13]. Because many patients with liver tumors have

impaired liver function, it is essential to assess the reserve capacity of the liver prior to CIRT in order to accurately estimate the post-therapeutic residual reserve capacity.

There are some standard methods for evaluating preoperative liver reserve capacity, including indocyanine green (ICG) clearance [15, 16], Child-Pugh classification [16, 17], model for end-stage liver disease (MELD) score [16, 17]. These conventional methods reflect total liver function; therefore, they cannot always accurately assess or estimate the impact of treatments. ^{99m}Tc-galactosyl human serum albumin (^{99m}Tc-GSA), which binds specifically to the asialoglycoprotein receptor, is only expressed in normal hepatocytes and has been widely used to estimate the reserve capacity of the liver [18-20]. As Mizutani et al. and other investigators reported previously, ^{99m}Tc-GSA liver scintigraphy is clinically useful imaging evaluating liver function before surgery of liver tumors [21-25].

The maximal removal rate of ^{99m}Tc-GSA (GSA-Rmax), which is calculated by a kinetic analysis using the compartment model developed by Kawa et al., is useful for the evaluation of preoperative liver reserve capacity and for the prediction of postoperative outcomes [21-25]. Based on these prior studies, we hypothesized that this technique has a potential utility of liver functioning evaluation in patients with liver tumors before undergoing CIRT. However, there has been no report evaluating pre-treatment liver function using ^{99m}Tc-GSA scintigraphy in

patients with various liver tumors who are going to receive CIRT.

The aim of this study was to evaluate the ability of ^{99m}Tc-GSA scintigraphy to accurately estimate the residual reserve capacity of the liver in patients treated with CIRT for liver tumors.

Materials and Methods

Study patients

This study was approved by our institutional review board (#19-027). This study is registered in the University Hospital Medical Information Network Clinical Trials Registry (#UMIN000038328), and written informed consent was obtained from each patient. This study conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. And this study has been reported based on the Standards for Reporting of Diagnostic Accuracy guidelines. Data generated or analyzed during this study are available from the corresponding author by request.

This retrospective study analyzed 114 potential patients (with a total of 179 ^{99m}Tc-GSA scintigraphy examinations) who were scheduled to undergo CIRT for various liver tumors between December 2018 and September 2020. Of the 114 patients, those were considered eligible for inclusion in this study if they (1) were clinically diagnosed with a liver tumor and

scheduled to undergo CIRT, (2) underwent ^{99m}Tc-GSA scintigraphy and gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRI within 1 month before CIRT, and (3) underwent ^{99m}Tc-GSA scintigraphy 3 months after CIRT. Patients were excluded from this study if they (1) refused to participate or (2) did not undergo ^{99m}Tc-GSA scintigraphy from 3 months after CIRT. Figure 1 shows the flowchart of the patient population.

Patients' characteristics

As Figure 1 shows, 64 patients were eventually excluded. Characteristics of 50 patients treated with CIRT were as follows. Thirty-six patients were diagnosed with hepatocellular carcinoma, 2 with cholangiocellular carcinoma, 1 with mixed hepatocholangiocellular carcinoma, 11 with metastatic liver tumor, and another with giant hemangioma. The total exceeds 100% because one patient had two types of tumors. All patients were classified by liver function according to Child-Pugh classification previously reported [26]. Regarding the history of liver treatment before this study, twelve partipants had undergone surgery, eight had undergone radiofrequency ablation, six had undergone transcatheter arterial chemoembolization, five had undergone CIRT, and another had undergone microwave ablation. Some patients had

undergone more than one treatment. None of the 50 patients underwent ICG clearance test.

^{99m}Tc-GSA dynamic scintigraphy and SPECT procedure

All patients underwent ^{99m}Tc-GSA scintigraphy using a gamma camera (E.CAM, Canon Medical, Tokyo, Japan) equipped with a low-medium-energy general purpose collimator centered over the liver and the precordium. Dynamic images were acquired immediately after intravenous injection of 185 MBq of ^{99m}Tc-GSA (Nihon Medi-Physics, Tokyo, Japan) at a rate of 30 seconds per frame for the first 30 minutes. Single-photon emission computed tomography (SPECT) images of the liver were acquired in 90 steps, with a 360-degree rotation at 3.3 seconds per view and a matrix size of 128 × 128 pixels. SPECT image reconstruction was performed with an ordered subset expectation maximization method.

MRI procedure

For reference with SPECT-MRI fusion images, hepatobiliary phase images acquired 20 minutes after contrast agent administration were selected. We used Gd-EOB-DTPA-enhanced MRI as reference images, not treatment planning computed tomography (CT), because MRI showed higher sensitivity and diagnostic accuracy than CT for the detection and the

determination of the margin of liver tumors [27, 28]. In addition, because CIRT-treatment planning CT had not been obtained at the time of evaluation of reserve capacity of the liver in all patients, we could not use the planning CT images as a reference of fusion images. Therefore, using SPECT-MRI fusion images combined with contrast-enhanced MRI, which provides high contrast between the tumor and the normal liver tissue, we simulated the estimated post-treatment liver reserve capacity prior to CIRT.

All MRI examinations were performed before CIRT using the 1.5-T Achieva dStream (Philips Healthcare, Best, the Netherlands). The hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI was acquired using axial three-dimensional gradient-echo imaging with breath-hold examination. The MRI protocol for the spectral attenuated inversion-recovery T1-weighted sequence was as follows: repetition time msec/echo time msec, 5.0/2.4; echo train length, 38; 12° flip angle; 5-mm slab thickness; 256 × 256-matrix; and a 350 × 350-mm field of view.

Analysis of reserve capacity of the liver

The GSA-Rmax was calculated by a nuclear medicine physician (with 12 years of experience), with application of ^{99m}Tc-GSA dynamics of the heart and liver to a radiopharmacokinetic model composed of five compartments, including the extrahepatic blood,

hepatic blood, hepatocytes, interstitial fluid, and urine, as developed by Ha-Kawa [21]. Liver SPECT images were then fused with the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI using the 'Fusion Viewer' image-analysis software (AZE, Kawasaki, Japan). Rectangular volumes of interest (VOIs) were drawn on the fusion images to include the whole liver. Elliptical VOIs were then drawn around the tumor and an approximately 15-mm margin based on CIRT planning. Kasuya et al. have previously described that the planning target volume can be defined as the gross tumor volume plus a 10-mm margin, with the whole planning target volume covered by at least 95% of the prescribed irradiation dose [12]. Therefore, we determined VOIs of the CIRT planning area by estimating the gross tumor volume plus a 15-mm margin as the area in which hepatocytes lose liver function after CIRT. Using radioisotope counts within these VOIs, the GSA-Rmax of the estimated residual liver (GSA-RL) was calculated as follows, with reference to the modified method reported by Shuke et al. [29]:

GSA-RL [mg/min] = GSA-Rmax [mg/min] × {(RI count of whole liver) − (RI count of CIRT planning area)} / (RI count of whole liver)

All fusion images were analyzed by a consensus of two nuclear medicine physicians (with 10 and 24 years of experience, respectively), a radiologist specializing in body imaging (with 12 years of experience), and two radiation oncologists (with 9 and 5 years of experience in

radiation oncology). Then, ^{99m}Tc-GSA scintigraphy 3 months after CIRT was also performed to evaluate the accuracy of the pre-treatment estimated values. Values before CIRT and at 3 months after CIRT were compared for all eligible patients stratified by both GSA-RL group and Child-Pugh classification.

Statistical analysis

Normally distributed continuous variables are expressed as mean ± standard deviation, and non-normally distributed variables are expressed as median and range. The variables were compared using non-parametric Wilcoxon signed-rank test, with linear regression analysis of the relationship between GSA-RL values before CIRT and GSA-Rmax values 3 months after CIRT. *P*-values <.05 were considered statistically significant. Sample size estimations were not performed because no previously published applicable data were available. Statistical analysis was performed using JMP statistical software (SAS Institute, Cary NC, USA).

Results

Of the 114 potential patients, 2 refused to participate in the study, 5 did not undergo MRI before CIRT, 60 did not undergo ^{99m}Tc-GSA scintigraphy 3 months after CIRT, and 4 of them

did not undergo both. One patient had circulatory failure due to cardiovascular disease, which prevented proper analysis of the GSA-Rmax both before and after CIRT. Therefore, this patient was excluded from this study. Ultimately, 50 patients were included in this study (mean age ± standard deviation, 73 years ± 11; range, 29–89 years), with 35 men (74 years ± 8) and 15 women (71 years ± 15). All 50 patients underwent ^{99m}Tc-GSA scintigraphy 3 months (median, 96.5 days; range, 81–126 days) after CIRT. Patients' demographics and characteristics are presented in Table 1, and a summary of clinical information is in Table 2.

Imaging assessment

Hepatic uptake of ^{99m}Tc-GSA after CIRT was reduced or absent at irradiated sites, which was somewhat consistent with planning target volumes and gross tumor volumes and an approximately 15-mm margin compared to the dose distribution of the treatment-planning CT. On the other hand, uptake outside of irradiation sites seemed to be preserved, although the degree of ^{99m}Tc-GSA uptake was dependent on liver functions.

Analysis of reserve capacity of the liver

These results are shown in Table 3. The median GSA-Rmax before CIRT for all patients was

0.460 [range, 0.061–0.795] mg/min. Depending on tumor volumes and number of tumors, the post-treatment liver reserve capacity, calculated from the SPECT-MRI fusion images, was estimated to be 91 [range, 57–98] % of the GSA-Rmax before CIRT. The median GSA-RL, calculated as an estimated value after CIRT, was 0.393 [range, 0.057–0.729] mg/min for all patients. The median GSA-Rmax 3 months after CIRT for all patients was 0.369 [range, 0.037–0.780] mg/min. When comparing the GSA-RL before CIRT and the GSA-Rmax 3 months after CIRT in all patients, there was no statistically significant difference ($P = .40$).

Each patient was classified into the following three groups based on their GSA-RL value, with a GSA-RL ≥ 0.50 considered 'Excellent,' a GSA-RL < 0.50 and ≥ 0.25 considered 'Fair,' and a GSA-RL < 0.25 considered 'Poor.' A GSA-RL of < 0.25 corresponds to the value that Mizutani et al. suggested should cause patients to forego liver surgery [23]. Based on the GSA-RL groups described above, the GSA-RLs before CIRT and the GSA-Rmax 3 months after CIRT were compared as follows: Excellent group, GSA-RL was 0.587 [range, 0.500–0.729] mg/min, GSA-Rmax after CIRT was 0.547 [range, 0.228–0.780] mg/min, $P = .27$; Fair group, GSA-RL was 0.405 [range, 0.292–0.484] mg/min, GSA-Rmax after CIRT was 0.375 [range, 0.236–0.636] mg/min, $P = .96$; and Poor group, GSA-RL was 0.178 [range, 0.057–0.246] mg/min, GSA-Rmax after CIRT was 0.157 [range, 0.037–0.379] mg/min, $P = .55$.

Based on Child-Pugh classification, the GSA-RLs before CIRT and the GSA-Rmax 3 months after CIRT were compared as follows: score 5 (grade A), GSA-RL was 0.454 [range, 0.203–0.729] mg/min, GSA-Rmax after CIRT was 0.427 [range, 0.168–0.780] mg/min, $P = .55$; score 6 (grade A), GSA-RL was 0.223 [range, 0.090–0.552] mg/min, GSA-Rmax after CIRT was 0.379 [range, 0.037–0.449] mg/min, $P = 1.0$; and score 7–9 (grade B), GSA-RL was 0.107 [range, 0.057–0.351] mg/min, GSA-Rmax after CIRT was 0.109 [range, 0.045–0.336] mg/min, $P = .06$), respectively.

The linear regression equation representing the relationship between the GSA-RL before CIRT and the GSA-Rmax 3 months after CIRT was $y = 0.05 + 0.84x$ ($R^2 = 0.67$, $P < .0001$). Focusing on the 'Poor' group only, the linear regression equation was $y = - 0.02 + 1.09x$ ($R^2 = 0.62$, $P = .0005$). It was possible to estimate post-treatment liver reserve capacity even in Poor group patients. There was a positive correlation between the estimated and actual post-treatment values for all patients, as well as in the group with impaired liver reserve capacity (Figure 4). One patient had a more than two-fold elevation in alkaline phosphatase than that of normal levels and was diagnosed with classic radiation-induced liver disease 2 months after CIRT, with a GSA-RL of 0.090 mg/min and a GSA-Rmax 3 months after CIRT of 0.037 mg/min [30]. No other patients had apparent worsening of the liver function by serological testing.

Representative cases are shown in Figure 5.

Discussion

The present study clearly showed the clinical utility of pre-carbon-ion radiotherapy (CIRT) ^{99m}Tc-galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy to estimate the residual liver reserve capacity of the liver in patients who were scheduled to receive CIRT for liver tumors. There has been no study that estimate post-treatment liver reserve capacity quantitatively and compare actual liver reserve capacity using ^{99m}Tc-GSA scintigraphy after various treatment for liver tumor patients. In the present study, we have collected pre- and post-treatment data from a total of 50 patients. Our data demonstrated pre-treatment GSA-RL calculated from ^{99m}Tc-GSA scintigraphy was consistent with post-treatment liver reserve capacity. In the surgical treatment of liver tumors, investigators have reported that pre-treatment ^{99m}Tc-GSA scintigraphy was useful in predicting posthepatectomy liver failure [22, 23]. To the best of our knowledge, our present study would be the first report describing a detailed comparison of preoperative prediction and postoperative residual liver function by ^{99m}Tc-GSA scintigraphy. For assessing the relationship between pre-treatment estimated residual liver reserve capacity and actual post-treatment liver reserve, there was a significant linear relationship between the maximal removal

rate of ^{99m}Tc -GSA (GSA-Rmax) of the estimated residual liver (GSA-RL) and the GSA-Rmax after CIRT ($R^2 = 0.67$, $P < .0001$). Our estimations were in good agreement with the actual liver reserve capacity 3 months after CIRT.

When examined by classifying by pre-treatment liver function status, there was a significant linear relationship with the estimated value between actual values not only in the group with a good liver reserve capacity of 0.50 ≤ GSA-RL, but also in the group with poor liver reserve capacity with a GSA-RL of < 0.25 ($R^2 = 0.62$, $P = .0005$), corresponding to the group that Mizutani et al. suggested should avoid liver surgery [23]. Even inoperable patients with low liver reserve capacity were able to receive CIRT safely without acute radiation-induced liver disease except for 1 patient. Besides, the classification based on patients' pre-treatment GSA-RL could contribute to the prediction of patients who would require careful medical management after treatment. Thus ^{99m}Tc-GSA scintigraphy could accurately estimate liver reserve capacity after CIRT regardless of the degree of liver function, and our proposed method may facilitate preemptive identification of patients who will need careful follow-up.

The advantage of this proposed method compared with the conventional liver function test should be discussed. Our method could evaluate the regional liver function, which is difficult to assess with the Child-Pugh classification and the ICG clearance test. Previously reported liver

function assessments have included serological tests, Child-Pugh classification system, ICG clearance, all of which are widely used techniques in clinical practice. These methods reflect total liver function; therefore, they cannot always accurately assess or estimate the impact of CIRT, which provides localized treatment for individual lesions. Assessment of the liver and tumor volumes by CT (CT volumetry) is known to be another option for pretreatment [31] . However, an accurate assessment of liver reserve capacity is difficult to obtain using this strategy because it cannot reflect the heterogeneity of normal and dysfunctional hepatocytes in the liver [23, 32, 33]. ^{99m}Tc-GSA kinetic analysis of HH15 (retention rate in blood) and LHL15 (hepatic uptake rate) are other widely used indices of liver function [18]; however, these values are obtained from planar images and do not allow for the accurate assessment of anatomy [34]. In clinical practice of radiation therapy, it is desirable to have radiation dose on tumor as high as possible to the extent that damage of surrounding normal liver parenchyma is kept to the minimal.

The present study demonstrated that a SPECT-MRI fused imaging method could easily estimate the liver reserve capacity in each lobe of liver while also taking into account the anatomy of individual patients. This can be accomplished by combining the advantages of SPECT and Gd-EOB-DTPA-enhanced MRI. The former can assess regional liver reserve capacity, while the

latter can distinguish tumors from non-tumor areas with high contrast. Therefore, this method might have a clinical utility for patients who receive CIRT for various liver tumors.

Regarding the indication criteria for CIRT for liver tumors, it is determined by staging with CT, MRI, ^{99m}Tc-GSA scintigraphy, and blood tests. CIRT is then performed using the planning CT of treatment dose distribution. The semi-quantitative evaluation of GSA-RL calculated from the pre-treatment ^{99m}Tc-GSA scintigraphy proposed in the present study would be of important clinical significance in the accurate determination of CIRT indication for liver tumors.

In ongoing study with longer observation period, we are planning to determine clear indication criteria of CIRT for liver tumor by a combination of this GSA-RL method with other important prognostic factors.

Our study had several limitations. First, we did not compare GSA-RL and post-treatment GSA-Rmax with ICG clearance, which was considered to be one of the standards and the most accurate liver function test so far. Some patients have checked ICG-clearance in the other hospital before coming to our institution. However, ICG clearance was not a routine examination in our institution. The accuracy and feasibility of ^{99m}Tc-GSA scintigraphy should be confirmed for further study. Second, there are technical limitations with the use of SPECT, including errors in radioisotope counting between superficial and deep areas of the liver due to

the large size of this organ. Technical verification is needed using a scanner with a high spatial resolution, such as digital SPECT/CT, which will facilitate accurate attenuation correction. Third, outcomes after a longer-term follow-up are unknown. As acute outcomes after radiotherapy for liver tumors, patients usually present with fatigue, abdominal pain, weight gain, hepatomegaly, anicteric ascites as symptoms of acute classic radiation-induced liver disease. As for acute radiation-induced liver disease after CIRT, Komatsu and Kasuya reported they observed no severe adverse events in the liver, only required controllable management in a few patients [12, 35]. Further study was needed to confirm the relationship between our method using ^{99m}Tc-GSA and more longer-term outcome of liver reserve capacity because ^{99m}Tc-GSA scintigraphy is generally performed in patients with a low liver reserve capacity.

In conclusion, this study demonstrated that ^{99m}Tc-galactosyl human serum albumin scintigraphy has potential clinical utility for estimating the residual reserve capacity of the liver in patients undergoing treatment with carbon-ion radiotherapy for liver tumors.

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Author contributions

Kana Yamazaki and Ryuichi Nishii were responsible for the research, wrote the main manuscript text as the first author (Kana Yamazaki) and the corresponding author (Ryuichi Nishii) responsible for this study, and coordinated and supervised the entire study. Yoshiharu Isobe, Toshiaki Tani and Masato Kobayashi are radiological technologists responsible for SPECT scans and provided technical advice for SPECT and MRI imaging. Kana Yamazaki, Yoichi Mizutani and Tamasa Terada were calculated and analyzed all of GSA-related parameters using the dynamic imaging data and SPECT/MRI fused images. Hirokazu Makishima, Takashi Kaneko, Masaru Wakatsuki and Hiroshi Tsuji are radiation oncologists responsible for planning patient examinations, therapy, and subsequent management of patients. Kana Yamazaki, Kentaro Tamura and Etsuko Imabayashi interpreted SPECT images. Masato Kobayashi and Tatsuya Higashi were responsible for the statical analysis and provided technical advice for data management. All authors conducted this study and also read and approved the final version of the manuscript.

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Table 1. Characteristics of Study Participants Before Carbon-ion Radiotherapy

Characteristic	Participant data (*n* = 50)
Sex [*]	
Male	35 (70)
Female	15 (30)
Age (y) [†]	
Overall	73 ± 11 [29–89]
Men	74 ± 8 [52–89]
Women	71 ± 15 [29–85]
Pathology of tumors treated with CIRT [*‡]	
Hepatocellular carcinoma	36 (72)
Cholangiocellular carcinoma	2 (4)

Mixed hepatocholangiocellular carcinoma	1 (2)
Metastatic liver tumor	11 (22)
Giant hemangioma	1 (2)
Child-Pugh classification *	
5 (grade A)	37 (74)
6 (grade A)	5 (10)
7 (grade B)	6 (12)
8 (grade B)	1 (2)
9 (grade B)	1 (2)
History of liver treatment before this study*§	
Surgery	12 (24)
Radiofrequency ablation	8 (16)
Transcatheter arterial chemoembolization	6 (12)
CIRT	5 (10)
Microwave ablation	1 (2)

Continuous variables are expressed as mean ± standard deviation.

CIRT = carbon-ion radiotherapy

[*] Data in parentheses are percentages.

[†] Data in brackets are ranges.

[‡] The total exceeds 100% because one participant had two types of tumors.

[§] Some participants had undergone more than one treatment.

Table 2. Summary of clinical information

Number of lesions treated with CIRT [*]	
Solitary	40 (80)
Multiple	10 (20)
Median tumor max diameter (mm) [†]	38 [9−160]
CIRT total dose, Gy (RBE) / fractions, No. [*‡]	
60 Gy/4 Fr	25 (50)
48 Gy/2 Fr	25 (50)
58 Gy/1 Fr	6 (12)

RBE = relative biologically effectiveness

[*] Data in parentheses are percentages.

[†] Data in brackets are ranges.

[‡] The total exceeds 100% because five participants underwent more than one dose.

Table 3. Comparison of the Reserve Capacity of the Liver Before and 3 months After CIRT

Characteristic	Number (*n*)	GSA-Rmax before CIRT [*†]	GSA-RL [*†]	GSA-Rmax after CIRT [*†]	*P*-value [‡]
Overall patients	50	0.460 [0.061–0.795]	0.393 [0.057–0.729]	0.369 [0.037–0.780]	.40
GSA-RL classification [§]					
Excellent	12	0.679 [0.527–0.795]	0.587 [0.500–0.729]	0.547 [0.228–0.780]	.27
Fair	24	0.466 [0.340–0.574]	0.405 [0.292–0.484]	0.375 [0.236–0.636]	.96
Poor	14	0.199 [0.061–0.391]	0.178 [0.057–0.246]	0.157 [0.037–0.379]	.55
Child-Pugh classification					
5 (grade A)	37	0.480 [0.226–0.795]	0.454 [0.203–0.729]	0.427 [0.168–0.780]	.55
6 (grade A)	5	0.381 [0.095–0.691]	0.223 [0.090–0.552]	0.379 [0.037–0.449]	1.0

7–9 (grade B)	8	0.118 [0.061–0.362]	0.107 [0.057–0.351]	0.109 [0.045–0.336]	.06

Continuous variables are expressed as median.

CIRT = carbon-ion radiotherapy, GSA-Rmax = maximal removal rate of ^{99m}Tc -GSA, GSA-RL = GSA-Rmax of the estimated residual liver.

* Unit: mg/min

† Data in brackets are ranges.

‡ Comparison of GSA-RL and GSA-Rmax after CIRT.

§ Definition of GSA-RL classification system: 0.50 ≤ GSA-RL is 'Excellent,' 0.25 ≤ GSA-RL < 0.50 is 'Fair,' and GSA-RL < 0.25 is 'Poor' group.

May 16, 2022

Arturo Chiti, MD, PhD
Editor-in-Chief
European Journal of Nuclear Medicine and Molecular Imaging

Dear Dr. Chiti:

I wish to submit an original research article for publication in the *European Journal of Nuclear Medicine and Molecular Imaging*, titled "Estimation of Post-therapeutic Liver Reserve Capacity Using ^{99m}Tc-GSA Scintigraphy Prior to Carbon-ion Radiotherapy for Liver Tumors." The paper was coauthored by Kana Yamazaki, Yoichi Mizutani, Hirokazu Makishima, Takashi Kaneko, Yoshiharu Isobe, Tamasa Terada, Kentaro Tamura, Etsuko Imabayashi, Toshiaki Tani, Masato Kobayashi, Masaru Wakatsuki, Hiroshi Tsuji, and Tatsuya Higashi.

This study aimed to determine the ability of ^{99m}Tc-GSA scintigraphy to accurately estimate the hepatic residual reserve capacity in 50 patients undergoing carbon-ion radiotherapy (CIRT) for liver tumors who underwent ^{99m}Tc-GSA scintigraphy before and after CIRT.
We believe that our study makes a significant contribution to the literature because we found no significant differences between the maximal removal rate of ^{99m}Tc-GSA (GSA-Rmax) of the estimated residual liver (GSA-RL) and the actual GSA-Rmax after CIRT, suggesting that ^{99m}Tc-GSA scintigraphy can accurately estimate liver reserves after CIRT.

Further, we believe that this paper will be of interest to the readership of your journal because we also divided our study population based on the degree of liver reserve and the Child-Pugh classification, demonstrating no significant differences between the maximal removal rate of ^{99m}Tc-GSA (GSA-Rmax) of the estimated residual liver (GSA-RL) and the actual GSA-Rmax after CIRT between subgroups. These findings suggest that ^{99m}Tc-GSA scintigraphy can accurately estimate liver reserves after CIRT regardless of the severity of illness.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Figures

Figure 1

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Figure 2

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Figure 3

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Figure 4

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Figure 5

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