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Evaluation of liver functionality after liver Stereotactic Body Radiation Therapy (SBRT) using blood tests and imaging examinations

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ABSTRACT

Background: Several studies have shown that liver function can be evaluated after hepatic Stereotactic Body Radiation Therapy (SBRT) using Galactosyl Human Serum Albumin (GSA) liver scintigraphy and Gd-EOB-DTPA-enhanced magnetic resonance imaging EOB. However, there are no reports investigating the relationship (including Chile-Pugh classification) between imaging and blood tests. Therefore, we investigated the changes that occur in the liver between before and after SBRT by combining imaging (GSA, Computed Tomography (CT), and MRI) with and without EOB enhancement) with blood tests that assess total liver function (Albumin-Bilirubin (ALBI) grade, ICG-R15). We decided to find a method that could assess liver reserve capacity locally and globally.

Methods: Of the 23 patients who underwent hepatic SBRT, 12 patients underwent GSA, MRI, and ICG-R15 testing before treatment, 1 month after treatment, and 3 months after treatment. All patients underwent imaging studies and blood tests at the beginning of treatment, 1 month after treatment, and 3 months after treatment ended. The evaluation items were as follows: 1) changes over time in Child–Pugh classification, ICG-R15, and ALBI values before and after SBRT; 2) changes over time in GSA count and ICG; and 3) selection of the optimal sequence for recognizing radiation hepatitis on MRI.

Results: The ICG values were 14.4 before RT, 17.1 after 1 month, and 17.6 after 3 months. ICG worsened after 1 month of treatment, but was similar after 3 months. ALBI values were −2.61 before RT, −2.67 after 1 month, and −2.71 after 3 months. ALBI worsened slightly over time.

Conclusion: Regarding the ICG-R15, there was an average worsening of 2.8 after 1 month of treatment compared with before SBRT, but only of 0.5 between 1 month and 3 months after SBRT. Therefore, evaluation using ICG-R15 after SBRT after 1 month alone may be sufficient.

Clinical trial registration: UMIN000035026

Keywords: hepatocellular carcinoma, ICG-R15, GSA liver scintigraphy, child-pugh classification, Gd-EOB-DTPA-enhanced MRI

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INTRODUCTION

Hepatocellular Carcinoma (HCC) is a leading cause of cancer-related death worldwide [1]. HCC has a high recurrence rate, rendering its treatment modalities and the assessment of liver function after therapy of significant interest to the medical community [2]. Currently, although there are many treatment methods for hepatocellular carcinoma, radiation therapy, surgery, and radiofrequency ablation are among the treatments that are used locally to treat this cancer [3-5].

Radiation-Induced Liver Disease (RILD) determines the liver tolerance dose of radiotherapy for liver cancer. RILD is a radiation liver injury characterized by fibrous occlusion of the small hepatic veins caused by radiation, resulting in congestion and hepatocellular depletion, and presenting within 3 months of radiotherapy [3, 4]. If these changes occur over a wide area, they lead to liver failure; however, if they occur only partially, they merely leave atrophic scars in that part of the organ, and liver failure can be avoided.

Previously, it was believed that the maximum tolerable radiation dose to the liver was about 30 Gy. This guideline was based on past reports of whole-liver irradiation, and it was considered impossible to administer radical doses. However, recent research revealed that, for Stereotactic Body Radiation Therapy (SBRT), the tolerable dose is higher, especially in the case of partial liver irradiation.

SBRT is a computer-controlled treatment that concentrates doses from multiple directions. The success of this treatment has led to its application not only to the brain, but also to tumors of the body, such as those of the lung. However, because SBRT emits beams from multiple directions, it also damages the normal liver tissue that surrounds the tumor. Theoretically, it is considered a local treatment for liver cancer, similar to liver resection. Therefore, it can be used as a pretreatment evaluation method for SBRT, in addition to the preoperative Indocyanine Green Retention test 15 minutes (ICG-R15) and Galactosyl Human Serum Albumin (GSA) scintigraphy [6-13]. In the case of liver resection, deterioration of liver function is observed at the time of surgery using blood tests (ALBI, GSA, and ICG-R15). However, in the case of SBRT, post-treatment Computed Tomography (CT) cannot measure local functional deterioration of the liver. This is because the Hounsfield units are similar in non-enhanced CT for both normal and functionally impaired partial livers.

However, it has been reported that decreased accumulation of GSA by radiation therapy and abnormal signals can be detected by Magnetic Resonance Imaging (MRI) [14-17].

Functional imaging is useful for planning the second SBRT or liver resection for new hepatocellular carcinoma [6-10]. At present, there are many uncertainties in the planning of SBRT of the liver based on GSA and MRI alone. The goal of this study was to examine the relationship between blood tests (ALBI and ICG-R15) measuring total liver function pre and post SBRT in liver cancer and GSA images reflecting functional images (CT and MRI with and without EOB enhancement).

MATERIALS AND METHODS

In this study, we assessed the following:

- Changes over time in Child-Pugh classification, ICG-R15, and ALBI values before and after SBRT (overall liver evaluation);
- The correlation between the changes in GSA count and ICG-R15 over time (correlation); and
- The optimal MRI sequence for recognizing radiation hepatitis.

Patients

This study was approved by the Institutional Review Board, and the national registration number is UMIN000035026. Of the 23 patients who underwent liver SBRT at our hospital between 2019 and 2022, 11 received only imaging examinations (GSA, CT, and MRI) and blood tests before treatment, 1 month after treatment, and 3 months after treatment; and 12 received ALBI and ICG-R15 in addition to the imaging. Moreover, 10 patients of the 12 patients had to undergo Trans Arterial Chemoembolization (TACE) within 1 month before SBRT. At our hospital, we first perform TACE on HCC, and then perform SBRT on areas where embolization was not possible. The patient backgrounds are shown in table 1.

Tab. 1. Baseline patient characteristics

Characteristics	
Avg. age in years at SBRT (range)	71 (68-82)
Sex	
Male	9
Female	3
Cirrhosis	
Yes	11
No	1
No. of prior liver therapies (range)	1 (0-2)
TACE (TAE)	10
Liver Disease	
HCV	10
Other	2
Liver Dose	
44 Gy/4 fractions	8
40 Gy/4 fractions	4

TACE, Trans catheter arterial chemoembolization; TAE, trans catheter embolization

Imaging

An Elekta Synergy Linear Accelerator (Elekta AB, Stockholm, Sweden) with coplanar volume-modulated arc therapy was used for all patients. This approach delivers personalized, safe, efficient, and high-quality radiation with enhanced dose conformance appropriate to the tumor's size, shape, and pathology. Each patient was immobilized in a stereotaxic frame and underwent a 4-dimensional CT scan with 2 mm sections. Scanning was performed using an external respiration monitoring system (Apex Medical, Inc., Tokyo, Japan) during breath-holding. Respiratory phase data were transferred to a treatment planning system (MOSAIQ; Elekta AB). For some patients, fiducial markers were not used.

Plain CT (16-row multidetector CT; Alexion, Toshiba Medical System; Otawara, Japan) and MRI (MRI, Achieva; Philips Medical Systems; Best, Netherlands) were used to investigate the extent of tumor development. The CT parameters were as follows: slice thickness =2 mm, field of view =50 cm × 50 cm, and settings of 150 mA and 120 kV. The T2-weighted MRI (T2-WI) parameters were as follows: fast spin-echo; repetition time (TR)/echo time (TE) in ms =433/80; the number of Sample Signals Averaged (NSA) =1; and matrix =256 × 204. The DWI parameters were: EPI; TR/TE in ms=1200/65; NSA=5; matrix =80 × 142; and B-value=1000. The signal intensity in the gastric wall on DWI was assessed immediately after RT (pre), 1 month after RT, and 3 months after RT. The Gd-EOB-DTPA-enhanced MRI (EOB) parameters were as follows: gradient echo, TR/TE1/TE2 in ms=5.1/1.82/3.4, NSA =1, ACQ matrix =1.45 × 1.85, and FA=10.

Radiotherapy planning

The small intestine (including the duodenum), stomach, pancreas, kidneys, and spinal cord were set as OARs. The GTV was the entire tumor; the Clinical Tumor Volume (CTV) added a 2 mm margin to the GTV. The Planning Target Volume (PTV) was the same as the CTV. We treat tumors smaller than 2 cm (n=9) with 40 Gy/4fx, and tumors larger than 2 cm (n=3) with 44 Gy/4fx. However, if the pre-treatment CP classification or ICG-R15 re-

sults are poor, the prescribed dose may not be met in all cases. The treatment plan was carried out by a medical physicist with 15 years of experience and was approved by a radiation oncologist.

Statistical analyses

Wilcoxon signed-rank test for statistical analyses of the recorded data were performed using the Excel statistical software package (Excel-statistics 2015; Social Survey Research Information Co., Ltd., Tokyo, Japan). A p-value of <0.05 was regarded as a statistically significant difference.

RESULTS

Table 2, figure 1, and figure 2 depict the changes in liver function over time in patients who underwent SBRT.

- In the Child-Pugh classification, the median deteriorated from 6 to 7 (Table 2).
- The ICG-R15 values were 14.4 before RT, 17.1 after 1 month, and 17.6 after 3 months, which indicated a worsening at 1 month, but a similar result after 3 months (Figure 1).
- The ALBI values were -2.61 before RT, -2.67 after 1 month, and -2.71 after 3 months. ALBl worsened slightly over time (Figure 2).

Tab. 2. Summary of the outcomes in patients who underwent SBRT

Outcome	Value	(Range)
Baseline CP	6	(6-7)
CP 3 months after treatment	7	(6-7)
CP Change (Baseline to 3 Months After Treatment)		
≦ 0	10	-
1+	2	-
2+	0	-
Baseline ICG-R15 score	14.4	(3.0-39.4)
ICG-R15 score 1 month after treatment	17.1	(5.0-43.0)
ICG-R15 score 3 months after treatment	17.6	(7.0-46.0)
ICG-R15 score change (baseline to 3 months after treatment)	-	-
ICG-R15 score change (baseline to 3 months after treatment) >1	-	-
Baseline ALBI score	-2.61	(-1.97 to -3.46)
ALBI score 1 month after treatment	-2.67	(-1.96 to -3.33)
ALBI score 3 months after treatment	-2.71	(-1.92 to -3.44)
ALBI score change (baseline to 3 months after treatment)	-	-
ALBI score change (baseline to 3 months after treatment) >1	-	-

CP; Child-Pugh classification, ICG-R15: Indocyanine Green Retention test (15 minutes)
ALBI; Albumin-Bilirubin (ALBI) grade
ALBI score= (log10 bilirubin (μmol/L) × 0.66) + (albumin(g/L) × -0.085)
Grade 1: ≤ -2.60; Grade 2: <-2.60 to ≤ -1.39; Grade 3: >-1.39

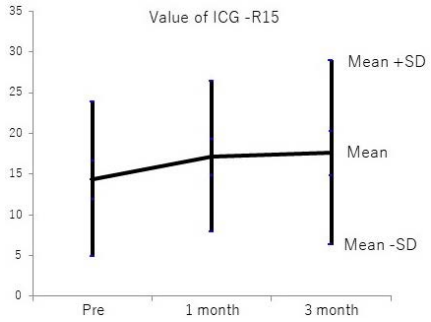

Fig. 1. Changes in ICG before radiation therapy (Pre), 1 month after radiation therapy (1 month), and 3 months after radiation therapy (3 months)

The mean ICG-R15 was 14.4 before radiotherapy, 17.1 1 month after the treatment, and 17.6 3 months after the treatment.

Although there was no significant difference between the values obtained before radiotherapy and those obtained at 1 month after radiotherapy (p=0.071), deterioration of liver function was observed.

Although there was no significant difference between the values obtained before radiotherapy and those obtained at 3 months after radiotherapy (p=0.10), deterioration of liver function was observed.

There was no significant difference between the values obtained at 1 and 3 months after radiotherapy (p=0.81).

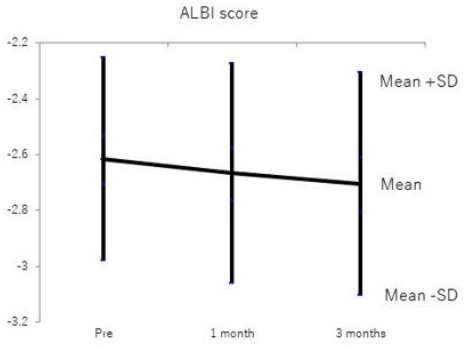

Fig. 2. Changes in ALBI before radiation therapy (Pre), 1 month after radiation therapy (1 month), and 3 months after radiation therapy (3 months). The mean ALBI was -2.61 before radiotherapy, -2.67 at 1 month after the treatment, and -2.71 at 3 months after the treatment. However, no significant difference was observed among the three groups

Changes over time in the imaging of the site at which SBRT was performed

Figure 3 shows the changes over time in CT and MRI between before and after the treatment. After SBRT, contrast-enhanced CT showed focal enhancement in the arterial phase and low intensity on Gd-EOB-DTPA-enhanced MRI (EOB). Regarding EOB, the low intensity persisted for a long time after treatment; however, in many cases, the hyperintense areas disappeared on contrast-enhanced CT.

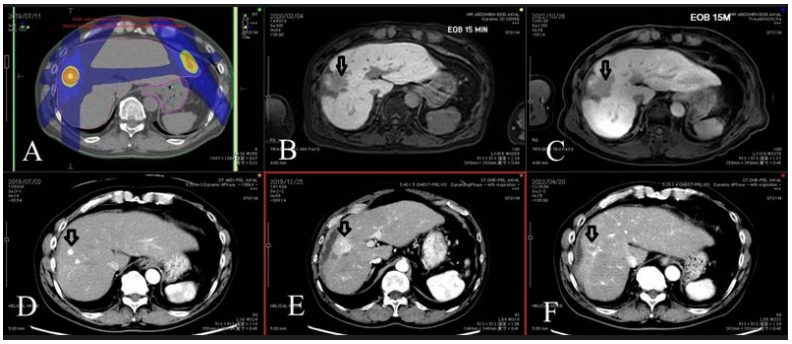

Fig. 3. Changes in hepatic SBRT over time (Arrow: tumor A: SBRT for hepatocellular carcinoma: two (1 cm in size in the left lobe, 2 cm in size in the right lobe) yellow areas irradiated with 40 Gy/4 fx. The areas in blue received 50% of the prescribed dose. B: EOB image acquired at 8 months after SBRT: a decrease in signal intensity was observed consistent with the irradiated area. C: EOB image acquired at 3 years and 4 months after SBRT: the hypo intensity in the irradiated area persisted. D: Contrast-enhanced CT before radiotherapy. Persistent lipiodol by TACE. E, at 5 months after SBRT, contrast-enhanced CT showed deep staining in the irradiated area. F: at 2 years and 3 months after SBRT, loss of lip iodol and contrast enhancement was observed)

Abnormal signals were observed on MRI, consistent with the accumulation defect sites on GSA scintigraphy (Figure 4). However, the most useful sequence among the four sequences was EOB (15 min), followed by fat suppression-T2-weighted imaging (Table 3).

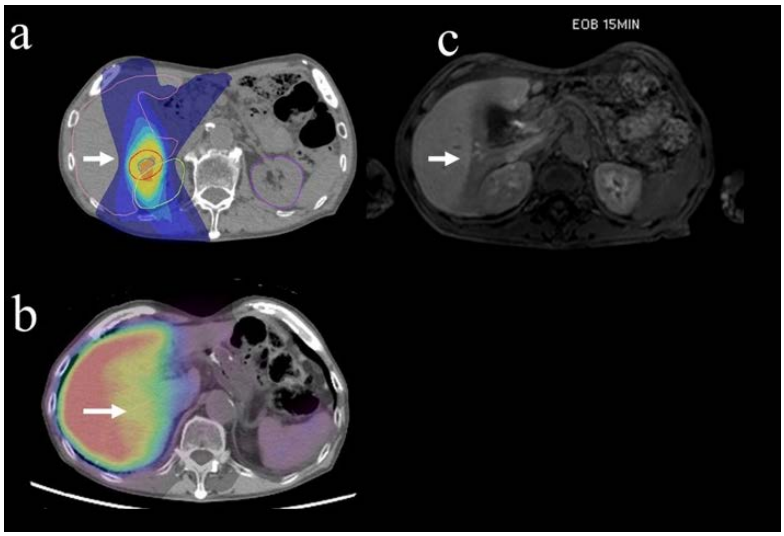

Fig. 4. A, SBRT for hepatocellular carcinoma: 1 cm in size in the left lobe. Yellow areas irradiated with 40 Gy/4 fx. The areas in blue received 50% of the prescribed dose. White allows; irradiated area. B, 99mTc-Galactosyl Human Serum Albumin (99mTc-GSA) scintigraphy; Three months after SBRT, there is a decrease in counts consistent with areas irradiated with GSA. C, MR image (EOB); A decrease in signal is observed consistent with the radiation-irradiated sites

Tab. 3. MRI evaluation

	Observer 1		
	Contrast	**Borderline**	**Area**
T1-WI	3.5	3.25	3.5
T2-WI	3	2.75	3.5
FS-T2-WI	3	2.25	3
EOB	4.25	4	4
	Observer 2		
	Contrast	**Borderline**	**Area**
T1-WI	3.8	3	3.4
T2-WI	2.2	2.8	4
FS-T2-WI	3.2	3.2	4
EOB	3.8	3	3.6

Two medical physicists evaluated the four imaging sequences shown below, with a score of 1 indicating the worst imaging quality and a score of 5 indicating the best imaging quality; a score of 3 indicated a level of imaging that can be recognized by an average radiotherapist or medical physicist, a score of 2 represented a middle value between 1 and 3, and 4 represented a middle value between 3 and 5.

Contrast is the difference in visual signal between the lesion and normal tissue.

Borderline is the clarity of the distinction between the lesion and normal tissue.

Area is the degree of recognition of the site with the lesion.

Correlations between GSA scintigraphy and blood tests

We assessed the correlation between imaging examinations (GSA) and blood tests (ICG-R15 and ALBI) reflecting liver function. There was no correlation between GSA counts and ICG-R15 values (Figures 5-19).

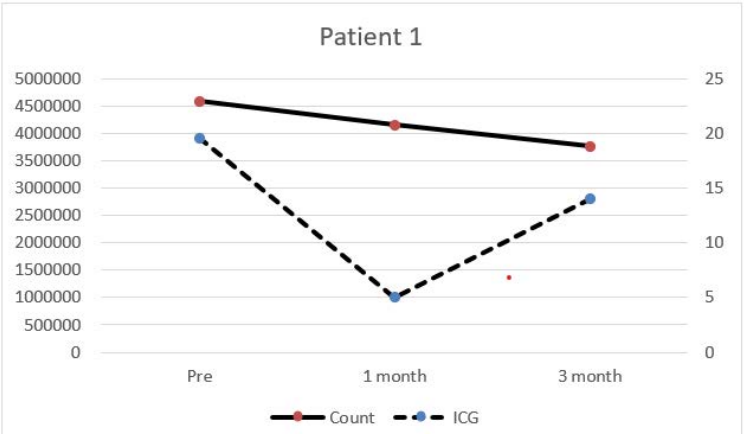

Fig. 5. Patient 1- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

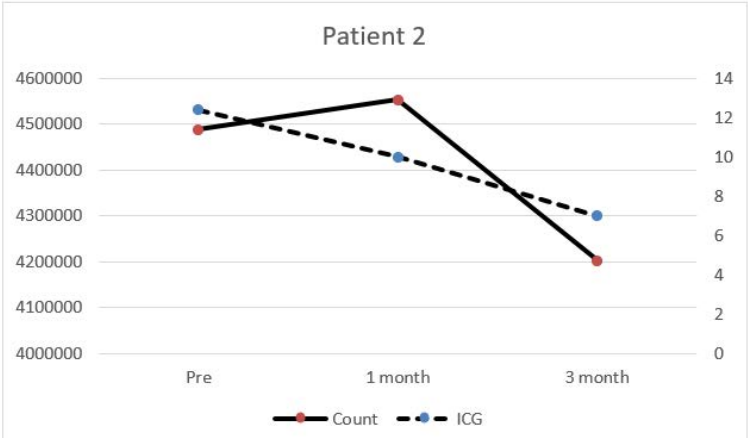

Fig. 6. Patient 2- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

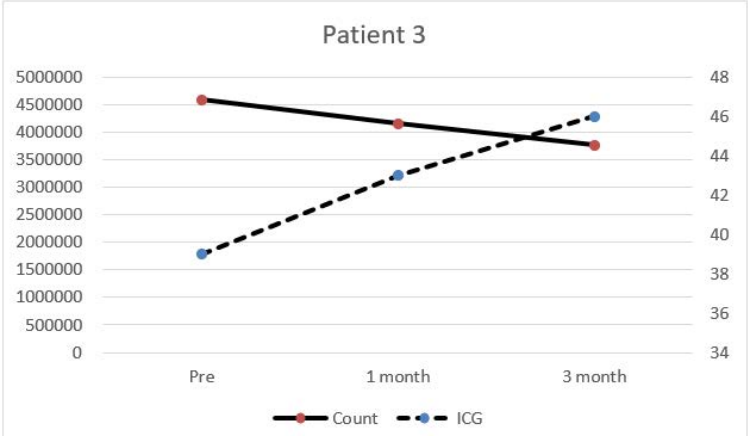

Fig. 7. Patient 3- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

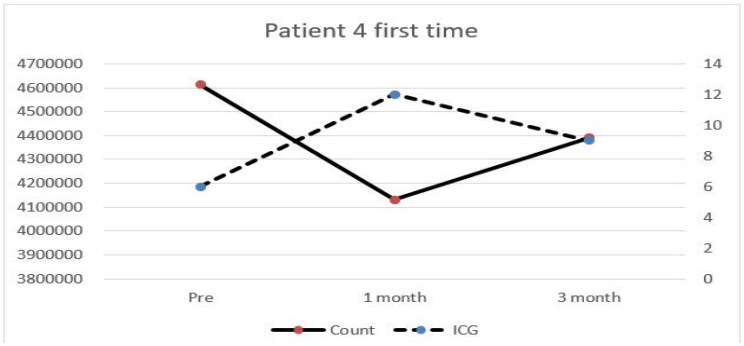

Fig. 8. Patient 4 first time- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

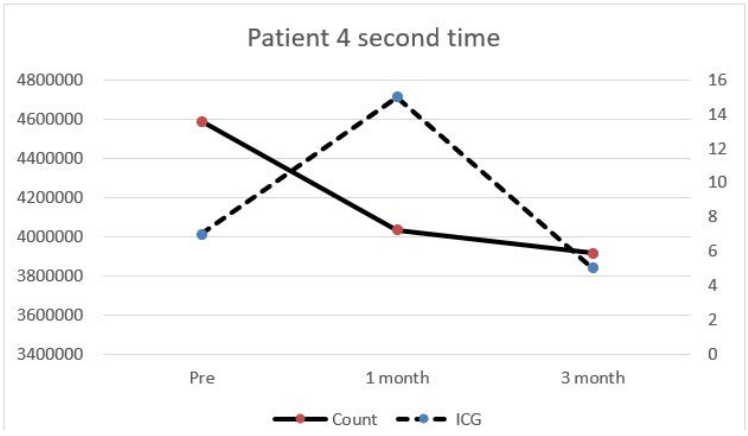

Fig. 9. Patient 4 second time- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

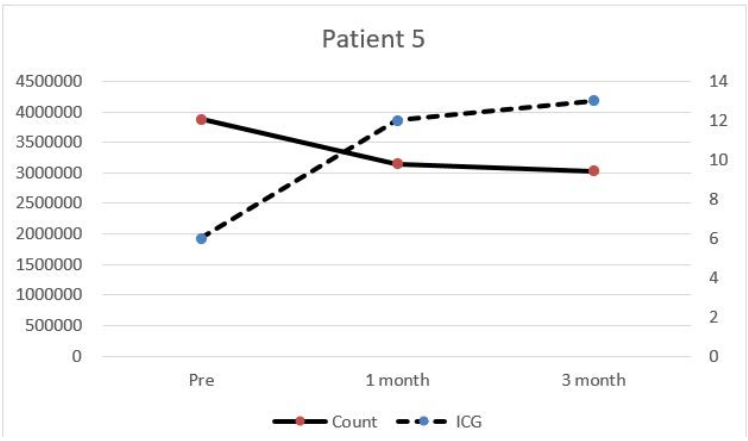

Fig. 10. Patient 5- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

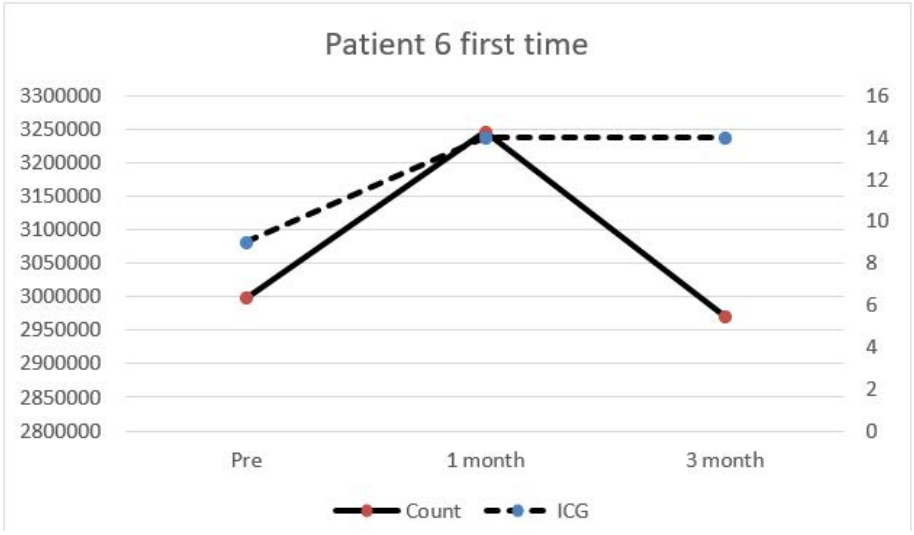

Fig. 11. Patient 6 first time- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

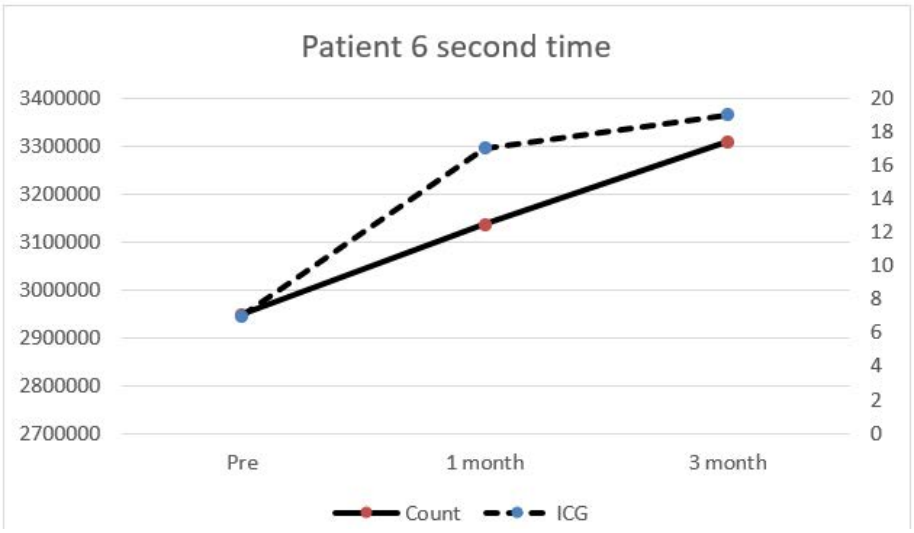

Fig. 12. Patient 6 second time- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

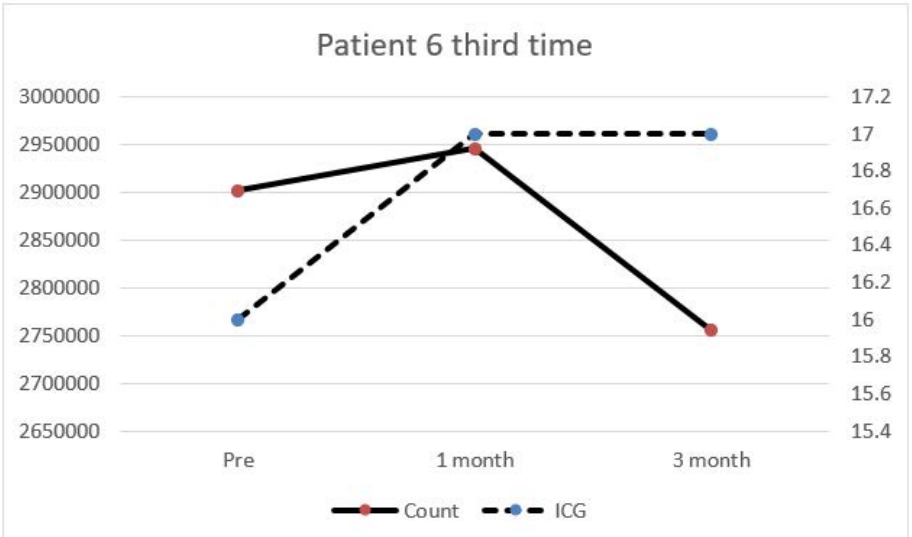

Fig. 13. Patient 6 third time- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

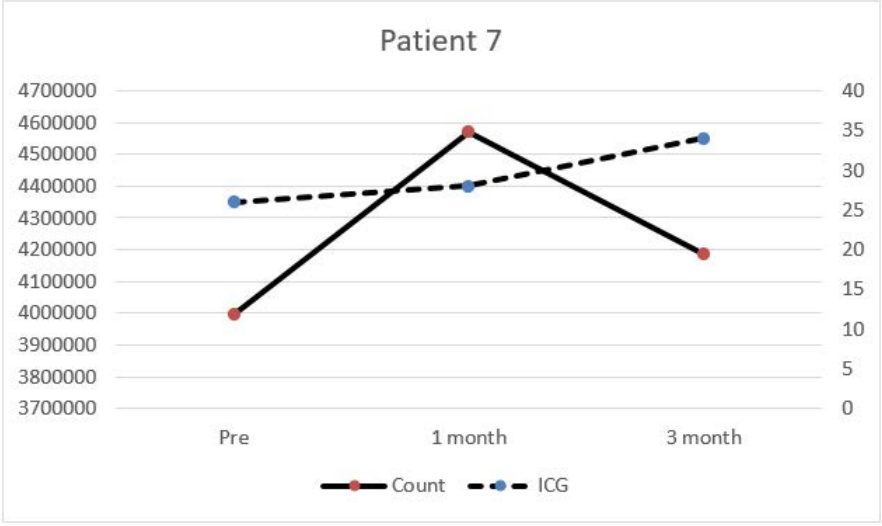

Fig. 14. Patient 7- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

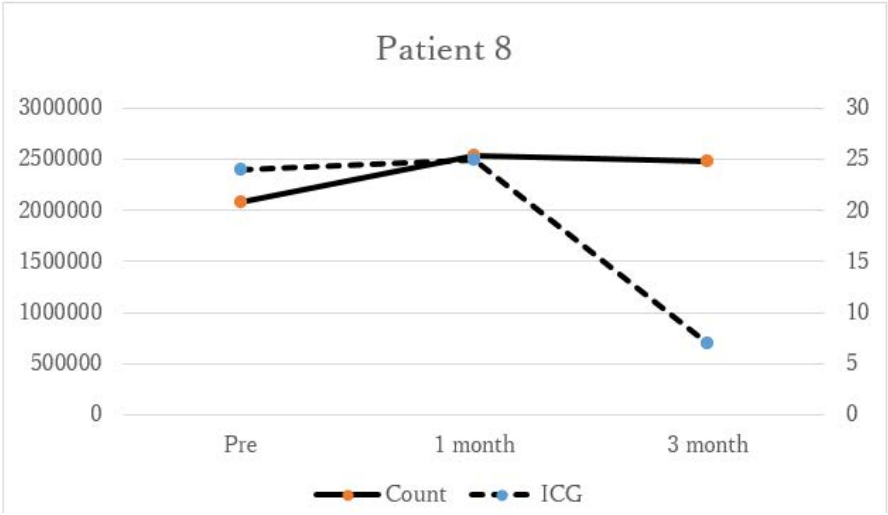

Fig. 15. Patient 8- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

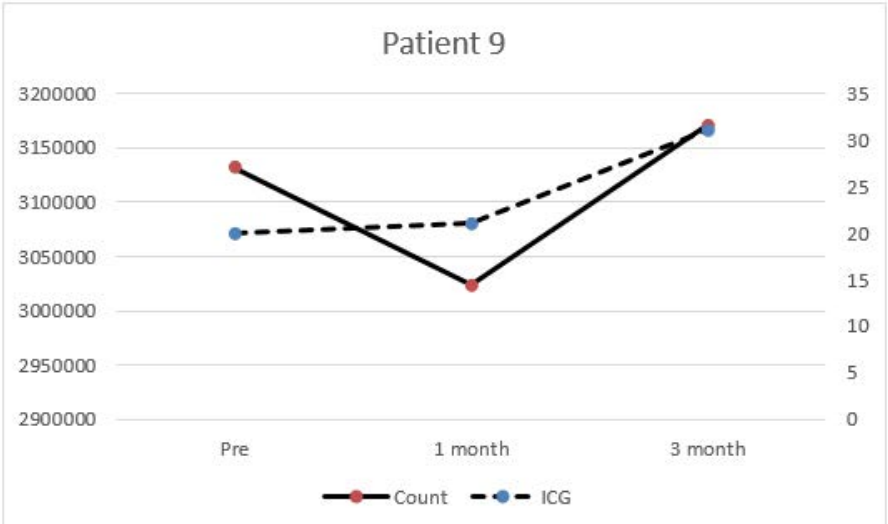

Fig. 16. Patient 9- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

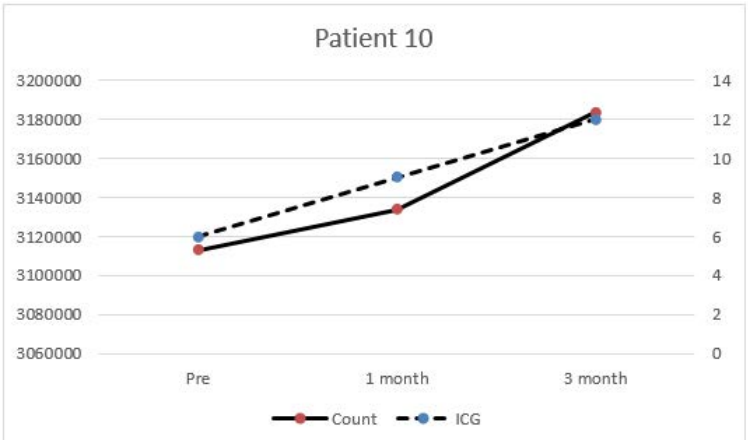

Fig. 17. Patient 10- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

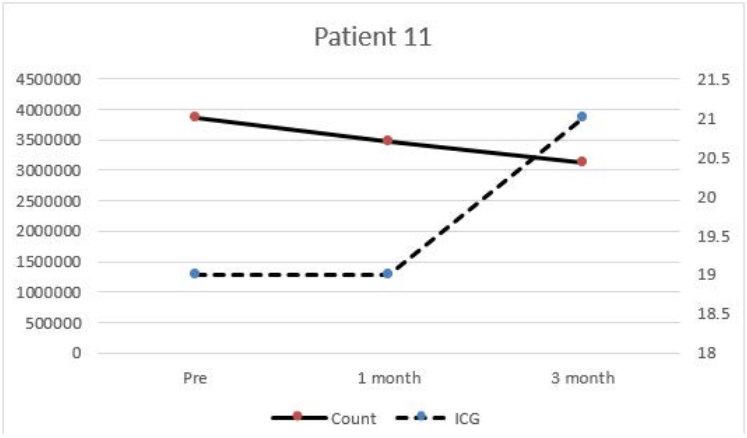

Fig. 18. Patient 11- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

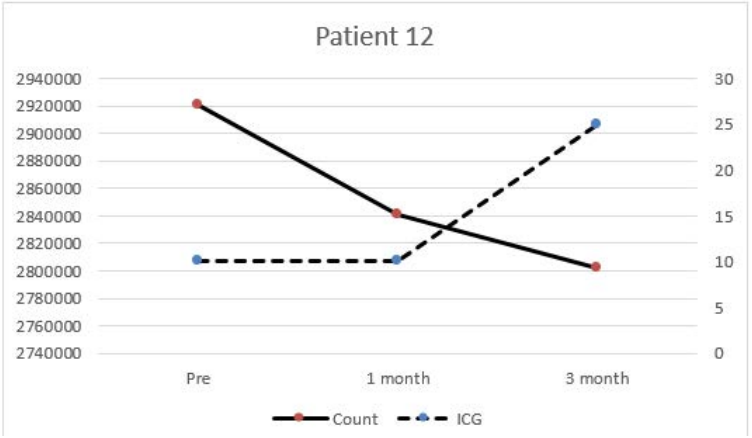

Fig. 19. Patient 12- Results of the indocyanine green retention test (ICG-R15) and counts on 99mTc-Galactosyl human Serum Albumin (99mTc-GSA) scintigraphy (Count)

No correlation was observed between tumor size and changes in ICG-R15. However, because large tumors may have had poor CP classification and ICG-R15 test results from the beginning, one case in which it was difficult to prescribe a sufficient radiation dose resulted in a PR.

DISCUSSION

Blood tests and time course of liver reserve after SBRT

The goal in this study was to determine the method that can evaluate the future liver reserve capacity locally and globally. From this investigation we observed that the ICG-R15 blood test worsened by an average of 2.8 at 1 month of treatment, but changed by only 0.5 between 1 month and 3 months after the end of treatment. The effects of radiotherapy usually become apparent after 1 month-3 months. Because the liver has a high regenerative capacity, the effects of radiation may already have disappeared after 3 months. Specifically, although Patients 4 and 6 in the present study underwent SBRT more than once, there was almost no difference between the ICG values at 3 months after the first treatment and those detected after the second treatment. It is possible

that a phenomenon similar to the enlargement of the liver after liver resection may occur. Twelve patients were included in this analysis, and no statistically significant difference was observed using the Wilcoxon signed-rank test. It is expected that differences will become apparent if the number of cases is increased.

The standard deviation was large because the pretreatment ICG values were inconsistent. In the future, it would be worthwhile to increase the number of cases and divide the ICG before treatment into three groups (e.g., 0-10, 10-20, and 20-30) and observe the changes. Similarly, changes in the signal delivered to the liver depending on the size (mm) of the tumor and the range/dose of the irradiation are significant.

We believe that the ALBI score is also very useful for evaluation after SBRT. On average, scores decrease slowly after irradiation. Although we only examined the patient up to 3 months later, the GSA scintigram defect is clearly visible after 3 months. This means that the local normal liver is dying, and it may be better to measure the ALBI after 3 months.

We treat tumors smaller than 2 cm (n=9) with 40 Gy/4fx, and tumors larger than 2 cm (n=3) with 44 Gy/4fx. When evaluating the treatment effect after 3 months, CR was achieved in all cases (n=9) for tumors smaller than 2 cm. The response rate for tumors larger than 2 cm was CR in 2 cases and PR in 1 case. We believe that the reason why we were able to control with 40 Gy to 44 Gy was because 10 patients out of 12 patients received TACE before SBRT.

In regions that received low-dose irradiation, GSA accumulation and MRI abnormal signals become gradations, thus rendering boundaries unclear. Because the liver has a high regenerative capacity, its regeneration can be expected if there is little damage. The low-dose region of this gradation may be a reproducible part. In this way, the effects of radiotherapy change over time, and the responses of organs change accordingly.

In recent years, the number of reports on the usefulness of re-irradiation has increased. We believe that a variety of modalities can be used to plan re-irradiation, as determined based on liver imaging and blood tests [6, 8, 10, 11].

Imaging

SBRT is a computer-controlled treatment that concentrates doses from multiple directions. The success of this treatment has led to its application not only to the brain, but also to tumors of the body, such as those of the lung. SBRT is also theoretically a local therapy; i.e., it is the same as RFA (Radiofrequency Ablation), TACE, and surgery, and is a treatment that damages the normal liver, to some extent. This is why pretreatment ICG-R15 is necessary for surgical resection, and has been found to be useful for SBRT. ICG-R15 detects the deterioration of liver function immediately after surgery, whereas liver damage caused by radiation becomes apparent later. However, RILD appears within 3 months, and, conversely, liver function is thought to plateau after 3 months [3, 4].

Therefore, the following changes were observed on imaging in this study as changes pre and post SBRT:

- GSA: A decrease in counts was observed consistent with the irradiated site.
- Contrast-enhanced MRI (comparison of the four sequences): A decrease in signal was observed in EOB imaging consistent with the irradiated area. EOB images were the most useful. However, FS-T2WI was useful when contrast imaging was not possible.
- Contrast-enhanced CT: Contrast-enhanced effects in the hepatic arterial phase were observed in some cases, consistent with the irradiated area; however, the darkened area disappeared over time (the duration of this effect is unknown).

GSA indicates a decrease in normal hepatocyte counts, and EOB similarly reflects a decrease in normal hepatocyte counts. Although the mechanism of hepatic arterial phase enhancement in contrast-enhanced CT is unknown, the follow-up of hepatocellular carcinoma is often performed using MRI, because this modality is more sensitive than CT [4, 5, 13-16]. Nevertheless, because there are patients who cannot undergo MRI, it is necessary to discover the mechanism of contrast-enhanced CT in the future.

LIMITATIONS

We could not perform evaluations in all patients, because contrast-enhanced CT was not used in all patients. Contrast-enhanced CT may have an early contrast-enhancing effect, which, if combined with the MRI signal, will allow the determination of further post-treatment changes.

To date, although the usefulness of functional imaging (GSA and MRI) to assess radiation hepatitis has been reported, there are no studies including blood tests. HCC often recurs, and SBRT is used more frequently than TACE and RFA. It is desirable to evaluate the changes in imaging after each treatment in greater detail in a larger number of patients. Because the small number of cases in each study, it is necessary to consider increasing the number of cases in future studies for better elucidation of the potential connection between changes in GSA counts and blood test results (ICG-R15, ALBI).

CONCLUSION

ICG-R15 assessment at 1 month after SBRT may be a sufficient blood test to determine post-SBRT liver function after treatment. However, the changes in ICG-R15 levels were most drastic at only after 1 month after the treatment ended. On the other hand, ALBI score is gradually decreased. MRI assessment of radiation hepatitis was clearest at EOB. Contrast-enhanced CT revealed a contrast-enhancing effect in the early phase, matching the site of post-treatment radiation hepatitis in some cases, but disappeared after more than 1 year in some cases. Abnormal signals in EOB were detectable at more than 1 year after treatment.

LIST OF ABBREVIATIONS

ALBI-Albumin-Bilirubin (ALBI) grade

CT-Computed Tomography

EOB-Gd-EOB-DTPA-Enhanced Magnetic Resonance Imaging

GSA-Galactosyl Human Serum Albumin

Gy-Gray (radiation unit of absorbed dose)

HCC-Hepatocellular Carcinoma

ICG-R15-Indocyanine Green Retention test 15 minutes

MRI-Magnetic Resonance Imaging

RFA-Radiofrequency Ablation

RILD-Radiation-Induced Liver Disease

SBRT-Stereotactic body radiation therapy

DECLARATIONS

A statement to confirm that all methods were carried out in accordance with relevant guidelines and regulations (Declaration of Helsinki).

Ethics approval and consent to participate

- This study was approved by the Institutional Review Board (Asahi University Hospital, Medical Ethics Review Committee), and the national registration number is UMIN000035026
- Written informed consent was obtained from all patients and their legal guardians.

Consent to publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

- Osamu Tanaka- Conduct entire study
- Takuya Taniguchi- Conduct entire study
- Shuto Nakaya- Data collection
- Kousei Adachi- Data collection
- Takuji Kiryu- Image analysis
- Chiyoko Makita- Review and literatures collection
- Masayuki Matsuo- Review
- All the authors have read and approved the study

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Conflict of interest

None

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