

Original paper

## Evaluation of patients who underwent percutaneous transhepatic portal vein embolisation by Tc-99m GSA scintigraphy

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### Abstract

**Purpose:** To analyse the correlation between the fold change in residual liver volume (RLV) and residual liver uptake at 15 (RLU15) before and after percutaneous transhepatic portal vein embolisation (PTPE).

**Material and methods:** Between August 2010 and December 2016, 20 patients who underwent PTPE were retrospectively selected. Before and three weeks after PTPE, contrast-enhanced computed tomography (CECT) and Tc-99m GSA scintigraphy were performed to analyse the fold changes in RLV and RLU15, respectively, as well as their correlation.

**Results:** After PTPE, a significant increase was observed in the RLV (before:  $464 \pm 99$  ml; after:  $573 \pm 118$  ml,  $p = 0.004$ ) and the RLU15 (before:  $11.0 \pm 2.9\%$ ; after:  $17.7 \pm 3.8\%$ ,  $p = 5 \times 10^{-7}$ ). The fold increase of RLV and RLU15 in all patients was  $1.25 \pm 0.15$  and  $1.66 \pm 0.33$ , respectively. No significant correlation was observed in the fold increase in both RLV and RLU15 ( $r = 0.14$ ,  $p = 0.66$ ). In patients no. 3 and 9, who were outliers, the increase in RLV was minimal and RLU15 increased greatly, and these 2 patients underwent radical hepatectomy after PTPE.

**Conclusions:** No correlation was observed between the fold increase in RLV and RLU15 before and after PTPE. In order to accurately evaluate the residual liver function, it should be considered necessary to evaluate not only by morphological CECT volumetry, but also by functional outcome of Tc-99m GSA scintigraphy. Residual liver volume may not necessarily reflect RLF. It may be possible to improve the radical resection rate by detecting the potential increase of RLF with RLU15 of Tc-99m GSA scintigraphy.

**Key words:** PTPE, Tc-99m GSA scintigraphy, LU15, future remnant liver, sinusoidal obstructive syndrome, chemotherapy-associated steatohepatitis.

### Introduction

Recently, advances in medical technology have led to active and aggressive major hepatectomies. However, hepatic failure is still a fatal complication and is seen in 2.5% to 12.9% of patients [1-3]. Preoperative percutaneous transhepatic portal vein embolisation (PTPE) is known as an effective means of preventing hepatic failure by functional

residual liver hypertrophy and is often performed. However, a variety of hepatic injuries, such as liver cirrhosis, as well as post-systemic chemotherapy, greatly affect the outcomes of PTPE. Although morphological computed tomography (CT) volumetry has been widely used as an easy method of evaluation before and after PTPE, it is not suitable for accurately measuring functional residual liver volume.

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### Authors' contribution:

A Study design · B Data collection · C Statistical analysis · D Data interpretation · E Manuscript preparation · F Literature search · G Funds collection

To date, the usefulness of Tc-99m galactosyl human serum albumin (GSA) scintigraphy for more accurate evaluation of underlying liver diseases, such as cirrhosis [4,5], during both the preoperative [2,3,6] and peri-PTPE period [7,8], have been reported. A variety of radionuclide parameters can be used for Tc-99m GSA scintigraphy, depending on the institute. Residual liver uptake at 15 minutes (RLU15), which was reported by Koizumi *et al.*, is the cumulative residual liver accumulation rate of a GSA tracer 15 minutes after its injection, and it indicates residual liver function [9]. To safely perform hepatectomies, it has been reported that the RLU15 should theoretically [10] and clinically [2] be 13 or more. A co-author of the present manuscript has already reported the usefulness of using RLU15 to predict liver failure [2]; however, to date, there has been no evaluation of the effectiveness of PTPE using RLU15. We report herein a correlation between morphological residual liver volume (RLV) and

RLU15 before and after PTPE in 20 patients, and also compare the rate of increase in RLV and RLU15 between two groups, diagnosed and evaluated as having pathological cirrhosis vs. non-cirrhosis, and post-chemotherapy vs. non-chemotherapy.

## Material and methods

### Patient characteristics and underlying liver disease

Patient characteristics are listed in Table 1. Between August 2010 and December 2016, 30 patients underwent preoperative PTPE. Ten of them were excluded because data on either contrast-enhanced computed tomography (CECT) or Tc-99m GSA scintigraphy were missing, and therefore 20 patients (14 men and six women, median age: 72 years, range 42-78 years) were selected as subjects for the present study. Six patients were diagnosed as having

**Table 1.** Patient characteristics

Patient no.	Age (years)/Sex	Diagnosis	Embolised portal vein branch	Underlying liver disease		Interval to follow-up imaging from PTPE procedure (days)	
				Pathological cirrhosis and fibrotic grade	Chemotherapy, type (no. of cycles), and pathological findings	To CECT	To Tc-99m GSA scintigraphy
1	71/M	HCC	Right	No	No	22	22
2	77/M	MT	Right	No	No*	27	48
3	73/M	CC	Right	No	No	13	14
4	61/M	HCC	Right	Yes, 3	No	21	21
5	74/M	CC	Right	No	No	21	20
6	64/M	HCC	Right	Yes, 4	No	24	25
7	42/F	MT	Right	No	Yes, 0 (6), mild CASH	17	17
8	70/F	MT	Right	No	Yes, 0+1 (2), mild SOS	21	18
9	76/M	HCC	Right	No	No	25	29
10	49/M	MT	Right	No	Yes, 0 (6), moderate CASH	27	27
11	68/M	MT	Right	No	Yes, 0 (6), moderate SOS	18	17
12	72/M	CC	Right	No	No	18	20
13	72/F	CC	Right	Yes, 3	No	7	17
14	72/M	CC	Right	No	No	21	15
15	72/F	CC	Left + Ante	–	No	17	17
16	78/M	CC	Left + Ante	No	No	52	25
17	79/M	HCC	Left + Ante	–	No	23	23
18	75/F	CC	Right	–	No	25	25
19	73/M	HCC	Post + P4	No	No	28	28
20	77/F	MT	Right	No	Yes, 0 (4), moderate SOS	13	13
Median	72					21.0	20.5

HCC – hepatocellular carcinoma; CC – cholangiocarcinoma; MT – metastasis from colorectal cancer; Ante – Anterior; Post – Posterior; P4 – portal vein into segment 4; CECT – contrast-enhanced computed tomography; PTPE – percutaneous transhepatic portal vein embolization; 0 – oxaliplatin-based chemotherapy; 0+1 – irinotecan-based chemotherapy followed by oxaliplatin-based chemotherapy; CASH – chemotherapy-associated steatohepatitis; SOS – sinusoidal obstructive syndrome

\*Heterochronous metastasis was detected and the patient did not receive systemic chemotherapy before PTPE. The other patients with MT all had homochronous metastasis and received systemic chemotherapy before PTPE.

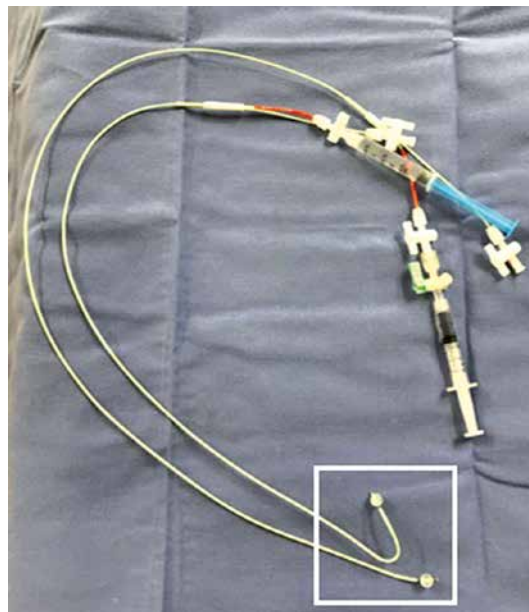
hepatocellular carcinoma (HCC), six were diagnosed as having cholangiocarcinoma, and eight were diagnosed as having metastases from colorectal cancer (MT). Five out of six MT patients underwent systemic chemotherapy before PTPE.

### Interventional radiology devices and embolic agents

A 6-Fr long sheath and a J-curved and loop-shaped 5.5-Fr balloon catheter (Selecon MP catheter II, Terumo, Tokyo, Japan) were used in every procedure (Figure 1). Absolute ethanol (Absolute Ethanol™, FUSO Pharmaceutical Industries, Ltd., Osaka, Japan) was used as an embolic material in all cases and was also used for the ethanol-lipiodol mixture, which contained 2 ml of ethiodised oil (Lipiodol™, Guerbet Japan, Tokyo, Japan) and 8 ml of ethanol. The maximum dose of ethanol was decided to be less than 0.2 ml/kg of body weight, which was considered a safe dose. Gelatine sponges (GS, Serescue™ Nippon Kayaku Co., Ltd., Tokyo, Japan) were used for approach tract embolisation.

### PTPE procedure

A routine method by which we perform embolisation of the portal vein branch of the right hepatic lobe is described below, which is similar to the PTPE outline using absolute ethanol reported by Satake *et al.* [11]. In all cases, the percutaneous transhepatic and ipsilateral approach was used. The portal vein of segment no. 5 (P5) or P6 was usually punctured with a 21-G needle under ultrasound guidance. A 6-Fr long sheath and a 5.5-Fr loop-shaped balloon catheter was coaxially inserted and advanced to the main trunk of the portal vein. Digital subtraction angiography (DSA) was performed, and whole portal vein images were confirmed (Figure 2A). A loop was made at the tip of the balloon catheter within the splenic vein. The tip of the catheter was inserted into the anterior branch of the portal vein and the balloon was inflated at the beginning of the anterior branch. Selective DSA was performed from this point (Figure 2B), which was also a test injection. The ethanol and lipiodol mixture was carefully and slowly injected to avoid backflow, particularly back into the left portal branch (Figure 2C). The dose of the embolic material was set at approximately the same as that of the test injection. Next, a 10-minute wait was necessary, until the endothelium of the portal vein became damaged and an embolic effect appeared. The balloon catheter was removed, DSA was performed from the sheath, and we confirmed that the embolised anterior branch of the portal vein was not displayed on the image. Next, the other J-curved balloon catheter was inserted into the portal vein trunk, and the tip of the balloon was placed on the beginning of the posterior branch as distally as possible because this makes portal vein reconstruction easier for the surgeon during hepatectomy. Selective DSA (test injection)



**Figure 1.** Photographs of the balloon catheters that were used. The size of the catheters was 5.5 Fr, and 2 types of tips, namely J-shaped and loop-shaped, were used

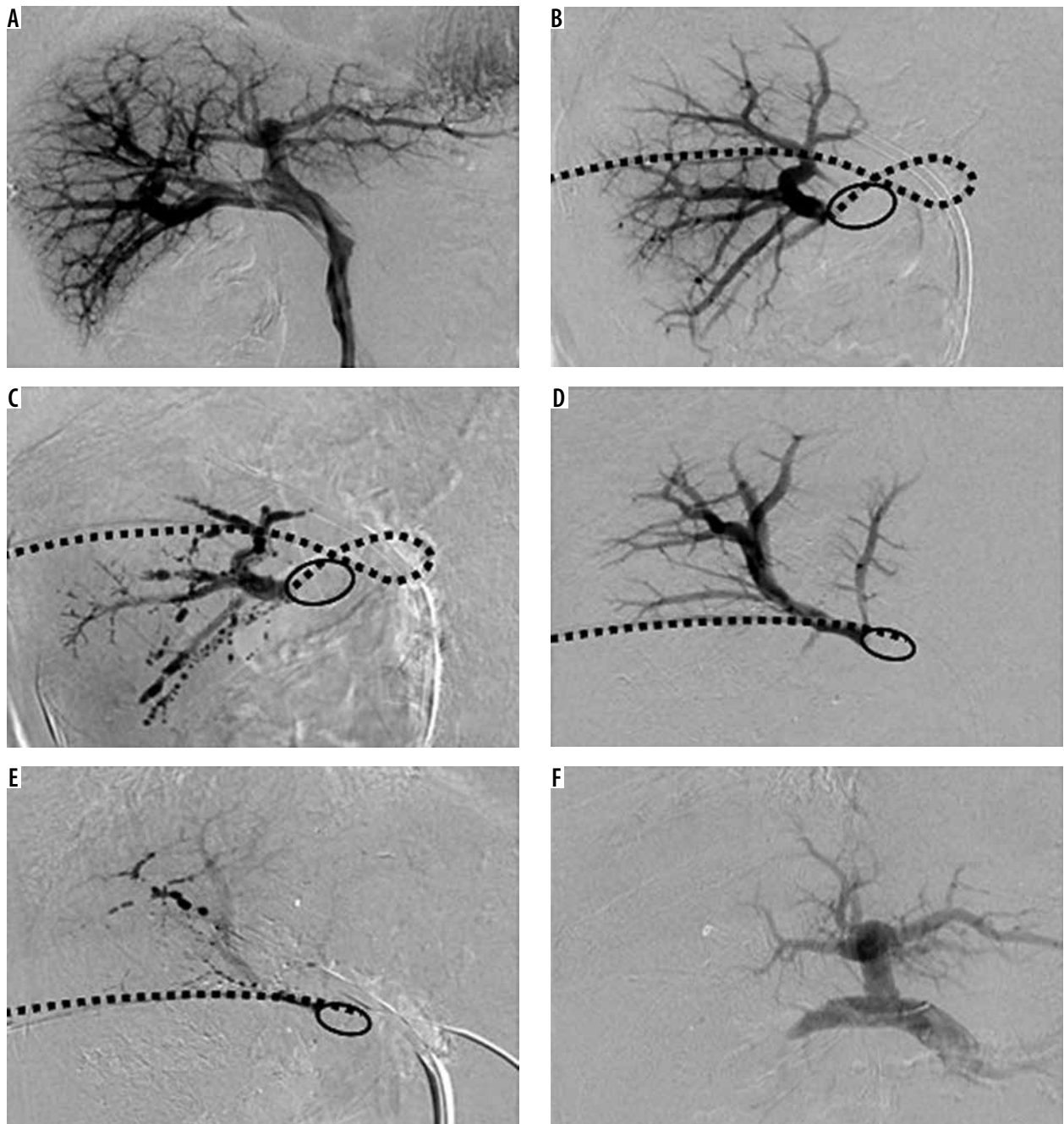
was performed during balloon occlusion (Figure 2D). The ethanol-lipiodol mixture was injected from the sheath at the same dose as the test injection (Figure 2E). Finally, access tract embolisation was necessary to prevent bleeding from the puncture site (Figure 3). A GS was cut into equal-sized thin strips, which were rounded into a cylindrical shape (Figure 3C). A second sheath was prepared and cut at approximately 5 cm intervals (Figure 3D), and the cylindrical shaped GS was put into the cylindrical cut sheath. The cut sheath within the GS was inserted from behind of the first sheath, and the GS was pushed into the tract by the inner cylinder with a guidewire from behind the first sheath, and the tract was packed with GS in the form of a mould (Figure 3E).

### Parameters and evaluation items

Before and approximately three weeks after PTPE, CECT and Tc-99m GSA scintigraphy were performed. The RLV and the RLU15 were used as the main parameter. CT volumetry, including RLV, was calculated by Synapse Vincent (Fujifilm Holdings Corporation, Tokyo, Japan). Liver uptake at 15 minutes (LU15) is the ratio of cumulative liver uptake from 15 to 16 minutes after GSA administration divided by the total GSA dose, and its formula is as below [9].

$$\text{LU15} = \frac{\int_{15}^{16} C(t) dt}{\text{total injected dose}} \times 100 (\%)$$

C (t) is the time-activity curves in which the region of interest is set in the liver in a continuous image taken from the anterior surface. RLU15 is the value obtained by multiplying LU15 by the residual count ratio calculated from single-photon emission computed tomography.



**Figure 2.** Digital subtraction angiography (DSA) during the percutaneous transhepatic portal vein embolisation (PTPE) procedure. **A)** The tip of the sheath was placed on the trunk of the portal vein, and contrast material was injected into the liver. The entire portal vein trunk and branches were displayed. **B)** A loop-shaped balloon catheter was turned back at the splenic vein and then its tip was inserted into the anterior segment branch, and after balloon occlusion, DSA of the anterior segment branch was performed. **C)** The ethanol-lipiodol mixture was carefully injected into the anterior segment branch while confirming the absence of reflux. **D)** A J-shaped balloon catheter was inserted into the beginning of the posterior branch, the balloon was occluded, and the contrast material was injected from the sheath. **E)** The ethanol-lipiodol mixture was carefully injected into the posterior segment branch while confirming the absence of reflux. **F)** In the final image, the portal vein of the right lobe was completely embolised, and only the portal vein of the left lobe was visualised

When evaluating residual liver function before hepatectomy, the desirable RLU15 value is reported to be more than 13 [10].

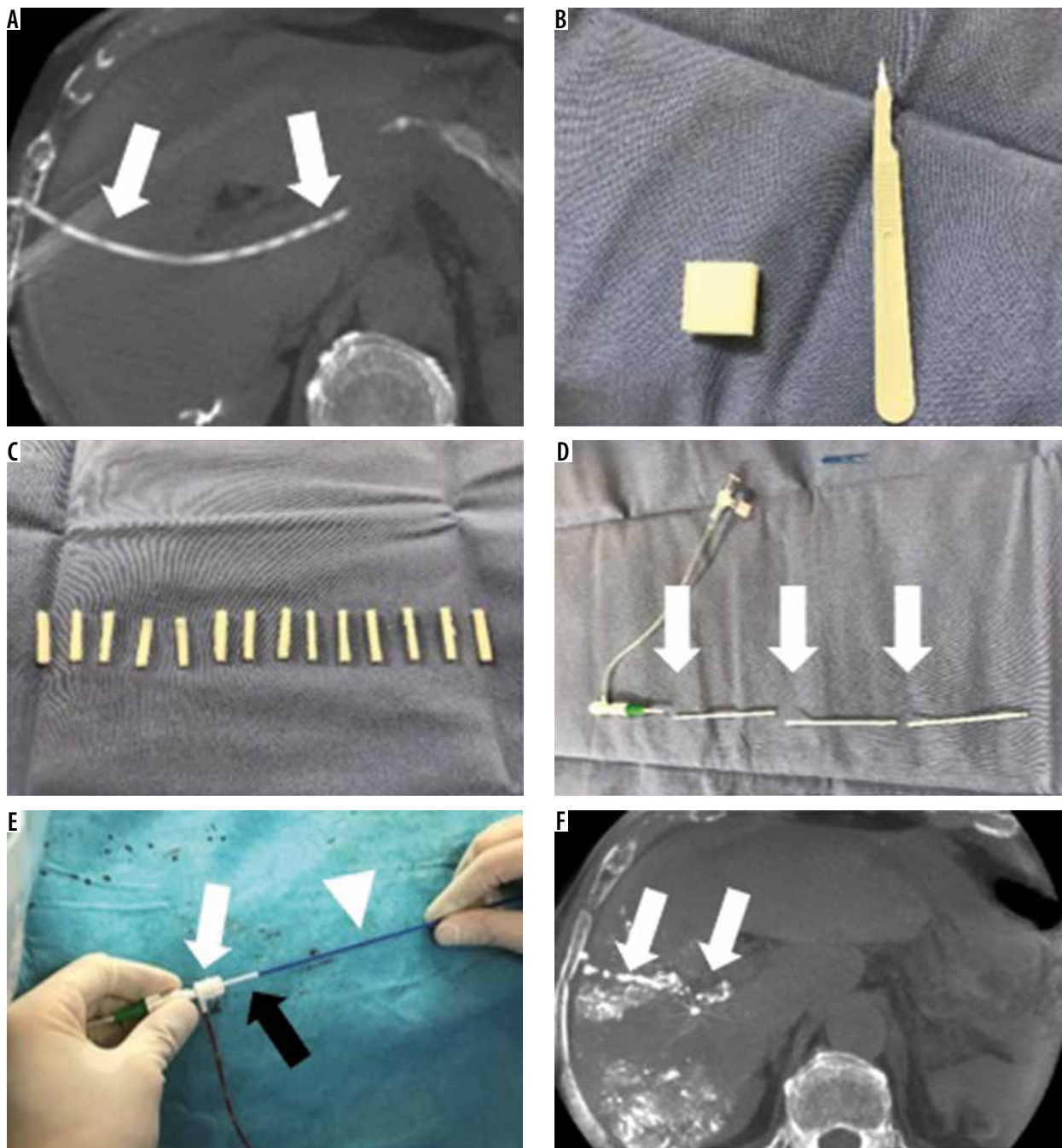
As the primary endpoint, RLV, RLU15, the fold change in RLV ( $\Delta$ RLV), the fold change in RLU15 ( $\Delta$ RLU15), and correlation between  $\Delta$ RLV and  $\Delta$ RLU15 were obtained.  $\Delta$ RLV and  $\Delta$ RLU15 were calculated as follows:

$$\Delta\text{RLV} = \frac{\text{after RLV}}{\text{before RLV}}, \Delta\text{RLU15} = \frac{\text{after RLU15}}{\text{before RLU15}}$$

The samples of 16 patients who underwent radical hepatectomy were histopathologically evaluated. The liver cirrhosis group was defined as cases of fibrosis grade (F) 3 or F4 pathologically diagnosed according to the classification reported by Desmet *et al.* [12].

Sinusoidal obstructive syndrome (SOS) and chemotherapy-associated steatohepatitis (CASH) are well-known hepatic impairments caused by systemic chemotherapy for colorectal cancer, and they were evaluated





**Figure 3.** Photographs demonstrating tract embolisation. **A)** The percutaneous transhepatic tract (arrows) is embolised to prevent bleeding from the puncture site. **B)** A gelatine sponge (GS) and a sharp disposable pointed scalpel. **C)** The GS was cut into 2-mm rectangular strips and manually rounded into a cylindrical shape. **D)** A new sheath was divided into three equal parts of about 5 cm (arrows), and the cut GS was put into the cut sheath. The GS was soaked with a small amount of contrast agent. **E)** This cut sheath (black arrow) was inserted into the first sheath (white arrow) and pushed with the inner tube (white arrowhead) under fluoroscopy. **F)** The tract was embolised completely in the shape of the mould (arrows)

based on the scores reported by Rubbia-Brandt *et al.* [13].  $\Delta$ RLV and  $\Delta$ RLU15 were compared between the two groups, i.e. the cirrhosis group ( $n = 3$ ) vs. the non-cirrhosis group ( $n = 13$ ), and the chemotherapy group ( $n = 5$ ) vs. the non-chemotherapy group ( $n = 15$ ).

As a secondary endpoint, % future remnant liver (FRL) change rates (increase %FRL) were calculated using the following formulas:

$$\%FRL = \frac{FRLV}{TLV-TV} \times 100\%, \Delta\%FRL = \frac{\text{after \%FRL} - \text{before \%FRL}}{\text{before \%FRL}}$$

(FRLV – future remnant liver volume; TLV – total liver volume; TV – tumour volume)

Adverse events were evaluated using CTCAE v4.0 software.

### Statistical analysis

Ratios were expressed as means and standard deviations. For the differences in increases in RLV and RLU15 before and after PTPE, Student’s *t*-test was used. For two-group

comparisons, Wilcoxon's rank sum test was used. A *p*-value less than 0.05 was considered to indicate a significant difference between two groups.

## Results

The median amount of ethanol used was 7.5 (3.67-10.0) ml. The embolic areas were the right lobe in 16 patients and the three segments in four patients. Of these four patients three were embolised in the left lobe and anterior segment, and one was embolised in the right lobe and segment 4. The median intervals from PTPE to CECT, to Tc-99m GSA scintigraphy, and to surgery were 21 (7-52) days, 21 (13-48) days, and 31 (20-56) days, respectively. Radical resection was performed in 16 patients (curative hepatectomy rate: 80%), and these patients were pathologically evaluated. In the other four patients (nos. 15, 17, 18, and 19), hepatectomy was not performed because the progression of the original disease was seen (Table 2).

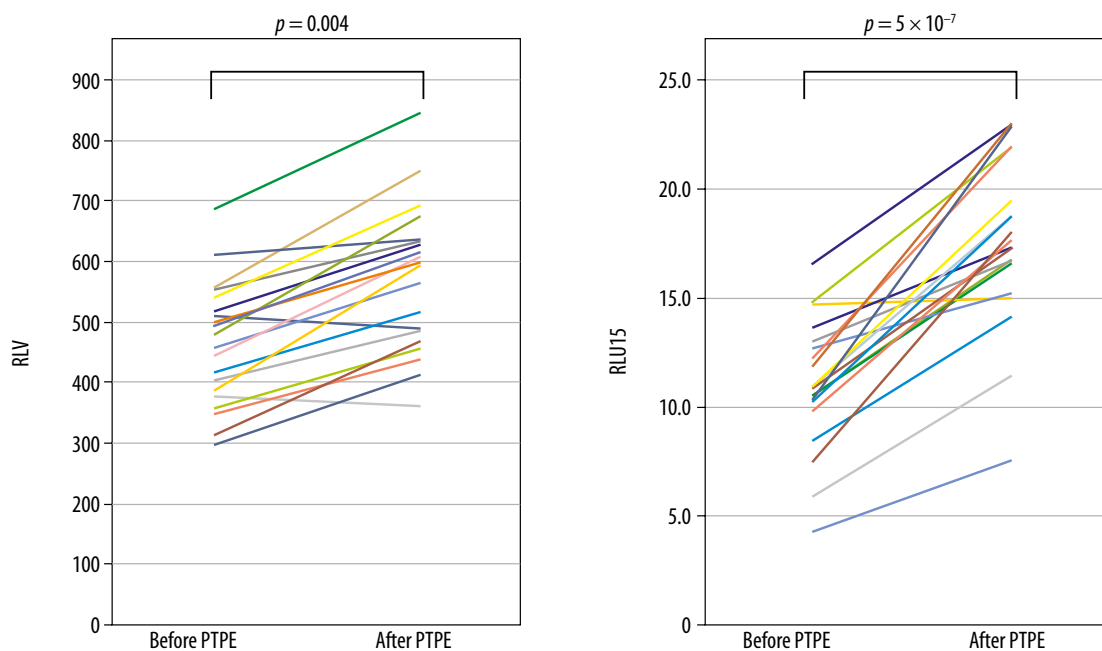
## Primary endpoint

Total liver volume before and after PTPE were  $1304 \pm 278$  ml and  $1249 \pm 254$  ml, respectively, and no significant difference was seen ( $p = 0.53$ ). A significant increase was observed in the RLV ( $464 \pm 99$  ml and  $573 \pm 118$  ml,  $p = 0.004$ , Figure 4) before and after PTPE.  $\Delta$ RLV in all cases was  $1.25 \pm 0.15$ . Total liver LU15 before and after PTPE were  $28.8 \pm 4.9\%$  and  $27.3 \pm 4.9\%$ , respectively, which indicated no significant difference ( $p = 0.35$ ). The RLU 15 before and after PTPE were  $11.0 \pm 2.9\%$  and  $17.7 \pm 3.8\%$ , respectively, with a significant increase ( $p = 5 \times 10^{-7}$ , Figure 4).  $\Delta$ RLU15 in all cases was  $1.66 \pm 0.33$ . No significant correlation was observed in either RLV or RLU15 before and after PTPE ( $r = 0.14$ ,  $p = 0.66$ , Figure 5A), although both RLV and RLU15 were significantly increased. Outliers were patients nos. 3, 9, and 16, and after these patients were excluded, the correlation coefficient increased to 0.76 ( $p = 0.005$ , Figure 5B). The results

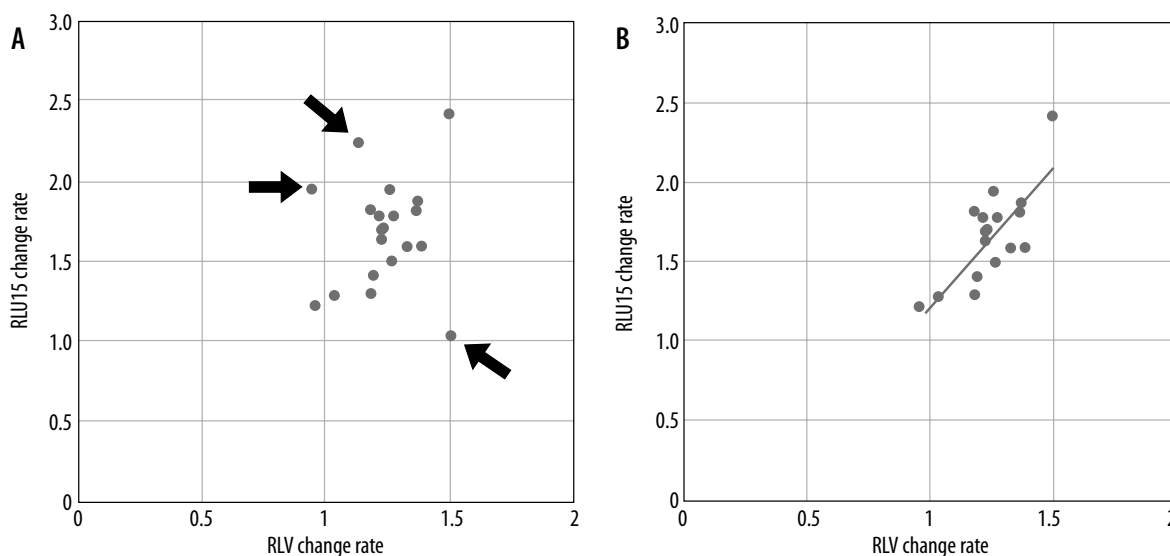
**Table 2.** Morphological and functional parameters obtained from PTPE, PTPE complications, and follow-up

Patient no.	RLV (ml)			RLU15 (%)			Complications	Radical resection*	Reason that radical resection could not be performed
	Before PTPE	After PTPE	$\Delta$ RLV	Before PTPE	After PTPE	$\Delta$ RLU15			
1	418	516	1.23	8.5	14.2	1.67	–	Yes	–
2	501	598	1.19	9.8	17.6	1.80	–	Yes	–
3	378	360	0.95	5.9	11.4	1.93	–	Yes	–
4	541	693	1.28	11.0	19.4	1.76	–	Yes	–
5	459	562	1.22	4.3	7.6	1.77	–	Yes	–
6	481	675	1.40	10.6	16.8	1.58	–	Yes	–
7	519	625	1.20	16.5	22.9	1.39	–	Yes	–
8	313	470	1.50	7.5	18.0	2.40	–	Yes	–
9	553	633	1.14	10.3	22.9	2.22	–	Yes	–
10	558	748	1.36	10.9	17.2	1.58	ALT and AST elevation (grade 4)	Yes	–
11	612	637	1.04	13.6	17.3	1.27	–	Yes	–
12	687	845	1.23	10.3	18.6	1.61	–	Yes	–
13	495	616	1.24	11.0	22.0	1.69	–	Yes	–
14	445	609	1.37	12.2	22.0	1.80	–	No	Multiple dissemination
15	406	484	1.19	13.0	16.7	1.28	–	Yes	–
16	391	592	1.51	14.7	15.0	1.02	Cholangitis (grade 3)	No	Tumour progression
17	509	492	0.97	12.7	15.2	1.20	–	No	Tumour progression
18	358	456	1.27	14.8	21.9	1.48	–	No	Tumour progression
19	297	411	1.38	10.1	18.8	1.86	–	Yes	–
20	348	437	1.26	11.9	23.9	1.93	–	Yes	–
Mean	$464 \pm 99$	$573 \pm 118$	$1.25 \pm 0.15$	$11.0 \pm 2.9$	$17.7 \pm 3.8$	$1.66 \pm 0.33$			

PTPE – percutaneous transhepatic portal vein embolisation; RLV – residual liver volume; RLU15 – residual liver uptake at 15 minutes



**Figure 4.** Changes in residual liver volume (RLV) and residual liver uptake at 15 minutes (RLU15) before and after PTPE. The RLV (before:  $464 \pm 99$  ml; after:  $573 \pm 118$  ml,  $p = 0.004$ ) and RLU 15 (before:  $11.0 \pm 2.9\%$ ; after:  $17.7 \pm 3.8\%$ ,  $p = 5 \times 10^{-7}$ ) were significantly increased after PTPE



**Figure 5.** Correlation between rates of changes in RLV and RLU15. **A)** When all patients were analysed, no correlation was observed ( $r = 0.14$ ,  $p = 0.66$ ). The three outliers were patients nos. 3, 9, and 16 (arrows). **B)** When the three outliers were excluded, a positive correlation was obtained ( $r = 0.76$ ,  $p < 0.005$ )

**Table 3.** Outliers of the RLV and RLU15 results

	Patient no.	$\Delta$ RLV	$\Delta$ RLU15	Outcomes
Outliers of the RLV results	3	0.95	1.93	Radical hepatectomy was performed
	9	1.14	2.22	
An outlier of the RLU15 results	16	1.51	1.02	Progression of the present disease was confirmed during surgery and hepatectomy could not be performed

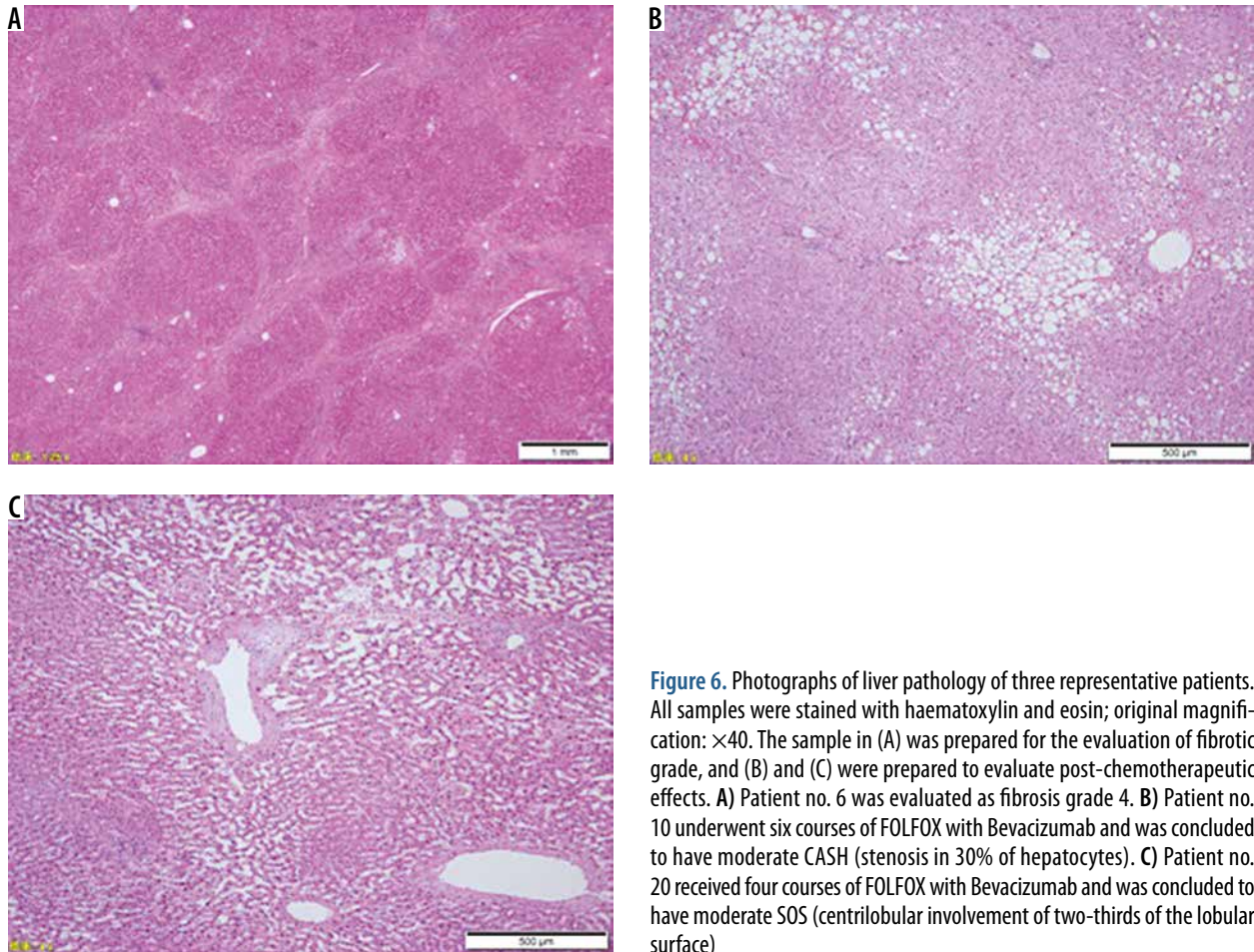
of these three outliers are shown in Table 3. In patients nos. 3 and 9 there was a minimal increase in RLV and a large increase in RLU15, and these two patients were able to undergo radical hepatectomy after PTPE. Patient no. 16 showed a large increase in RLV and a small increase

in RLU15, and radical hepatectomy could not be completed because of tumour progression. The outcomes of the two-group comparisons are listed in Table 4. Pathological cirrhosis was observed in patients nos. 5, 7, and 14 (Figure 6A), and the other 13 patients, including those with



**Table 4.** Outcomes of patients with cirrhotic liver vs. non-cirrhotic liver and patients undergoing systemic chemotherapy vs. no systemic chemotherapy before PTPE

	Cirrhotic (3) vs. non-cirrhotic (13)	<i>p</i> -value	Chemo (5) vs. no chemo (15)	<i>p</i> -value
ΔRLV	1.28 vs. 1.22	0.12	1.26 vs. 1.23	0.76
ΔRLU15	1.69 vs. 1.77	0.59	1.58 vs. 1.69	0.97

**Figure 6.** Photographs of liver pathology of three representative patients. All samples were stained with haematoxylin and eosin; original magnification:  $\times 40$ . The sample in (A) was prepared for the evaluation of fibrotic grade, and (B) and (C) were prepared to evaluate post-chemotherapeutic effects. A) Patient no. 6 was evaluated as fibrosis grade 4. B) Patient no. 10 underwent six courses of FOLFOX with Bevacizumab and was concluded to have moderate CASH (stenosis in 30% of hepatocytes). C) Patient no. 20 received four courses of FOLFOX with Bevacizumab and was concluded to have moderate SOS (centrilobular involvement of two-thirds of the lobular surface)

HCC, had no obvious fibrosis. There were no significant differences between cirrhotic and non-cirrhotic groups regarding both  $\Delta$ RLV (1.28 vs. 1.22,  $p=0.12$ ) and  $\Delta$ RLU15 (1.69 vs. 1.77,  $p=0.59$ ). Five patients (nos. 7, 8, 10, 11, and 20) underwent two to six courses of systemic chemotherapy before PTPE. Oxaliplatin-based chemotherapy was performed in these five patients. Only one patient (no. 8) switched to irinotecan-based chemotherapy because of an allergy to oxaliplatin (Table 1). No significant differences were observed between chemotherapy and non-chemotherapy groups in both  $\Delta$ RLV (1.26 vs. 1.23,  $p=0.76$ ) and  $\Delta$ RLU 15 (1.58 vs. 1.69,  $p=0.97$ ).

### Secondary endpoint

The % FRL increase was  $34.4 \pm 25.2\%$ . At the time of injection of ethanol, local abdominal pain was recognised in all patients; however, it was under self-control by the

administration of analgesics. Major adverse events are listed in Table 2. Grade 3 cholangitis, which requires endoscopic retrograde biliary drainage (ERBD), was found in one patient. Grade 4 alanine aminotransferase (ALT) and aspartate transaminase (AST) elevation were observed in one patient, grade 3 ALT elevation in 10 patients, grade 3 AST elevation in seven patients, grade 3 bilirubin elevation in one patient, and grade 3 thrombocytopenia in one patient; however, these symptoms were adequately treated by conservative treatments. Regarding postembolic syndromes, grade 1 fever was observed in five patients, grade 2 nausea in five patients, and grade 1 vomiting in one patient.

### Discussion

Some studies have compared morphological RLV with residual liver function (RLF), which is another radionu-



clide parameter that is different from RLU15 obtained from Tc-99m GSA scintigraphy, before and after PTPE [7,8,14]. The fold change in RLV and RLF were 1.28 to 1.32 and 1.63 to 1.7, respectively, and generally, the increase in the rate of change in RLF is known to be much greater than that of RLV [3,6,8,15]. In the present study, the fold changes in RLV and RLU15 were  $1.25 \pm 0.15$  and  $1.66 \pm 0.33$ , respectively, which is equivalent to those of previous reports. No correlation was seen between the fold change in RLV and RLU15 in all patients. Kono *et al.* reported that no correlation was observed between morphological RLV and residual liver R max (a radionuclide parameter) before and after PTPE in all patients ( $r=0.105$ ,  $p=0.803$ ) [8]. A good correlation between these parameters was observed when the patients were narrowed down to the good response group that showed a large increase in R max ( $r=0.826$ ,  $p=0.037$ ). Nanashima *et al.* found a good correlation between CT volumetry before PTPE and RI volumetry ( $r=0.69$ ); however, a very weak correlation was found between CT volumetry and RI volumetry after PTPE ( $r=0.03$ ) [15]. From these previous reports, it is suggested that although PTPE increases both RLV and RLF, these parameters may not be simply well correlated. Therefore, it is clinically important and desirable to analyse both parameters for more accurate evaluation of liver function. We divided the outliers into two types. Type A, comprising two of the three outliers, showed a small increase in RLV but a large increase in RLU15 (Table 3A). Type B, comprising one of the three outliers, showed a large increase in RLV but a small increase in RLU15 (Table 3B). Compared with morphological RLV, RLF values obtained from GSA scintigraphy are known to be better correlated with postoperative albumin level [15], prothrombin time [10], total bilirubin [10,15], preoperative indocyanine green retention rate at 15 min (ICGR 15) [9,10], and postoperative indocyanine green [6,15]. Therefore, in patients of type A, even if only a small increase in RLV is observed, a large increase in RLU15 is likely to indicate sufficient regeneration of the residual liver. As a result, we were able to perform surgery on all type A patients. On the other hand, in type B, two hypotheses were clinically inferred. The first hypothesis was that the underlying liver disease was much worse, and liver regeneration might take a comparatively long time. The remnant liver is known to continue to undergo hypertrophy after PTPE and postoperatively [3,15]. The second hypothesis was that there was rapid progression of the present liver disease and that regeneration itself was poor. In the case of patient no. 16, the latter hypothesis was thought to be true because progression of the present disease was found during surgery and hence curative operation was not performed. Many studies have reported that sufficient RLV and RLF increases in patients with liver cirrhosis may not be observed after PTPE [3,16-19]. In the present study, the fold change in RLV appeared to be good (1.28), but the RLU15 remained at 1.69. In the case of cirrhotic patients,

Kono *et al.* speculated that an increase in RLV reflects not an increase in the number of functional hepatocytes but instead an increase in the interstitial area [8]. This hypothesis suggests that in patients with liver cirrhosis, even if a good increase in RLV is observed, careful evaluation is required. To our knowledge, there are few studies comparing RLF in post-chemotherapy and non-chemotherapy groups before and after PTPE. Patients undergoing systemic chemotherapy after PTPE did not show a significant decrease in the rate of increase in RLV compared with the non-chemotherapy group [17,20,21]. On the other hand, de Baere *et al.* found that the rate of increase in RLV significantly decreased in the patient group, using the platinum formulation [22]. Narita *et al.* reported that the rate of increase in RLV significantly decreased in the SOS group ( $16.8 \pm 24.0$  vs.  $55.6 \pm 32.5$ ,  $p < 0.001$ ) [23]. The median number of chemotherapy cycles was 10 (range, 2-44), and the grades of SOS were mild in five patients, moderate in four patients, and severe in two patients. Ninety per cent of the patients with SOS received more than six cycles of chemotherapy and/or underwent oxaliplatin-based chemotherapy. In the present study, the chemotherapy group had equivalent outcomes in both RLV and RLU15 compared with the non-chemotherapy group, and consequently, curative hepatectomy was performed. Five cases in the chemotherapy group were pathologically evaluated, as follows: Moderate SOS was found in patients nos. 11 and 20, mild SOS in patient no. 8, moderate CASH was seen in patient no. 10, and mild CASH was seen in patient no. 7. No severe cases of both SOS and CASH were observed. An insufficient increase in RLU15 was observed only in patient no. 11. Thus, for up to six cycles of chemotherapy, it seems that systemic chemotherapy before PTPE might not affect increases in RLV and RLU15.

According to a systematic review of PTPE, % FRL was used for calculating the hypertrophy response of residual liver in 68.2% of reported studies [17]. The average and width of % FRL volume increase were used in  $37.9 \pm 0.1\%$  and 20.5% to 69.4%, respectively. Sakuhara *et al.* reported that, in a study of 143 patients who underwent PTPE using ethanol, the % FRL volume increase and resection rate were 33.6% and 84%, respectively [24]. In the present study, the % FRL volume increase and resection rate were  $34.4 \pm 25.2\%$  and 80%, respectively, which were similar to the previous study. The rate of PTPE complications was reported as 2.2% to 15% [25-27]. As a mild complication that is specific to the use of ethanol, pain at the time of injection may be reported. However, in our present study, most cases of pain were relieved within a few minutes with or without analgesics, similarly to a previous publication [24]. Pneumothorax, cholangitis, PVT, etc. were reported as major complications [25-27]. Rare but fatal cases of pulmonary embolism and cholangitis after PTPE have been reported [28]. In the present study, patient no. 16 had cholangitis on day 12 after PTPE, and although ERBD had been performed 14 days before PTPE, it was

performed again. Radical hepatectomy was attempted after two months; however, the tumour was unresectable due to tumour progression. A serious complication after PTPE was only observed in this patient.

## Limitations

This study has several limitations. Firstly, it is a retrospective study with only a few patients. All pathological specimens were obtained after surgery, and therefore they were affected by both PTPE and surgery. As hypertrophy of the residual liver continues even after hepatectomy, the final postoperative residual liver function was not evaluated. The outcomes after hepatectomy appear to most greatly affect the patients' prognosis; however, the success rate of the operation depends not only on residual liver function but also on operation time, amount of bleeding, and whether or not vascular reconstruction was performed. In the present study, the effect of pure PTPE was evaluated.

## Conclusions

No correlation was found between rates of changes in RLV and RLU15 both before and after PTPE. Outliers in which RLU15 increased despite a small increase in RLV suggested that these may be cases in which to consider surgery. Severe liver injury did not occur upon systemic chemotherapy for up to six cycles, and the effects of PTPE were similar to those in patients with liver cancer, who did not receive chemotherapy.

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## Conflict of interest

The authors report no conflict of interest.

## References

- Shindoh J, Tzeng CW, Aloia TA, et al. Safety and efficacy of portal vein embolization before planned major or extended hepatectomy: an institutional experience of 358 patients. *J Gastrointest Surg* 2014; 18: 45-51.
- Chiba N, Shimazu M, Takano K, et al. Predicting hepatic failure with a new diagnostic technique by preoperative liver scintigraphy and computed tomography: a pilot study in 123 patients undergoing liver resection. *Patient Saf Surg* 2017; 11: 29.
- Yumoto Y, Yagi T, Sato S, et al. Preoperative estimation of remnant hepatic function using fusion images obtained by 99mTc-labelled galactosyl-human serum albumin liver scintigraphy and computed tomography. *Br J Surg* 2010; 97: 934-944.
- Kokudo N, Vera DR, Koizumi M, et al. Recovery of hepatic asialoglycoprotein receptors after major hepatic resection. *J Nucl Med* 1999; 40: 137-141.
- Wu J, Ishikawa N, Takeda T, et al. The functional hepatic volume assessed by 99m Tc-GSA hepatic scintigraphy. *Ann Nucl Med* 1995; 9: 229-235.
- Mitsumori A, Nagaya I, Kimoto S, et al. Preoperative evaluation of hepatic functional reserve following hepatectomy by technetium-99m galactosyl human serum albumin liver scintigraphy and computed tomography. *Eur J Nucl Med* 1998; 25: 1377-1382.
- Kasai Y, Hatano E, Iguchi K, et al. Prediction of the remnant liver hypertrophy ratio after preoperative portal vein embolization. *Eur Surg Res* 2013; 51: 129-137.
- Kono Y, Kariya S, Komemushi A, et al. Comparison of Tc-99m GSA scintigraphy and CT volumetry for evaluation in portal vein embolization. *Minim Invasive Ther Allied Technol* 2014; 23: 241-246.
- Koizumi K, Uchiyama G, Arai T, et al. A new liver functional study using Tc-99m DTPA-galactosyl human serum albumin: evaluation of the validity of several functional parameters. *Ann Nucl Med* 1992; 6: 83-87.
- Uetake M, Koizumi K, Yagawa A, et al. Use of Tc-99m DTPA galactosyl human serum albumin to predict postoperative residual liver function. *Clin Nucl Med* 1999; 24: 428-434.
- Satake M, Hayashi T, Iwata R, et al. Percutaneous transhepatic portal vein embolization using absolute ethanol. *Nichidoku-Iho* 2007; 52: 94-99. (Japanese)
- Desmet VJ, Gerber M, Hoofnagle JH, et al. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; 19: 1513-1520.
- Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol* 2004; 15: 460-466.
- Nishiyama Y, Yamamoto Y, Hino I, et al. 99mTc galactosyl human serum albumin liver dynamic SPET for pre-operative assessment of hepatectomy in relation to percutaneous transhepatic portal embolization. *Nucl Med Commun* 2003; 24: 809-817.
- Nanashima A, Tobinaga S, Abo T, et al. Relationship of hepatic functional parameters with changes of functional liver volume using technetium-99m galactosyl serum albumin scintigraphy in patients undergoing preoperative portal vein embolization: a follow-up report. *J Surg Res* 2010; 164: e235-e242.
- Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg* 2003; 237: 208-217.
- Van Lienden KP, Van den Esschert JW, De Graaf W, et al. Portal vein embolization before liver resection: a systematic review. *Cardiovasc Intervent Radiol* 2013; 36: 25-34.
- Cotrono AR, Innocenti P, Marano G, et al. Pre-hepatectomy portal vein embolization: single center experience. *Eur J Surg Oncol* 2009; 35: 71-78.

19. Ko GY, Sung KB, Yoon HK, et al. Preoperative portal vein embolization with a new liquid embolic agent. *Radiology* 2003; 227: 407-413.
20. Zorzi D, Chun YS, Madoff DC, et al. Chemotherapy with bevacizumab does not affect liver regeneration after portal vein embolization in the treatment of colorectal liver metastases. *Ann Surg Oncol* 2008; 15: 2765-2772.
21. Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. *Ann Surg* 2008; 247: 451-455.
22. de Baere T, Teriitehau C, Deschamps F, et al. Predictive factors for hypertrophy of the future remnant liver after selective portal vein embolization. *Ann Surg Oncol* 2010; 17: 2081-2089.
23. Narita M, Oussoultzoglou E, Chenard MP, et al. Sinusoidal obstruction syndrome compromises liver regeneration in patients undergoing two-stage hepatectomy with portal vein embolization. *Surg Today* 2011; 41: 7-17.
24. Sakuhara Y, Abo D, Hasegawa Y, et al. Preoperative percutaneous transhepatic portal vein embolization with ethanol injection. *AJR Am J Roentgenol* 2012; 198: 914-922.
25. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg* 2008; 247: 49-57.
26. Di Stefano DR, de Baere T, Denys A, et al. Preoperative percutaneous portal vein embolization: evaluation of adverse events in 188 patients. *Radiology* 2005; 234: 625-630.
27. Kodama Y, Shimizu T, Endo H, et al. Complications of percutaneous transhepatic portal vein embolization. *J Vasc Interv Radiol* 2002; 13: 1233-1237.
28. Giraudo G, Greget M, Oussoultzoglou E, et al. Preoperative contralateral portal vein embolization before major hepatic resection is a safe and efficient procedure: a large single institution experience. *Surgery* 2008; 143: 476-482.