

Coil volume embolization ratio for preventing recanalization after portal vein embolization

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PURPOSE

The purpose of this study was to evaluate the optimum volume embolization ratio (VER) for the prevention of recanalization after portal vein embolization (PVE) and the influence of recanalization on future liver remnant (FLR) function using technetium-99m galactosyl human serum albumin single-photon emission computed tomography (^{99m}Tc -GSA SPECT/CT) fusion imaging.

METHODS

We analyzed procedural data of 18 patients who underwent PVE from 2015 to 2018. A total of 29 portal branches were embolized (12 anterior branch, 11 posterior branch, 4 left branch, 2 right branch) with absolute ethanol and coils. Portal vein recanalization was evaluated three weeks after PVE by contrast-enhanced CT. We classified the treated portal branches as non-recanalized and recanalized. VER was compared between the groups. In addition, for each patient, we calculated and evaluated the ratio of FLR volume to total liver volume (volumetric %FLR), FLR count to total liver count on ^{99m}Tc -GSA SPECT/CT fusion imaging (functional %FLR), and functional-volumetric ratio (functional %FLR/ volumetric %FLR).

RESULTS

Twenty-six portal branches showed no recanalization (non-recanalized group, $n=26$, 89.7%), while three portal branches showed recanalization (recanalized group, $n=3$, 10.3%). The median VER was 4.94% (3.12%–11.1%) in the non-recanalized group and 3.49% (2.76%–4.32%) in the recanalized group, which was significantly different between the groups ($p = 0.045$, Mann–Whitney U test). The median functional-volumetric ratio was 1.16 (1.03–1.50) in non-recanalized patients ($n=15$, 83.3%) and 1.01 (0.96–1.13) in recanalized patients ($n=3$, 16.7%), and it was significantly higher in the non-recanalized patients ($p = 0.021$, Mann–Whitney U test).

CONCLUSION

The VER for preventing recanalization after PVE was approximately 5% ($> 4.94\%$). ^{99m}Tc -GSA SPECT/CT fusion imaging revealed a decrease in FLR function due to recanalization after PVE.

Patients with malignant hepatic cancer are often treated by hepatectomy for tumor removal. The safety of major hepatectomy can be increased by inducing compensatory hypertrophy of the remaining liver through portal vein embolization (PVE) (1). Many reports have supported the clinical use of PVE before major hepatectomy. However, satisfactory embolization of the hepatic portal branches is necessary before performing extended hepatectomy, because partial PVE and recanalization after PVE can result in insufficient hypertrophy of the remaining liver after surgery. However, there is no obvious endpoint during embolization because portal vein flow is lost after PVE.

Prediction of remaining liver function after hepatectomy has been reported to be facilitated by the use of technetium-99m galactosyl human serum albumin single-photon emission computed tomography (^{99m}Tc -GSA SPECT/CT) fusion imaging, which is also useful for identifying hepatectomy candidates (2–7). However, the influence of recanalization on future liver remnant (FLR) function has not been evaluated in previous studies.

Therefore, we conducted the present retrospective clinical study to evaluate the optimum coil volume embolization ratio (VER) for prevention of recanalization after PVE and the influence of recanalization on FLR function.

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Methods

Patients

We analyzed 18 patients who underwent PVE with absolute ethanol and coils before major hepatectomy at our institution from 2015 to 2018. The underlying disease was cholangiocarcinoma in 12 patients, hepatic cancer in 4 patients, and metastatic carcinoma in 2 patients. Table 1 summarizes the characteristics of the subjects. PVE was performed using absolute ethanol combined with detachable coils. This was a single-center study, and approval from the local ethics committee (study number: 3568) was acquired before study initiation. All participants provided informed consent.

PVE procedure

PVE was conducted in patients who were scheduled for major hepatectomy, if they had a %FLR <35% or an expected remaining liver plasma clearance rate of less than 0.07 on indocyanine green (ICGK-F) testing (8, 9). PVE was performed using the trans-ileocecal method. After laparoscopic guidance was provided by the surgeons, the actual techniques were performed by interventional radiologists (S.A., 17 years of experience; M.N., 23 years of experience).

Occlusion was performed via the ileocecal vein using a 7 F sheath and a 6 F balloon catheter (9–20 mm Selecon MP catheter; Terumo). A balloon catheter was inserted first and digital subtraction portography was then conducted. This was followed by catheterization of the target branches before placement of embolic materials, such as absolute ethyl alcohol (anhydrous ethanol, Mylan) and detachable coils.

We determined the amount of absolute ethyl alcohol required to perform embolization administering a trial injection of

Table 1. Patient characteristics and laboratory findings

Variables	All patients (n=18)	Reference range
Age (years), mean±SD	68.8±7.49	-
Sex (male/female), n (%)	14 (77.8)/ 4 (22.2)	
Serum total bilirubin (mg/dL), mean±SD	1.05±0.58	0.4–1.5
Serum albumin (g/dL), mean±SD	3.22±0.60	4.1–5.1
Platelet count (10 ⁴ /μL), mean±SD	18.8±8.69	15.8–34.8
PT-INR, mean±SD	1.07±0.14	0.90–1.10

SD, standard deviation; PT-INR, international normalized ratio of prothrombin time.

contrast medium while keeping the balloon inflated in the target branches. We confirmed the absence of portal vein shunt or arterio-portal shunt by performing digital subtraction portography under balloon occlusion. Occlusion of the target veins was considered to be the endpoint of embolization with absolute alcohol on direct portography 10 minutes after the procedure. Coil embolization was then added to the primary branches or the proximal part of the right anterior/posterior segmental branches. When coil embolization was performed in the right or left primary branch, it was not conducted at the segmental branch level. We inserted a two-marker microcatheter (Progreat β, Terumo Clinical Supply) coaxially into the target vessel through the balloon catheter. The coils used for embolization were either a bare coil (Target 360, Stryker Japan) or a second-generation hydrocoil (AZUR CX, Terumo). The bare coil was used for anchoring and framing. The second-generation hydrocoil was used for filling. When no contrast flow distal to the coils was observed after injection of contrast medium on direct portography, the endpoint of coil embolization was considered to be reached.

Non-recanalization or recanalization after PVE

Portal vein recanalization was evaluated three weeks after PVE by contrast-enhanced CT. All patients were subjected to four-phase 320-detector row CT (Aquilion One, Canon Medical Systems) three weeks prior to and following the procedure. The patients were administered with iodinated nonionic contrast medium (600 mgI/kg) over 30 seconds with the help of a power injector. One unenhanced and three enhanced images were acquired. For each phase, the scanning parameters were as follows: slice thickness 0.5 mm, collimation 0.5

mm, reconstruction interval 0.3 mm, 120 kV, and auto-mA. After PVE, contrast-enhanced CT images were reconstructed with the application of the single-energy metallic artifact reduction (SEMAR) algorithm (Canon Medical Systems Corp.) (10, 11).

We divided the treated portal branches into two groups. Embolized portal branches with no enhancement observed on portal venous phase contrast-enhanced CT at three weeks after PVE were classified as not showing recanalization (non-recanalized group), whereas embolized branches with enhancement at three weeks after PVE were classified as showing recanalization (recanalized group).

Volume embolization ratio

The diameter of the target vessel was measured before PVE at its base in two extreme dimensions in the short axis direction on CT scans (window level and window width: 128 HU) and the mean diameter was calculated. The length of the coil embolization site was measured on curved planar reformation images using a three-dimensional (3D) image analysis system (SYNAPSE VINCENT, Fujifilm). CT images with SEMAR reconstruction (window level and width of 4000 HU and 8000 HU, respectively) after PVE were used for evaluation. An example case is depicted in Fig. 1.

The target vessel volume was calculated using the formula given below, assuming that the vessel was cylindrical:

Target vessel volume = $\pi \times (\text{target vessel diameter}/2)^2 \times \text{length of the coil embolization site}$.

The coil volume was then calculated as follows:

Coil volume = $\pi \times (\text{outer coil diameter}/2)^2 \times \text{coil length}$.

Main points

- The optimum volume embolization ratio (VER) for preventing recanalization after portal vein embolization (PVE) was approximately 5% (> 4.94%).
- Technetium-99m galactosyl human serum albumin single-photon emission computed tomography (99mTc-GSA SPECT/CT) fusion imaging revealed a decrease in future liver remnant function as a result of recanalization after PVE.
- Adequate coil embolization may prevent recanalization after PVE and achieve more effective hepatic hypertrophy.

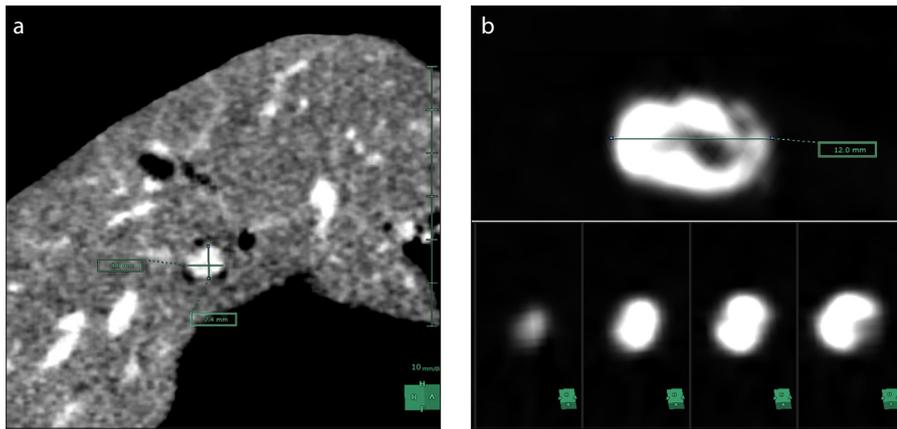


Figure 1. a, b. Target vessel diameter (a) and length of coil embolization site (b) on CT images. Oblique image (a) shows the short axis direction of the target vessel; the diameter of the target vessel was measured at its base in two extreme dimensions in the short axis direction on CT scans, and the mean diameter was calculated. Image (b) with curved planar reformation shows the long axis direction; the length of the coil embolization site was measured on curved planar reformation images using a three-dimensional image analysis system (SYNAPSE VINCENT; Fujifilm). CT images with single-energy metallic artifact reduction (SEMAR) reconstruction after portal vein embolization (PVE) were used for evaluation.

If multiple coils were used, the volume of the coils was calculated as the total of all coil volumes.

Finally, the VER was deciphered as follows:

$$\text{VER} = (\text{coil volume}/\text{target vessel volume}) \times 100 (\%).$$

We investigated the VER required to prevent recanalization by comparing the non-recanalized and recanalized vessels.

Functional-volumetric ratio

Before PVE and three weeks after PVE, ^{99m}Tc -GSA SPECT/CT fusion imaging was performed using the Discovery NM/CT 670 pro (GE Healthcare). The patient was given a 185-MBq/3-mg dose of ^{99m}Tc -GSA (Nihon Medi-Physics) by injection into a forearm vein after an overnight fast. Acquisition of SPECT data was initiated 20 minutes after injection using a low-energy, high-resolution collimator (90 steps at 15 s/step, 360°, 128×128 matrix). Reconstruction of SPECT images was performed using a 3D ordered subset expectation maximization algorithm with correction for both scatter and attenuation. Unenhanced CT scans (120 kV, 10 mA, and slice thickness of 3.5 mm) were obtained, and images were reconstructed using a standard algorithm with a 500 mm field of view of the target sites. The SPECT slices were then transformed to CT-like data, and then using Xeleris 3.1 (GE Healthcare), the SPECT and CT images were automatically fused.

Subsequently, resection lines were set on a composite display of the ^{99m}Tc -GSA SPECT and CT images by employing a 3D image analysis system (12), after which the functional %FLR on ^{99m}Tc -GSA SPECT/CT fusion imaging was calculated as follows:

$$\text{Functional \%FLR} = \text{FLR count}/\text{total liver count} \times 100.$$

The FLR volume as well as the total liver volume (TLV) were calculated at three weeks after PVE. The calculation of the ratio of the FLR volume to TLV (volumetric %FLR) was performed using the following formula:

$$\text{Volumetric \%FLR} = \text{FLR (mL)}/[\text{TLV (mL)} - \text{tumor volume (mL)}] \times 100.$$

Finally, the functional-volumetric ratio was calculated as follows:

$$\text{Functional-volumetric ratio} = \text{functional \%FLR}/\text{volumetric \%FLR}.$$

Patients in whom the embolized portal branch was not enhanced on portal venous phase contrast-enhanced CT at three weeks after PVE were classified as showing non-recanalization, whereas patients in whom the embolized portal branch was enhanced at three weeks after PVE were classified as showing recanalization. After all 18 patients were classified into the non-recanalized and recanalized groups, we compared the functional-volumetric ratio between them.

Statistical analysis

Descriptive statistics of the data are presented with n (%). Non-normalized variables are shown as median (min–max), and normal distributions are shown as mean±SD. Shapiro–Wilk test was used to check whether the variables are normally distributed. If variables were not normally distributed, differences between the non-recanalized and recanalized groups of vessels or the non-recanalized and recanalized patients were determined by the Mann–Whitney U test. If variables were normally distributed, t tests were performed. Statistical analysis was conducted using SPSS Statistics version 22.0 (IBM Corp.), and $p < 0.05$ was considered statistically significant.

Results

All PVE procedures were conducted successfully. Embolization was performed for the anterior portal branch (n=12, 41.4%), posterior branch (n=11, 37.9%), left branch including P4 (n=4, 13.8%), and right branch (n=2, 6.9%). A total of 29 portal branches were embolized. Coil embolization was performed at the proximal part of 23 secondary branches (anterior or posterior, n=23, 79.3%), and the proximal part of 6 primary branches (right or left, n=6, 20.7%). The mean target vessel diameter was 7.40 ± 1.40 mm, the mean length of coil embolization was 18.2 ± 6.7 mm, and the median volume of absolute ethanol was 4.5 mL (2.5–10.0 mL). Twenty-six portal branches did not show recanalization (non-recanalized group, n=26, 89.7%), but three portal branches (one anterior branch, one posterior branch, and one right branch) showed recanalization (recanalized group, n=3, 10.3%; Table 2). The median VER was 4.94% (3.12%–11.1%) for the non-recanalized group and 3.49% (2.76%–4.32%) for the recanalized group, and it was significantly higher in the non-recanalized group ($p = 0.045$, Mann–Whitney U test; Fig. 2).

^{99m}Tc -GSA SPECT/CT fusion imaging showed diminished uptake of ^{99m}Tc -GSA in the liver segments corresponding to the embolized portal branches, whereas ^{99m}Tc -GSA uptake was preserved when the portal branch underwent recanalization (Fig. 3). The median functional-volumetric ratio was 1.16 (1.03–1.50) in the 15 non-recanalized patients (n=15, 83.3%) and 1.01 (0.96–1.13) in the 3 recanalized patients (n=3, 16.7%), and it was significantly higher in the non-re-

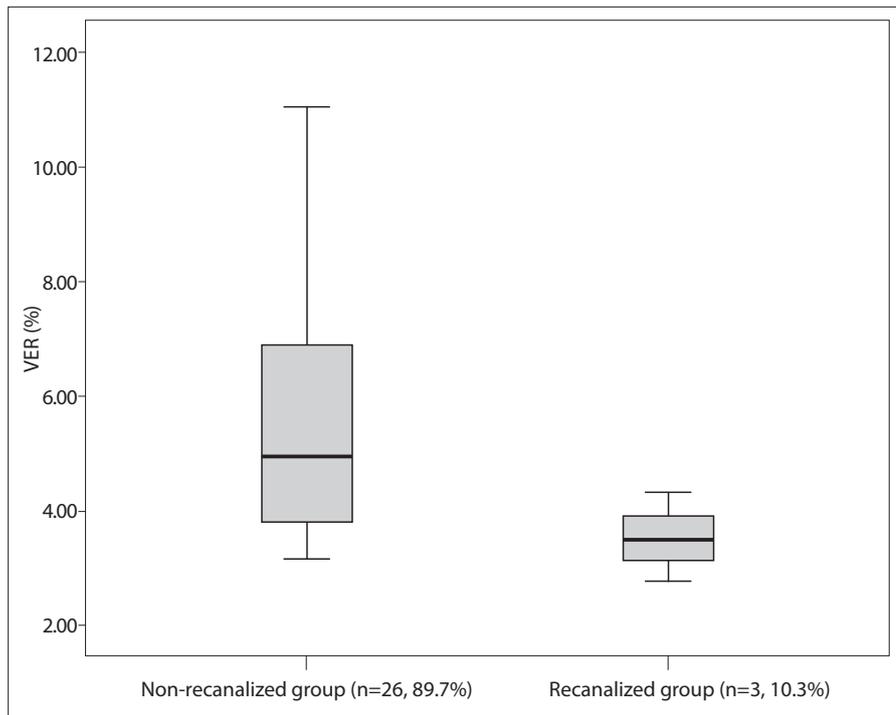


Figure 2. Box plot shows the comparison between the coil volume embolization ratio (VER) of non-recanalized group (n=26, 89.7%) and that of the recanalized group (n=3, 10.3%) ($p = 0.045$, Mann-Whitney U test).

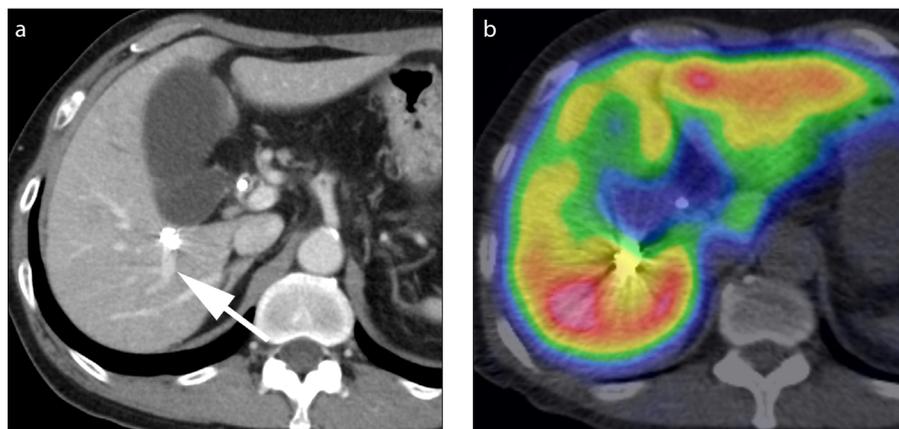


Figure 3. a, b. Contrast-enhanced CT and ^{99m}Tc -GSA SPECT/CT fusion imaging of a patient with recanalized portal branch. Contrast-enhanced CT image (a) with SEMAR reconstruction three weeks after both PVE and coil embolization: although coil embolization of both the anterior branch and posterior branch were performed, the posterior branch was recanalized (arrow). ^{99m}Tc -GSA SPECT/CT fusion imaging (b) shows preserved uptake of ^{99m}Tc -GSA in the liver segment corresponding to the recanalized portal branch.

canalized patients ($p = 0.021$, Mann-Whitney U test) (Fig. 4).

Discussion

The present study demonstrated that the VER for prevention of recanalization after PVE was approximately 5% (> 4.94%) and ^{99m}Tc -GSA SPECT/CT fusion imaging showed that recanalization decreased FLR function. To our knowledge, the VER for

preventing recanalization and the influence of recanalization on future remaining liver function have not been reported before. Adequate embolization of portal branches is crucial when patients are scheduled to undergo extended hepatectomy, because partial embolization can lead to insufficient hypertrophy, which affects the function and volume of the future remaining liver. It has been reported that PVE with an additional

central plug and/or coil embolization leads to a significantly greater increase in FLR volume than PVE alone (13). Among the many embolic agents, except for n-butyl-2-cyanoacrylate, absolute ethanol shows much higher hypertrophy effect (14). It has been reported that in the absence of balloon catheter blockade of blood flow, both absolute ethyl alcohol and n-butyl-2-cyanoacrylate flowed back at about 1% to the nontarget vessel (15). Balloon catheters are known for preventing flowing back. However, if n-butyl-2-cyanoacrylate is used balloon adhesion is a concern. Because of this, we have used absolute ethyl alcohol as the embolic agent.

In the present study, the recanalized patients (n=3, 16.7%) did not use antiplatelet drugs or anticoagulants. In two patients, both the anterior and posterior branch were embolized with coils and the VER of the recanalized branch was smaller than that of other branch in both patients. Accordingly, adequate coil embolization may prevent recanalization after PVE and achieve more effective hepatic hypertrophy. It might be necessary to distinguish between true recanalization after PVE and failure due to proximal embolization of the target vessel. When performing PVE, we first obtained complete occlusion of the target portal branches by injection of absolute ethanol and then added coil embolization to the proximal part of each target vessel. That is, to avoid proximal embolization, coil embolization was performed after injection of absolute ethanol. Arterio-portal or portal vein shunts could promote recanalization by allowing inflow of blood into the embolized portal vein. In the present study, we excluded the presence of arterio-portal or portal vein shunts by performing digital subtraction portography under balloon occlusion before embolization.

When postintervention CT and CT angiography are performed, a combination of physical effects causes the appearance of bright and dark streaks on the images (16), which leads to diminished visualization of the nearby tissues and coils (17). Anatomical structures are often obscured by streaks caused by the coils after PVE, escalating the risk of omitting the associated observations and restricting the diagnostic value of examinations (18, 19). To decrease artifacts and obtain more information concerning the underlying structures on CT, various algorithms for reduction of metal artifacts have been introduced into clinical practice,

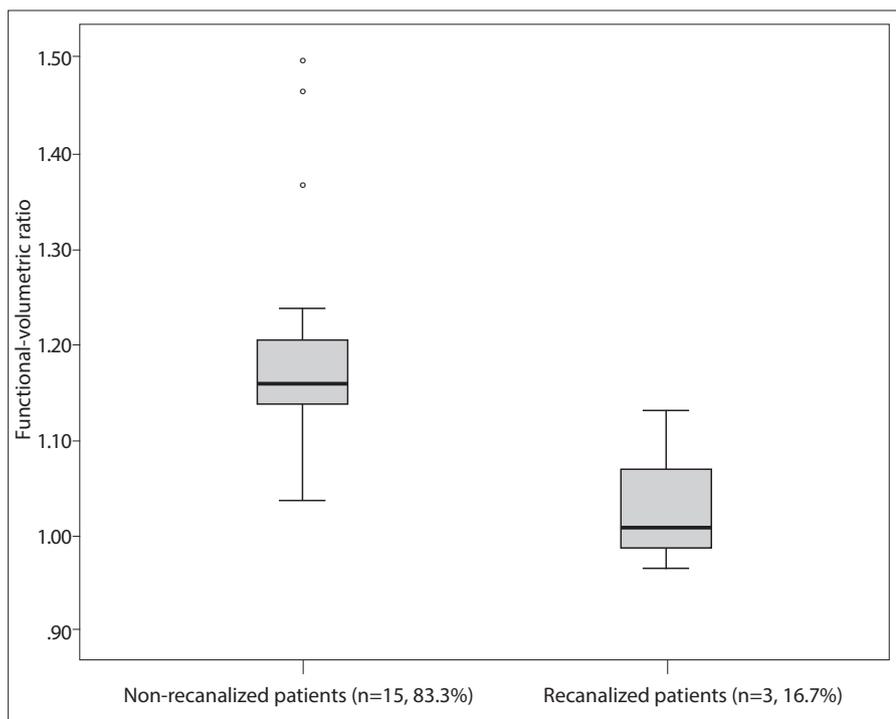


Figure 4. Functional-volumetric ratio. Box plot shows the comparison between the functional-volumetric ratio of the non-recanalized patients (n=15, 83.3%) and that of the recanalized patients (n=3, 16.7%) ($p = 0.021$, Mann–Whitney U test). Functional-volumetric ratio = functional %FLR/volumetric %FLR.

Table 2. Comparison of embolization parameters in non-recanalized and recanalized groups				
	All	Non-recanalized group	Recanalized group	p
Patients, n (%)	18 (100)	15 (83.3)	3 (16.7)	-
Branches, n (%)	29 (100)	26 (89.7)	3 (10.3)	-
VER (%), median (min–max)	4.77 (2.76–11.1)	4.94 (3.12–11.1)	3.49 (2.76–4.32)	0.045 ^a
Target diameter (mm), mean±SD	7.40±1.40	7.34±1.44	7.90±1.08	0.523 ^b
Embolization length (mm), mean±SD	18.2±6.7	18.5±7.0	15.3±3.5	0.451 ^b
Ethanol (mL), median (min–max)	4.5 (2.5–10.0)	4.25 (2.5–10.0)	5.0 (4.0–5.0)	0.799 ^a

When coil embolization was performed in the right or left primary branch of the portal vein, it was not conducted at the segmental branch level.
 VER, volume embolization ratio; SD, standard deviation.
^aMann-Whitney U test; ^bt test.

such as the SEMAR algorithm (10, 11). These algorithms employ numerous data interpolation and segmentation steps, together with reiterative forward and backward projection. It has been reported that SEMAR is efficient for decreasing metal artifacts, but little is known about its effectiveness for suppressing artifacts due to coils or improving the imaging of anatomical structures surrounding the coils on postinterventional CT (20). As far as we know, there has been

no previous report on the use of SEMAR to reduce artifacts caused by coils after PVE. We found that SEMAR was effective for this purpose and allowed us to assess recanalization and measure the extent of coil embolization.

^{99m}Tc-GSA is a specific ligand for asialoglycoprotein receptors located only on hepatocytes. The quantity of functional hepatocytes is reflected by the number of asialoglycoprotein receptors, and their decline

is noticed in patients suffering from hepatic damage (3). It was reported that ^{99m}Tc-GSA SPECT/CT fusion imaging is valuable for predicting outcomes after major hepatectomy (4). Several studies have shown that ^{99m}Tc-GSA SPECT/CT is more efficient for assessing the function of FLR than CT volumetry (21–24), and it can be employed to evaluate the adequacy of the procedure. If PVE is inadequate, the functional shift from the embolized liver to the future remaining liver will be incomplete. Accordingly, the functional-volumetric ratio was smaller in our recanalized patients (n=3, 16.7%) than in our non-recanalized patients (n=15, 83.3%), emphasizing that it is important to prevent recanalization after PVE.

There were several limitations to this study. First, it was a retrospective investigation conducted at a single center with a small number of subjects. Thus, our current observations should be taken as preliminary, and confirmatory future studies are required. In addition, other embolic materials for preventing recanalization after PVE were not evaluated. Furthermore, ^{99m}Tc-GSA SPECT/CT fusion imaging cannot be used in clinical application in many countries, even though there have been several reports about the use of this radiopharmaceutical method in Japan and elsewhere.

In conclusion, the results of the present study demonstrated that the optimum VER for preventing recanalization after PVE was approximately 5% (>4.94%). In addition, ^{99m}Tc-GSA SPECT/CT fusion imaging revealed a decrease in future remaining liver function as a result of recanalization after PVE.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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