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ORIGINAL ARTICLE

EFFICACY AND SAFETY OF PREOPERATIVE PORTAL VEIN EMBOLIZATION WITH MICROFIBRILLAR COLLAGEN FOR HEPATOBILIARY MALIGNANCY

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Abstract Purpose: To evaluate the clinical efficacy and safety of preoperative percutaneous transhepatic portal vein embolization (PVE) with an ipsilateral approach, using microfibrillar collagen (MFC) as an embolic material for carcinomas of the biliary tract and liver metastases of colorectal carcinoma.
Materials and methods: PVE using MFC was performed in 35 consecutive patients (29 men and 6 women; mean age 64 years, range 44–81 years) with small estimated future liver remnants (FLRs) after planned major hepatectomy. Patient malignancies included bile duct carcinoma (n = 20), gallbladder carcinoma (n = 5), and metastases of colorectal carcinoma (n = 8). In one patient preoperatively diagnosed with gallbladder carcinoma, the pathological diagnosis of xanthogranulomatous cholecystitis was confirmed after resection. PVE was performed with ultrasound guidance (ipsilateral approach, 35; contralateral approach, 1). Total liver volume (TLV) and FLR changes, hypertrophy ratio before and after PVE, and procedure-related complications were analyzed retrospectively.
Results: PVE was successful in all patients. There were no major procedure-related complications. Mean absolute FLR volume increased significantly ($p < 0.001$) from 434 to 524 cm^3, as did the standardized FLR to TLV ratio ($p < 0.001$), from a mean of 37.9% to 46.1%. The mean ratio of standardized FLR increase was 8.2%. The hypertrophy ratio was 23%. In the group receiving selective embolization in a centripetal direction, the increase in FLR/TLV ratio was 9.5%, while the hypertrophy ratio was 27%. Neither puncture-related complications nor deterioration of liver function were observed.
Conclusion: MFC was a safe and effective embolic material for preoperative PVE in patients with hepatobiliary malignancies, resulting in sufficient hypertrophy of FLRs.

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Key words: Portal vein; embolization; microfibrillar collagen; liver metastases; bile duct carcinoma.

原 著

肝胆道悪性疾患に対する微線維コラーゲンを用いた術前門脈塞栓術の有用性と安全性についての検討

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抄録 目的：胆道癌と大腸癌肝転移に対する大量肝切除後残存予定肝(FLR)の肥大を目的に，微線維コラーゲン(MFC)を用いた術前門脈塞栓術(PVE)について有用性と安全性について検討した．
対象と方法：MFC を用い，術前門脈塞栓を施行した胆道癌と大腸直腸癌肝転移の連続35症例(男：女＝29：6，平均64歳，胆管癌：肝内胆管癌：胆嚢癌：肝転移＝20：2：5：8，1例は術後黄色肉芽腫性胆嚢炎と確定，のべアプローチ同側：対側＝35：1)の全肝容量(TLV)，FLR の変化，肥大率，合併症について後方視的に検討した．
結果：全例で成功し，FLRは前後で434 cm^3から524 cm^3，標準化 FLR の TLV 比は37.9%から46.1%に増加した．平均標準 FLR 増加率は8.2%，肥大率は23%であった．求心性選択塞栓 group は標準 FLR 増加率が9.5%，肥大率は27%と優れていた．重大な合併症は認めなかった．
結論：胆道癌，大腸癌肝転移症例に対する MFC による術前門脈塞栓術は安全で十分な肥大が得られ，有用である．

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キーワード：門脈塞栓術；微線維コラーゲン；肝転移；胆道癌．

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Introduction

For primary or secondary hepatobiliary malignancies of the liver, extended liver resection is often necessary when a cure is desired. This leads to the removal of a large portion of the hepatic functional mass. Preoperative portal vein embolization (PVE) has been used to minimize complications after extended liver resection. Several authors[1-6] have described the technique, results, and effectiveness associated with percutaneous transhepatic PVE prior to major hepatectomy. Several reports have also described the use of various embolic materials in PVE, including gelatin sponges, polyvinyl alcohol[1, 4-5], cyanoacrylate[7], coils[1, 4, 6], and fibrin glue[8], alone or in combination with other materials.

Microfibrillar collagen (MFC) (Integran; Koken, Tokyo, Japan) is atelocollagen prepared from purified bovine hide collagen. It has been used as a hemostatic agent for controlling bleeding in various situations during surgery. This material is a cotton-like substance that mixes readily with contrast agent, forming a fine radio-opaque slurry that is easily injected through a catheter. Kaufman et al.[9] first suggested its potential efficacy in transcatheter embolization based on experimental studies in swine in 1978. Several studies on the intravascular use of MFC as an embolic material have subsequently been performed in both animals and patients. Diamond et al.[10] reported on preoperative embolization in five patients with large vascular lesions, including four renal cell carcinomas and one arteriovenous malformation (AVM) of the left shoulder, and embolization for hemostasis in four patients with bleeding malignancies and diseases, including one rectal carcinoma, two bladder carcinomas, and one case of esophageal varices. To our knowledge, however, there have been no reports so far regarding preoperative PVE using MFC as an embolic material.

This study is the first report on PVE using intravascular MFC injected as an embolic material through angiographic catheters. Our aim was to evaluate the efficacy and safety of percutaneous transhepatic PVE using MFC to induce desirable hypertrophy of future liver remnants (FLRs) before major hepatectomy in patients with hepatobiliary malignancies.

Material and Methods

Patients

This retrospective study assessed percutaneous transhepatic PVE procedures that used MFC as an embolic material and that were performed consecutively between January 2008 and March 2011. We reviewed the medical and imaging records of patients in our institution. Thirty-five patients with hepatobiliary malignancy who were scheduled for major hepatic lobectomy underwent percutaneous transhepatic PVE for the purpose of inducing adequate hypertrophy of FLRs, because calculated FLRs on three-dimensional (3D) computed tomography (CT) volumetry prior to PVE were estimated to be low. Twenty-nine males and six females with a mean age of 64 years (range 44 to 81 years) were included in this study. The preoperative diagnoses were gallbladder cancer (n = 5), bile duct cancer (n = 20), intrahepatic cholangiocellular carcinoma (ICC, n = 2), and liver metastases secondary to colorectal cancer (n = 8). Diagnoses were based on CT, magnetic resonance imaging (MRI), ultrasound sonography (US), endoscopic cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and brush cytology. One patient, although confirmed pathologically as having xanthogranulomatous cholecystitis, was included in this study because the preoperative diagnosis was advanced gallbladder carcinoma. Of 35 patients, 11 underwent internal or external biliary drainage because intrahepatic biliary dilatation was identified on initial evaluation CT. After biliary

drainage, serum total bilirubin returned to baseline values in six patients, but jaundice persisted in five patients. New elevation of serum total bilirubin value was subsequently observed in seven patients. Overall, therefore, jaundice was identified in pre-PVE biochemical analyses in 12 of 35 (34%) patients.

Two clinical groups were included in this study. One group consisted of 11 patients who underwent PVE with MFC involving balloon occlusion of the right main portal vein between January 2008 and March 2009 (bPVE group). The second group consisted of 24 patients who also underwent PVE with MFC, but with embolization performed selectively (peripheral branches only) in a centripetal direction, using 2.7-F microcatheters, between April 2009 and March 2011 (sPVE group). In two patients in the bPVE group, FLRs were estimated as insufficient on follow-up 3D CT volumetry after initial PVEs. One of these patients underwent additional PVE using balloon occlusion, and the other underwent selective PVE in which embolization was performed in a centripetal direction using a microcatheter. Thirty-seven PVE procedures in 35 patients were ultimately assessed in this study. Written informed consent was obtained from all patients or their families for PVE using MFC. Much hepatobiliary cancer patients were referred to our institusion for the purpose of an immediate operation from neighboring associated facilities. Because it was in danger of missing an opportunity of the surgery when approval of our institutional review board took considerable time, the application to an institutional review board was not made. However we are currently taking the necessary procedures of institutional review board approval.

Procedure

Before PVE, written informed consent was obtained from all patients or their families by a member of either the interventional radiology faculty or the hepatobiliary and pancreatic surgery faculty.

Hydroxyzine hydrochloride 25 mg was administered intravenously for sedation, and 1% lidocaine hydrochloride was used as a local anesthetic. In 34 patients, the portal venous system was accessed with an ipsilateral (right-sided) percutaneous transhepatic approach, and in the one remaining patient a contralateral (left-sided) percutaneous transhepatic approach was used. Under ultrasonographic and fluoroscopic guidance, the selected peripheral branch of the portal venous system (usually the P5 or P6 portal vein branch) was punctured with a 21-gauge percutaneous transhepatic cholangiography drainage needle (Top, Tokyo, Japan) by experienced members (Y.T., colleagues) of the hepatobiliary and pancreatic surgery faculty. A 0.018-inch hair wire (SKATER introducer set; Sheen Man, Osaka, Japan) was introduced into the portal vein branch through the needle, and a 6-F coaxial dilator (SKATER introducer set; Sheen Man, Osaka, Japan) was inserted into the right portal vein. A 0.035-inch guidewire (coil wire; Sheen Man, Osaka, Japan) was then introduced through the dilator into the main portal vein and the introducer system was exchanged with a 6-F angiographic sheath (Brite-tip SHEATH introducer; Cordis, Johnson & Johnson, Tokyo, Japan).

A 4.2-F angiographic catheter with multiple side holes (pigtail-shaped EN catheter; Hanaco, Saitama, Japan) was inserted into the main portal trunk through the 6-F catheter sheath, and flush portography was conducted to assess anatomical variation in the intrahepatic portal tree. MFC, a cotton-like substance, was cut into small fragments then mixed with non-ionic contrast agent, forming a mixture that could be easily injected through catheters.

From January 2008 through March 2009, balloon catheters were used in PVE. A 5-F occlusion balloon catheter (Moiyan; Tokai

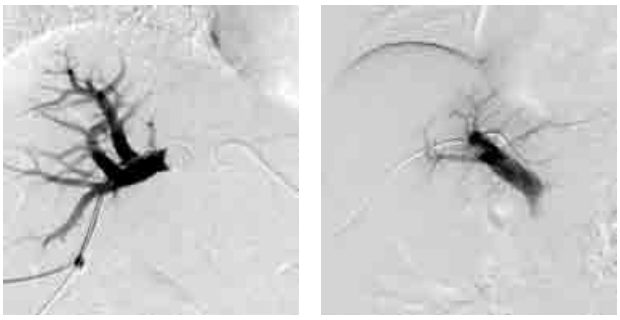

Figure 1 a **Figure 1 b**

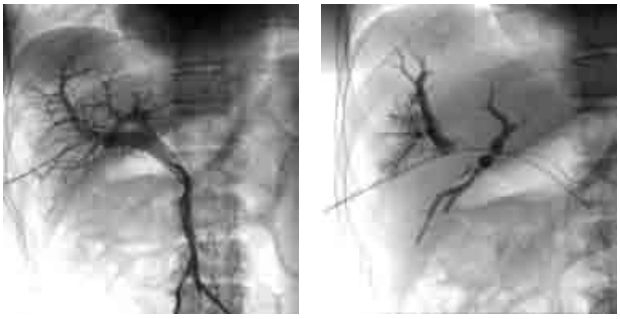

Figure 1 c **Figure 1 d**

Figure 1 Percutaneous transhepatic portography (with balloon occlusion) before (a) and after (b) embolization. A 6-F sheath was inserted into the main right portal vein and a 5-F balloon catheter was inflated at the proximal main right portal vein. The left portal venous tree was not visualized. MFC was then injected through the sheath lumen. A PVE portogram demonstrated complete occlusion of the right portal venous system. (c) Transhepatic portography. (d) A 4.2-F reverse-curve catheter was inserted through the P5 portal vein branch to the main portal vein. Using a coaxial catheter system, a 2.7-F microcatheter was selectively inserted into the other P5 portal vein and MFC was injected in a centripetal direction. P8, P7, and P6 portal vein branches were embolized, and the radioopaque MFC mixture was stagnant.

Medical Products, Aichi, Japan) or a 5.5-F three-lumen balloon catheter (Selecon MP catheter II; Terumo Clinical Supply, Gifu, Japan) was inserted into the main trunk of the right portal vein, and an aqueous suspension of MFC (Integran; Koken, Tokyo, Japan) was injected simultaneously through the 7-F sheath lumen and the side hole located proximal to the balloon. In 11 patients, comprising what we defined as the bPVE group, the occlusion balloon was inflated during injection to avoid reflux of MFC into the FLR. Beginning in April 2009, portal vein branches were selectively embolized under fluoroscopic surveillance according to the Couinaud classification using a 2.7-F microcatheter (Turtle Crane; Hanaco, Tokyo, Japan) placed coaxially through a 4.2-F reversed-curve angiographic catheter (modified SHK EN catheter; Hanaco, Tokyo, Japan). A 2.7-F microcatheter was placed distally into the right portal vein branch. The mixture of MFC and non-ionic contrast agent, which formed a radio-opaque aqueous suspension, was injected until occlusion of the distal branches was achieved (analogous to replacement of luminal blood by the embolic mixture) while pulling back the microcatheter to the proximal segment. The selective embolization of other peripheral branches was also performed in a centripetal direction in the remaining 23 patients; these individuals comprised what we defined as the sPVE group. After the embolization of predesignated portal vein branches, cessation of portal venous flow to the corresponding branches was confirmed by flush portography. The puncture route was sealed with MFC to prevent

bleeding or bile leakage from the puncture path while pulling the sheath. Embolization procedures were performed by an experienced, senior interventional radiology faculty member (Fig. 1).

Volumetric evaluation

All patients underwent helical CT to evaluate liver volume before and after PVE. Three multidetector row CT scanners were available at our institution, as follows: Lightspeed QXi (GE Yokogawa Medical Systems, Tokyo, Japan), SOMATOM Definition (Siemens, Erlangen, Germany), and Discovery 750HD (GE Healthcare, Tokyo, Japan). Multiple transverse helical CT images were obtained before and after intravenous bolus administration of non-ionic contrast agent at multiphase flow rates ranging from 3 to 5 mL/second, consisting of an arterial dominant phase (usually only a late arterial dominant phase, with addition of an early arterial dominant phase if necessary), a portal dominant phase, and an equilibrium phase. Volumetric thin-section CT images were simultaneously obtained during both the arterial dominant phase and the portal dominant phase, and evaluated for the extent of hepatobiliary disease, the presence or absence of extrahepatic disease, and the presence or absence of anatomical variation in the portal venous tree and visceral arteries. The CT parameters included collimation of 0.625 mm, 1.0 mm, 1.25 mm, or 2.5 mm, and reconstruction intervals of 0.625 mm, 1.0 mm, or 1.25 mm.

Volumetric images from portal dominant phases were analyzed with a commercially available imaging workstation (Synapse Vincent; FujiFilm, Tokyo, Japan), and total liver and FLR volumes were calculated before and after PVE with manual and semiautomated segmentation techniques based on thresholding and morphologic filtering on the workstation. The FLR volume was calculated based on non-embolized portions of the left liver (segments I–IV according to the Couinaud classification). In patients with hepatic metastases, tumor volume was not excluded from total liver or hemi-liver calculations because the number of patients with colorectal liver metastases was small in this study and the contours of metastatic tumors were so obscure that delineating the contours of all metastatic tumors was thought to be impossible. Right- and left-lobe FLRs were calculated after virtual hepatectomy by manual delineation of a resection border in the craniocaudal direction performed using the middle hepatic vein and gallbladder fossa as landmarks. The same author (K.S.) retrospectively measured the liver volume in each procedure twice, and the average value was adopted.

The hypertrophy ratio was calculated using the following formula:

$$\frac{{}_{\text{postPVE}}\text{FLR} - {}_{\text{prePVE}}\text{FLR}}{{}_{prePVE}FLR} \times 100$$

Similarly, the atrophy ratio was calculated using the following formula:

$$\frac{{}_{\text{prePVE}}\text{embolized lobe} - {}_{\text{postPVE}}\text{embolized lobe}}{{}_{prePVE}\text{embolized lobe}} \times 100$$ [11].

Standardized FLR volume

The method used to measure FLR volume can influence the results of studies on liver volume. The most accurate approach is to standardize remnant size to individual patient size to account for the reality[1, 3, 12-14]. With this method, FLR volume is measured directly with volumetric CT images, but the total liver volume is estimated (TELV; total estimated liver volume) using a formula derived from the close association between liver size and patient size based on body weight and body surface area (BSA).

The formula used to determine TELV is as follows:

$$TELV = -404.8 + 961.3 \times BSA\ (m^2)$$

$$BSA = \frac{\sqrt{height\ (cm) \times weight\ (kg)}}{3600}$$ [15].

The standardized FLR volume is expressed as a percentage of the TELV, specifically, as FLR volume from CT / formula-derived TELV (henceforth referred to as the FLR/TELV ratio). The FLR/TELV ratio provides a volumetric estimate of FLR function. Shirabe et al.[16] described the importance of standardizing liver volume to patient size (based on BSA). To evaluate the degree of hypertrophy, the FLR/TELV ratio was calculated before and after PVE.

Postprocedural follow-up

Patients required several hours of bed rest after the procedure and were admitted to the hepatobiliary and pancreatic surgery ward for routine postprocedural care. Postembolization syndrome, which included pain, fever, and abnormal blood counts and liver function tests (total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were assessed before, 1 day after, and 4 – 7 days after PVE. Prothrombin time, serum albumin, alkaline phosphatase, and cholinesterase were also assessed before and after PVE.

Analysis

Technical success was defined as the complication-free introduction of an angiographic catheter into the portal vein and the embolization of predesignated portal vein branches. Clinical success was defined as completion of the surgical procedure. SPSS software (version 11.0; SPSS, Chicago, IL) and Aabel 3 (Version 3; Gigawiz, Tulsa, OK) were used for statistical analysis. Nonpaired data were tested with the Mann-Whitney U test, and the Wilcoxon test and paired t-test were used for paired data. Cross-tables and χ^2 tests were used for analysis of categoric data. All tests were two-sided with a 5% significance level. Results are expressed as means ± SDs (median, range).

Results

Technical and clinical success

Preoperative transhepatic PVE using MFC was technically successful in all 37 procedures in 35 patients (100%). The right portal vein was embolized with an ipsilateral approach in 32 patients and a contralateral approach in one patient. Two patients (one with hilar bile duct cancer and the other with intrahepatic cholangiocellular carcinoma) who were scheduled for extended left lobectomy based on their tumor locations, had stenoses of the left portal vein and underwent embolization of the right anterior segment branches.

No major procedure-related complications occurred, including subcapsular hematoma, hemobilia caused by inadvertent puncture, peritoneal bleeding, portal thrombosis, or pneumothorax. Ten patients developed moderate transient fever (29%, 10/35) that was treated with cooling or antipyretic analgesics. No patients experienced abdominal pain requiring medication, and none developed fulminant liver insufficiency after PVE.

The clinical success rate was 77% (27/35). Surgery was performed on 27 of the 35 patients who underwent PVE. The procedures included extended right lobectomy (n = 6), extended right lobectomy with resection of the caudate lobe (n = 11), extended right lobectomy with additional partial resection (n = 1), right lobectomy (n = 1), right lobectomy with partial resection (n = 3), right lobectomy with resection of the caudate lobe (n = 1), multiple partial resection (n = 1), right trisegmentectomy (n = 2), and left trisegmentectomy (n = 1). The mean interval between PVE and surgery was 27 ±

12 days (25, 15–74 days). Surgery was cancelled eight times due to either refusal (n = 1) or disease progression (n = 7). In six of the seven patients with disease progression, peritoneal carcinomatosis was observed at surgery.

Recanalization of the portal vein

Recanalization of the portal branches was observed on follow-up volumetric CT after a mean of 16 ± 6.3 days (14, 4 – 33 days). The recanalization rate per procedure was 55.6% (20/36 procedures). This rate was significantly higher in the bPVE group (83.3%, 10/12) than in the sPVE group (41.7%, 10/24) (p = 0.018). We also used a scoring system to assess recanalization of the portal venous system from the first- to the third-order branches. Occluded branches were assigned a score of 0, while patent branches were assigned a score of 1. Overall recanalization scores consist of the sums of each score from the first- to the third-order branches (Fig. 2). The overall mean score was 1.9 ± 2.2 (2, 0 – 7). The recanalization score in the bPVE group was 3.8 ± 2.5 (4, 0 – 7), which was significantly higher than the 1.0 ± 1.4 (0, 0 – 7) score in the sPVE group (p = 0.002). This indicated that recanalization had progressed to the second- or third-order peripheral branches in the bPVE group, but only to the first- or second-order branches in the sPVE group (Table 1).

Liver volume changes

We assessed morphologic changes of the liver after PVE with MFC. The mean interval between PVE and CT volumetric evaluation was 16 ± 6.3 days (14, 4 – 33 days). One patient with surgically confirmed peritoneal dissemination was excluded from volumetric analysis because a slight degree of jaundice was demonstrated by biochemical analysis, and marked intrahepatic biliary dilatation and diffusely enlarged liver were identified on initial volumetric CT. In this case, PVE caused atrophy of the entire liver,

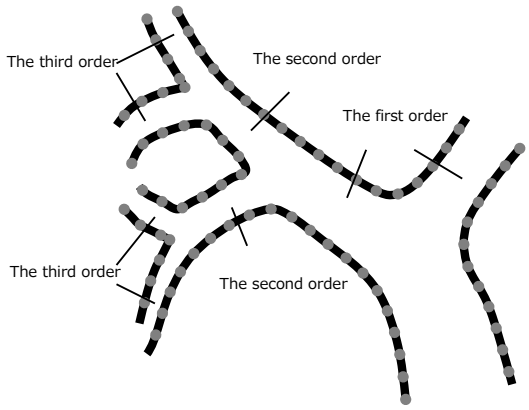

Figure 2 a

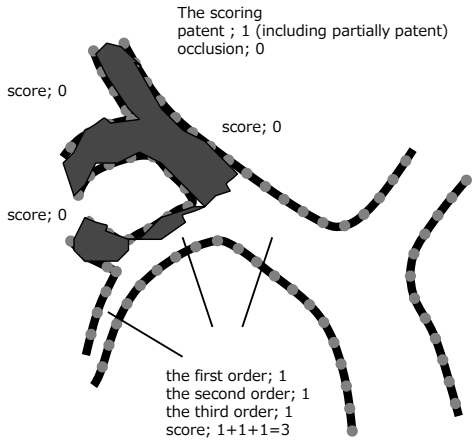

Figure 2 b

Figure 2 Anatomy of the portal venous system and recanalization scoring
Anatomy of the portal venous system (a). First-order veins include the proximal portal vein branches. Second-order veins include the anterior and posterior segmental branches. Third-order veins include the peripheral (sebsegmental) branches. Example: Recanalization scores are expressed as the sum of the scores for first-, second-, and third-order portal veins. The recanalization score for the example presented above is 3 (b).

and it was therefore thought to be inappropriate to assess FLR volume changes. Volumetric measurements were carried out for a total of 36 PVE procedures in 34 patients.

The preembolization total liver volume (TLV) was 1231 ± 304 cm^3 (1175, 761 – 2218 cm^3), which was not significantly different from the postembolization TLV, which was 1231 ± 261 cm^3 (1195, 723 – 2030 cm^3). The calculated

Table 1 Recanalization rates and scores

	Recanalization rates after a mean of 16 days post-PVE			Recanalization scores		
overall	55.6 %	(20/36)		1.9 ± 2.2	(2, 0-7)	
bPVE	83.3 %	(10/12)	p = 0.018	3.8 ± 2.5	(4, 0-7)	p = 0.002
sPVE	41.7 %	(10/24)		1.0 ± 1.4	(0, 0-4)	

bPVE: patients who underwent PVE with MFC under balloon occlusion of the right main portal vein.
sPVE: patients who underwent PVE with MFC selectively (peripheral branches only) in a centripetal pattern.

volume of the right lobe decreased significantly, from 797 ± 201 cm^3 (776, 481 – 1393 cm^3) before PVE to 706 ± 179 cm^3 (686, 355 – 1127 cm^3) after PVE ($p < 0.001$). The atrophy ratio was 10.7 ± 12.2% (11.2, −28.2 – 24.4). The calculated FLR volume increased significantly, from 435 ± 124 cm^3 (437, 269 – 835 cm^3) before PVE to 525 ± 124 cm^3 (511, 331 – 902 cm^3) after PVE ($p < 0.001$). The hypertrophy ratio was 23.3 ± 17.6% (24.0, −13.0 – 58.9).

The TELV was 1148 ± 174 cm^3 (1165, 751 – 1482 cm^3). The preembolization FLR/TELV ratio was 37.9 ± 8.8% (35.8, 21.7 – 67.3), while the postembolization FLR/TELV ratio was 46.1 ± 9.8% (43.4, 28.8 – 73.6). The increase in the FLR/TELV ratio was 8.2 ± 6.1% (7.3, −4.9 – 21.2) ($p < 0.001$).

The preembolization FLR volume in the bPVE group was 455 ± 147 cm^3 (461, 269 – 826 cm^3), which increased to 513 ± 148 cm^3 (506, 331 – 902 cm^3) after PVE ($p = 0.015$). The hypertrophy ratio was 15.2 ± 18.3% (9.8, −13.9 – 43.4). The FLR/TELV ratio in the bPVE group increased significantly, from 40.8 ± 11.5% (39.2, 26.5 – 67.3) before PVE to 46.3 ± 12.5% (42.7, 30.5 – 73.6) ($p = 0.011$). The increase in the FLR/TELV ratio was 5.6 ± 6.3% (6.0, −4.9 ± 16.6).

In the sPVE group, the FLR volume significantly increased from 425 ± 113 cm^3 (428, 269–648 cm^3) before PVE to 530 ± 114 cm^3 (519, 358 – 784 cm^3) after PVE ($p < 0.001$). The hypertrophy ratio was 27.4 ± 16.1% (30.8, −3.9 – 58.9). The FLR/TELV ratio in the sPVE group increased significantly, from 36.4 ± 7.0% (34.5, 21.7 ± 47.0) before PVE to 45.9 ± 8.5% (44.4, 28.8 ± 62.6) after PVE ($p < 0.001$). The increase in the FLR/TELV ratio was 9.5 ± 5.7% (8.9, −1.7 – 21.3). There was no significant difference between the bPVE and sPVE groups in terms of increase in FLR/TELV ratio ($p = 0.069$). A summary of the above data is shown in Table 2.

Laboratory findings

A slight, transient elevation in white blood cell count and serum AST and ALT values was observed at day 1 after PVE, but these values returned to pretreatment levels within a week (NS; Bonferroni correction). A transient decrease in platelet count was observed at day 1 after PVE, but this also returned to pretreatment values within a week (NS; Bonferroni correction). Serum total bilirubin was slightly elevated before PVE, and appeared to decline gradually after PVE, but the difference was not significant (NS; Bonferroni correction). Although the prothrombin time also appeared to decrease slightly after PVE, it remained above 90% of pretreament value. A significant decrease was observed in serum albumin ($p = 0.016$) and cholinesterase ($p = 0.008$) levels, but these remained within normal limits. No significant changes were observed in serum alkaline phosphatase or lactate dehydrogenase before and after PVE. Laboratory findings are summarized

Table 2 Volumetric data before and after PVE with MFC

PVE with MFC	TELV	Before PVE with MFC		After PVE with MFC		FLR/TELV increase (%)	Hypertrophy ratio (%)	Atrophy ratio (%)
		FLR	FRL/TELV (%)	FLR	FLR/TELV (%)			
overall (n = 36)	1148	435	38	525	46	8.2	23	10.7
bPVE (n = 12)		455	41	513	46	5.6	15	
sPVE (n = 24)		425	36	530	46	9.5	27	

PVE, portal vein embolization; MFC, microfibrillar collagen; TELV, total estimated liver volume; bPVE, patients undergoing portal vein embolization under balloon occlusion; sPVE, patients undergoing portal vein embolization via selective catheterization of branches in a centripetal pattern.

Table 3 Laboratory findings before and after PVE

	Before PVE mean ± SD (median, range)			1 day after PVE mean ± SD (median, range)			4-7 days after PVE mean ± SD (median, range)		
WBC, $\times 10^3$/ml	5.8 ± 1.8	(5.4, 3.4-10.5)	(n = 36)	6.2 ± 2.8	(6.3, 4.8-13.1)	(n = 36)	5.7 ± 1.3	(5.8, 3.3-8.9)	(n = 30)
Platelet count, $\times 10^3$/ml	235 ± 76	(220, 71-411)	(n = 36)	219 ± 76	(211, 100-436)	(n = 36)	249 ± 56	(240, 155-399)	(n = 30)
TB, mg/dl	2.9 ± 4.6	(0.9, 0.3-20)	(n = 36)	2.8 ± 3.4	(1.4, 0.4-18)	(n = 36)	2.4 ± 3.4	(1.2, 0.3-16.9)	(n = 31)
AST, U/L	53 ± 57	(39, 13-275)	(n = 36)	71 ± 52	(52, 23-247)	(n = 36)	56 ± 52	(47, 16-298)	(n = 31)
ALT, U/L	88 ± 114	(36, 15-584)	(n = 36)	103 ± 102	(75, 21-417)	(n = 36)	85 ± 73	(69, 18-387)	(n = 31)
PT, %	100 ± 12	(98, 80-122)	(n = 20)		NA		97 ± 12	(98, 77-119)	(n = 16)
ALP, U/L	720 ± 703	(472, 178-3851)	(n = 34)		NA		764 ± 531	(550, 255-2218)	(n = 32)
LDH, U/L	197 ± 53	(183, 113-348)	(n = 34)		NA		195 ± 61	(177, 121-400)	(n = 32)
Alb, mg/dl	3.9 ± 0.4	(4.0, 2.9-4.5)	(n = 34)		NA		3.8 ± 0.4	(3.7, 3.1-4.5)	(n = 32)
ChE, U/L	239 ± 55	(235, 152-364)	(n = 32)		NA		229 ± 57	(222, 137-382)	(n = 32)

AST, serum aspartate aminotransferase; ALT, serum alanine aminotransferase; ALP, alkaline phosphatase; TB, total bilirubin; WBC, white blood cell count, PT, prothrombin time; LDH, lactate dehydrogenase; Alb, serum albumin; ChE, cholinesterase; NA, not applicable.

in Table 3.

Discussion

As a result of advances in hepatobiliary surgical techniques, preoperative PVE is the most widely accepted and validated technique for use in patients with primary or secondary hepatobiliary malignancy. It provides desirable contralateral hypertrophy in curative large-volume hepatic resection when small FLR volumes are predicted. During the last decade, a number of authors have reported on the safety and effectiveness of preoperative PVE, as well as the techniques involved[1–6], and the procedure is well established at this point in time.

PVE can be performed using any of the following three standard approaches: transhepatic contralateral, ipsilateral, and transileocolic venous. Most often, the ipsilateral approach to the portal venous system is selected and performed under ultrasonographic and fluoroscopic guidance. With the ipsilateral approach, the puncture site and embolized lobe are on the same side[17]. The advantage of this approach is that the anticipated liver remnant is not exposed to surgical instruments[1,17], while the disadvantage of the contralateral approach is the risk of injury to the FLR. The most worrisome complication of the contralateral approach is complete portal vein thrombosis resulting from catheter maneuvers[18]. Reported disadvantages of the ipsilateral approach are that it requires complicated maneuvers using reverse-curve catheters (with or without microcatheters) as well as the use of specially prepared three- or four-lumen balloon catheters to avoid the reflux of embolic materials into the FLR[8, 18]. In using a balloon catheter as

previously described, one should be careful to select the proper embolic materials. In our experience, it was not difficult to maneuver a coaxial catheter system, and we expect it to be easy to embolize segment IV portal branches if necessary. The transileocolic approach requires general anesthesia and that the ileocolic vein be exposed surgically for cannulation, and is thus quite invasive. It is an alternative, however, when the percutaneous transhepatic approach is considered to be contraindicated.

With respect to complications, Kodama et al.[19] reported that iatrogenic effects occurred in 14.7% of subjects, and that these included pneumothorax, subcapsular hematoma, pseudoaneurysm, hemobilia, and one case of pseudoaneurysm that required transcatheter arterial embolization. The same report revealed that the rate of complications related to contralateral and ipsilateral methods were 18.1% and 13.9%, respectively[19]. Di Stefano et al.[18] reported that adverse events, which occurred in 12.8% (24/180) of subjects, included complete portal thrombosis (n = 1), inadvertent n-butyl-2-cyanoacrylate migration to the FLR (n = 2), hemoperitoneum (n = 1), hemobilia (n = 1), rupture of metastasis (n = 1), and liver failure (n = 6). In contrast to the above reports, no patients in the present study experienced complications.

Serum transaminase values showed a slight transient elevation but soon returned to pretreatment values about 1 week after PVE. The same trends have been reported regarding liver enzymes[2, 20]. According to Hong et al.[21], the hepatic lobe in which portal vein embolization was performed showed histological changes that corresponded to apoptosis rather than to necrosis. Since PVE necrosis has not been demonstrated in experimental animals, therefore, PVE is considered to be extremely non-invasive as a preoperative procedure, infrequently causing fever-up or pain[1, 4, 5, 18].

Numerous embolic materials have been described in the literature, including gelatin sponge and thrombin, coils, fibrin glue, n-butyl-2-cyanoacrylate, polyvinyl alcohol, and absolute alcohol, alone or in combination with other materials. PVE has recently been performed using implantation of the Amplatzer Vascular Plug[22, 23]. MFC is purified bovine collagen that has primarily been used to control capillary bleeding in surgical suites. In our institution, commercially prepared MFC is a cotton-like substance. It is easily mixed with non-ionic contrast agent, forming a radio-opaque suspension. In practice, before MFC is mixed with contrast agent it must be cut into small pieces that can be injected through an angiographic catheter, similar in this regard to gelatin sponge. MFC is highly thrombogenic, and has been shown to be effective despite heparinization and intrinsic clotting defects[24].

An ideal embolic agent should have the following characteristics: (1) be effective in causing vascular obstruction, (2) be safe for long-term implantation, (3) be persistent, (4) be able to pass easily through small, flow-directed catheters, and (5) be suitable for use regardless of the degree of arteriovenous shunting that exists within a particular vascular bed[25]. To ensure adequate liver regeneration, embolization of portal branches should be as complete as possible so as to minimize the recanalization of occluded portal branches[6]. Gelatin sponge is readily available, safe, and inexpensive, and most interventional radiologists are familiar with its handling, but it is associated with quite a high rate of early portal vein branch recanalization[6]. The use of gelatin sponge alone seems to have only limited efficacy. Combination use with iodized oil, coils, fibrin glue, polyvinyl alcohol, or polidocanol has been reported in the literature[21].

Although absolute alcohol is an alternative, alcohol is a cytotoxic agent that causes inflammation and sclerosis of the vascular endothelium on

contact. Dose-dependent periportal fibrosis and necrosis[5] have been reported in experimental animals, and in clinical use elevated transaminase values have been observed after PVE[26]. MFC in a semiliquid suspension passes easily through small catheters. The adjustment of both concentration and viscosity is straightforward. Platelet aggregation has been readily observed after MFC exits the catheter. MFC seems to exert its effects largely[24]. Given that MFC is expected to prolong obstruction and to induce adequate hypertrophy of FLRs, and that its use alone seems to be feasible, it has come to be the preferred embolic agent in our institution.

We initially performed PVE under balloon occlusion using an ipsilateral approach. MFC was injected through a side hole proximal to the balloon of a 5.5-F three-lumen balloon catheter and also simultaneously through a 7-F sheath lumen. The occlusion of the main right portal vein was confirmed on angiography after PVE, but follow-up volumetric CT revealed a recanalization rate of 83.3%. The hypertrophy ratio of FLRs after PVE was 15%, and the mean increase in the FLR/TELV ratio was 5.6%. These initial results were inadequate, and were inferior to those reported previously. The reason for early recanalization was postulated to be that MFC rapidly formed a large luminal thrombus in the proximal main right portal vein because of its thrombogenicity, while the peripheral branches remained patent. Daniels et al.[27] observed recanalization of the occluded vessels as early as one week after embolization with MFC, and consequently concluded that MFC should be considered a medium-duration embolic agent, similar in this respect to gelatin sponge[24]. Noncirrhotic human livers regenerate at rates of 12–24 cm^3/day at 2 weeks[17, 26]. To obtain adequate hypertrophy of the FLR, the portal vein occlusion must continue for at least 2 weeks. Since April 2009, therefore, in order to occlude the peripheral smaller branches, we have performed PVE with a coaxial system consisting of a 4.2-F reverse-curve catheter and a 2.7-F microcatheter, selectively embolizing in a centripetal direction from the peripheral to the proximal branches. Bae et al.[7] reported that in their PVE study with n-butyl-2-cyanoacrylate combined with gelatin sponge, they performed procedures in the same strategic manner. Selective PVE in a centripetal direction reduced the recanalization rate to 41.7%. The mean recanalization score was 1.0 ± 1.4 (0, 0 – 7), indicating that recanalization, if it existed, was limited to the first- and second-order branches.

Two CT volumetric techniques are commonly used[1, 12]. In the present study we employed standardized volumetry[13–15]. With this method the FLR volume is calculated actually, and TELV is calculated using a formula based on BSA. This formula might be a better fit for calculating TELV in Japanese adults by Hashimoto et al.[15], and allows for uniform comparison of FLR volumes before and after PVE. In the present study, elevated serum total bilirubin levels were identified in 12 of 35 patients (34%) before PVE, but calculation of the FLR volume after PVE did not require determining the presence or absence of either biliary dilatation or hepatic enlargement. Pamecha et al. reported an alternative method of FLR volumetry that involves calculating measurable tumor volume and subtracting this from total liver volume, tumor growth after PVE[28]. However, this approach is controversial. Tashiro[29] reported that tumor growth was accelerated after hepatectomy and that PVE or PV ligation resulted in marked contralateral hypertrophy and significant reduction in tumor growth in the non-embolized lobe. In the present study, the mean pre-PVE standardized FLR volume was 37.9%; the literature would suggest no need for PVE. Patients with normal livers and large liver remnants are unlikely to benefit from PVE[3]. We considered the FLR to be the non-embolized liver, including the

Table 4 Comparison of Embolic material, the FLR/TLV ratio, hypertrophy ratio, or increase ratio in the literature

Study Reference		No. of Patients	Embolic material	pre-PVE FLR/TLV (TELV) (%)	post-PVE FLR/TLV (TELV) (%)	FLR hypertrophy ratio(%)	FLR/TLV (TELV) increase ratio(%)	PVE	
Imamura et al., 1999	[2]	84	GS/Lipiodol mixture	32.2	42.4	NA	NA	rightPVE	
Madoff et al., 2003	[4]	26	PVA + Coils	18.1	25.8	NA	7.7	rightPVE+IV	†
Covey et al., 2005	[5]	58	PVA	39	48	24.3	9	rightPVE	†
Madoff et al., 2005	[3]	23	PVA	17	23.8	NA	6.9	rightPVE+IV	†
		21	Trisacryl microsphere	14.9	24.6	NA	9.7		
Kakizawa et al., 2006	[31]	14	GS/Lipiodol mixture	39	47	NA	7.9	rightPVE	
Tsuda et al., 2006	[6]	22	GS + coils	31.3	39.9	NA	8.5	rightPVE	
Gibo et al., 2007	[8]	8	Fibrin glue	NA	NA	30	NA	rightPVE	
Radeleff et al., 2007	[30]	15	Ethibloc/Lipiodol mixture	40 *	50 *	25 *	24 *	rightPVE	
Bent et al., 2009	[23]	16	Nitinol Plug + NBCA/ Lipiodol mixture	NA	NA	34	NA	rightPVE	
				NA	NA	NA	NA		
Bae et al., 2009	[7]	11	GS, NBCA/Lipiodol mixture	NA	NA	30	10	rightPVE	†
Baere et al., 2010	[32]	70	NBCA/Lipiodol mixture	25	39	NA	14	rightPVE	
		37		22	35	NA	13	rightPVE+IV	
Deneke et al., 2011	[33]	25	PVA	16.2 *	23 *	34.8 *	5.2	rightPVE	
Hong et al., 2011	[21]	14	GS, thrombin, polidocanol	19.8	27.2	NA	7.3	rightPVE	
Present study		34	MFC	38	46	23	8.2	rightPVE	
		24		36	46	27	9.5		

PVE, portal vein embolization; FLR, future liver remnant; TLV, total liver volume; TELV, total estimated liver volume; PVA, polyvinyl alcohol, GS, gelatin sponge; NBCA, n-butyl-2-cyanoacrylate; MFC, microfibrillar collagen; NA, not applicable,
*Median value.
†Total estimated liver volume was used for the evaluation.

caudate lobe, and that this did not necessarily correspond to the extent and complexity of the planned resection by the surgeon. To determine the indication for PVE, the planned extent of resection and extrahepatic procedures such as pancreaticoduodenectomy must be considered[1, 3]. Pre- and post-FLR/TELV, hypertrophy ratio, and FLR/TELV increase ratio in the present study and in previous reports are shown in Table 4. The hypertrophy ratio and FLR/TELV increase ratio of this study's sPVE group (selective embolization in a centripetal direction using MFC) are comparable with those of previous reports.

Madoff et al.[1, 3] reported durable PV occlusion that theoretically resulted from the occlusion of outflow vessels by PVA particles and occlusion of the inflow vessels by coils. We hypothesize that a similar luminal environment is created by centripetally directed selective embolization using MFC, as injected MFC replaces blood in the luminal space.

One limitation of the present study is its retrospective design, which may decrease its statistical strength. Furthermore, the number of patients was insufficient to allow for definite conclusions. Further prospective studies using larger numbers of patients will be necessary to clarify the oncological benefit of PVE. Finally, pathological examination could not be presented in this study.

In conclusion, although our experience was limited, preoperative PVE using MFC as a sole embolic material in patients with primary or secondary hepatobiliary malignancy was safe and feasible. No major complications required further medical procedures or led to prolonged hospital stays. PVE performed by selectively catheterizing peripheral branches in a centripetal direction effectively induced adequate

hypertrophy of the FLR. The FLR/TELV ratio, hypertrophy ratio, and FLR/TELV increase ratio in the present study were comparable to those in previous studies using other embolic materials.

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