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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 CT images showing routes of venous flow from the spleen after portal vein–superior mesenteric vein confluence resection (Word document)

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CASE REPORT

Esophageal stenting after penetrating complete esophageal obstruction using a trocar stylet via a gastrostomy route: a case report

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Abstract Complete esophageal obstruction developed after radiation and endoscopic submucosal dissection therapy for a cervical esophageal cancer in a 77-year-old woman. After failure to recanalize the esophageal obstruction by endoscopic and catheterization techniques, the esophageal obstruction was penetrated using a trocar stylet needle via a gastrostomy route. A covered stent was placed across the esophageal obstruction, letting her take water and liquid food until she died 2 months later. There was no complication related to the procedures except transient chest discomfort and pain that subsided with symptomatic treatment.

Keywords Esophageal obstruction · Esophageal stent · Trocar stylet needle of TIPS kit

Introduction

Complete esophageal obstruction (CEO) can result from both benign and malignant disorders [1] and occurs in 23 % of patients after radiation therapy [2]. CEO leads to an inability to swallow saliva, which induces major discomfort and causes serious problems such as aspiration and pneumonia. In the past, treatment options were limited to surgical resection or nutritional support through a gastrostomy or jejunostomy, but neither is ideal. In particular, surgical repair is extremely difficult in most patients after radiation therapy [3]. More recently, the usefulness of expandable esophageal stents has been well established [1]. Despite making full use of some techniques, there are occasionally patients in whom recanalization is difficult due to the CEO. Various useful techniques under endoscopic or fluoroscopic guidance to pass a guidewire through a CEO or severe stricture have been reported [3–7]. Several reports have already noted that the retrograde approach via a gastrostomy under endoscopic guidance with recanalization devices such as biopsy forceps, a needle knife, and an endoscopic ultrasound needle is a useful technique for resolving this problem [5, 6]. A few other studies have reported the high success rate (83–86 %) of combined endoscopic antegrade and retrograde dilation for the treatment of CEO [3, 7].

We herein report our experiences of treating complete esophageal obstruction that was refractory to all the above mentioned techniques.

Case report

A 77-year-old woman developed a CEO due to inflamm - tion after treatment for cervical esophageal cancer, and she was referred for possible stenting. She had a complete response to chemo-radiotherapy for an advanced cervical esophageal cancer 6 years earlier and also underwent ESD for an early esophageal cancer that arose just proximal to the initial lesion 2 years earlier. The esophageal stenosis occurred a year after the ESD. Endoscopic balloon

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dilatation was performed, but mediastinitis occurred due to esophageal perforation. She was managed conservatively using a central venous implantable port and surgical gastrostomy, and then she became well enough to ingest liquid foods. However, the stricture progressed, and oral intake became impossible again. Despite the situation, she desired oral ingestion. Unfortunately, since treatment via endoscopic guidance was impossible, an interventional radiology procedure under fluoroscopic guidance was performed after obtaining the patient's written, informed consent.

The cranial end of the CEO was located at the level of the superior border of the second thoracic vertebral body. Recanalization of the obstruction by a transnasal approach under fluoroscopic guidance was tried first, but it was unsuccessful, and esophageal perforation occurred again. After conservative treatment for 8 days, a retrograde approach via the existing gastrostomy was performed. The CEO was too rigid to pass the guidewire even using the tip of the guidewire tail. Since the antegrade and retrograde esophagograms revealed that the obstruction was rather straight and the length was no more than 5 mm (Fig. 1), it was decided to penetrate it using the 0.038-inch trocar stylet needle of the Rösch-Uchida Transjugular Liver Access Set, TIPS kit (Cook, Bloomington, IN, USA).

A 7-French angiographic sheath was inserted in the lower thoracic esophagus from the gastrostomy, and the trocar stylet needle within the 5-French catheter was carefully advanced, with needle tip positioned just beneath the obstruction (Fig. 2). By pushing the needle up with a slight force, it was possible to easily penetrate the obstruction under fluorosco y in one direction and to pass the guidewire up to the nose. Then, a 14-French, 60-cm-long tube (PTCS catheter; Sumitomo Bakelite, Akita, Japan) was inserted as a bougie from the nose to the distal esophagus, because the stricture was very tight. Four days later, a 16.5-French stent delivery catheter could be easily passed through the stricture, and a 10-cm-long Niti-S covered esophageal stent with a body diameter of 18 mm (Taewong Medical, Seoul, Korea) was successfully placed at the obstruction (Fig. 3). A covered stent was used because esophageal perforation occurred prior to this procedure. All procedures were performed under local anesthesia and mild sedation. A follow-up esophagography, 9 days after the stent placement, showed full expansion and patency of the stent. Although the patient had discomfort and slight pain in the chest after the procedure, it improved with symptomatic treatment for several days with her being able to take water and liquid food. This patient was transferred to a convalescent hospital 2 months after the procedure, and then she died from a suspected cardiac disorder in that hospital a few days later.

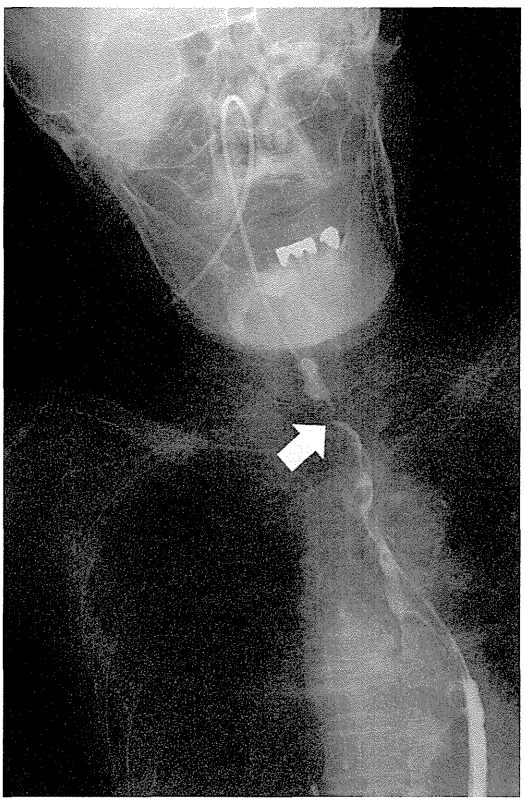

Fig. 1 Antegrade and retrograde esophagograms reveal that the obstruction (*arrow*) is straight and 5 mm in length

Discussion

A sharp recanalization technique using a trocar stylet needle of a TIPS kit under endoscopic guidance has been described in two case reports [8, 9]. These reports indicated that the procedure using this needle could be performed safely when the direction of puncture was verified exactly. In the present case, it was possible to ensure that the trocar stylet needle penetrated the true lumen under fluorosco y in one direction, because the obstruction was rather straight and short. However, it might be necessary to verify the exact puncture site and the relationship with the surrounding organs on CT or fluorosco y in multiple directions, when this needle is used for a longer obstruction or a lesion at a curvilinear site, such as the esophagogastric junction, because of the difficulty in adjusting needle direction. Furthermore, in order to perform a safe puncture of the CEO via the gastrostomy, the device is required to have an appropriate length and thickness to reach and penetrate the obstruction. This needle was sufficient to meet these requirements

In fact, the transgastric approach was chosen for penetrating the obstruction because it was more suitable for a linear approach than the oral route. Although a transgastric approach was relatively easy because the gastrostomy

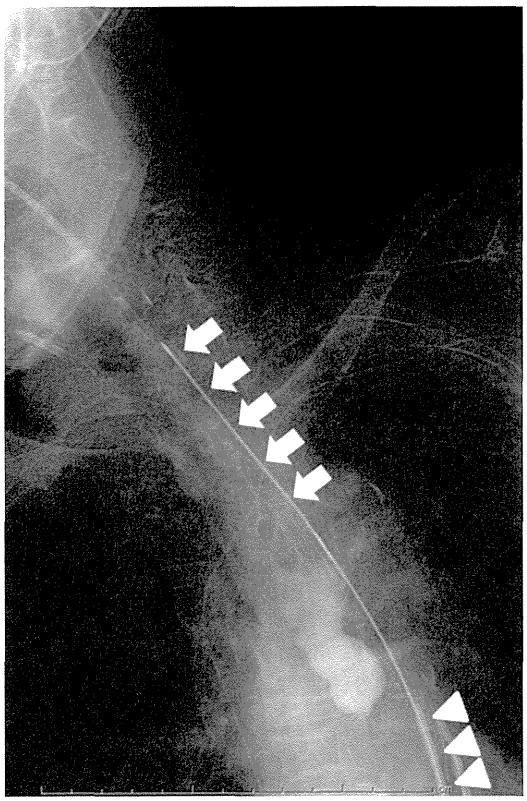

Fig. 2 Fluoroscopic image shows successful penetration of the obstruction using a trocar stylet needle within a guiding catheter (*arrows*) inserted through the angiographic sheath (*arrow heads*) via a retrograde route

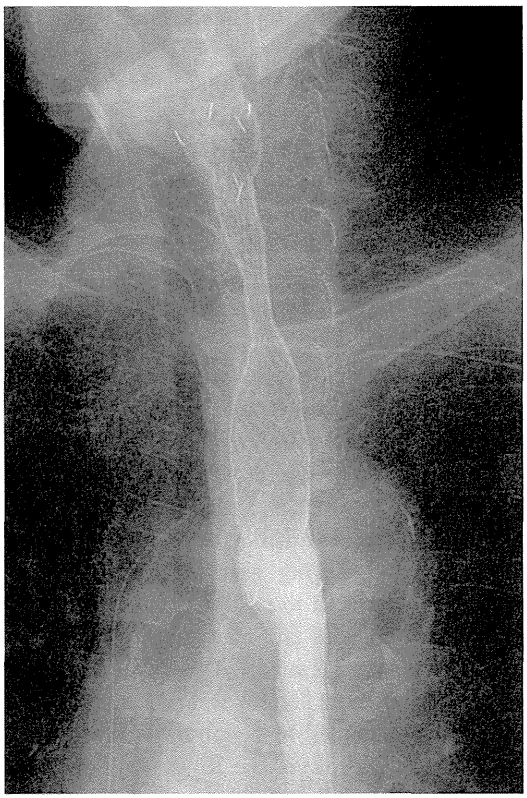

Fig. 3 A Niti-S covered esophageal stent has been successfully placed at the obstruction

had been previously created surgically in this case, a direct transgastric approach can be implemented with ultrasound or CT guidance even in such CEO patients. Inaba et al. [10] reported the feasibility of the percutaneous radiologic gastrostomy procedure in CEO cases.

Our experience suggested that a trocar stylet needle of a TIPS kit could be useful for penetrating a rigid esophageal obstruction that was resistant to any conventional recanalization procedures.

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Prognosis of patients with intermediate-stage hepatocellular carcinomas based on the Child-Pugh score: subclassifying the intermediate stage (Barcelona Clinic Liver Cancer stage B)

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Abstract
Purpose Retrospective evaluation of intermediate-stage hepatocellular carcinoma (HCC) patient survival after undergoing chemoembolization based on the Child-Pugh score.
Materials and methods Data of intermediate-stage HCC patients undergoing chemoembolization were gathered from 43 centers in Japan. Overall survival rates were compared with Child-Pugh scores.
Results Of the 329 patients examined in this study, Child-Pugh scores were 5 (CP-5) in 136 patients (41.3 %), 6 (CP-6) in 101 patients (30.7 %), 7 (CP-7) in 58 (17.7 %), 8 (CP-8) in 22 (6.7 %), and 9 (CP-9) in 12 (3.6 %). Two-year survival rates were 77.5 % in CP-5 patients ($p = 0.047$ vs. CP-6), 65.1 % in CP-6 patients ($p = 0.038$ vs. CP-7), 51.3 % in CP-7 patients ($p = 0.30$ vs. CP-8, $p = 0.034$ vs. CP-9), 50.3 % in CP-8 patients ($p = 0.0065$ vs. CP-9), and 16.7 % in CP-9 patients. Two-year survival rates were 77.2 % in 139 patients meeting the 4 tumors of 7 cm criterion with Child-Pugh class A (B1) ($p < 0.0001$ vs. B2), 59.5 % in 178 patients other than B1 and B3 (B2)

On behalf of the Clinical Research Group of the Japanese Society for Transcatheter Hepatic Arterial Embolization.

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($p = 0.0014$ vs. B3), and 16.7 % in 12 patients with Child-Pugh score 9 (B3).
Conclusion The Child-Pugh score is a useful prognostic factor to stratify intermediate-stage HCC patients.

Keywords Hepatocellular carcinoma · Chemoembolization · Child-Pugh score · Prognosis · Stage

Introduction

Hepatocellular carcinoma (HCC), the fifth most common cancer in the world, shows increasing incidence worldwide [1]. Curative therapies, including resection, liver transplantation, and percutaneous ablation such as radiofrequency ablation (RFA), are applicable in only 30–40 % of HCC patients [1]. Other HCC patients undergo palliative treatments because of advanced tumor stage or poor hepatic functional reserve. Transarterial chemoembolization has been used widely for the treatment of Barcelona Clinic Liver Cancer (BCLC) stage B HCC, which is defined as an intermediate-stage disease [2] that consists of highly heterogeneous patients having Child-Pugh grade A and B liver function with four or more tumors irrespective of size, or 2–3 tumors larger than 3 cm maximum diameter, in the absence of cancer-related symptoms, macrovascular invasion, or extrahepatic spread [3]. Although the survival benefit of undergoing chemoembolization has been demonstrated in comparison with the best supportive care [4–6], it remains unclear whether there might be any subgroup stratification for which chemoembolization can provide better prognosis than others [3, 7]. A movement is underway to divide intermediate-stage HCC patients into substages to stratify patients based on their respective prognoses following chemoebolization. Some factors such as the up-to-7 criteria, the four tumors of 7 cm criterion (4-of-7-cm criterion), and Child-Pugh score have been used as favorable prognostic factors to subclassify the intermediate stage [3, 7, 8]. However, adverse prognostic factors have not been well investigated yet. Furthermore, although the the Child-Pugh score is regarded as a key to stratify the intermediate stage, prognosis based on Child Pugh scores has not been well elucidated in intermediate-stage HCC patients [9].

This retrospective study was conducted to evaluate the survival of intermediate-stage HCC patients undergoing chemoembolization based on the Child-Pugh score and to subclassify the intermediate stage.

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Materials and methods

Study design

The Clinical Research Group of the Japanese Society of Transcatheter Hepatic Arterial Embolization sent questionnaire sheets to 255 training centers accredited by the Japanese Society of Interventional Radiology to take part in this study. Patient data were gathered from the 43 institutions (16.9 %, 43/255) that agreed to participate [7, 10]. At each institution, IRB approval was obtained for this study. Because of the retrospective nature of this study, the requirement of obtaining informed consent to take part in this study was waived at all but two institutions, where informed consent was obtained from surviving patients.

Data of patients who had Child-Pugh grade A or B liver profiles and who had received chemoembolization as the initial treatment for intermediate-stage HCCs during 2003–2004 were gathered in October 2011 and were updated in June 2014. Patients who were followed less than 3 months and for whom the Child-Pugh score was not assigned were excluded.

Patients

In 2003 and 2004, 1290 patients received chemoembolization as the initial treatment of unresectable HCCs. Of those, 329 patients (25.5 %, 329/1290) met the inclusion criteria and were enrolled in this study.

The HCC diagnosis was made, based mainly on imaging modalities using ultrasonography, contrast-enhanced computed tomography (CT), magnetic resonance (MR) imaging, and angiography, in addition to elevation of tumor markers such as α-fetoprotein and des-γ-carboxyl prothrombin. The typical HCC was depicted as an enhanced tumor in the arterial phase and washout in the delayed phase in contrast-enhanced CT and MRI, and as a hypervascular tumor in digital subtraction angiography [11].

The 86 women and 243 men examined in this study were of mean age of 69.3 ± 8.6 [standard deviation (SD)] years (range 37–87 years). Patients were divided into five groups based on Child-Pugh numerical scores (CP-5–9)

Table 1 Patient and tumor backgrounds based on Child-Pugh scores

	CP-5	CP-6	CP-7	CP-8	CP-9
n	136	101	58	22	12
Male/female	101/35	74/27	43/15	17/5	8/4
Age (years)	70.1 ± 8.8	69.3 ± 8.8	69.2 ± 8.0	64.6 ± 7.0[*1]	68.6 ± 7.4
Hepatitis C virus/others	93/43	75/26	49/9	16/6	7/5
Albumin (g/ml)	4.0 ± 0.3	3.4 ± 0.4[*2]	3.2 ± 0.4[*3]	3.1 ± 0.4	2.8 ± 0.4
Bilirubin (mg/dl)	0.8 ± 0.3	1.1 ± 0.4[*4]	1.2 ± 0.6	1.9 ± 0.8[*5]	1.8 ± 0.7
% Prothrombin time (%)	89 ± 11	78 ± 14[*6]	73 ± 15[*7]	60 ± 11[*8]	60 ± 22
Ascites (±)	136/0	93/8[*9]	44/14[*10]	13/9	2/10[*11]
Encephalopathy (±)	136/0	101/0	57/1	20/2	10/2
Maximum tumor diameter (cm)	4.1 ± 2.5	4.4 ± 2.9	4.5 ± 2.5	4.1 ± 2.4	4.7 ± 4.7
Tumor number(≤4/≥5)	82/54	67/34	37/21	13/9	7/5
Hemilobe/bilateral lobe	55/81	32/69	20/38	6/16	3/9
α-Fetoprotein (±)	59/77	29/72[*12]	16/42	5/17	3/9
Up to 7 (in/out)	64/72	41/60	25/33	7/15	4/8
4–7 cm (in/out)	77/59	62/39	33/25	12/10	6/6
Selective embolization/non-selective embolization	88/48	54/47	38/20	16/6	9/3

[*1] $p = 0.012$ vs. CP-7;
[*2] $p < 0.0001$ vs. CP-5;
[*3] $p = 0.0001$ vs. CP-6;
[*4] $p < 0.0001$ vs. CP = 5;
[*5] $p < 0.0001$ vs. CP-7;
[*6] $p < 0.001$ vs. CP-5;
[*7] $p = 0.0082$ vs. CP-6;
[*8] $p = 0.001$ vs. CP-7;
[*9] $p = 0.0009$ vs. CP-5;
[*10] $p = 0.0075$ vs. CP-6;
[*11] $p = 0.030$ vs. CP-8;
[*12] $p = 0.022$ vs. CP-5

(Table 1). The tumors were uncountable because of the overly large number (>10) in 65 patients (19.8 %, 65/329).

Chemoembolization

Chemoembolization was performed using iodized oil and anticancer drugs such as epirubicin and mitomycin. A gelatin sponge was used as an embolic material. Chemoembolization was performed in the segmental artery or more peripherally in 194 patients (59.0 %, 194/329) and more proximally in the other 135 patients (41.0 %, 135/329) (Table 1).

Assessments and statistical analysis

Patient and tumor backgrounds were compared between each patient group. A Mann-Whitney *U* test was used to compare the numerical data and Fisher's exact test was used to compare the categorical data. The data were expressed as mean ± SD. A p value of 0.05 was regarded as statistically significant. Liver function was compared between adjacent groups. Overall survival rates were obtained based on the Child-Pugh scores using the Kaplan-Meier method and were compared using the log-rank test to evaluate whether the Child-Pugh score can be a prognostic factor. If a Child-Pugh score was shown to have adverse effects on survival, then all patients were divided into three substages based on the 4-of-7-cm criterion and Child-Pugh class.

All statistical analyses were conducted using software (Statistical Analysis System, SAS version 8.02; SAS Inc. Cary, NC).

Results

Patient tumor backgrounds

Patient backgrounds were similar except for liver function and age between the CP-7 and CP-8 patient groups (Table 1). The tumor backgrounds were also similar except for the patient percentage of positive AFP between the CP-5 and CP-6 patient groups (Table 1). No significant difference in embolization procedures was found among patient groups.

Overall survival rate

The 1-, 2-, 3-, and 5-year overall survival rates were 86.1 % (95 % CI 82.2–89.9 %), 65.3 % (95 % CI 59.8–70.7 %), 45.8 % (95 % CI 39.8–51.8 %), and 24.2 % (95 % CI 18.6–29.7 %) in all patients.

The 2-year survival rates and median survival times were 77.5 % [95 % confidence interval (CI) 70.1–84.9 %] and 39.7 months in CP-5, 65.1 % (95 % CI 55.5–74.8 %) and 32.4 months in CP-6, 51.3 % (95 % CI 37.4–65.2 %) and 24.1 months in CP-7, 51.3 % (37.4–65.2 %) and 33.4 months in CP-8, and 16.7 % (95 % CI 0–37.8 %) and 13.0 months in CP-9 patient groups (Fig. 1). Significant differences were found in the survival between CP-5 and CP-6 ($p = 0.047$), between CP-6 and CP-7 ($p = 0.0378$), between CP-7 and CP-9 (0.034), and between CP-8 and CP-9 ($p = 0.0065$) patient groups (Fig. 1). No significant difference was found in the overall survival between CP-7 and CP-8 patient groups ($p = 0.30$) (Fig. 1).

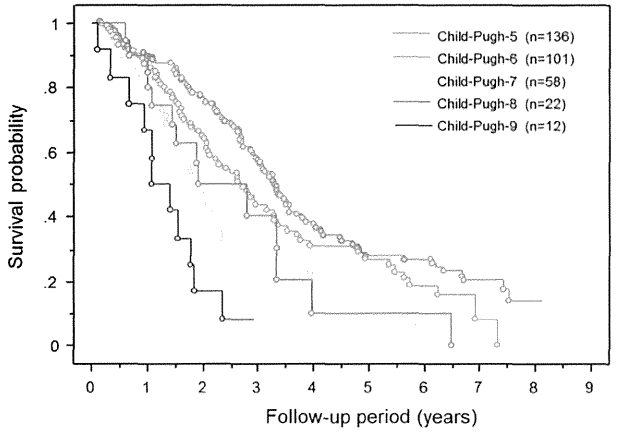

Fig. 1 Overall survival rates based on Child-Pugh score. Two-year survival rates and the median survival times were 77.5 % [95 % confidence interval (CI) 70.1–84.9 %] and 39.7 months in CP-5, 65.1 % (95 % CI, 55.5–74.8 %) and 32.4 months in CP-6, 51.3 % (95 % CI 37.4–65.2 %) and 24.1 months in CP-7, 51.3 % (37.4–65.2 %) and 33.4 months in CP-8, and 16.7 % (95 % CI 0–37.8 %) and 13.0 months in CP-9. Significant differences were found in survival between CP-5 and CP-6 ($p = 0.047$), between CP-6 and CP-7 ($p = 0.0378$), between CP-7 and CP-9 (0.034), and between CP-8 and CP-9 ($p = 0.0065$) patient groups. No significant difference was found in overall survival between CP-7 and CP-8 patient groups ($p = 0.30$)

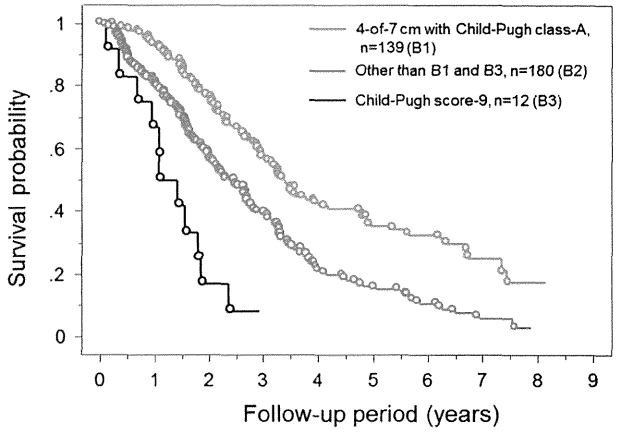

Fig. 2 Subclassification of the intermediate stage. Patients were divided into three new substages. One substage (B1) consisted of Child-Pugh grade A patients with HCC lesions within the 4-of-7-cm criterion. The second substage (B2) included patients other than B1 and B3. The third substage (B3) included patients with Child-Pugh score 9 (equal to the CP-9 patient group). Significant differences were found in overall survival between patient groups: B1 vs. B2 ($p < 0.0001$) and B2 vs. B3 ($p = 0.0014$). Two-year survival rates and the median survival time were 77.2 % (95 % CI 69.8–84.5 %) and 40.5 months in 139 patients meeting the 4 tumors of 7 cm criterion with Child-Pugh class A (B1), 59.5 % (95 % CI 51.8–67.1 %) and 28.1 months in 178 patients other than B1 and B3 (B2), and 16.7 % (95 % CI 0–37.8 %) and 13.0 months in 12 patients with Child-Pugh score 9 (B3). CP, Child-Pugh

During the mean follow-up of 31.2 months ± 22.8 (range 3.0–97.2 months), 219 patients (66.6 %, 219/329) died. Cancer progression was the most frequent cause of death, followed by liver failure, other diseases, gastrointestinal hemorrhage, tumor rupture, and unknown causes (Table 2). Although CP-9 patients were more likely to die of cancer progression (41.7 %) and liver failure (33.3 %), no significant difference from other patient groups was found.

Substaging of intermediate stage

Patients were divided into three new substages. One substage (B1) consisted of Child-Pugh grade A patients with HCC lesions within the 4-of-7-cm criterion. The second substage (B2) included patients other than B1 and B3. The third substage (B3) included patients with Child-Pugh score 9 (equal to the CP-9 patient group) (Fig. 2). Significant differences were found in overall survival between patient groups: B1 vs. B2 ($p < 0.0001$) and B2 vs. B3 ($p = 0.0014$) (Fig. 2). Two-year survival rates and the median survival time were 77.2 % (95 % CI 69.8–84.5 %) and 40.5 months in 139 patients meeting the 4 tumors of 7 cm criterion with Child-Pugh class A (B1), 59.5 % (95 % CI 51.8–67.1 %) and 28.1 months in 178 patients other than B1 and B3 (B2), and 16.7 % (95 % CI 0–37.8 %) and 13.0 months in 12 patients with Child-Pugh score 9 (B3).

Discussion

This study showed that the Child-Pugh numerical score is useful for stratifying intermediate-stage HCC patients undergoing chemoembolization.

Table 2 Causes of death based on Child-Pugh scores

	A5	A6	B7	B8	B9
Number of deaths	89 (65.4 %)	66 (65.3 %)	39 (67.2 %)	14 (63.6 %)	11 (91.7 %)
Cause of death					
Cancer progression	46 (33.8 %)	32 (31.7 %)	20 (34.5 %)	5 (22.7 %)	5 (41.7 %)
Liver failure	24 (17.6 %)	17 (16.8 %)	8 (13.8 %)	5 (22.7 %)	4 (33.3 %)
Other disease	9 (6.6 %)	7 (6.9 %)	4 (6.9 %)	2 (9.1 %)	1 (8.3 %)
Gastrointestinal bleeding	3 (2.2 %)	6 (5.9 %)	3 (5.2 %)	1 (4.5 %)	0 (0 %)
Tumor rupture	2 (1.5 %)	3 (3.0 %)	3 (5.1 %)	0 (0 %)	0 (0 %)
Unknown	5 (3.7 %)	1 (1.0 %)	1 (1.7 %)	1 (4.5 %)	1 (8.3 %)

Bolondi et al. advocated division of the intermediate-stage into four substages based on the up-to-seven criteria and Child-Pugh scores (5–7 vs. 8–9) [3]. Recently, one study validated this substaging. Difficulty in stratifying the patient group that benefits least from chemoembolization was reported [12]. Aside from the up-to-seven criteria, the 4-of-7-cm criterion and Child-Pugh class A were identified as favorable prognostic factors in patients with intermediate-stage HCCs undergoing chemoembolization [7]. However, difficulty lies in distinguishing a patient group that benefits least from chemoembolization even using the 4-of-7-cm criterion and Child-Pugh class in the same way. These findings allowed us to detect adverse prognostic factors that may be useful in distinguishing a patient group that benefits least from chemoembolization.

Piscaglia et al. [9] evaluated the survival of intermediate-stage HCC patients with a Child-Pugh class-B liver profile. Although they reported longer median survival times after chemoembolization in Child-Pugh score-7 patients than Child-Pugh score-8 patients (22.0 months vs. 6.0 months), they were unable to identify any clinical variable suggesting a better outcome in the former patient group than in the latter [9]. By the same token, we also were unable to find a survival difference between the CP-7 and CP-8 patient groups in this study. An overlap between these patients appears to be caused by a wave of liver function. Selection bias might be another explanation. Piscaglia et al. reported that chemoembolization (or ablation) was applied in 68.8 % of Child-Pugh score-7 patients, 50 % of Child-Pugh score-8 patients, and 0 % of Child-Pugh score-9 patients. We gathered data of patients who underwent chemoembolization, but we had no data about how many intermediate-stage HCC patients underwent therapeutic options other than chemoembolization based on each Child-Pugh score. Irrespective of the overlap between the Child-Pugh score-7 and score-8 patients, it is noteworthy that Child-Pugh score 9 was found to be a significant adverse prognostic factor in this study. Significant survival differences were found between the CP-7 and CP-9 patient groups and CP-8 and CP-9 patient groups.

Llovet et al. performed a randomized control trial and verified survival benefits of chemoembolization compared with conservative treatment in mostly intermediate-stage HCC patients [6]. The 2-year survival rates were 63 % in the chemoembolization group and 27 % in the symptomatic treatment group. Cabibbo et al. evaluated the natural history of HCC patients and reported a similar 2-year survival rate of 22 % with median survival time of 17.4 months in intermediate-stage HCC patients. They also emphasized the influence of liver function reserve on the natural course of HCC patients. The median survival times of untreated HCC patients were, respectively, 9.8, 6.1, and 3.7 months in Child-Pugh classes A, B, and C.

Both the 2-year survival rates (50.3–77.5 %) and median survival times (24.1–39.7 months) achieved in this study were better than the natural history of intermediate-stage HCC patients (22–27 % and 17.4 months) when Child-Pugh scores were 5–8. However, the 2-year survival rate (16.7 %) achieved in Child-Pugh score-9 patients was not higher than the natural history, although the median survival time (13.0 months) showed survival benefits against the natural history of HCC patients with Child-Pugh class B (6.0 months).

Therefore, the possibility exists that chemoembolization does not benefit intermediate-stage HCC patients with Child-Pugh score 9.

We divided the intermediate stage into three subgroups (B1–B3) using favorable (4-of-7-cm criterion and Child-Pugh class A) and adverse (Child-Pugh score 9) prognostic factors. Results revealed clear patient stratification based on survival. However, the retrospective nature is a limitation of this study, in addition to the patient selection bias mentioned above. Additional studies must be conducted to verify our results and identify suitable therapeutic alternatives such as radiofrequency ablation and transarterial infusion chemotherapy for patients with intermediate-stage HCCs based on substages.

In conclusion, the Child-Pugh score is a significant prognostic factor for intermediate-stage HCC patients who undergo chemoembolization. Moreover, it is a useful factor for stratifying intermediate-stage HCC patients.

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Prospective Evaluation of the Optimal Duration of Bed Rest After Vascular Interventions Using a 3-French Introducer Sheath

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Abstract
Purpose To assess optimal bed-rest duration after vascular intervention by way of the common femoral artery using 3F introducer sheaths.
Materials and Methods Eligibility criteria for this single-center, prospective study included clinically necessary angiography, no coagulopathy or anticoagulant therapy, no hypersensitivity to contrast medium, age >20 years, and written, informed consent. Enrolled patients were assigned to one of three groups (105/group) with the duration of bed rest deceased sequentially. A sheath was inserted by way of the common femoral artery using the Seldinger technique. The first group (level 1) received 3 h of bed rest after the vascular intervention. If no bleeding or hematomas developed, the next group (level 2) received 2.5 h of bed rest. If still no bleeding or hematomas developed, the final group (level 3) received 2 h of bed rest. If any patient had bleeding or hematomas after bed rest, the study was terminated, and the bed rest of the preceding level was considered the optimal duration.
Results A total of 105 patients were enrolled at level 1 between November 2010 and September 2011. Eight patients were excluded from analysis because cessation of bed rest was delayed. None of the remaining subjects experienced postoperative bleeding; therefore, patient enrollment at level 2 began in September 2011. However, puncture site bleeding occurred in the 52nd patient immediately after cessation of bed rest, necessitating study termination.
Conclusion To prevent bleeding, at least 3 h of postoperative bed rest is recommended for patients undergoing angiography using 3F sheaths.

Keywords Bed rest duration · 3-French introducer sheath · Non-coronary intervention

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Introduction

The duration of bed rest after angiography varies from 4 to 24 h among institutions in Japan. With many angiography procedures, the length of bed rest is based on the clinical experience of each institution or operator [1, 2]. A meta-analysis of bed-rest duration that was performed using 20 studies (including coronary angiography) involving 4,019 participants reported 47 bleeding events after the procedure using 4F to 7F catheters [3].

In contrast, if the use of 3F introducer sheaths markedly decreases the need for postoperative bed rest, not only would patient discomfort be decreased but angiography would be feasible on an outpatient basis compared with conventional angiography requiring hospitalization in Japan. Decreasing bed-rest time would also be beneficial in terms of use of health care resources; however, it is unclear whether vascular interventional radiology (VIR) procedures using 3.5F catheters can also be performed with 3F introducer sheaths. It is well established that the smaller the gauge of the parent catheter, the more difficult it is to guide the catheter to its destination.

This study was designed both to examine the feasibility of angiography using 3F introducer sheaths and to determine whether the duration of postoperative bed rest can be decreased. The primary end point was the optimal duration of bed rest, and secondary end points were feasibility of the procedure and occurrence adverse events.

Materials and Methods

This study was approved by the Clinical Research Ethics Committee of our institution, and all patients gave written, informed consent before enrollment. This study was registered in the UMIN Clinical Trial Registry (UMIN000007134).

Inclusion and Exclusion Criteria

Patients were eligible for enrollment in the study if they met the following inclusion criteria: (1) angiography for abdominal malignant tumor or other reason; (2) no clinical bleeding tendency or blood clotting disorder [platelets $\geq$75,000/μL; this is grade 0 of the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0], (3) prothrombin time-international normalized ratio (PT-INR) $\geq$1.7 (this is point 0 of the Child-Pugh Score); (4) no hypersensitivity to contrast agents; (5) age $\geq$20 years; (6) able to understand the prescribed duration of bed rest; and (7) no contraindications for angiography. Patients were excluded if severe atherosclerosis (narrowing of the lumen, vascular tortuosity, or presence of intramural thrombus) had been identified by previous angiography or computed tomography. Patients were also excluded if they were on anticoagulant or antiplatelet drugs or if postoperative ambulation appeared unlikely. Patients who met all of the inclusion criteria and none of the exclusion criteria were enrolled in the study. Multiple enrollments of the same patient were not permitted.

Angiographic Procedures

In this study, angiography was defined as a VIR procedure using a 3F introducer sheath inserted into the common femoral artery using the Seldinger technique. After the intended procedure, the catheter and sheath were removed from the common femoral artery. Hemostasis at the site of sheath puncture was obtained by manual compression, and ambulation occurred after the designated duration of bed rest.

The materials used for the VIR procedures were 3F introducer sheaths: (1) Sheath Introducer Kit [(3F) Create Medic, Kanagawa, Japan]; (2) S1 sheath [(3F) Terumo Clinical Supply, Gifu, Japan], and (3) 3.5F angiographic catheters [Fansac IV; Terumo Clinical Supply (Phoenix, AZ) and Create Medic]. The outer diameter/inner diameters of the introducer sheath and catheter were 1.60/1.23 and 1.17/0.85 mm, respectively. Therefore, the 3.5F catheter could pass through the 3F introducer sheath. The use of microcatheters compatible with 3.5F catheters for selecting peripheral blood vessels was permitted.

Determination of the Optimal Duration of Bed Rest

Manual compression was continued for a sufficient period of time until no further bleeding occurred after compression cessation. Thereafter, compression was continued with a gauze role and elastic dressing during the period of bed rest. Sandbag compression was not performed. Patients were in the supine position during bed rest, and rolling over was not permitted.

The optimal duration of bed rest was determined using the following protocol. First, the presence/absence of postoperative bleeding was evaluated in 105 patients after 3 h of bed rest (level 1). If no bleeding occurred in any of these 105 patients at the end of the 3-h bed-rest period, another 105 patients were examined for the presence/absence of bleeding after 2.5 h of postoperative bed rest (level 2). If no bleeding occurred in these 105 patients, another 105 patients were examined for bleeding after 2 h of postoperative bed rest (level 3). If bleeding was observed after the designated bed rest period in any patient, the bed rest duration of the previous level was considered the optimal bed-rest duration. Therefore, if bleeding occurred in any of the 105 patients at level 3, the study would be terminated. Likewise, if bleeding occurred after bed rest in any of the patients at level 2, the study would be terminated.

The following definitions were used in this study: (1) operative time = time between initiation of cleansing of the femoral region and completion of manual compression hemostasis; (2) compression time = time between sheath removal and completion of manual compression hemostasis based on the operator's experience; and (3) duration of bed rest = time between completion of manual compression hemostasis in the femoral region and end of the bed-rest period.

Evaluation of Secondary End Points

The VIR procedure was judged to be incomplete if any of the following events occurred: (1) difficulty inserting the 3F sheath; (2) difficulty choosing the target vessel with the 3.5F angiographic catheter; (3) injury to the target vessel requiring treatment (e.g., celiac trunk, common hepatic artery, proper hepatic artery); (4) instrument breakage; (5) occurrence of serious adverse events during the procedure; and (6) any circumstance in which the operator deemed it necessary to discontinue the procedure.

Adverse events were evaluated by grading according to the JCOG/JSCO Japanese version of CTCAE version 3.0. In this study, adverse events were defined as worsening by one or more grades according to CTCAE version 3.0 compared with the grade before study enrollment. The grade of each adverse event was determined by applying the closest grade based on the definitions of grades 0 though 4.

Statistical Analysis

A dose-escalation design was used. If no patients experienced bleeding at a level of the duration of postoperative bed rest, escalation to the next level was permitted. A precision-based sample size calculation was performed. If none of the 100 patients experienced bleeding at a level, the upper limit of the one-sided 95 % confidence interval for the estimated probability of bleeding would be no greater than a threshold value of 3 %, which was within the accepted range in many studies [1, 2, 4–6]. A total of 105 patients were required at each level to allow for patients who might be ineligible.

A 4-h period of bed rest was not evaluated in the present study. If bleeding occurred after 3 h of bed rest (level 1), the study was discontinued without enrolling patients at levels 2 or 3, and it was assumed that the optimal duration of bed rest was 4 h. This was performed because the current procedure using 3F sheaths includes 4 h of bed rest, and because 4 h of bed rest for 4F sheath procedures is commonly used in clinical practice in other institutions.

Table 1 Patient characteristics (level 1)

Female/male	24/81
Median (range) age (year)	71 (40–89)
Underlying disease	
Hepatocellular carcinoma	86
Metastatic liver cancer	18
Other	1
Concomitant diseases	
Hypertension	41
Diabetes mellitus	27
Pulmonary emphysema	1
ECOG performance status (0/1/2)	98/6/1
Laboratory tests	
Platelets ($\times 10^4/\mu L$)	12.9 (7.6–47.8)
PT-INR	1.08 (0.90–1.42)
APTT (second)	28.7 (21.2–47.9)
Fibrinogen (mg/dL)	246 (125–707)
VIR procedure	
TACE	73
Cisplatin-HAI	5
Redistribution for/with HAI-port	20
Angiography without treatment	7

ECOG Eastern Cooperative Oncology Group, *HAI* hepatic arterial infusion, *APTT* activated partial prothrombin time

Operators for Angiography and Manual Compression Hemostasis

Angiography and manual compression hemostasis were performed by T.A., M.M., and E.B., and their experience performing angiography was 19, 15, and 3 years, respectively.

Results

In total, 105 patients were enrolled at level 1 between November 2010 and September 2011. Table 1 lists the characteristics of level 1 patients. At this level, there was delayed cessation of bed rest due to unpredicted errors in 8 patients, who were subsequently excluded from further evaluation. None of the remaining 97 patients experienced postoperative bleeding. Based on the absence of postoperative bleeding, the statistical risk of bleeding was estimated to be 3.04 %. This result was judged as nearly equal to 3 % clinically, and enrollment at the next level was started.

After the level 1 study was completed, enrollment of patients at level 2 began in September 2011. Table 2 lists the characteristics of level 2 patients. At this level, bleeding from the puncture site occurred immediately after the

Table 2 Patient characteristics (level 2)

Female/male	11/41
Median (range) age (year)	69 (28–82)
Underlying disease	
Hepatocellular carcinoma	41
Metastatic liver cancer	11
Other	0
Concomitant disease	
Hypertension	18
Diabetes mellitus	9
Interstitial pneumonia	1
ECOG performance status (0/1/2)	45/6/1
Laboratory tests	
Platelets ($\times 10^4/\mu L$)	14.4 (7.5–43.9)
PT-INR	1.10 (0.98–1.30)
APTT (second)	27.4 (21.0–37.8)
Fibrinogen (mg/dL)	248 (142–496)
VIR procedure	
TACE	31
Cisplatin-HAI	3
Redistribution for/with HAI	15
Angiography without treatment	3

ECOG Eastern Cooperative Oncology Group, *HAI* hepatic arterial infusion, *APTT* activated partial prothrombin time

cessation of bed rest in the 52nd patient, necessitating study termination. This patient had neither a hemorrhagic diathesis, such as a bleeding tendency, nor atherosclerosis; in addition, no complications were observed during the VIR procedure and manual compression. This patient underwent 25 minutes of manual compression and 6 h of additional bed rest thereafter to prevent further bleeding. Neither subsequent additional bleeding nor serious complications, such as pseudoaneurysm formation, were observed.

All of the 157 patients underwent the intended VIR procedure. None of the 157 patients at levels 1 and 2 required transition to the use of a 4F or thicker sheath catheter. Median numbers of punctures at levels 1 and 2 were 1 (range 1–10) and 1 (range 1–2); operative times for the two levels were 90 min (range 30–255) and 117.5 min (range 30–260), respectively; and compression times for the two levels were 10 min (range 5–25) and 10 min (range 6–20), respectively. None of the 157 enrolled patients had any serious adverse events.

Discussion

Previous studies that investigated bed-rest duration after angiography were performed using 7F [4], 6F [5], 5F [6], and 4F sheaths [1]. Lau et al. reported that postoperative bleeding occurred in 6 (4 %) patients after 6 h of bed rest after angiography using 7F sheaths. Wood et al. reported pseudoaneurysm development after 2.5 h of bed rest in two patients undergoing angiography with 6F sheaths. Ishiyama et al. reported three cases of postoperative bleeding after 2.5 h of bed rest after angiography using 4F sheaths, and they indicated that this duration of bed rest was safe. These investigators reported that a bleeding risk of 3–5 % was safe [1, 4–6]. Although these four studies had a prospective design, the rationale for calculating the number of patients was not described, and this resulted in a degree of uncertainty in the statistical analyses. In addition, the frequency of complications, particularly postoperative bleeding, in these reports would not be acceptable with current VIR procedures. Based on these reports, it was determined that 99 patients in each group would be required to assess the effectiveness of bed rest for the prevention of bleeding (the calculated risk of bleeding would be <3 % if no cases with bleeding were present among the 99 patients).

At level 1, delayed cessation of bed rest occurred in 8 of 105 patients, all of whom were subsequently excluded from evaluation. Because no postoperative bleeding occurred in the remaining 97 patients, it was concluded that the intended risk was no more than approximately 3 %, and enrollment of patients at level 2 was started. At level 2, postoperative bleeding occurred in the 52nd patient, and the study was terminated based on our prospective criteria. No hemorrhagic diathesis, including problems with platelets or clotting ability or other bleeding disorders, were noted in this patient. We suspect that postoperative bleeding might be more likely with a duration of bed rest of only 2.5 h. Therefore, at least 3 h of postoperative bed rest appears to be necessary, and this is the policy that has since been adopted by our hospital.

Concerning the catheter procedures, thinner catheters are less stable and may impact the feasibility of VIR procedures. Nevertheless, the procedural feasibility rate in this study was 100 % (157 of 157 cases) for the following reasons: (1) we had a period of nearly 1 year from the adoption of 3F sheaths at our institution until initiation of this study, which allowed us to acquire the skills necessary to perform the procedure; (2) particularly for VIR procedures, we basically insert a 3.5F catheter into the common hepatic artery or a more distal artery, or aberrant right, and/or left hepatic artery arising from the superior mesenteric artery or the left gastric artery to ensure catheter stability, and then we performed the procedure, including the difficult cases, e.g., superselective transcatheter arterial chemoembolization (TACE), embolization of the right gastric artery to prepare placement for a hepatic arterial infusion port; and (3) we used a 2.2F to 2.0F microcatheter to helps selection of and insertion into fine branches (deep insertion

of the 3.5F catheter is required because the 3.5F catheter is unstable if the catheter is placed at the axis of the branches, e.g., the celiac trunk).

No serious adverse events related to the angiographic procedures were reported. This may have been because there were numerous VIR procedures that had targeted abdominal organs. Previously reported serious adverse events included ischemic changes due to VIR procedures on the coronary arteries [4]. These adverse events appear to be rare in the upper abdominal organs. In addition, the use of microcatheters was relatively uncommon when these past reports were published. These differences may have contributed to the comparatively low incidence of complications in the present study.

None of the patients enrolled in this study required transition to the use of a catheter thicker than 3.5F; however, the inner diameter of a 3.5F catheter (diameter of the matched guidewire) is currently 0.032 inches, and a wide assortment of compatible embolization coils and other devices is lacking. Development of VIR devices compatible with 3.5F catheters is desirable.

The major limitation of this study was the small sample size. None of the 97 patients evaluated at level 1 experienced postoperative bleeding, and the statistical risk of bleeding was no more than 3.04 %. To approach our goal of "exactly 0 %," a larger-scale study is needed.

Conclusion

It was found that 2.5 h was an insufficient duration of postoperative bed rest and that at least 3 h of bed rest is recommended for patients undergoing angiography using 3F sheaths. In addition, this is feasible for VIR.

Conflict of interest Takeshi Aramaki, Michihisa Moriguchi, Emima Bekku, Masahiro Endo, Koiku Asakura, Narikazu Boku and Kenichi Yoshimura do not have any conflict of interest or financial disclosures.

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An Early-stage, Non-hypervascular HCC Successfully Treated by Superselective, Bland Transarterial Embolization Using 40-μm Microspheres

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Abstract. *Transcatheter embolization is considered to be less effective for early-stage hepatocellular carcinomas (HCCs) without a hypervascular arterial supply. In the present case report, a 65-year-old male with hepatitis type C and non-hypervascular HCC located in the hepatic hilum was successfully treated by bland transarterial embolization (TAE). After the temporary protective embolization of normal liver tissue using large gelatin particles, diluted 40-μm microspheres were injected via the tumor-feeding artery. The tumor shrank, and the patient has survived for 25 months without recurrence.*

Superselective transarterial chemoembolization (TACE) and transarterial embolization (TAE) are effective local treatments for hepatocellular carcinoma (HCC). Theoretically, TACE and TAE are useful for hypervascular tumors. HCC frequently involves multi-step sequential development. During the multi-step process of hepatocarcinogenesis, the source of the vascular supply switches from the portal vein to the hepatic artery (1). In early-stage HCC, tumors have no hypervascular arterial supply, only fine-feeding arteries. Therefore, TACE and TAE are generally considered less effective for early-stage HCC (2).

For non-hypervascular, early-stage HCC, tumor ablation, including radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI), are frequently-used treatments. However, ablation therapies are occasionally contraindicated due to tumor location or ascites. Therefore, the development of an effective intra-arterial treatment for non-hypervascular, early-stage HCC is necessary.

Previously, Miyayama *et al.* reported the usefulness of superselective lipiodol-TACE for hypovascular HCC. Their report demonstrated that lipiodol could be distributed into the hypovascular tumor portion. In their series, approximately 60% of tumors, which did not have hypervascular arterial supply with decreased the portal blood flow, obtained the dense lipiodol retention (3).

Currently, precisely-calibrated, small-size microspheres are available in Europe and the United States. We considered that embolization using small-size microspheres could occlude fine tumor feeding arteries, as well as lipiodol, and be effective for non-hypervascular, early-stage HCC. Thus, a case of non-hypervascular, early-stage HCC successfully treated by superselective bland TAE using 40-μm microspheres is reported. To the best of our knowledge, there have been no reports to date regarding bland TAE using microspheres for non-hypervascular HCC.

Case Report

A 65-year-old male with hepatitis type C was found to have a liver nodule, 2.4 cm in diameter, on gadolinium ethoxybenzyl diethylene-triamine-pentaacetic-acid (Gd-EOB-DTPA)-enhanced MRI during a routine follow-up examination. In the arterial phase of Gd-EOB-DTPA-enhanced MRI, a slightly hypo-intense nodule, containing a hyper-intense spot, was seen (Figure 1a). In the hepatobiliary phase, the nodule was depicted as a hypointense area (Figure 1b). From these findings, the nodule was diagnosed as non-hypervascular, early-stage HCC containing hypervascular foci. For the treatment of this tumor, surgical resection and radiofrequency ablation (RFA) were considered. However, firstly, the patient refused surgery, and secondly, ultrasonography did not depict the tumor. In addition, due to the location of the tumor in the right hepatic hilum adjacent

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Key Words: Transcatheter arterial embolization, hepatocellular carcinoma, microspheres, Bland-TAE.

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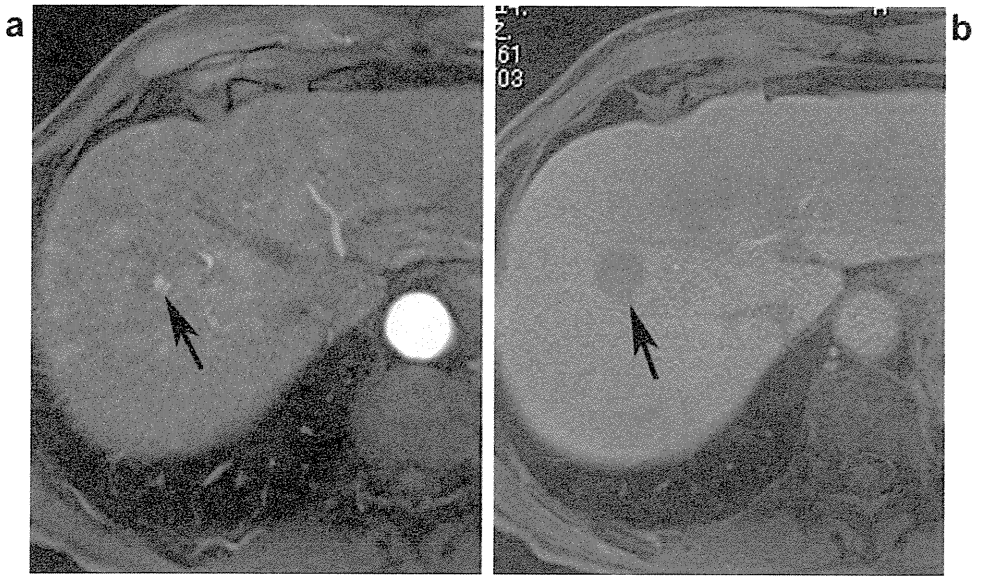

Figure 1. *a. The arterial phase of Gd-EOB-DTPA-enhanced MRI before bland TAE shows a slightly hypointense nodule containing a hyperintense spot, which is a hypervascular foci (arrow). b. The hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI before bland TAE shows a markedly hypointense nodule (arrow).*

to the bile duct and portal vein, RFA could be considered to cause bile duct injury and a heat sink effect could lead to incomplete ablation. Therefore, transarterial embolization became the treatment of choice for this tumor. To precisely observe the blood flow into the tumor, CT during angiography was conducted using a hybrid CT/angio system (Aqullion 16/ Infinix Celeve, Toshiba, Tokyo, Japan). The CT during arterial portography (CTAP) showed that the tumor had no portal vein supply (Figure 2a). CT during hepatic arteriography (CTHA) showed that the tumor had a similar or smaller arterial supply compared to normal hepatic parenchyma, except for the hypervascular foci (Figure 2b). On digital subtraction arteriography (DSA), tumor stain was not depicted (Figure 2c). The patient had good liver function (Child-Pugh A). Although superselective lipiodol-TACE could be considered to be effective for this tumor from Miyayama's report (3), we determined to use recent small microspheres.

The treatment strategy was as follows: (i) tumor-feeding arteries were confirmed using selective CT during arteriography because the DSA could not depict the tumor stain; (ii) the "temporary protective embolization" technique was used to avoid complications caused by embolization with small microspheres in a large liver area because of the tumor location in the hepatic hilum (4); and (iii) small microspheres, calibrated to be 40-μm in size, were used because the non-hypervascular tumor could have fine tumor vessels.

Firstly, a 2.0-Fr microcatheter (Estream; Toray Medical, Tokyo, Japan) was inserted into the anterior branch of the right hepatic artery. The selective CTHA showed that the tumor was located within the enhanced area, and a large hepatic volume was supplied from this artery (Figure 3a). Secondly, the microcatheter was inserted into the distal hepatic branches (A5 and A8), and gelatin particles, 1 mm in size, (Gelpart; Nippon Kayaku, Tokyo, Japan) were injected at the distal sites of the tumor feeding arteries to block the distal branches. Thirdly, 40-μm microspheres (Embozene; CeloNova BioSciences, Newnan, GA, USA), diluted 60 times with contrast material (iopamidol 150 mgI/mL), were injected slowly *via* the proximal site of the anterior branch of the right hepatic artery with a 1-mL syringe. During the injection, a slight tumor stain was seen on fluoroscopy (Figure 3b). The microsphere injection was stopped when the anterior branch of the right hepatic artery was completely occluded. Non-enhanced CT obtained immediately after TAE showed high density within the tumor, which could indicate that microspheres were present within the tumor.

The liver enzymes and C-reactive protein levels before and after TAE showed no remarkable changes (Table I). CT obtained one week after TAE showed that the area inside the tumor had a slightly higher density on non-enhanced CT, and a remarkably lower density area inside tumor was seen on contrast-enhanced CT. Perfusion CT demonstrated decreased arterial vascularity of the tumor (Figure 4). Shrinkage of the tumor was seen on the follow-up CTs obtained 1 and 3 months after TAE (Figure 5). Currently, this patient has no local recurrence 25 months after TAE.

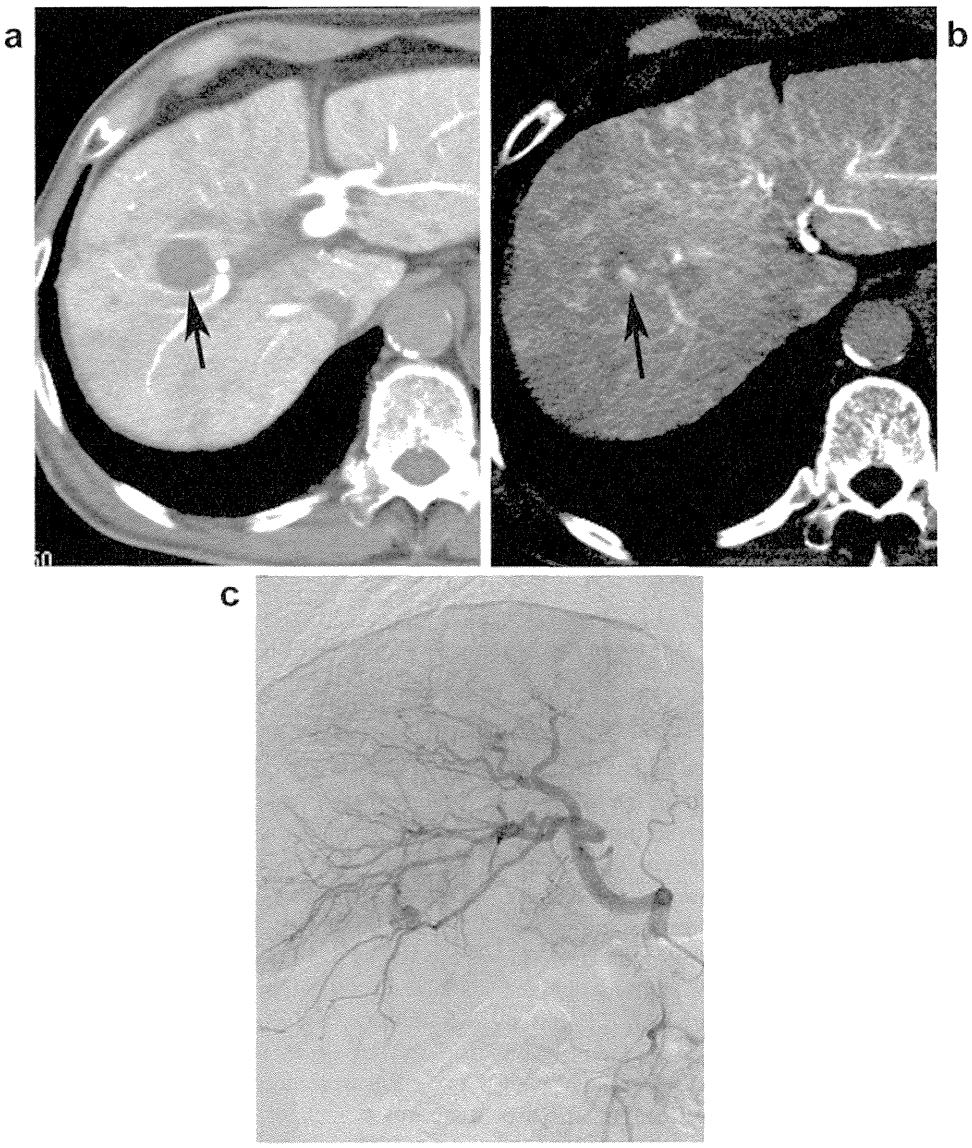

Figure 2. *a. CT during arterioportography (CTAP) shows the hypodense nodule without a portal supply (arrow). b. CT during hepatic arteriography (CTHA) shows the hyperdense spot within the slightly hypodense nodule (arrow). c. Tumor stain is not depicted on the hepatic arteriography.*

Discussion

Early HCC was clearly defined in the international consensus meeting on small nodular lesions in the cirrhotic liver (5). Although indications for treatment of early HCC remain controversial, tumors with hypo-intensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI, decreasing portal blood flow on CTAP, or over 1.5 cm in diameter should be treated (6). The tumor in the present case had all of the above. A tumor biopsy was not performed before treatment due to the risk of causing arterial-portal or arterial-venous shunts after the needle puncture.

Table I. *Laboratory test results before and after bland-TAE.*

	Pre	1 day	3 days	7 days
CRP (mg/dl)	0.0	1.1	0.5	0.5
AST (U/L)	36	38	28	29
ALT (U/L)	35	46	34	29
LDH (U/L)	192	266	265	199
ALP (U/L)	230	273	231	227

CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase. LDH: Lactate dehydrogenase, ALP: alkaline phosphatase.

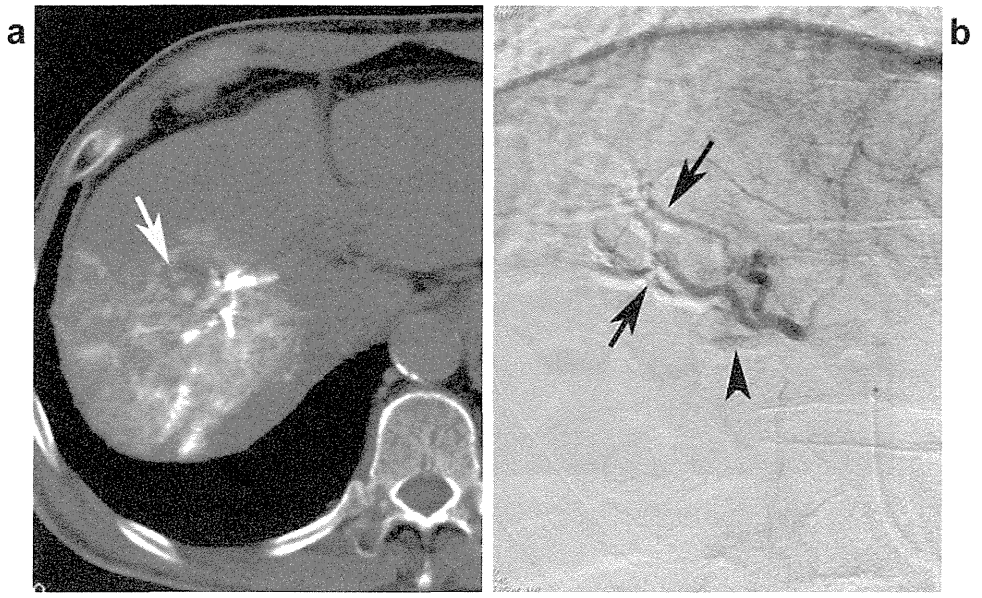

Figure 3. *a. Selective CT during arteriography shows that the tumor is located within the enhanced area (arrow), and a large hepatic volume is supplied from this artery. b. Angiography during the injection; the distal hepatic branches (A5 and A8) were embolized by gelatin particles (arrows). A slight tumor stain can be seen on fluoroscopy (arrowhead).*

Treatment of early HCC by TACE/TAE is a major challenge because the response to arterial embolization depends primarily on the development of tumor vessels. However, Miyayama's report showed that tumors with a hypovascular portion could be successfully treated by superselctive lipiodol TACE in many cases (3). When we use microspheres in such cases, the selection of the size of microspheres could be a key issue. In general, non-hypervascular tumors have fine tumor feeding vessels. Therefore, small-size microspheres could be effective for early-stage HCC. In the present case, 40-μm microspheres, the smallest size commercially available, were chosen. However, further studies to investigate the optimal size of microspheres are necessary. Highly-diluted microspheres were injected to avoid proximal occlusion of the hepatic artery.

Regarding the necessity of chemo-agents, Osuga *et al.* previously reported that bland TAE using microspheres was effective for hypervascular HCC (7). To date, there is no consensus regarding the efficacy of chemo-drugs in the embolization of HCC. However, TACE using newly-developed, small-size, drug-eluting microspheres, *i.e.* 40-μm Embozene TANDEM (CeloNova BioSciences) and 75-150-μm DC Bead^{M1} (Biocompatible, Farnham, UK), should be promising, with a stronger effect than bland TAE (8).

Embolization of a large hepatic volume using small-size microspheres could cause liver dysfunction and biliary damage (9). Therefore, a temporary protective embolization technique with 1-mm gelatin particles was used prior to injection of the microspheres. As a result, the present patient had less toxicity. Protection using degradable starch microspheres (DSM) was also possible (4).

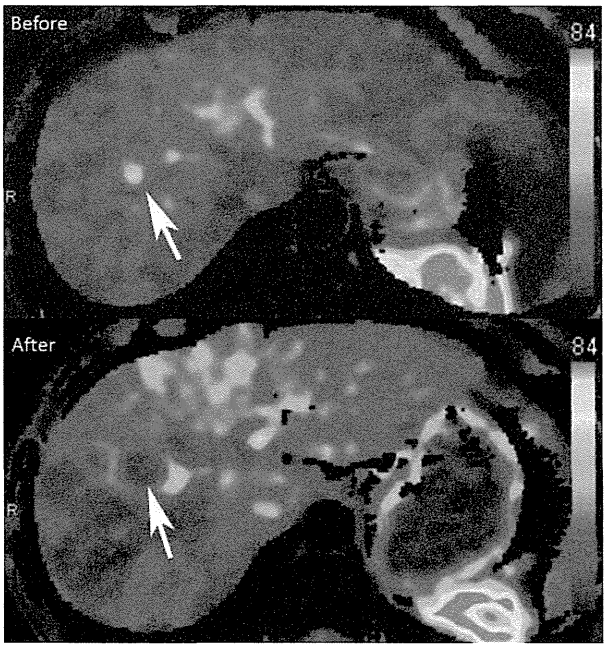

Figure 4. *Perfusion CTs before and 1 week after bland TAE demonstrate the decrease of the arterial vascularity of the tumor after bland-TAE (arrows).*