little activity in patients with advanced HCC, although this regimen was generally well tolerated. These findings do argue against the use of this regimen in clinical practice.

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Conflict of interest statement

None declared.

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MR imaging of hepatic metastasis in patients with malignant melanoma: Evaluation of suspected lesions screened at contrast-enhanced CT

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ABSTRACT

Purpose: To evaluate the magnetic resonance (MR) imaging feature of suspected hepatic metastasis in patients with malignant melanoma which showed intermediate findings on screened contrast-enhanced computed tomography (CECT).

Materials and methods: MR imaging was performed in 38 patients (22 men, 16 women; mean age, 58 years) whose CECT findings were intermediate. Hepatic metastases had been diagnosed on MR imaging in 23 of the 38 patients. Verification of hepatic metastasis was made by histological examination: ultrasonographic-guided needle biopsy ($n=3$), autopsy ($n=3$), and surgical resection ($n=1$), or by an obvious progression in number and/or size of the lesions on follow-up MR imaging ($n=24$). Two diagnostic radiologists reviewed MR images by consensus. The median follow-up duration was 14.2 months.

Results: Abnormal findings were detected in 31 patients on MR images, and undetected in the remaining seven patients resulting in false-positive on CECT. The mean size of the lesion was 11.0 mm. False-positive results were obtained in two lesions which disappeared on follow-up MR imaging. In six patients, lesions were considered as hepatic cysts on MR images. As a result, a total of 35 hepatic metastases were detected on MR images. Of these, 18 patients demonstrated typical melanotic appearance on MR images which showed shortened T1 and T2 relaxation times, and five patients demonstrated atypical melanotic appearance. In 16 patients, extra-hepatic metastases were also developed.

Conclusion: MR imaging could rule out hepatic metastasis in patients with malignant melanoma which showed intermediate findings on screened CECT, and could detect additional extra-hepatic metastases.

1. Introduction

Hepatic metastasis is a common feature signaling the advanced stage of malignant melanoma. Detection of hepatic metastases provides valuable prognostic information and critical impact for the planning of therapies. Moreover, the precise localization of hepatic metastasis has influenced decisions on the appropriateness of surgical options for the treatment of the localized hepatic metastasis [1–4].

Although hepatic metastasis in patients with malignant melanoma could be assessed by imaging studies, a simple, reliable, and non-invasive method to diagnose hepatic lesion in patients with advanced stage would be preferable. Imaging modalities used for assessment of hepatic metastases include ultrasonography (US), computed tomography (CT), [F-18] fluorodeoxyglucose (^{18}FDG)-positron emission tomography (PET), and magnetic resonance (MR) imaging.

CT has been commonly used to detect hepatic metastasis in patients with malignant melanoma, and was more sensitive modality compared with US in regard to diagnostic performance [1]. However, CT can provide a limited specificity for the detection of hepatic metastasis and data relating its utility in patients with malignant melanoma are also limited. Although clinical impact exists in ^{18}FDG-PET for the staging of malignant melanoma and the detection of hepatic metastasis [2], the effectiveness for the detection of hepatic metastasis of malignant melanoma remains controversial [3,4]. Moreover, ^{18}FDG-PET often underestimates hepatic metastases of malignant melanoma, because there is limitation in spatial resolution and high background activity of normal hepatic tissue affects to detect smaller lesions.

Some studies suggested that MR imaging is more sensitive imaging technique than contrast-enhanced CT (CECT) for the detection

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of hepatic metastasis [5,6], and MR imaging was useful in screening for the detection of hepatic metastasis in patients with malignant melanoma [7]. MR imaging features of hepatic metastasis of malignant melanoma typically display shortened T1 and T2 relaxation times and the presence of T1 shortening closely related to the melanin content of the lesion [8–11]. However, the diagnostic accuracy of assessing hepatic metastasis using MR imaging, when we evaluate intermediate lesion on CECT, has not been determined elsewhere.

The purpose of this study was to evaluate the MR imaging feature of suspected hepatic metastasis in patients with malignant melanoma which showed intermediate findings on screened CECT.

2. Materials and methods

2.1. Study population

This study was conducted in accordance with the amended Helsinki Declaration. The ethics committee at our institution deemed that approval of this study was unnecessary because of retrospective nature. Between January 2006 and December 2008, 69 consecutive patients with malignant melanoma were examined on screened CECT for the detection of metastasis. Of the 69 patients, 38 were suspected solitary hepatic metastasis which showed intermediate findings on CECT, examined on MR imaging for differentiation, and included in this retrospective study. The patient population included 22 men and 16 women who ranged in age from 15 to 80 years (mean age, 58 years). None of the patients had received previous treatment for hepatic metastases. Informed consent for the imaging examinations was obtained from all the patients. Clinical information was extracted from the patient files regarding patient age, gender, symptoms, treatment, associated conditions, and final disease status.

Hepatic metastases had been diagnosed in 23 of the 38 patients who were underwent MR images. The assessment of hepatic metastasis was confirmed by histological examination: ultrasonographic-guided needle biopsy ($n = 3$), autopsy ($n = 3$), surgical resection ($n = 1$), or by an obvious progression in number and/or size of the lesions on follow-up MR images ($n = 16$). The surgical procedure or biopsy was performed within 16 days (mean, 10 days) after MR images.

2.2. CT imaging protocol

CT was performed with a multi-detector row helical CT unit (Aquilion; Toshiba Medical Systems, Tokyo, Japan) that had 16 detector rows, a 0.5-s rotation time, and exposure factors of 120 kV and 250–300 mA s for all scans. The contrast material injection rate was set at 2.7 ml/s, and the contrast material ((Iopamiron 300/370; Bayer Schering Pharma, Osaka, Japan) was injected into an antecubital vein with an automatic power injector (DUAL SHOT GX; Nemoto, Tokyo, Japan) through a 22-gauge intravenous catheter. The examinations were performed in a cephalocaudal direction starting at the top of the liver, and each examination included non-enhanced scanning and contrast-enhanced scanning.

Before the contrast material was injected, a non-enhanced scanning was performed in transverse section. CECT was performed 70 s after intravenous administration of 100 ml of contrast material. The parameters for the scans obtained during non-enhanced and contrast-enhanced scanning were set at a 2-mm collimation, pitch of 5, and 5-mm reconstruction interval. Image reconstruction was performed in a 25–35 cm display field of view according to the patient's physique in our clinical protocol setting.

2.3. MR imaging protocol

MR imaging was performed after CECT with follow-up of a mean of 3 days (range, 1–6 days) with a super-conducting magnet system at 1.5-T scanner (Signa; General Electric Medical Systems, Milwaukee, WI and Visart; Toshiba Medical Systems, Tokyo, Japan) using an 8-channel body phased-array coil.

Fat-suppressed T1-weighted gradient-echo (GRE) images were obtained in coronal and transverse planes by using a 24–30 cm field of view, 7–9 mm section thickness, 105–139/1–4 (repetition time ms/echo time ms, [TR/TE]), 224–256 × 256 matrix, two signals acquired. Fat-suppressed T2-weighted fast spin-echo (FSE) images were performed in transverse plane by using a 24–35 cm field of view, 8–9 mm section thickness, 2050/120 (effective repetition time ms/effective echo time ms, [TR_{eff}/TE_{eff}]), 224–256 × 256 matrix, two signals acquired. T2-weighted single shot fast spin-echo acquisitions were performed in coronal plane by using a 24–35 cm field of view, 8–9 mm section thickness, 21,700–23,700/80, 224–256 × 256 matrix, one signal acquired. Contrast-enhanced fat-suppressed T1-weighted GRE images were obtained 70 s after intravenous administration of contrast material in coronal and transverse planes by using a 24–30 cm field of view, 7–9 mm section thickness, 105–139/1–4, 224–256 × 256 matrix, two signals acquired. Contrast material (gadopentetate dimeglumine, 0.1 mmol/kg) was manually injected intravenously as a rapid volus through a 22-gauge intravenous catheter.

2.4. Image analysis

Two diagnostic radiologists with 16 and 9 years of experience reviewed the CECT and MR images by consensus. All images were reviewed on a 1536 × 2048 picture archiving and communication systems monitor (PACS; Radi CS, Nihon IBM, Tokyo, Japan). The readers were aware of the overall goal of the study before the reading session and knew that the patients had malignant melanoma, but were unaware of any other information.

Intermediate findings on CT were defined as follows: focal areas of high attenuation on non-enhanced CT which did not show significant enhancement on CECT, or focal areas of low attenuation on non-enhanced CT whose enhancement were equivocal on CECT.

MR images were evaluated for predominant signal intensity characteristics (low, intermediate, high). On fat-suppressed T1-weighted GRE images and fat-suppressed T2-weighted FSE images, low signal intensity was defined as signal intensity less than that of normal liver parenchyma, intermediate signal intensity was defined as similar to that of normal liver parenchyma, and high signal intensity was defined as more than that of normal liver parenchyma. A melanotic metastasis was defined as focal high signal intensity relative to adjacent normal liver parenchyma on fat-suppressed T1-weighted GRE images and focal low signal intensity relative to adjacent normal liver parenchyma on fat-suppressed T2-weighted FSE images. Lesions with low signal intensity on fat-suppressed T1-weighted GRE images and high signal intensity on fat-suppressed T2-weighted FSE images were evaluated with subsequent contrast-enhanced fat-suppressed T1-weighted GRE images. When heterogeneous enhancement was observed, these lesions were considered as metastases. Lesions with low or intermediate signal intensity on fat-suppressed T1-weighted GRE images and high signal intensity on fat-suppressed T2-weighted FSE images were also evaluated with subsequent contrast-enhanced fat-suppressed T1-weighted GRE images. When heterogeneous enhancement was observed after contrast-enhancement, these lesions were also considered metastases. Furthermore, when the results of subsequent contrast-enhanced fat-suppressed T1-weighted GRE images were not

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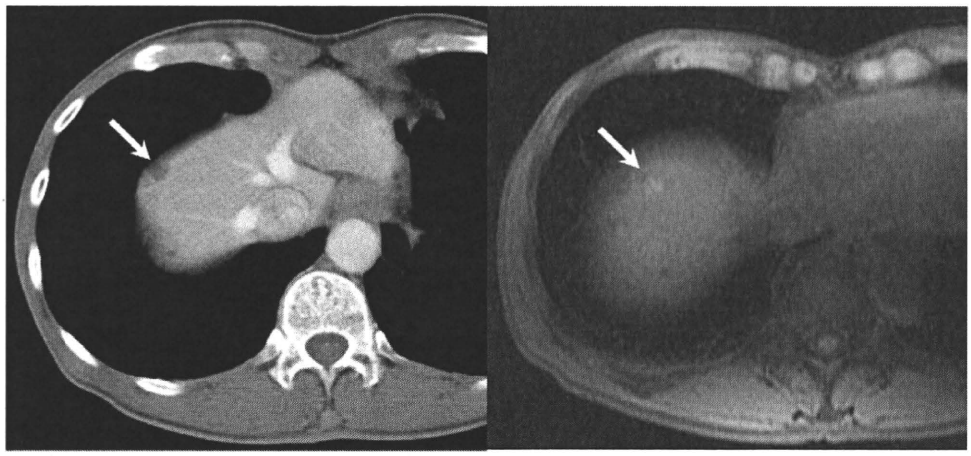

A B

Fig. 1. A 66-year-old woman with malignant melanoma of the left leg. The patient received surgical resection and sentinel lymph node sampling. (A) Follow-up contrast-enhanced spiral CT is detected a low attenuation nodule of the liver in segment 8 (arrow), and the enhancement of the lesion is obscure. (B) Fat suppressed transverse T1-weighted gradient-echo image shows high signal intensity nodule in segment 8 (arrow). The lesion showed obviously growth after 6 months watchful waiting. Hence, the lesion was considered to be a true hepatic metastasis.

confirmed as metastases, follow-up MR images was performed 6 months after and was re-evaluated.

2.5. Statistical analysis

Clinical variables including age, follow-up duration, and size of the lesion were compared by means of the two-tailed Student's *t* test with two sample equal variance. Survival was calculated for one-dependent end point. The primary endpoint was the overall survival (OS) that was defined as the time in month from the date of initial MR examination until the date the patient was last known to be alive. Any death from any cause was considered a failure. Univariate analysis was performed by comparing Kaplan–Meier survival curves and carrying out log-rank tests. All analyses were conducted using software package (SPSS for Windows, version 12.0, SPSS, Chicago, IL). A p value less than 0.05 was considered to indicate a statistically significant difference.

3. Results

MR images showed no significant abnormalities in seven of the 38 patients (18%), and the seven false-positive lesions on CECT were attributed to three partial volume artifacts or four unexplained areas at retrospective review. In 20 of 31 patients (65%), lesions showed high signal intensity on T1-weighted gradient-echo with fat saturation images and low signal intensity on T2-weighted fast spin-echo images. Of these, hepatic metastases were identified in 18 patients (58%, Fig. 1). Two lesions with melanotic signal pattern disappeared on follow-up MR images. In 11 of 31 patients (36%), lesions showed low signal intensity on T1-weighted images gradient-echo with fat saturation and high signal intensity on T2-weighted fast spin-echo images (Fig. 2). Of these, five lesions (16%) showed heterogeneous enhancement on subsequent contrast-enhanced T1-weighted gradient-echo with fat saturation images and diagnosed as having hepatic metastases. No significant enhancement was found in the other six patients (20%) on subsequent contrast-enhanced T1-weighted gradient-echo with fat saturation images. These lesions were considered as hepatic cysts. As a result, in 23 of 38 patients (60%) who were suspected hepatic metastasis which showed intermediate findings on CECT, a total of 35 hepatic metastases were confirmed on MR images, and four of these 23 patients had detected a total of 12 additional hepatic metastases. The sizes of the 35 hepatic metastases ranged from 0.8 to 2.2 cm (mean, 1.1 cm ± 0.3). The clinical characteristics of study patients are summarized in Table 1.

The size of lesions with false positive results on MR examinations was 8.5 ± 2.5 mm, which was smaller than those (11.4 ± 0.7 mm) with true positive results but its degree was not statistically significant ($p = 0.219$). The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) to detect hepatic metastasis using MRI were 100%, 86.7%, 94.7%, 92.0%, and 100%, respectively.

Of note, 16 of 31 patients also developed extra-hepatic metastases (Fig. 3). The extra-hepatic metastases were not detected on CECT, because these lesions were not conspicuous due to small in size and poor contrast. The sites of extra-hepatic metastases were summarized in Table 2. Not abdominal extra-hepatic metastases including lung, heart, brain, parotid gland, and skin were detected by the other examinations, after detected abdominal extra-hepatic metastases on MR imaging. Most frequent site of

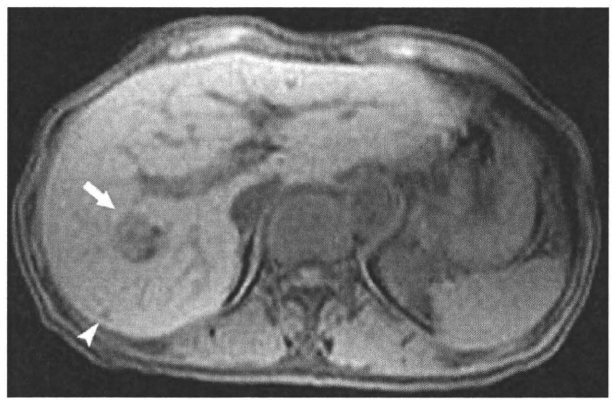

Fig. 2. A 68-year-old woman with malignant melanoma of the anus. The patient received surgical resection and lymph node dissection. Contrast-enhanced CT showed low attenuation nodule of the liver in segment 7 which was intermediate findings. Fat suppressed transverse T1-weighted gradient-echo image obtained 3 months after operation shows two nodules with low signal intensity. The lesion is 22 mm in the diameter (arrow), and additional tiny nodule is depicted in segment 7 (arrowhead).Ultrasonographic-needle biopsy was performed for the larger nodule, and hepatic metastasis was confirmed.

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Table 1
Clinical characteristics of patients with hepatic metastasis.

Parameter	Value
Age, year	
Mean ± SD	57 ± 16
Range	15–80
Gender	
Male:female	13:10
Primary site	
Uvea	8
Conjunctiva	2
Thigh	2
Rectum	2
Foot	2
Finger	2
Back	2
Upper arm	1
Anus	1
Esophagus	1
Following treatment	
Chemotherapy	11
TAE	7
Additional RT	2
No treatment	3
Outcome	
DOD	11
AWD	12

Note: SD, standard deviation; TAE, transarterial embolization; RT, radiotherapy; DOD, dead of disease; AWD, alive with disease.

metastasis was lymph node (n = 10%, 29%). Treatments consisted of systemic chemotherapy (n = 11%, 48%) and TAE (n = 7%, 30%). Subsequent additional radiotherapy (RT) was performed in two patients (9%). In three patients with advanced disease, supportive care was performed. The median follow-up duration was 14.2 months. Clinical outcome of 23 patients included died of disease (DOD; n = 11%, 48%) and alive with disease (AWD; n = 12%, 52%). The 2-year overall survival of all patients was 46%. Patients with hepatic metastasis showed poorer 2-year survival than those without hepatic metastasis, but there was not statistically significant difference (38% vs. 75%, p = 0.07, Fig. 4). However, patients with distant metastasis showed poorer 2-year survival than those without distant metastasis (36% vs. 100%, p = 0.035, Fig. 5).

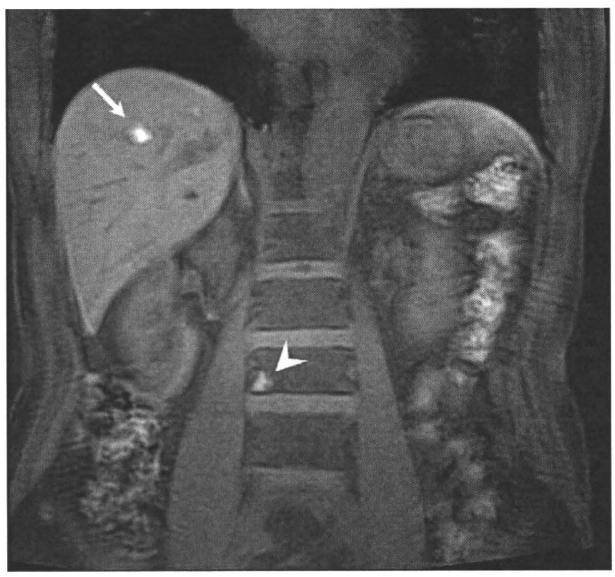

Fig. 3. A 62-year-old man with malignant melanoma of uvea. The patient received radiotherapy for the right uveal melanoma. Contrast-enhanced CT showed intermediate lesion of the liver in segment 8.Fat suppressed coronal T1-weighted gradient-echo image obtained 2 years after radiation shows hepatic lesion with high signal intensity (arrow). Also noted is high signal intensity in the vertebra (arrowhead), which showed obviously growth on follow-up imaging and confirmed as spinal metastasis.

Table 2
The sites of extrahepatic metastases.

Parameter	Value
Lymph node	10
Lung	5
Bone	4
Skin	4
Stomach	3
Brain	2
Kidney	1
Parotid gland	1
Spinal cord	1
Spleen	1
Heart	1
Bowel	1

4. Discussion

The results of this study demonstrated that MR imaging could differentiate hepatic metastasis from intermediate hepatic lesions on screened CECT with high diagnostic performance, and detect additional extra-hepatic metastases. This finding indicates that MR imaging has the capability of higher diagnostic performance for assessing suspicious small hepatic metastasis than CECT and potentially superior detectability for extra-hepatic metastases.

In this study, MR imaging could detect precisely hepatic metastasis in 23 of 38 patients, with high PPV. Of these, 18 patients demonstrated typical melanotic appearance on MR images which showed shortened T1 and T2 relaxation times. This T1-shortning effect might be caused by a cytoprotective function as a paramagnetic intracellular scavenger of free metals [14]. A majority of lesions which exhibit typical MR signal pattern have increased melanin content within the tumors, and T1-weighted GRE images are better to visualize melanotic lesions [8–11]. On the other hand, two false-positive lesions which showed typical melanotic findings on MR images were detected in our study. Although it is extremely

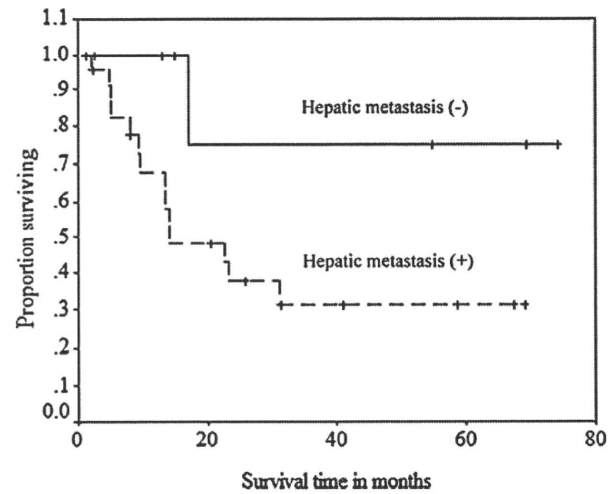

Fig. 4. Kaplan–Meier estimate of overall survival according to the presence of hepatic metastasis or not. Solid line: hepatic metastasis (−), dash line: hepatic metastasis (+). Tumors without hepatic metastasis show a longer overall survival than those with hepatic metastasis, but this did not show statistically significant difference (p = 0.07).

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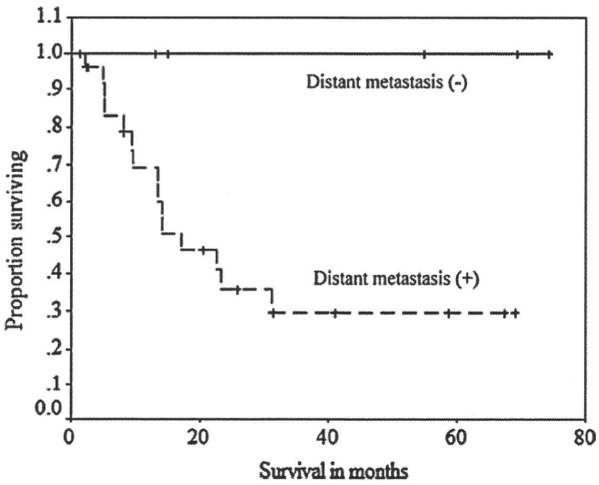

Fig. 5. Kaplan–Meier estimate of overall survival according to the presence of distant metastasis or not. Solid line: distant metastasis (−), dash line: hepatic metastasis (+). Tumors without distant metastasis show a longer overall survival than those with distant metastasis ($p = 0.035$).

rare, we should consider that T1-shortning effects on T1-weighted images may be caused by extracellular methemoglobin, fat, and high protein content except for melanin, and such lesions often contain malignant hepatic lesions including hepatocellular carcinoma, multiple myeloma, carcinoid, metastatic tumors from ovary, colon, and pancreas [15].

Atypical melanotic patterns, which showed low/intermediate intensity on fat-suppressed T1-weighted GRE images, high intensity on fat-suppressed T2-weighted FSE images, and heterogeneous enhancement on subsequent contrast-enhanced fat-suppressed T1-weighted GRE images, were identified in five patients. These results agree with the previous study [7]. When atypical melanotic patterns exist for lesions on MR imaging, additional contrast-enhanced MR study is helpful for the differentiation of hepatic metastases.

The results of this study indicated that 16 of 31 patients had extra-hepatic metastases, and systemic chemotherapy, TAE, and RT were performed for following treatment. However, the 2-year overall survival of all patients was only 46%. The result of overall survival suggests that earlier detection of distant metastasis is required to improve patients' outcome [13]. Improved gradient performance enables whole-body MR imaging which has the potential to detect melanotic lesion with high anatomic resolution. Although technical problems arise as a result of long examination time for whole-body MR imaging, the development of ultrafast pulse sequences can decrease the scanning time [12]. We propose that whole-body MR imaging using fat-suppressed T1-weighted GRE sequence will be effective for screening of distant metastasis in patients with malignant melanoma. In addition, the advantage of MR imaging is that it does not involve ionizing radiation and it makes use of smaller amounts of gadolinium chelates, which have an even better safety profile than iodinated contrast agents.

Our study had several limitations. First, although hepatic metastases were detected in 23 of 38 patients, not all lesions were confirmed surgically and pathological verification was performed only in seven patients. This may have resulted in overestimation of the actual sensitivity by reducing the number of false-negative lesions. Second, there was no comparison of diagnostic performance between CECT and MR imaging for the detection of hepatic metastases in patients with malignant melanoma. Further validation studies are needed to clarify the role of MR imaging for the detection of metastases in patients with malignant melanoma.

In conclusion, MR imaging could be used to rule out hepatic metastasis of malignant melanoma which showed intermediate findings on screened CECT, and could be detected additional extra-hepatic metastases. These results potentially demonstrated its advantages in comparison with CECT.

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Hepatic Arterial Infusion of 5-Fluorouracil for Patients With Liver Metastases From Colorectal Cancer Refractory to Standard Systemic Chemotherapy: A Multicenter, Retrospective Analysis

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Abstract

Introduction: This retrospective study evaluated the safety and efficacy of hepatic arterial infusion chemotherapy (HAIC) with 5-fluorouracil (5-FU) for patients with liver metastases from colorectal cancer refractory to standard systemic chemotherapy. **Patients and Methods:** Fifty-five patients who had shown disease progression during the prior standard systemic chemotherapy with oxaliplatin, irinotecan, and 5-FU were enrolled. The treatment was weekly HAIC with 5-FU 1000 mg/m^2/5 hours through an indwelling catheter-port system. **Results:** No major adverse reaction was observed other than grade 3 leukocytopenia (3.6%) and hyperbilirubinemia (1.8%). The overall response rate and disease control rate were 18.2% and 70.9%, respectively. The median progression-free survival and median overall survival (OS) were 2.8 months, and 6.7 months, respectively. The initial sites of disease progression were liver in 14, other than liver in 27, and both in 6. Multivariate analysis identified Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 and number of extrahepatic metastatic sites (NMS) ≤ 1 as favorable prognostic factors for OS (hazard ratio [HR], 8.277; 95% CI, 3.60-19.0; P = .000 for ECOG PS; and HR, 2.456; 95% CI, 1.30-4.61; P = .005 for NMS). **Conclusion:** HAIC with 5-FU may be a safe and effective treatment for patients with colorectal liver metastases refractory to standard systemic chemotherapy.

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Keywords: 5-FU, Alkaline phosphatase, Prognostic factor, Third-line chemotherapy

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide and remains a major cause of cancer-related deaths. For advanced CRC, irinotecan and oxaliplatin are widely used in both first-line and second-line treatments, in combination with 5-fluorouracil (5-FU) and leucovorin (LV). This approach has yielded improvements in response rates and survival.[1,2] The treatment options for disease refractory to these standard treatments are limited, although cetuximab benefits some patients during third-line chemotherapy.[3,4] In clinical practice, novel approaches need to be developed and established to improve prognoses further.

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About half of CRC patients develop liver metastases during the course of their disease. Moreover, more than half of the patients who die of CRC manifest liver metastases at autopsy, and the majority of these patients die of liver failure.[5] Several randomized studies showed that hepatic arterial infusion chemotherapy (HAIC) during first-line therapy is associated with a higher tumor response rate, but not significantly prolonged survival.[6-8] On the other hand, positive data are also available for the effects of HAIC on survival. Kemeny et al reported on the advantages of HAIC in a well-designed randomized study.[9] Unfortunately, they did not use irinotecan and oxaliplatin, key drugs in standard systemic chemotherapy, as the initial treatment in their systemic group. Thus, it remains to be proven that hepatic arterial therapy results in longer survival compared with recent standard systemic chemotherapy. However, because the direct infusion of antitumor agents into tumors at a higher concentration than with systemic chemotherapy using HAIC can enhance antitumor effects and reduce toxicity,

HAIC may be effective for patients with liver metastases from CRC refractory to standard systemic chemotherapy. Therefore, we conducted a multicenter, retrospective study to evaluate the efficacy and tolerability of HAIC with 5-FU and to analyze prognostic factors in these patients.

Patients and Methods

Patient Selection

Four participating centers in Japan provided the data of 55 patients with liver metastases from CRC treated with HAIC and 5-FU between April 2005 and March 2008. All selected patients fulfilled the criteria of (1) histologically confirmed colorectal adenocarcinoma, (2) predominant disease with liver metastases, (3) previous exposure to and failure of the 3 drugs oxaliplatin, irinotecan, and 5-FU, (4) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 3, (5) adequate bone marrow and renal/hepatic function, and (6) the performance of HAIC with single-agent 5-FU. This study received the approval of the Institutional Review Board at the center that required it.

Treatment

Under local anesthesia, an indwelling catheter with a sidehole was inserted from the left subclavian artery or right femoral artery. The catheter tip was inserted into the gastroduodenal artery and fixed to the vascular wall by metallic coils and a mixture of n-butyl cyanoacrylate (NBCA) and iodized oil, and the sidehole was placed within the common hepatic artery. The proximal end of the catheter was connected to an implanted port and embedded subcutaneously. When an aberrant hepatic artery was found, hepatic arterial blood flow was redistributed, using coils to convert multiple hepatic arteries to a single arterial blood supply. If necessary, extrahepatic arterial branches arising from the hepatic artery and parasitic arteries with hepatopetal blood flow were also occluded, using coils and a mixture of NBCA and iodized oil. The appropriate drug distribution through the indwelling catheter was confirmed according to computed tomography (CT) via the injection of contrast material through the implanted port before the initiation of therapy.[10-12]

As treatment, 5-FU (1000 mg/m^2) was administered via continuous 5-hour infusion once a week, using a continuous-infusion device.[13] Treatment was repeated weekly until the appearance of unacceptable toxicity, the progression of hepatic lesions, or a marked enlargement of extrahepatic lesions.

Evaluation

During treatment, a blood cell count and liver function tests were performed every week. Intravenous contrast-enhanced CT and CT arteriography via the implanted port were performed every 1-2 months. Toxicities were graded according to the Common Toxicity Criteria for Adverse Events, version 3.0, and the responses limited to a liver metastasis were evaluated regardless of the disease outside the liver. A sum of the longest diameters for all target legions of liver metastasis was compared with that before treatment. Hepatic response was classified as a partial when a 30% or more reduction in the sum without new lesions in the liver was obtained, and as progressive when a 20% or greater enlargement or new lesions in the liver was evident. Otherwise, hepatic disease was classified as stable. Hepatic progression-free survival (H-PFS) was defined as the date from the initiation of HAIC to the date of hepatic progression or death from any cause.

Overall survival (OS) was calculated from the date of initiating HAIC to death, and was censored on the date of the last follow-up of a surviving patient. Overall progression-free survival (PFS) was defined as the time from initiating HAIC to the documented progression of disease at any site or to date of death from any cause, according to the Response Evaluation Criteria for Solid Tumors.

Statistical Analysis

Statistical analyses were conducted using Dr. SPSS II, version 11.0.1J (SPSS, Inc.; Chicago, IL). The OS, PFS, and H-PFS were estimated using the Kaplan-Meier method, and 95% confidence intervals (CIs) were provided for proportions. Univariate and multivariate Cox regression analyses were performed to assess factors prognostic of OS, including age, ECOG PS, number of extrahepatic metastatic sites, location of primary site, history of primary resection, synchronicity or metachronicity of a liver metastasis, number of previous regimens, and data from clinical laboratory tests (eg, alkaline phosphatase [ALP], carcinoembryonic antigen [CEA], and white blood cell count [WBC]). Multivariate analysis was undertaken for variables demonstrating $P < .10$ after univariate analysis, and $P < .05$ was considered statistically significant. The relationships between H-PFS and OS were analyzed using simple linear regression. Multiple correlation coefficients (r) were calculated to draw regression lines.

Results

Patient Characteristics

The baseline characteristics of the 55 patients in this study are summarized in Table 1. The median age was 62 years (range, 30-78 years). Thirteen patients (23.6%) demonstrated an ECOG PS of 2 or 3. Thirty-six patients (65.5%) had synchronous hepatic metastases, and 45 (81.8%) had extrahepatic disease. The median baseline ALP, CEA, and WBC values were 781 IU/L (range, 228-3916 IU/L), 808 ng/mL (range, 9-36,787 ng/mL), and 7020/mm^2 (range, 2090-21,100/mm^2), respectively. Twenty-four patients (43.6%) had previously received 3 or more regimens. All patients had received oxaliplatin, irinotecan, and 5-FU, and these agents had proven ineffective. All patients had received FOLFOX (5-FU plus LV with oxaliplatin), 44 patients had received FOLFIRI (5-FU plus LV with irinotecan), and 5 patients had received irinotecan alone, 5 patients had received a 5-FU bolus plus LV with irinotecan, and 1 patient had received a combination of irinotecan and S-1.

Treatment Course

A catheter-port system was implanted successfully in all patients. The routes of catheter insertion included the left subclavian artery in 41 patients and the right femoral artery in 14 patients. The median number of hepatic arterial infusion courses was 12 (range, 1-58 courses), and the median duration of treatment was 3.3 months (range, 0.3-17.2 months). During the treatment period, abnormalities of drug distribution to the liver were observed via follow-up CT arteriography in seven patients (12.7%). The development of a collateral blood supply to the liver (inferior phrenic artery in 5 patients, gastroduodenal artery in 2 patients, adrenal artery in 1 patient, and

Table 1 Patient Characteristics

Characteristic	Patients (N = 55)
Sex (Male/Female)	32/23
Age, Years (≤ 60/> 60)	23/32
PS (ECOG) (0/1/2/3)	24/18/9/4
Extrahepatic Metastatic Site (0/1/≥ 2)	10/24/21
Primary Site (Colon/Rectum)	34/21
Primary Resection (No/Yes)	12/43
Liver Metastases (Metachronous/Synchronous)	19/36
Number of Previous Regimens (2/≥ 3)	31/24
Previous Therapy Using FOLFOX	55
Previous Therapy Using Regimen Containing Irinotecan (FOLFIRI/Others)	55 (11/44)
Baseline ALP, IU/L (≤ 300/> 300)	6/49
Baseline CEA, ng/mL (≤ 50/> 50)	7/48
Baseline WBC, /mm^2 (≤ 10,000/> 10,000)	42/13

Abbreviations: ALP = alkaline phosphatase; CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil/leucovorin/irinotecan; FOLFOX = 5-fluorouracil/leucovorin/oxaliplatin; PS = performance status; WBC = white blood cell

Table 2 Adverse Events

Adverse Event	Grades 1 and 2 (%)	Grade 3 (%)
Leukocytopenia	0	2 (3.6)
Thrombocytopenia	1 (1.8)	0
Nausea	1 (1.8)	0
Stomatitis	1 (1.8)	0
Hyperbilirubinemia	0	1 (1.8)

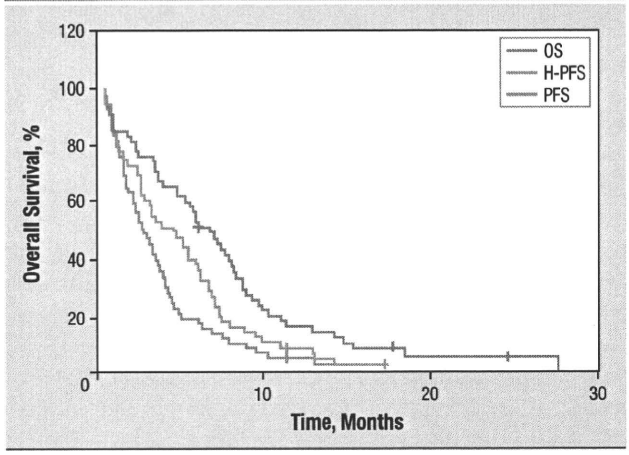
Table 3 Response and Survival

Response Measure	Patients (N = 55; %)
CR	0
PR	10 (18.2)
SD	29 (52.7)
Disease Control (Complete Response + Partial Response + Stable Disease)	39 (70.9)
PD	10 (18.2)
Not Evaluable	6 (10.9)
Survival, Months (95% CI)	
PFS	2.8 (2.0-3.6)
H-PFS	4.6 (2.8-6.3)
OS	6.7 (4.8-8.5)

Abbreviations: CR = complete response; H-PFS = hepatic progression-free survival; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease

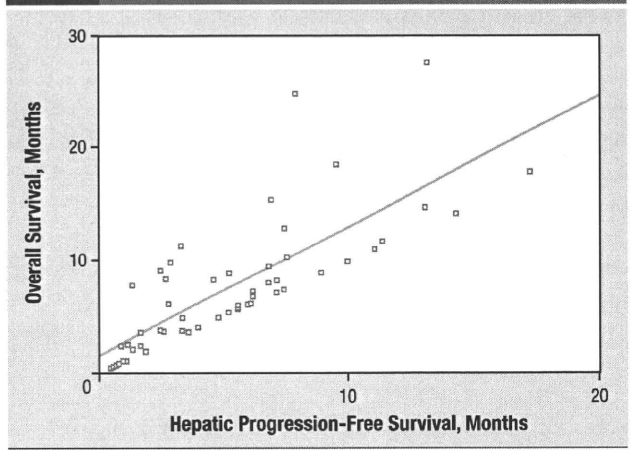
replaced left hepatic artery in 1 patient) was detected, and these collateral vessels were embolized using interventional radiology techniques in all of these patients, and HAIC was then continued. In 4

Figure 1 Kaplan-Meier Curve for Overall Survival, Hepatic Progression-Free Survival, and Progression-Free Survival



Abbreviations: H-PFS = hepatic progression-free survival; OS = overall survival; PFS = progression-free survival

Figure 2 Linear Regression Line (y = 1.19x + 1.54) and Corresponding Correlation (r^2 = 0.54) for Relationship Between Hepatic Progression-Free Survival and Overall Survival



patients (7.3%), HAIC was terminated because of hepatic arterial occlusion 1.2-8.5 months after initiating treatment. Two of these patients underwent HAIC with mitomycin C from a collateral artery, and 1 underwent systemic chemotherapy (FOLFOX plus bevacizumab) as subsequent therapy. The remaining 2 patients underwent no subsequent anticancer therapy.

Toxicity

Toxicities related to HAIC are listed in Table 2. No life-threatening toxicity was evident. Hematologic toxicities were generally mild, with grade 3 leukocytopenia in 2 patients (3.6%) and grade 2 thrombocytopenia in 1 patient (1.8%). Nonhematologic toxicities were also mild, with grade 3 hyperbilirubinemia in 1 patient (1.8%) and grade 1 nausea and stomatitis in 1 patient each (1.8%).

Efficacy

The hepatic tumor response is listed in Table 3. Six of 55 patients (10.9%) could not be evaluated because they died within 1 month

Table 4 Prognostic Factors

Variable	Overall Survival					
	Univariate			Multivariate		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age (≤ 60 Years/> 60 Years)	0.749	0.41-1.35	.339	–	–	–
PS (0 or 1/≥ 2)	7.943	3.48-18.1	.000	8.277	3.60-19.0	.000
Number of Extrahepatic Metastatic Sites (0 or 1/≥ 2)	2.592	1.39-4.82	.003	2.456	1.30-4.61	.005
Primary Site (Rectum or Colon)	0.627	0.34-1.13	.126	–	–	–
Primary Resection (No or Yes)	1.129	0.56-2.27	.734	–	–	–
Hepatic Metastasis, Synchronous (No or Yes)	0.657	0.36-1.18	.165	–	–	–
Number of Previous Regimens (2/≥ 3)	0.88	0.49-1.55	.661	–	–	–
ALP, IU/L (≤ 300/> 300)	1.232	0.52-2.91	.635	–	–	–
CEA, ng/mL (≤ 50/> 50)	2.278	0.88-5.83	.086	1.857	0.71-4.86	.207
WBC, /mm^2 (10,000/> 10,000)	1.291	0.65-2.54	.46	–	–	–

Abbreviations: ALP = alkaline phosphatase; CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; PS = performance status; WBC = white blood cell

after initiating HAIC and had undergone no follow-up CT. No patients manifested the disappearance of a liver metastasis, and 10 patients demonstrated a hepatic partial response, resulting in a hepatic response rate of 18.2%. In addition, 29 patients had stable disease, resulting in a hepatic disease control rate of 70.9%. Ten (18.2%) exhibited hepatic progressive disease.

After a median follow-up of 6.1 months (range, 0.5-27.5 months), 53 patients had experienced progressive disease or died, and the remaining 2 patients continued their HAIC without progression for 11.3 and 17.2 months. The median overall PFS and H-PFS were 2.8 months (95% CI, 2.0-3.6 months) and 4.6 months (95% CI, 2.8-6.3 months), respectively (Figure 1). The initial sites of disease progression in these 47 patients included the liver in 14, sites other than the liver in 27, and both in 6. The median OS was 6.7 months (95% CI, 5.0-8.3 months; Figure 1).

Correlation Between Hepatic Progression-Free Survival and Overall Survival

Among the 47 patients who died or whose disease progressed, the relationship between OS and H-PFS, as assessed by a simple linear regression analysis, yielded a multiple correlation coefficient (r^2) of 0.54. The formula for the resulting regression line was $y = 1.19x + 1.54$ (Figure 2).

Prognostic Factors

A univariate analysis of OS showed that ECOG PS, number of extrahepatic metastatic sites, and serum CEA level significantly affected patients' prognoses. The results of Cox regression analyses of various prognostic factors are given in Table 4. A multivariate analysis revealed that ECOG PS and the number of extrahepatic metastatic sites were independent prognostic factors (hazard ratio [HR], 8.277; 95% CI, 3.60-19.0; and $P = .000$ for ECOG PS; and HR, 2.456; 95% CI, 1.30-4.61; and $P = .005$ for number of extrahepatic metastatic sites).

Discussion

Systemic chemotherapy for advanced CRC has improved considerably in recent years. The combination of infusional 5-FU and LV with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) is considered standard therapy during first-line treatment, with a crossover to irinotecan-containing or oxaliplatin-containing second-line regimens.[1,2,14] The use of all 3 active drugs reportedly contributes to prolonged survival.[2] In addition, the systemic administration of new targeted agents such as bevacizumab and cetuximab has brought further increases in antitumor activity.[15-17]

Despite these recent advances, the clinical courses of patients after the failure of 5-FU, oxaliplatin, and irinotecan are not satisfactory.[18,19] Before the approval of cetuximab in Japan, a dihydropyrimidine dehydrogenase–inhibitory oral fluoropyrimidine, known as S-1 was a treatment option for patients with CRC refractory to these 3 key drugs. However, S-1 produced no objective response and a median OS of only 4.8 months.[20] In clinical trials, monotherapy with cetuximab yielded a survival benefit with a response rate of 10.8% and a median OS of 6.9 months over best supportive care with a median OS of 4.6 months, and cetuximab combined with irinotecan produced a favorable response of 20% and a median OS of around 10 months.[4,5,21,22] To the best of this author's knowledge, no reports have described HAIC with 5-FU for advanced CRC refractory to the above 3 cytotoxic agents. This study demonstrated that the hepatic response rate for HAIC with 5-FU was 18.2%, and the median OS was 6.7 months. These results seem compatible with those of cetuximab alone, which is a standard therapy after 5-FU, oxaliplatin, and irinotecan have failed. Furthermore, HAIC could be placed in a fourth-line regimen after the failure of cetuximab for patients with predominantly liver metastases.

Some studies reported that the level of ALP is a useful prognostic factor in patients with metastatic CRC.[23,24] The present results suggest that the prognosis of patients with hepatic dysfunction because of liver metastases may be poor. In this study, 89.1% of the patients had high levels of ALP (≥ 300 U/L). All manifested uncontrolled liver metastases that had been considered the prognosis-limiting factor. In addition, 23.6% of the patients had an ECOG PS ≥ 2, and 43.6% had previously received 3 or more regimens of

systemic chemotherapy. Despite these poor patient baseline characteristics, HAIC demonstrated a survival value compatible with that of cetuximab alone.

To determine the indications for HAIC, especially in patients with extrahepatic disease, is very difficult. Kemeny et al reported that if extrahepatic metastases were absent, some patients with extensive hepatic metastases previously treated by systemic chemotherapy became resectable with combined therapy using HAIC and systemic chemotherapy.[25] However, combined systemic chemotherapy with 5-FU, oxaliplatin, and irinotecan is usually used as first-line treatment, and thus many patients with both extensive hepatic metastases and extrahepatic metastases have already been treated with these drugs. The methods of treating such patients thus remain an unresolved issue. In the present study, although 81.8% of the patients also had metastases at extrahepatic sites, HAIC was administered because the hepatic lesion was considered to be the prognosis-limiting factor. The correlation between H-PFS and OS in this study suggests that the control of liver metastases, even in patients with extrahepatic disease, may be important in prolonging OS. On the other hand, a multivariate analysis indicated that patients with ≥ 2 extrahepatic metastatic sites had a significantly poorer prognosis, with a median OS of only 4.8 months. These results suggest that the indications for HAIC should be limited by the extent of extrahepatic metastases.

Recently, some clinical studies of HAIC combined with systemic chemotherapy were conducted, and demonstrated remarkable efficacy.[26,27] Gallagher et al reported that HAIC plus systemic irinotecan showed promising results in patients with colorectal liver metastases previously treated with systemic oxaliplatin, resulting in a response rate of 44% and MST of 20 months.[28] In the present study, patients had been refractory to both oxaliplatin and irinotecan and were therefore treated with HAIC alone. In terms of further investigation, HAIC combined with molecular targeted agents could be undertaken.

In third-line and subsequent treatments, clinicians should be especially vigilant regarding adverse effects, because these patients often manifest complications, with various symptoms attributable to their disease and the toxicities of previous therapy. Reportedly, 10%-42% of patients develop grade 3-4 toxicities during third-line systemic chemotherapy.[4,5,18-22] In contrast, in this study, grade 3 toxicities were evident in only 5.5% of patients. Therefore, HAIC may be feasible in heavily pretreated patients, if indicated.

Conclusion

In conclusion, our multicenter, retrospective study demonstrated that HAIC with 5-FU may benefit patients with liver metastases from CRC refractory to standard systemic chemotherapy. Patients with a good PS and limited extrahepatic metastases seem to be optimal candidates for this therapy. This study was clearly limited by its small number of patients and retrospective design. The role of HAIC in patients previously treated using standard, systemic chemotherapy should thus be evaluated in a prospective clinical trial. However, no reports, to the best of this author's knowledge, have described HAIC in this situation, and thus the present results offer background data for future trials. A large-scale, prospective study is required to clarify the clinical benefits of HAIC in this setting.

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Disclosures

The authors have no relevant relationships to disclose.

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Clinical Studies

Phase I/II Multiinstitutional Study of Uterine Artery Embolization with Gelatin Sponge for Symptomatic Uterine Leiomyomata: Japan Interventional Radiology in Oncology Study Group Study

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PURPOSE: This multicenter prospective study was conducted to evaluate the safety and the efficacy of uterine artery embolization (UAE) with gelatin sponge for symptomatic leiomyomas.

MATERIALS AND METHODS: Patients with symptomatic uterine leiomyomas were enrolled and treated with UAE. In phase I, nine patients were evaluated for safety. In phase II, 24 patients were accrued, and an intent-to-treat analysis was performed on all 33 patients. The primary endpoint was safety. Secondary endpoints included technical success, hospital stay, change in symptoms, leiomyoma volume on magnetic resonance (MR) imaging, and incidence of treatment failure.

RESULTS: UAE procedures were performed for all 33 patients. Two patients were lost to follow-up at 3 and 12 months. The median follow-up period was 33.4 months. Minor adverse events (AEs) occurred in 10 patients (33%); major AEs of permanent amenorrhea and leiomyoma expulsion occurred in two (6%). The most common AE was transient amenorrhea. Technical success was achieved in all patients. The median hospital stay was 5 days. At 12 months after UAE, menorrhagia had improved in 90% of patients, pelvic pain in 78%, and bulk-related symptoms in 97%. The mean reduction in leiomyoma volume on MR imaging at 12 months was 61%. Treatment failure occurred in one patient, who underwent hysterectomy for recurrent menorrhagia at 21 months.

CONCLUSIONS: UAE with gelatin sponge is safe, with efficacy comparable to other embolic agents based on published data. Gelatin sponge should be an option for UAE, but a prospective comparison versus other standard UAE embolic agents may be warranted.

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Abbreviations: AE = adverse event, FSH = follicle-stimulating hormone, PVA = polyvinyl alcohol, QOL = quality of life, SIR = Society of Interventional Radiology, TAGM = tris-acryl gelatin microsphere, UAE = uterine artery embolization

VARIOUS embolic agents have been used for uterine artery embolization (UAE); however, no definitive consensus exists regarding the choice of embolic agent. From previous reports, the choice of embolic agent seems to depend not only on its safety and efficacy, but also on its availability in each country.

Since the introduction of UAE in 1995, nonspherical polyvinyl alcohol (PVA) has been most widely used (1–4). Spherical agents such as tris-acryl gelatin microspheres (TAGMs) and

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spherical PVA particles were developed in the past decade, and recently, the use of TAGMs has been expanding. In the United States, European countries, and some other countries, several types of embolic agents are available for UAE. In contrast, no embolic agent is approved for UAE in Japan, and only gelatin sponge is available.

Gelatin sponge has been used for embolization in various fields for more than 30 years. In gynecology, it has been used as part of the standard interventional procedure to control the bleeding of obstetric hemorrhage or malignant tumors (5). In the early years of UAE, gelatin sponge was used, and favorable mid- and long-term outcomes were reported in retrospective and single-institutional studies (6,7). However, no clinical trial has yet prospectively investigated gelatin sponge for UAE. Therefore, we undertook a phase I/II multiinstitutional prospective clinical trial of UAE with gelatin sponge (Japan Interventional Radiology in Oncology Study Group trial 0302). In this study, we evaluated the safety and the efficacy of UAE with gelatin sponge for patients with symptomatic uterine leiomyomata.

MATERIALS AND METHODS

Patient Eligibility

Premenopausal women with symptomatic uterine leiomyomas confirmed by imaging studies were eligible. Symptoms uncontrolled with medical therapies, adequate organ function, and an Eastern Cooperative Oncology Group performance status of 0 to 1 were required.

Exclusion criteria included pregnancy, nursing, or desire for future pregnancy; active inflammatory disease; pelvic malignancy; hormonal therapy within 12 weeks; contraindication to magnetic resonance (MR) imaging; contraindication to iodized contrast material; uncontrolled comorbid disease; and adenomyosis confirmed with MR imaging.

This study was approved by the ethics committee of the Japanese Society of Interventional Radiology and the institutional review boards of the participating institutions. All patients provided written informed consent.

Study Endpoints

The primary endpoint was safety, and the secondary endpoints were clinical outcomes and the incidence and grade of adverse events (AEs).

Study Design

This was a multiinstitutional, single-arm, open-label, noncomparative trial. In phase I, nine patients were enrolled and evaluated for safety according the three-by-three method of the Japan Interventional Radiology in Oncology Study Group. This method has been described in detail elsewhere (8), and, briefly, consists of three phases with intervals of 4 weeks between phases. With three patients entered per phase, a total of nine patients were evaluated. This method was developed to assure the safety of a new treatment with a meticulous, step-by-step approach.

In phase II, an additional 24 patients were enrolled, and the study was completed with a total of 33 patients. All enrolled patients were included in the intent-to-treat analysis for the primary and secondary endpoints. A total of 10 institutions participated in this study. Patient accrual started in May 2004 and terminated in April 2006.

Embolic Material

We used gelatin sponge in this study. Gelatin sponge is absorbable embolic material that dissolves within several days to several weeks. At present, a number of types of gelatin sponge are on the market worldwide. In Japan, three products—Spongel (Astellas, Tokyo, Japan), Gelfoam (Pfizer Japan, Tokyo, Japan), and Gelpart (Nippon Kayaku, Tokyo, Japan)—are commercially available; however, Gelpart was not available at the time of the present study. The products are supplied in various forms: Spongel in blocks of two sizes (2.5 × 5 × 1 cm and 7 × 10 × 1 cm), Gelfoam in sheets of two sizes (8 × 12.5 × 1 cm and 2 × 6 × 0.7 cm), and Gelpart in 1-mm or 2-mm particles in bottles. We used a 2.5 × 5 × 1 cm Spongel block, which weighs approximately 235 mg. A block was cut into 1-mm cubes with a scalpel and scissors according to the previously reported procedure (6) and sterilized by ethylene oxide. This preparation was performed by the principal investigator, and the particles were distributed to coinvestigators.

UAE Procedure

The UAE was performed as follows. Bilateral uterine artery catheterization was performed under local anesthesia, and a vascular sheath was inserted from the unilateral or bilateral femoral arteries. A 4-F or 5-F angiography catheter was advanced into the internal iliac arteries and a coaxial microcatheter system was used to select the uterine arteries. Embolization of both uterine arteries was performed with 1-mm^3 gelatin sponge particles. The gelatin sponge was diluted with approximately 10 mL of nonionic contrast material and aspirated in 1-mL or 2.5-mL syringes. The embolic material was injected under fluoroscopy and saline solution was injected to avoid aggregation of the gelatin sponge in a microcatheter. The embolization endpoint was stasis of blood flow in the ascending branch of the uterine artery, as confirmed by injection of contrast material under fluoroscopy. Embolization of the ovarian artery was not allowed even if the supply from this artery to the leiomyomas was observed on angiography. Evaluation of pelvic arterial anatomy was performed with aortography during UAE or MR angiography before UAE in all patients. Pain management was administered according to local practice.

The size and type of microcatheter systems, use of prophylactic antibiotics, total amount of gelatin sponge used, and pain control procedures were reported. These data were collected with dedicated case report forms.

Outcome Measures

The primary endpoint was the incidence and type of AEs. AEs and their causality and severity were evaluated based on the Society of Interventional Radiology (SIR) classification (9).

Secondary endpoints were clinical outcomes, which included technical success; linear analog pain scale score at 6, 12, 18, and 24 hours and 2 and 7 days after UAE; hospital stay; change in symptom score ranging from 0 (marked worsening) to +10 (marked improvement) on a scale on which +5

represented no change; change in volume of dominant leiomyomas on MR imaging; ovarian function measured by follicle-stimulating hormone (FSH) and presence or absence of menstruation; and treatment failure, defined as the need for subsequent intervention for symptom control, including hysterectomy and repeated embolization. According to the SIR guidelines, the UAE was considered successful when bilateral UAE was confirmed (10). Unilateral UAE was considered successful if only single-sided uterine arterial flow was present.

Baseline clinical symptoms were scored before the UAE on a scale of 0 (no interference with daily life) to 10 (marked interference with daily life). Baseline imaging was obtained by MR imaging according to the standardized protocol at each hospital with or without contrast enhancement.

Symptom change was assessed by patients with a score divided into three levels: marked improvement (score 8–10), moderate improvement (score 5–8), and none (score 5 or lower).

We assessed outcome measures at 1, 3, 6, 9, and 12 months and annually thereafter, except for the postprocedural pain score. We present 12-month results, with the exceptions of major AEs and treatment failure, which were reported through the final analysis in September 2007.

All data were collected with case report forms. Adverse events were to be reported with other items on the schedule. Severe adverse events were to be reported immediately after the events.

Statistical Analysis

In phase I, a cohort of nine patients was considered to be adequate for quick termination when the incidence of severe AEs associated with UAE with gelatin sponge exceeded one third of the population. Throughout phase I and phase II, the study was designed to detect the incidence of AEs set at 10% for the least, 10% for the predicted, and 30% for the unacceptable, with a power of 80%. Therefore, the target number of patients to be accrued was calculated to be 33, including an anticipated dropout rate of 10%.

Demographic and baseline variables were summarized by descriptive statistics. Comparisons with baseline data were performed for the FSH level with paired *t* tests. The statistical significance level was set at .05. All statistical analyses were performed with SPSS software (version 11.01; SPSS, Chicago, Illinois).

RESULTS

Patients

A total of 33 patients were enrolled. All received UAE and were assessable for study endpoints. Patient characteristics are shown in **Table 1**. Two patients were lost to follow-up at 3 and 12 months. In one patient, MR imaging was not performed at 12 months. The median follow-up period was 33.4 months (range, 13.6–41.2 months).

Table 1
Baseline Characteristics of the Patients (N = 33)

Variable	Value
Age (y)	
Median	43
Range	37–54
Previous treatment	
Myomectomy	5 (15)
Hormonal therapy	11 (33)
Other medication	19 (58)
Dominant leiomyoma location	
Intramural	26 (79)
Submucosal	5 (15)
Subserosal	2 (6)
No. of leiomyomas	
1	9 (27)
2–5	14 (42)
> 5	10 (30)
Dominant leiomyoma volume (mL)	
Median	321
Range	64–1,922
Presenting symptom	
Menorrhagia	32 (97)
Severity score	6.9 ± 2.6
Pelvic pain	29 (88)
Severity score	4.6 ± 3.0
Bulk-related symptoms	32 (97)
Severity score	6.7 ± 2.5

Note.—Values in parentheses are percentages. Values expressed as mean ± SD, where appropriate.

Primary Outcome

During phase I, major AEs were not encountered; therefore, the study proceeded to phase II. Among all enrolled patients, minor AEs were reported in 10 patients (33%) and major AEs were reported in two patients (6%; **Table 2**). The most common AE was transient amenorrhea. Other AEs were observed in one patient each. Permanent amenorrhea occurred in one patient who was 46 years of age whose menstruation stopped 6 months after UAE. Leiomyoma expulsion occurred at 2 months in one patient with a submucosal leiomyoma, and the leiomyoma was removed successfully without hospitalization. Complications of angiography were not encountered, and no deaths occurred. Pelvic infection, postembolization syndrome requiring prolonged admission or readmission, radiation injury, adverse drug reactions, and pulmonary embolism were not encountered.

Secondary Outcomes

UAE procedures.—Technical success was achieved in all 33 patients. Dominant ovarian arterial supply to leiomyomas was not encountered. The median procedural time was 55 minutes (range, 29–120 min), and the median fluoroscopic time was 18 minutes (range, 6–44 min). The median mass of gelatin sponge used was 168 mg (range, 80–320 mg). The sizes of the microcatheters used were 2.3 F (Microferret [Cook, Bloomington, Indiana] or Tracker-18 [Boston Scientific, Natick, Massachusetts]; n = 7); 2.4 F (On-the-Road [Solution, Yokohama, Japan], n = 2); 2.5 F (FasTracker-18 [Boston Scientific]; n = 3); 2.6 F (Shirabe High Flow [Piolax, Yokohama, Japan]; n = 3); 2.7 F (Renegade Hi-Flo [Boston Scientific]; n = 17); and 2.8 F (Progreat Omega [Terumo, Tokyo, Japan]; n = 1). Thirty-two patients underwent UAE under local anesthesia and one underwent UAE under conscious sedation. Primary pain control methods were epidural analgesic agents in 17 patients, intravenous or subcutaneous opioid agents in 14 patients, and intramuscular pentazocine in two patients. Oral or suppository nonsteroidal antiinflammatory drugs were administered in combination with primary analgesic agents. A prophylactic antibiotic was used for 1–4 days in all patients. The type of antibiotics were cephazolin (n = 22), piperacillin (n = 7), fosfomycin (n = 2), flomoxef (n = 1), and faropenem (n = 1).

Pain score.—The mean and SD vi-

Table 2
Summary of AEs

Event	SIR Class	At ≤ 1 Month	At 1–12 Months
Major			
Leiomyoma expulsion	C	1 (3)	0
Permanent amenorrhea	E	NE	1 (3)
Minor			
Transient amenorrhea	A	NE	6 (18)
Anemia	B	0	1 (3)
Elevated ALP	A	1 (3)	0
Elevated ALT	A	1 (3)	0
Elevated bilirubin	A	0	1 (3)

Note.—Values in parentheses are percentages. ALP = alkaline phosphatase; ALT = alanine aminotransferase; NE = not evaluable.

Table 3
Changes in Symptom Scores

Symptom/Improvement	1 Month	3 Months	6 Months	12 Months
Menorrhagia	*n* = 32	*n* = 31	*n* = 31	*n* = 30
Marked	16 (50)	21 (68)	23 (74)	23 (77)
Moderate	10 (31)	6 (19)	5 (16)	4 (13)
None	6 (19)	4 (14)	3 (10)	3 (10)
Pelvic pain	*n* = 29	*n* = 28	*n* = 28	*n* = 27
Marked	14 (48)	14 (50)	16 (57)	17 (63)
Moderate	7 (24)	7 (25)	8 (29)	4 (15)
None	8 (28)	7 (25)	4 (14)	6 (22)
Bulk-related symptoms	*n* = 32	*n* = 31	*n* = 31	*n* = 30
Marked	15 (47)	26 (84)	22 (71)	26 (87)
Moderate	13 (40)	4 (13)	8 (26)	3 (10)
None	4 (13)	1 (3)	1 (3)	1 (3)

Note.—Values in parentheses are percentages.

sual analog scale score for pain was as follows: baseline, 0.5 ± 1.8; 6 hours, 5.8 ± 3.7; 12 hours, 4.8 ± 3.7; 18 hours, 3.7 ± 2.8; 24 hours, 2.7 ± 2.6; 2 days, 2.4 ± 2.3; and 7 days, 0.2 ± 0.2.

Length of hospital stay.—The median hospital stay was 5 days (range, 2–10 d). Readmission was not observed in any case.

Clinical outcome.—Symptomatic changes are summarized in **Table 3**. At 12 months after UAE, moderate to marked improvement was observed in terms of menorrhagia in 90% of patients, in pelvic pain in 78% of patients, and in bulk-related symptoms in 97% of patients.

Imaging outcome.—Dominant leiomyoma volume on MR imaging is presented in **Table 4**. At 12 months after UAE, the volume reduction was 61.4% (95% CI, 52.9%– 69.9%).

Ovarian function.—No statistically significant increase in FSH level was demonstrated (**Table 5**). In six patients with transient amenorrhea, the median baseline FSH level was 9.2 mIU/mL. In one patient with permanent amenorrhea, the FSH level showed an increase from a baseline of 11.4 mIU/mL to 152.5 mIU/mL at 12 months.

Treatment failures.—In one patient, hormonal therapy was performed for recurrent bleeding and anemia at 12 months; however, these symptoms were not controlled. This patient underwent hysterectomy at 21 months. No patients underwent repeat UAE. Therefore, the rate of treatment failure was 3% (ie, one of 33).

DISCUSSION

Data regarding UAE with nonspherical PVA, spherical PVA, and TAGMs have been published worldwide, but there have been few studies of gelatin sponge for UAE except for single-institution experiences from Japan (6,7). Follow-up procedures or intervals vary among studies; however, there are few differences in major clinical outcomes between studies that used gelatin sponge and studies that used other embolic agents. Therefore, UAE with gelatin sponge shows safety and efficacy similar to UAE with other widely distributed embolic agents.

Several studies comparing embolic materials for UAE have been reported. Spies and colleagues (11) conducted a randomized controlled trial comparing TAGMs with nonspherical PVA by measuring the recovery after UAE and the 3-month clinical outcome. No significant difference was noted between the two embolic materials in peri- and postprocedural symptoms, tumor infarction, patient satisfaction, symptom improvement, and quality of life (QOL). A difference was observed only in the incidence of microcatheter occlusion, which was more common with PVA. Subsequently, the investigators performed a similar randomized controlled trial (12) comparing TAGMs and spherical PVA. Although no significant differences were observed in symptom control, QOL, and AEs, 500–700-μm PVA spheres were associated with a significantly higher rate of failed tumor infarction, which resulted in the early termination of the trial. In response to these results, Rasuli and coworkers (13) performed a historical comparison of spherical versus nonspherical PVA particles for UAE; UAE with spherical PVA particles resulted in less leiomyoma shrinkage and less improvement in clinical symptoms than UAE with nonspherical PVA, which supported the results of the previous trials (11,12). In terms of the degree of tumor infarction after UAE, Siskin and colleagues (25) undertook a randomized study comparing TAGM with spherical PVA. They evaluated the degree of tumor infarction using contrast-enhanced MR imaging. UAE with TAGMs showed a significantly greater degree of tumor infarction than UAE with spherical PVA, and the authors concluded that TAGMs should be the preferred embolic material for UAE. Conceptually, the spherical shape of spherical PVA particles could improve the tendency of the material to clump in the catheter; however, previous clinical trials have demonstrated the clinical and

Table 4
Changes in Dominant Leiomyoma Volume

Value	Baseline	3 Months	6 Months	12 Months
No. of Pts.	33	32	32	30
Mean volume (mL)	298 (171–426)	180 (83–277)	157 (64–251)	138 (52–224)
Mean reduction (%)	NA	43.7 (36.6–50.8)	53.6 (45.7–61.4)	61.4 (52.9–69.9)

Note.—Values in parentheses are 95% CIs. NA = not applicable.

Table 5
Changes in FSH Levels

Interval	No. of Pts.	Mean FSH (mIU/mL)	*P* Value
Baseline	33	10.3 (6.8–13.5)	NA
3 Months	32	16.7 (7.5–25.9)	.065
6 Months	32	15.3 (8.6–21.9)	.056
12 Months	31	20.7 (5.9–35.4)	.708

Note.—Values in parentheses are 95% CIs. *P* values comparing data at baseline and each month were calculated with paired *t* tests. NA = not applicable.

imaging failure of spherical PVA (12,13). To our knowledge, no study has compared gelatin sponge versus another embolic material.

The incidence of severe AEs in the present study was 6%, which was similar to those of previous reports (0%–11%; **Table 6**) (2–4,6,7,11,14–17). Minor AEs occurred at a rate of 33% in the present study, which was also similar to those of the other studies (20%–53%). Transient amenorrhea, which was seen in 18% of patients, was the most frequent AE, although no significant elevation in FSH levels was observed. Hovsepian and colleagues (18) reported that, within a 6-month follow-up period, no significant difference in FSH levels or new-onset menopausal symptoms was observed among patients undergoing UAE, hysterectomy, or myomectomy in their prospective comparison. In the present study, one case of permanent amenorrhea occurred in a patient who was 46 years of age. Of the six patients who experienced the complication of transient amenorrhea, three were 45 years of age or older. The incidence of amenorrhea after UAE is highly age-dependent, and the reported occurrence in women 45 years of age or older is 26%–58% (18,19).

The technical success rate of 100% in the present study is comparable to those of previous reports (Table 6). No periprocedural complications were observed. We did not experience any case of aggregation of gelatin sponge particles in the microcatheters. Not only nonspherical PVA particles, but also spherical PVA particles, are known to have a tendency to aggregate in microcatheters and vessels (11,20). Gelatin sponge particles are also quoted to have the same tendency; however, the use of gelatin sponge differs depending on the gelatin sponge product, institute, or country. Our procedure of preparing the gelatin sponge (Spongel) was similar to that of Katsumori and coworkers (6) and consisted of manual shaving and cutting of a block into 500–1,000-μm particles. With gelatin sponge prepared by this technique, no microcatheter occlusion or proximal arterial occlusion was experienced in the present study.

In the present study, the average maximum visual analog scale score for subjective pain after UAE was 5.8. In previous randomized and nonrandomized comparison studies (11,12,21), the maximum score ranged from 3.0 to 5.9 after UAE, which was similar to that observed in the present study. In addition, there was no significant difference between nonspherical PVA particles and TAGMs.

Direct comparison of the cost of each embolic material in UAE practice is difficult because the availability varies greatly among countries. Dembek and colleagues (22) reported that the UAE procedure costs were significantly lower than those of myomectomy or hysterectomy in the United States, although no significant difference was noted in 12-month payer costs, mainly because of the high cost of follow-up imaging. In the present study, the UAE procedure costs were reported as a lump sum. The type and quantity of the embolic materials were not evaluated; therefore, the influence of the embolic materials on the total UAE cost was not determined. The price of embolic materials may vary depending on the country; however, the approximate price of one vial of TAGMs (Embosphere) is $240, whereas that of a block of gelatin sponge (Spongel) is $2. Given the variable use of each embolic material, the cost per procedure would be approximately $960 for TAGMs and $5 for gelatin sponge, approximately a 200-fold difference. Differences in local practices such as the length of hospital stay or the type of pain control may affect the total cost of UAE. Also, we did not perform a cost analysis in the present study; however, the low cost of gelatin sponge may have an impact on the medical cost of UAE. As long as the safety and efficacy are demonstrated in an evidence-based manner, the use of low-cost embolic materials is important to reduce the escalating health care cost of UAE.

Several weaknesses of the present trial should be acknowledged. First, this trial was not a randomized controlled trial, and therefore a direct comparison with other embolic materials was not possible. Spies (23) pointed out the importance of properly designed randomized controlled trial comparing the new embolic agents versus the established ones to answer the key question of symptom relief and tumor infarction predicting symptom recurrence. Nevertheless, our data are of value as a baseline for future randomized controlled trials of

Table 6
Comparison of Clinical Outcome of Embolic Agents in Symptomatic Leiomyomas (2–4,6,7,11,12,14–17)

Study, Year	Embolic Particle Size (μm)	Study Design	No. of Pts.	Technical Success (%)	AEs (%)	Symptom Improvement (%)	Leiomyoma Volume Reduction (%)
Nonspherical PVA							
Pelage et al (2), 2000	150–300	Prospective	76	95	Transient amenorrhea; 3; permanent amenorrhea, 5; prolonged postembolization syndrome, 9	95 (2 y)	52 (6 mo, US)
Spies et al (3), 2002	500–710	Prospective	291	99	Minor, 7; major, 4.3	NA	NA
Walker and Pelage (4), 2002	150–500	Prospective	395	99	Infection (hysterectomy), 1; leiomyoma passage, 2; permanent amenorrhea, 7; transient amenorrhea, 2	Menorrhagia, 84; pain, 79; bulk, 82	67 (6 mo)
Spies et al, (11) 2004	355–710	RCT*	46	99	17	Scores equivalent to TAGM (3 mo)	NA
Volkers (15), 2006	355–500	RCT†	88	82.7	Minor, 25.9; major, 4.9 (in-hospital); minor, 53.1; major, 11.1 (discharge 6 weeks)	Menorrhagia, 96.3 (2 y)	60.5 (2 y)
Spherical PVA							
Spies et al (12), 2005	500–900	RCT*	17	100	NA	QOL and symptom scores inferior to TAGM	NA
Siskin et al (25), 2006	500–1,200	Cohort	77	NA	26	88.3 (6 mo)	43.7 (6 mo)
TAGMs							
Spies et al (16), 2001	500–900	Prospective	30	100	Minor, 33; major, 0	Menorrhagia, 100 (6 mo)	—
Spies et al (11), 2004	500–900	RCT*	54	99	Minor, 20; major, 0	Scores equivalent to TAGM (3 mo)	NA
Spies et al (12), 2005	500–900	RCT*	19	95	NA	QOL and symptom scores superior to spherical PVA	NA
Lohle et al (17), 2006	500–1,200	Prospective	158		Permanent amenorrhea, 11; transient amenorrhea, 13; leiomyoma expulsion, 10	Menorrhagia, 91; pain, 92; bulk, 92 (12 mo)	66
Gelatin sponge							
Katsumori et al (6), 2002	500–1,000	Case series	60	98	Leiomyoma expulsion, 3; permanent amenorrhea, 2	Menorrhagia, 100; bulk, 100 (12 mo)	70
Katsumori et al (7), 2005	500–1,000	Prospective	96	NA	Minor, 23; major, 3	96 (1 y), 94.5 (2 y), 89.5 (3 y), 89.5 (4 y), 89.5 (5 y)	—
Present study, 2009	500–1,000	Prospective phase I/II	33	100	Permanent amenorrhea, 3; transient amenorrhea, 18; leiomyoma expulsion, 3	Menorrhagia, 90; bulk, 76; pain, 96 (12 mo)	61

Note.—NA = not available; RCT = randomized controlled trial.
* RCT comparing embolic agents in UAE.
† RCT comparing UAE versus other treatments.

embolic materials including gelatin sponge. Second, we did not measure QOL with preexisting QOL instruments. Although subjective symptom reports like those in the present study are essential for evaluation of the efficacy of UAE, QOL scores on instruments such as the Uterine Fibroid Symptom QOL questionnaire, Short Form–12, Short Form–36, or EuroQol have a positive meaning in the setting of the endpoints for UAE trials. Third, we did not evaluate contrast-enhanced MR imaging for follow-up imaging after UAE. Recently, this issue has been amplified with an increase in data with spherical PVA showing an unacceptably high rate of failed tumor infarction, and with data suggesting a relationship between incomplete tumor infarction and long-term clinical failure (20,24,25). As for UAE with gelatin sponge, Katsumori and coworkers (7,26) evaluated the association of tumor infarction on contrast-enhanced MR imaging with long-term clinical outcome. Of 221 cases, 100% infarction

was achieved in 142 (group A), 90%–99% in 74 (group B), and less than 90% in 5 (group C). The cumulative rates of symptom control at 5 years were 93%, 71%, and 60% in groups A, B, and C, respectively. According to these results, a high rate of tumor infarction was achieved with gelatin sponge in conjunction with a favorable long-term clinical outcome (7,26).

In conclusion, UAE with gelatin sponge is safe, with efficacy equivalent to previous data for other widely used embolic materials. Gelatin sponge should be an option for UAE, but randomized controlled trials including cost analysis will be needed to determine the impact of gelatin sponge on UAE clinical practice.

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Phase I/II Study of Hepatic Arterial Infusion Chemotherapy With Gemcitabine in Patients With Unresectable Intrahepatic Cholangiocarcinoma (JIVROSG-0301)

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Objectives: No established therapy exists for unresectable intrahepatic cholangiocarcinoma (ICC). We conducted a phase I/II study to ascertain the recommended dose (RD) of hepatic arterial infusion using gemcitabine (GEM) for ICC and to assess the efficacy and safety.

Methods: For patients with unresectable ICC, GEM was administered through the hepatic artery via the port system as a 30-minute infusion on days 1, 8, and 15 every 4 weeks for 5 cycles. In phase I, dosage for levels 1, 2, and 3 was set at 600, 800, and 1000 mg/m^2, respectively, and was increased in 3 to 6 patients at a time. Maximum tolerated dose was defined as a dosage resulting in dose-limiting toxicity in 2 of 3 patients or 3 of 6 patients, and RD was estimated during the first cycle. In the phase II, more RD patients were added to assess tumor response and toxicity.

Results: During the phase I, 16 patients were enrolled. Maximum tolerated dose was not reached. Assuming RD at 1000 mg/m^2, the phase II enrolled a total of 13 patients. The following Grade 3 toxicities were observed: neutropenia 20%, increased gamma-glutamyl transpeptidase 8%, increased aspartate aminotransferase 4%, increased alanine aminotransferase 4%, increased bilirubin 4%, nausea 4%, and fatigue 4%. The tumor response rate was 7.7% (complete response 0, partial response 1, stable disease 8, and progressive disease 4).

Conclusion: Whereas the toxicity of hepatic arterial infusion with 1000 mg/m^2 GEM for ICC was tolerable, expected efficacy could not be obtained, thus suggesting only minimal activity.

Key Words: intrahepatic cholangiocarcinoma, hepatic arterial infusion, gemcitabine, phase I/II study, clinical trial

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Intrahepatic cholangiocarcinoma (ICC) constitutes 5% to 15% of cases of the primary hepatic cancer in Japan. It is a cancer with a relatively low incidence, but is characterized by spread from the biliary epithelium to Glisson capsule. ICC has a high incidence of lymph node metastasis and vascular invasion and also tends to invade adjacent organs, so that in a fair number of cases it is already advanced and unresectable at the time of detection.[1–3] Chemotherapy is the treatment option for unresectable ICC, but no standard therapy has been established.[4,5] Typically, drug regimens centered on 5-fluorouracil (5-FU) have been used, but recently, gemcitabine hydrochloride (GEM) has appeared promising.[6]

Hepatic arterial infusion (HAI) chemotherapy is one local therapy for unresectable malignant hepatic tumors and its anticancer effect is obtained by raising the local concentration of the anticancer agent. Local therapy also reduces systemic adverse response and can increase the effect on the hepatic lesions by infusing the active medicinal agent into a hepatic artery.[7] In Japan, HAI with percutaneous placement of a catheter-port system is highly feasible,[8–10] and HAI of GEM can be continued systematically. If a local effect for ICC supplying from the hepatic artery can be obtained with HAI of GEM, this treatment may contribute to prolonging patient survival.

With this as background, we designed a phase I and II clinical trial to evaluate HAI chemotherapy with GEM for unresectable ICC, and a multicenter study was carried out by the Japan Interventional Radiology in Oncology Study Group.

MATERIALS AND METHODS

Study Design and Patient Eligibility

A phase I and II clinical trial at multiple institutions was designed to determine the dose-limiting toxicity (DLT) and recommended dose (RD) for HAI chemotherapy with GEM to treat unresectable ICC, as well as to evaluate its safety and tumor response effect. Dose-limiting toxicity and recommended dose of hepatic arterial infusion of GEM were determined as the primary end point, and the frequency and severity of adverse events, tumor response effect in the liver only, and tumor response effect in the whole body were the secondary end points. In phase I portion, DLT was assessed and RD was estimated, and in phase II portion, cases were added at the estimated RD, and the tumor response effect was evaluated. Toxicity assessment was conducted in all patients with HAI chemotherapy.

The inclusion criteria were the following conditions for cases of unresectable ICC:

1. Cases of histologically confirmed ICC (initial tumor or recurrence after resection), which was determined to be unresectable by a hepatic surgeon at each institution, or it was judged to be the prognosis-determining factor, even when metastasis was found as extrahepatic lesions.
2. Cases that were previously untreated with GEM or that were previously treated with agents other than GEM in the past, but had received no chemotherapy for at least 4 weeks from the last session, and were not responded by the chemotherapy.
3. Cases in which measurable lesions that corresponded to the target lesions on response evaluation criteria in solid tumors were located in the liver and had maximum tumor diameters of 20 mm or more

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