tumor cells and in the liver. Thymidine phosphorylase, which is significantly more active in tumor tissues than in adjacent normal tissues, finally converts 5′-DFUR to 5-FU (5,6). With each successive conversion step, the potential for systemic exposure to 5-FU is reduced while 5-FU delivery to tumor tissues is increased. Consequently, capecitabine avoids many of the gastrointestinal toxicities commonly observed with 5-FU.

Many clinical studies of capecitabine in MCRC have been conducted worldwide. In a Japanese phase I study using continuous administration of capecitabine, the maximum tolerated dose was 1255 mg/m^2 twice daily; skin fissures and gastric ulcers were noted as the dose-limiting toxicities (7). Another phase I study showed that a 1-week rest period appealed to patients and also maintained the activity of capecitabine therapy (8). From these findings, a 4-week intermittent regimen (3 weeks of capecitabine 828 mg/m^2 twice daily followed by a 1-week rest period) was recommended for Japanese phase II studies. This 4-week intermittent schedule of capecitabine was active and well tolerated in Japan, resulting in response rates of 25% (5/20) in a small pilot study (9), and 27% (15/56) in a phase II study (10) in patients with advanced or MCRC. However, it was a 3-week regimen of capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period) that was shown to have superior activity and improved safety over bolus 5-FU/LV (Mayo Clinic regimen) as the first-line therapy in two large randomized phase III studies (11–13), and has been approved for MCRC in Europe and in the United States. Since then, this 3-week regimen has been used as a platform for combination therapy with other active agents, such as irinotecan, oxaliplatin and bevacizumab (14–18).

To date, the efficacy and safety of the 3-week capecitabine regimen in Japan remains unclear. Therefore, we conducted this phase II trial as a registration trial, which included a pharmacokinetic analysis, of the 3-week capecitabine regimen in Japanese patients with previously untreated MCRC.

PATIENTS AND METHODS

Study Design

The primary endpoint of this open-label multicenter phase II study was response rate. Secondary endpoints were safety, time-to-tumor progression (TTP), survival and pharmacokinetic analysis. This study was conducted in accordance with the Good Clinical Practice guidelines for clinical trials in Japan and the Declaration of Helsinki. The study protocol was approved by the ethics committee of each institution. Written informed consent was obtained from all patients.

Patients

All patients had to have histologically confirmed colorectal adenocarcinoma with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) (19). Patients were also required to have the following laboratory values: neutrophils $\geq 1.5 \times 10^3/mm^3$; platelet count $>10 \times 10^4/mm^3$; serum creatinine $<1.5 \times$ upper limit of normal (ULN); serum bilirubin $<1.5 \times$ ULN; ALT (GPT), AST (GOT) $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN in the case of liver metastases); alkaline phosphatase $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN in the case of liver metastases or $\leq 10 \times$ ULN in the case of bone disease) and creatinine clearance >50 ml/min. Patients had received no chemotherapy for metastatic disease (excluding adjuvant chemotherapy completed more than 6 months before registration) and no radiotherapy to target lesions. Patients were not included if they had received radiotherapy within the previous 4 weeks, or had not fully recovered from the major surgery within 4 weeks. Other eligibility criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; expected survival time of more than 3 months and age at enrollment of 20–74 years.

Exclusion criteria were as follows: pregnant or lactating women; sexually active men/women unwilling to practice contraception during the study; a history of hypersensitivity to 5-FU; organ allografts; clinically significant cardiac disease or myocardial infarction within the last 12 months; metastases of the central nervous system; a history of epilepsy; psychiatric disability precluding compliance with oral drug intake or giving informed consent; history of another malignancy within the last five years, except for cured basal cell carcinoma of skin, cured carcinoma *in situ* of uterine cervix, or cured esophago-gastric carcinoma removed by endoscopic procedures; serious uncontrolled infection; malabsorption syndrome; participation in any investigational drug study within 4 weeks preceding the start of treatment.

Evaluation of Response and Safety

Anti-tumor efficacy was evaluated by the investigators according to RECIST guidelines (19). An Independent Review Committee (IRC) confirmed tumor responses. Adverse events were assessed according to the National Cancer Institute—Common Toxicity Criteria, Version 2.0 (20). Hand-foot syndrome (HFS) was classified as follows: grade 1 (numbness, dysesthesia, painless swelling or erythema not disrupting daily living activities); grade 2 (erythema with painful swelling or disruption of daily living activities) or grade 3 (moist desquamation, ulceration, blistering or severe pain, or any symptoms leading to an inability to work or to perform daily living activities).

Study Assessments

Tumor responses were assessed every 2 cycles up to the cycle 10, and then every 3 cycles. Tumor markers (CEA and CA19-9) were also assessed at these times. Laboratory tests were performed before treatment, on day 8 of cycle 1 and on day 22 of each cycle. Drug compliance was reviewed at regular patient visits by checking unused tablets. Survival in all patients was monitored for 2 years after the last patient was enrolled.

Dosage and Dose Modifications

Capecitabine (Xeloda®) 1250 mg/m^2 was taken orally twice daily within 30 min after breakfast and dinner. The actual dose of capecitabine administered was determined according to the patient's body surface area (BSA) as follows: 3000 mg/day if BSA was <1.33; 3600 mg/day if BSA was between 1.33 and 1.56; 4200 mg/day if BSA was between 1.57 and 1.80; and 4800 mg/day if BSA was >1.80. Each cycle of therapy consisted of 2 weeks of capecitabine administration followed by a 1-week rest period. Patients received treatment unless they had disease progression or unacceptable toxicity, or withdrew consent.

Treatment interruption or dose reductions were made if patients experienced grade 2–4 toxicities, but not if the toxicity was considered unlikely to become serious or life-threatening. Treatment was interrupted in cases of grade 2 or grade 3 toxicities and was not resumed until adverse drug reactions improved to grade 1. The dose of capecitabine was not reduced for the subsequent treatment cycle in cases of the first appearance of grade 2 toxicity. Capecitabine dose was reduced by 25% when patients experienced any grade 2 toxicity for a second time or for any grade 3 toxicity. It was reduced by 50% when patients experienced any grade 2 toxicity three times, any grade 3 toxicity twice, or any grade 4 toxicity. Treatment was discontinued if such toxicities were observed despite dose reduction.

Statistical Methods

The target number of patients for accrual was 60. Given an expected response rate of 25%, a threshold response rate of 10% and a one-tailed probability of 0.025, the statistical power was 80%. All eligible patients were included in the analysis of response. The 95% confidence interval (CI) of the response rate was calculated by the exact method, assuming a binomial distribution of data. Treatment duration was defined as days from the first day of drug administration to the last regulated rest day of the final cycle. Dose intensity was calculated by dividing the cumulative dose/treatment duration by BSA. TTP was calculated as the time from the first administration of capecitabine to disease progression or death if the patient died before progression. Overall survival was defined as the time from study enrolment to death. These endpoints were calculated by the Kaplan–Meier method. Safety was evaluated in all patients who received capecitabine treatment.

Pharmacokinetic Analysis

Blood sampling was performed in the first 20 patients who gave consent to participate in the pharmacokinetic study. On day 1, the evening dose of capecitabine was not administered in order to quantify urinary recovery of capecitabine and its metabolites over a 24 h collection period. On days 1 and 14, 5 ml blood samples were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8 and 11 h after the morning dose using vacutainers containing EDTA as an anticoagulant. Blood samples were centrifuged at 1500 *g* and 4°C for 10 min, and supernatant plasma was removed and stored in plastic tubes below −20°C until analysis. Urine was collected and pooled during the following time intervals: 0, 0–11 and 11–24 h on day 1; and 0–11 h on day 14. At the end of each interval, the total volume and the pH of urine were recorded; and a 15 ml aliquot was removed and stored at −20°C until analysis.

Plasma and urine concentrations of capecitabine and its metabolites were determined by a validated liquid chromatography with mass-spectrometry detection (LC/MS-MS). The lower limits of quantification (LLOQ) of capecitabine, 5′-DFCR, 5′-DFUR, 5-FU and α-fluoro-β-alanine (FBAL) in plasma were 0.01, 0.01, 0.05, 0.002 and 0.011 μg/ml, respectively. The LLOQ of capecitabine, 5′-DFCR, 5′-DFUR, 5-FU, α-fluoro-β-ureidopropionic acid and FBAL in urine were 0.02, 0.02, 0.02, 0.1, 0.02 and 0.1 μg/ml, respectively.

Pharmacokinetic parameters were assessed by standard non-compartment analysis, using WinNonlin® professional version 4.1 (Pharsight Corporation). Maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were determined. Apparent half-life ($t_{1/2}$) was estimated from ln2/λ, where the apparent rate constant of elimination, λ, was estimated by linear regression on the logarithm of the plasma concentration versus time data. The area under the plasma concentration time curve from time 0 to infinity (AUC) was estimated from the sum of AUC_{0-t} and C_{tlast}/λ, where AUC_{0-t} is the area under the curve from time 0 to the last sampling time (t_{last}) at which a concentration above the limit of quantification was measured (C_{tlast}). AUC_{0-t} was estimated using the linear-log trapezoidal rule. Percentage of dose recovered in urine as capecitabine or one of its metabolites was calculated based on the dose administered, urinary concentration and volume of urine collected.

RESULTS

Patient Characteristics

Sixty patients were enrolled at 11 centers between January 2003 and November 2003. All patients met the eligibility criteria and received at least one dose of capecitabine. Therefore, both tumor response and safety were assessed in 60 patients. The baseline characteristics of patients are shown in Table 1. Median age was 60 years (range 34–71 years). A total of 33 patients (55%) had colon cancer, and 26 (43%) had rectal cancer. Metastatic sites affected were liver (73%), lung (58%), lymph node (47%) and others (17%).

Treatment Duration and Intensity

The median duration of treatment was 186 days (range 8–508 days). The median cumulative dose of capecitabine was 370 g (range 27–1255 g). The planned dose intensity was 1667 mg/m^2/day and the actual median dose intensity was 1420 mg/m^2/day (range 940–2220 mg/m^2/day). Approximately 57 and 35% of patients completed 8 and 10 cycles of therapy, respectively. The reasons for treatment discontinuation were progressive disease (54 patients), adverse reactions (5 patients) and salvage surgical therapy (1 patient).

Table 1. Baseline patient demographics (intent-to-treat population)

Parameter	No. of patients	%
No. patients enrolled	60	100
Sex		
Male	33	55
Female	27	45
Age (years)		
Median	60	
Range	34–71	
Primary site		
Colon	33	55
Rectum	26	43
Colon/rectum	1	2
ECOG performance status		
0	42	70
1	17	28
2	1	2
Metastatic sites		
Liver	44	73
Lung	35	58
Lymph node	28	47
Other	10	17
Number of metastatic sites		
1	18	30
2	31	52
≥3	11	18
Resection		
Yes	54	90
No	6	10
Prior radiotherapy	1	2
Prior 5-FU or 5-FU analog-based adjuvant chemotherapy	10	17

The median dose per cycle was >75% of the planned dose up to 10 cycles.

Efficacy

The objective response rate according to the IRC assessment was 35% (95% CI, 23–48%) (Table 2). Twenty-one patients had a partial response, and 31 (52%) had stable disease. Partial responses were observed in 11 out of 44 patients (25%) with liver metastases, 14 out of 35 patients (40%) with lung metastases and in 8 out of 28 patients (29%) with lymph nodes metastases. The median TTP was 5.5 months (95% CI, 4.2–6.7 months) (Fig. 1). Survival follow-up was performed at the cut-off date of October 2005. Thirty-five patients died of disease progression and there were no treatment-related deaths. The median overall survival was 20.2 months (95% CI, 16.6–27.8 months) and the 1-year survival rate was 70% (Fig. 1).

Table 2. Tumor responses (N = 60)

Response	No. of patients (%)	
	Assessed by investigators	Confirmed by Independent Review Committee
Complete response (CR)	0 (0)	0 (0)
Partial response (PR)	19 (32)	21 (35)
Stable disease (SD)	33 (55)	31 (52)
Progressive disease (PD)	7 (12)	8 (13)
Not evaluable	1 (2)	0 (0)
Overall response rate	32% (95% CI, 20–45%)	35% (95% CI, 23–48%)
Disease control (CR + PR + SD)	87% (95% CI, 75–94%)	87% (95% CI, 75–94%)

CI: confidence interval.

Safety

The common adverse drug reactions (all grades) were HFS (73%), pigmentation (38%), diarrhea (37%), anorexia (37%), nausea (37%) and stomatitis (37%) (Fig. 2). The most frequent grade 3/4 adverse drug reaction was HFS (13%), but it was managed relatively easily by treatment interruption or dose reduction. No grade 4 diarrhea was observed, and grade 3 diarrhea was seen in only one patient. Ileus occurred in one patient. As for grade 3/4 laboratory abnormalities, the common events were elevated total bilirubin (12%) and elevated AST (10%). One patient had grade 3 leucopenia, and 5 patients had grade 3 neutropenia. One patient had grade 4 hyperglycemia.

Treatment was interrupted due to adverse drug reactions in 48 patients (80%). The median time to the first interruption was 43 days. The major cause of treatment interruption was HFS (25 patients). Dose reduction was needed in 32 patients (53%), and 10 patients had the second dose reduction. The median time to the first dose reduction was 78 days, and to second dose reduction was 162 days. Nineteen patients had dose reductions due to HFS. Five patients discontinued treatment because of adverse events: ileus (grade 4, treatment related); hepatitis C (grade 3, not related, an accidental acute infection); liver function abnormality (grade 2, not related, due to the progression of liver metastasis); hydronephrosis (grade 4, not related) and HFS (grade 3, treatment related).

Pharmacokinetics

Plasma concentrations for capecitabine and its metabolites (5′-DFCR, 5′-DFUR, 5-FU and FBAL) are shown in Fig. 3. The pharmacokinetic parameters are summarized in Table 3. Peak plasma concentrations of capecitabine and its metabolites

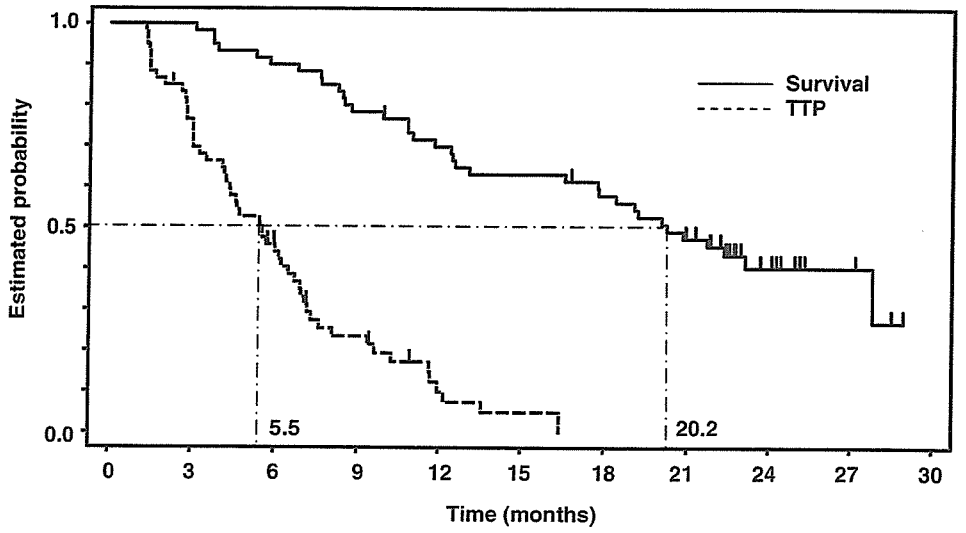

Figure 1. Time to disease progression (TTP) and overall survival.

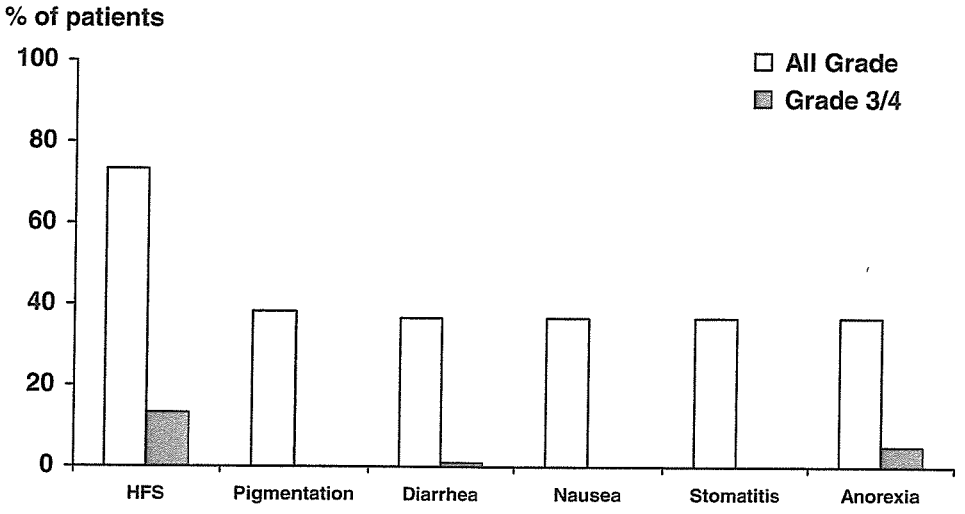

Figure 2. Common adverse drug reactions (≥20% of patients). HFS: hand-foot syndrome.

were reached rapidly at approximately 1.5–4 h after oral administration. Plasma concentrations of capecitabine, 5′-DFCR, 5′-DFUR and 5-FU were below the LLOQ at 8, 11, 8 and 8 h on day 1, respectively, and at 6, 11, 6 and 8 h on day 14, respectively. $T_{1/2}$ were generally short at <1 h, except for FBAL (around 2.5 h). After a single dose of capecitabine 1250 mg/m^2, the AUC for 5-FU was almost 30 times lower than its precursor 5′-DFUR on day 1. Comparing day 1 versus day 14, there was no significant accumulation of capecitabine and its metabolites except for 5-FU. The AUC for 5-FU on day 14 was 1.6 times higher than that on day 1.

The mean urinary excretion ratio of capecitabine and its metabolites are presented in Table 4. The mean proportions for the urinary recovery of capecitabine and its metabolites were 78% on day 1 and 80% on day 14. FBAL was the main urinary metabolite accounting for 50% on day 1 and 50% on day 14. The urinary excretion ratio of unmetabolized capecitabine was low at around 3%.

DISCUSSION

Two large randomized phase III studies have shown that capecitabine is more active than bolus 5-FU/LV in terms of tumor response (26 versus 17%), and equivalent to 5-FU/LV in terms of TTP and overall survival time in the first-line treatment of MCRC (11,13). Furthermore, a combined analysis of these randomized phase III studies revealed that capecitabine conferred a clinically meaningful advantage over 5-FU/LV in terms of safety (12). On the basis of these data, capecitabine was approved for the treatment of MCRC in Europe and in the US as an alternative to 5-FU/LV.

The results of the present study are similar to those observed in the pivotal phase III trials. The response rate in our study

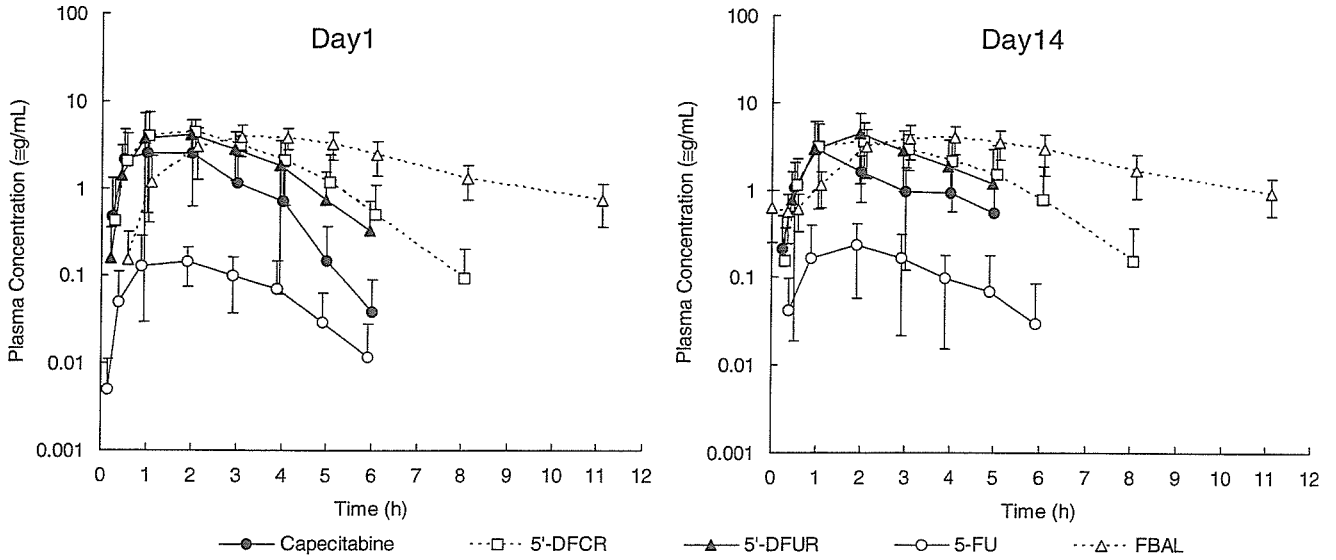

Figure 3. Plasma concentrations (mean ± standard deviation) for capecitabine and its metabolites 5′-deoxy-5-fluorocytidine (5′-DFCR), 5′-deoxy-5-fluorouridine (5′-DFUR) and α-fluoro-β-alanine (FBAL).

Table 3. Pharmacokinetic parameters of capecitabine and its metabolites

	Parameter	Day 1		Day 14	
		N	Mean ± SD	*N*	Mean ± SD
Capecitabine	C_{max} (μg/ml)	20	4.80 ± 1.75	19	4.19 ± 2.55
	T_{max} (h)	20	1.68 ± 0.99	19	1.90 ± 1.40
	AUC (μg·h/ml)	18	7.06 ± 2.46	15	6.73 ± 1.71
	$t_{1/2}$ (h)	18	0.545 ± 0.245	15	0.478 ± 0.152
5′-DFCR	C_{max} (μg/ml)	20	5.95 ± 2.50	19	5.20 ± 1.90
	T_{max} (h)	20	2.00 ± 1.07	19	2.53 ± 1.27
	AUC (μg·h/ml)	20	15.2 ± 4.32	19	14.1 ± 4.60
	$t_{1/2}$ (h)	20	0.810 ± 0.112	19	0.855 ± 0.199
5′-DFUR	C_{max} (μg/ml)	20	6.02 ± 2.49	19	6.59 ± 2.83
	T_{max} (h)	20	2.25 ± 1.16	19	2.69 ± 1.21
	AUC (μg·h/ml)	19	13.1 ± 3.69	17	13.2 ± 3.40
	$t_{1/2}$ (h)	19	0.711 ± 0.140	17	0.689 ± 0.199
5-FU	C_{max} (μg/ml)	20	0.217 ± 0.121	19	0.376 ± 0.211
	T_{max} (h)	20	2.30 ± 1.25	19	2.74 ± 1.20
	AUC (μg·h/ml)	19	0.455 ± 0.180	17	0.719 ± 0.235
	$t_{1/2}$ (h)	19	0.732 ± 0.291	17	0.755 ± 0.258
FBAL	C_{max} (μg/ml)	20	4.50 ± 1.01	19	4.84 ± 1.20
	T_{max} (h)	20	3.35 ± 1.09	19	3.85 ± 1.31
	AUC (μg·h/ml)	20	24.5 ± 7.40	16	27.0 ± 7.84
	$t_{1/2}$ (h)	20	2.56 ± 0.690	16	2.72 ± 0.506

5′-DFCR, 5′-deoxy-5-fluorocytidine; 5′-DFUR, 5′-deoxy-5-fluorouridine; FBAL, α-fluoro-β-alanine.

was 35%, which compares favorably with the combined response rate reported in the phase III studies (26%) (11,13) and in a previous Japanese phase II study (27%) using the 4-week regimen (10). Comparing the patients' background, the number of patients who had more than 3 metastatic sites in this study was less than that in the phase III studies (18 versus 52%) (12), and our patients had better PS (PS 0, 70%). These better backgrounds might bring out slightly higher response rate in our study. The rate of stable disease was 52% in the current study and 38% with the 4-week regimen (10). Consequently, the disease control rate was superior in the present study than with the 4-week regimen (87 versus 64%). Moreover, the median TTP was similar to that reported in the phase III studies (5.5 months versus 4.6 months) using the same 3-week schedule, and was longer than that in the previous Japanese phase II study (2.2 months, unpublished data) using the 4-week regimen. Notwithstanding the limitations of comparing data between trials, these data strongly suggest that the capecitabine 3-week regimen is superior to the 4-week regimen. One of the reasons for these better results might be attributed to the higher dose intensity of the 3-week regimen than that of the 4-week regimen.

In terms of safety, most adverse events were reversible and manageable, and the tolerability of this regimen in a Japanese patient population seemed similar to that observed in Western patient populations. Compared with the randomized phase III studies (12), the rate of HFS, the most frequently reported adverse drug reaction, was higher in the present study (73 versus 54%), but grade 3 HFS appeared a little lower (13 versus 17%). However, HFS was controlled easily by interruption or dose reduction and it is not a life-threatening toxicity. Only one patient withdrew from the study due to this adverse reaction (2%), but none of the patients required hospitalization for the treatment of HFS. In the phase III studies (12), 2% of patients withdrew because of HFS, a rate that was similar to our study. The rate of diarrhea (all-grade and grade 3/4) was less frequent in the present study compared with that of the phase III data (all-grade 37 versus 48%; grade 3/4

Table 4. Urinary excretion of capecitabine and its metabolites

	Urinary excretion (% of dose)			
	Day 1		Day 14	
	N	Mean ± SD	*N*	Mean ± SD
Capecitabine	16	3.21 ± 2.04	19	3.42 ± 1.48
5′-DFCR	16	8.39 ± 3.73	19	8.42 ± 3.44
5′-DFUR	16	12.1 ± 4.34	19	14.6 ± 5.35
5-FU	16	0.691 ± 0.835	19	0.782 ± 0.642
FUPA	16	2.78 ± 0.808	19	2.98 ± 1.05
FBAL	16	50.3 ± 9.66	19	49.5 ± 11.3
Total	16	77.5 ± 14.8	19	79.6 ± 16.9

5′-DFCR, 5′-deoxy-5-fluorocytidine; 5′-DFUR, 5′-deoxy-5-fluorouridine; FUPA, α-fluoro-β-ureidopropionic acid; FBAL, α-fluoro-β-alanine.

2 versus 13%) (12). Though pigmentation, which was not reported more than 5% in the phase III trials, was frequently observed in this study (38%), all events of pigmentation were grade 1 and did not lead to interruption or reduction. The rate of other adverse drug reactions in our study was almost identical to that reported in the phase III trials (12). With regard to severe abnormalities in laboratory parameters, AST elevation was more frequently observed in the present study (10 versus 1%), although the rate of hyperbilirubinemia was similar to phase III observations (12 versus 23%) (12). Dose reduction was executed more frequently than the phase III trials (53 versus 34%), but the rate of dose reduction to second level was almost similar (17 versus 12%). Median time to reduction to the first level was similar to phase III trials (2.6 months versus 2.5 months), and median time to reduction to the second level was longer in our study (5.3 months versus 3.6 months). From these results, the current 3-week regimen seems quite feasible for the treatment of MCRC in Japan.

The pharmacokinetic findings in the present study were basically similar to those reported in Caucasian patients (8,21). Pharmacokinetic analysis of plasma concentrations and urinary excretion showed rapid gastrointestinal absorption of capecitabine and efficient conversion to its metabolites. Peak concentrations of capecitabine and its metabolites, including 5-FU, were reached shortly after drug administration and declined exponentially with a half-life of approximately 1 h. Pharmacokinetic data obtained on days 1 and 14 showed no difference in pharmacokinetics over time and there was no clinically significant accumulation of capecitabine and its metabolites, except for 5-FU. The AUC of 5-FU on day 14 was 1.6 times higher than on day 1. A similar increase of 5-FU with multiple administration has been also reported in other clinical studies of capecitabine (7,8,21).

From these results, we conclude that the 3-week regimen of capecitabine is effective and well tolerated in Japanese patients with MCRC. Capecitabine has been reported to show good activity when combined with irinotecan (14,15) and oxaliplatin (16,17). Further investigation of this 3-week schedule is warranted in Japan.

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APPENDIX

List of participating centers: NHO Shikoku Cancer Center, National Cancer Center Hospital, National Cancer Center Hospital East, Cancer Institute Hospital, Aichi Cancer Center, Saitama Cancer Center, Kobe University Graduate School of Medicine, Kanagawa Cancer Center, Osaka Medical College, Kinki University, NHO Osaka National Hospital.

Staging performance of carbon-11 choline positron emission tomography/computed tomography in patients with bone and soft tissue sarcoma: Comparison with conventional imaging

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The present study was conducted to compare the diagnostic accuracy between carbon-11 choline (^{11}C-choline) positron emission tomography (PET)/computed tomography (CT) and conventional imaging for the staging of bone and soft tissue sarcomas. Sixteen patients who underwent ^{11}C-choline PET/CT prior to treatment were evaluated retrospectively for staging accuracy. Conventional imaging methods consisted of ^{99m}Tc-hydroxymethylene diphosphonate bone scintigraphy, chest CT and magnetic resonance imaging of the primary site. The images were reviewed and a consensus was reached by two board-certified radiologists who were unaware of any clinical or radiological information using hard-copy films and multimodality computer platform. Tumor stage was confirmed by histological examination and/or by an obvious progression in number and/or size of the lesions on follow-up examinations. Reviewers examining both ^{11}C-choline PET/CT and conventional imaging classified T stage in all patients. Interpretation based on ^{11}C-choline PET/CT, the Node (N) stage was correctly diagnosed in all patients, whereas the accuracy of conventional imaging in N stage was 63%. Tumor Node Metastasis (TNM) stage was assessed correctly with ^{11}C-choline PET/CT in 15 of 16 patients (94%) and with conventional imaging in eight of 16 patients (50%). The overall TNM staging and N staging accuracy of ^{11}C-choline PET/CT were significantly higher than that of conventional imaging ($P < 0.05$). ^{11}C-choline PET/CT is more accurate than conventional imaging regarding clinical staging of patients with bone and soft tissue sarcomas. A whole body ^{11}C-choline PET/CT might be acceptable for imaging studies of tumor staging prior to treatment. (*Cancer Sci* 2006; 97: 1125–1128)

The general diagnostic tools for staging bone and soft tissue sarcomas are clinical examination, magnetic resonance imaging (MRI) and X-ray of the primary tumor site, chest X-ray or computed tomography (CT), and bone scintigraphy.[1]

Positron emission tomography (PET) with [18F]-fluoro-2-deoxy-D-glucose (FDG) has been used in the evaluation of patients with bone and soft tissue sarcomas for grading and therapy monitoring.[2–7] Most of these studies reveal that ^{18}FDG-PET is superior in the assessment of grading and therapy monitoring compared with conventional imaging.

Recently, carbon-11 choline (^{11}C-choline) has been introduced as a new oncological positron-emitting radiopharmaceutical for evaluation of a variety of malignant tumors.[8–11] Choline is an essential component of the cell membrane, and choline uptake may be via a choline-specific transporter protein.[12] Choline kinase, which catalyzes the phosphorylation of choline, is upregulated in malignant cells. Some studies have demonstrated additional gains in diagnostic accuracy using ^{11}C-choline.[13] ^{11}C-choline uptake is significantly higher in malignant tumors than in benign tumors and correlates well with the degree of ^{18}FDG accumulation with the lesion, while the high background activity owing to excretion via urinary tract interferes with evaluation on ^{18}FDG-PET.[14,15] However, the role of ^{11}C-choline PET scan in the staging of bone and soft tissue sarcomas has not been clarified. To fully elucidate the role of ^{11}C-choline PET, the comparison with ^{18}FDG-PET and conventional imaging modalities are needed.

A new-modality PET/CT can improve the localization of tumors and accuracy of staging in patients because anatomic and molecular information can be coregistered precisely.[16] The aim of the current study was to compare the diagnostic accuracy between ^{11}C-choline PET/CT and conventional imaging for the staging of bone and soft tissue sarcomas.

Materials and Methods

Patient. We retrospectively reviewed ^{11}C-choline PET/CT results from September 2005 to March 2006 for patients with bone and soft tissue sarcomas, who subsequently underwent surgical resection, chemotherapy and/or radiotherapy within 2 weeks. ^{11}C-choline PET/CT was performed for initial staging in 12 patients and for restaging of recurrent disease in four patients. The study population consisted of 13 men and three women with a mean age of 44 years (range, 13–75 years). The clinical records of all of the patients were available for review. This study was conducted in accordance with the amended Helsinki declaration and the protocol was approved by the Institutional Review Board (National Cancer Center, Research Center for Cancer Prevention and Screening). All of the patients provided their written informed consent to participate in the present study and to review their records and images.

Radiopharmaceuticals. Carbon-11 choline was synthesized with a commercial module essentially using the method described by Hara and Yuasa.[17] $^{11}CO_2$ was converted to ^{11}C-methyl iodide by $LiAlH_4$/HI reaction. ^{11}C-methyl iodide was trapped in dimethylaminoethanol. After a washing step with ethanol and water, ^{11}C-choline retained on a cation exchange resin was eluted with saline. Radiochemical purity of the solution was evaluated by liquid chromatography radiodetector. The organic solvents were analyzed by gas chromatography. Endotoxin was assayed by the lysosomal acid lipase method.

PET/CT. Scans were acquired with a PET/CT device (Aquiduo; Toshiba Medical Systems, Tokyo, Japan) that consisted of a PET scanner (ECAT HR+; CTI, Knoxville, TN, USA) and 16-section CT scanner (Aquilion V-detector; Toshiba Medical Systems) with a whole-body mode implemented as the standard software. Prior to the ^{11}C-choline PET/CT study, the patients fasted for at least

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Table 1. Summary of patients and confirmed staging

Patient no.	Diagnosis	SUV	Size (mm)	Staging type	Location	TNM	Metastasis	Grade	Stage
1	Leiomyosarcoma	4.63	110	Initial	Retroperitoneum	T2bN0M1	Soft tissue	High	IV
2	Rhabdomyosarcoma	3.03	60	Initial	Perineum	T2bN1M0	Lymph node	High	IV
3	Pleomorphic malignant Fibrous histiocytoma	15.05	133	Initial	Chest wall	T2bN0M1	Bone, pleura, lymph node	High	IV
4	Leiomyosarcoma	4.10	80	Initial	Retroperitoneum	T2bN0M,P	Lung	Low	IV
5	Osteosarcoma	6.70	110	Initial	Iliac bone	T2N0M1b	Bone, lung	High	IVB
6	Clear cell sarcoma	13.03	80	Initial	Chest wall	T2bN0M1	Bone, lung, pleura, lymph node	High	IV
7	Myxoid liposarcoma	2.15	50	Initial	Leg	T1aN1M0	Lymph node	Low	IVB
8	Osteosarcoma	5.31	110	Initial	Tibia	T2N1M0	Lymph node	High	IV
9	Ewing sarcoma	3.46	95	Initial	Leg	T2bN0M0	N/A	High	III
10	Ewing sarcoma	9.86	102	Initial	Shoulder	T2N0M0	N/A	High	IIB
11	Ewing sarcoma	6.14	16	Initial	Spine	T1N0M0	N/A	High	IA
12	Chondrosarcoma	5.99	110	Initial	Iliac bone	T2N0M1b	Bone	High	IVB
13	Leiomyosarcoma	3.18	50	Restaging	Thigh	T1bN1M1	Bone, soft tissue, lymph node	High	IV
14	Osteosarcoma	4.95	75	Restaging	Jaw	T1N0M1a	Lung	High	IVA
15	Osteosarcoma	3.60	50	Restaging	Femur	T1N0M1b	Lung, bone	High	IVB
16	Alveolar soft part sarcoma	3.60	25	Restaging	Shoulder	T2N0M1	Bone	High	IV

N/A, not applicable; SUV, standardized uptake value; TNM, Tumor Node Metastasis.

6 h. CT was performed from the head to the mid-thigh according to a standardized protocol with the following setting: axial 3.0-mm collimation × 16 modes; 120 kVp; 100 mAs; and a 0.5-second tube rotation, pitch 11.0. Patients maintained normal shallow respiration during the three-dimensional acquisition of CT scans. No iodinated contrast material was administered. Emission scans from the base of the skull to the leg were obtained starting 5 min after the intravenous administration of 350–573 MBq of ^{11}C-choline. The acquisition time for PET was 2 min per table position. Images were reconstructed with attenuation-corrected ordered-subset expectation maximization with two iterations and eight subsets using emission scans and CT data.

Positron emission tomography, CT and coregistered PET/CT images were analyzed with dedicated software (e-soft; Siemens). The initial review of the attenuation-corrected PET images was performed using transaxial, coronal and sagittal planes. The images were reviewed and a consensus was reached by two board-certified radiologists who were unaware of any clinical or radiological information using a multimodality computer platform. ^{11}C-choline uptake was considered to be abnormal when it was substantially greater than the surrounding normal tissue. For ^{11}C-choline PET/CT, tumor sizes and T staging were determined by the CT part of PET/CT. ^{11}C-choline-avid lymph nodes or distant metastases on PET/CT were interpreted as positive for metastases regardless of size. Lymph nodes with abnormal uptake were deemed positive for metastases even when they were smaller than 10.0 mm in short axis nodal diameter. Lung nodules without abnormal uptake but highly suggestive of lung metastases on ^{11}C-choline PET/CT were considered to be positive for metastases. A pixel region of interest (ROI) was outlined within regions of increased ^{11}C-choline uptake and measured on each slice. For quantitative interpretations, standardized uptake value (SUV) was determined according to the standard formula, with activity in the ROI given in Bq per mL/injected dose in Bq per weight (kg). However, time decay correction for whole-body image acquisition was not conducted. A SUV of more than 2.5 was considered to characterize malignancy.

Conventional imaging. Conventional imaging methods, performed within 2 weeks of ^{11}C-choline PET/CT, either before or after, were ^{99,m}Tc-hydroxymethylene diphosphonate (HMDP) bone scintigraphy, chest CT and MRI of the primary site. ^{99,m}Tc-HMDP bone scintigraphy was performed 2 h after intravenous injection of 740 MBq of ^{99,m}Tc-HMDP. Both anterior and posterior whole-body planar images were obtained simultaneously with a dual-headed gamma camera (E.CAM; Siemens). Chest CT was performed using a multidetector scanner (Aquilion V-detector; Toshiba Medical Systems) with the following setting: axial 4.0-mm × 4 modes; 120 kVp, automated electric current; 0.5-second tube rotation; and pitch 5. Images were reconstructed with 10.0-mm slice thickness by means of a standard algorithm. MRI of the primary site was performed using a 1.5 Tesla system (Signa Horizon; GE Medical Systems, Milwaukee, WI, USA or Visart; MRI produced by Toshiba Medical Systems, Tokyo, Japan). Pulse sequences comprised T1-weighted spin echo (SE) images, T2-weighted fast spin echo (FSE) images, as well as post-contrast T1-weighted SE images with fat suppression after injection of contrast material. Pulse sequence parameters and slice orientation varied with the examined anatomic site. The images were reviewed and a consensus was reached by two board-certified radiologists who were unaware of any clinical or radiological information using hard-copy films and multimodality computer platform. The two readers for ^{11}C-choline PET/CT and those for conventional imaging were not the same persons.

Each tumor was staged according to the Tumor Node Metastasis (TNM) classification of the International Union Against Cancer for sarcoma of bone and the American Joint Committee staging protocol for sarcoma of the soft tissue.[18,19] T, N and M stages were assigned for both PET/CT and conventional imaging. T staging was confirmed by pathological evaluation using specimens obtained from surgical resection of the primary tumors. N staging was confirmed by pathological examinations in two patients using specimens obtained from sampling of regional nodes. In terms of extraregional nodes in two patients, nodal staging was confirmed by an obvious progression in number and/or size of the lesions on follow-up examinations. The mean follow-up period was 172 days (range, 44–322 days).

Statistical analysis. All valuables were assessed on a patient-by-patient basis. The McNemar test was used for paired comparisons between ^{11}C-choline PET/CT and conventional imaging. Statistical analysis was performed with the SPSS version 11 software program (SPSS, Chicago, IL, USA).

Results

There were eight bone sarcomas and eight soft tissue sarcomas (Table 1). The primary sites included shoulder ($n = 2$), chest wall

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Table 2. Staging of bone and soft tissue sarcoma

Variables	^{11}C-choline PET/CT	Conventional imaging	*P*-value
Overall stage			0.023
Correct	15 (94)	8 (50)	
Understaged	1 (6)	8 (50)	
Overstaged	0	0	
N stage			0.041
Correct	16 (100)	10 (63)	
Understaged	0	6 (38)	
Overstaged	0	0	
M stage			0.617
Correct	15 (94)	13 (81)	
Understaged	1 (6)	3 (19)	
Overstaged	0	0	

Note: Data are presented as number (*n*). Numbers in parentheses are percentages. CT, computed tomography; PET, positron emission tomography.

($n = 2$), retroperitoneum ($n = 2$), iliac bone ($n = 2$), leg ($n = 2$), thigh ($n = 1$), perineum ($n = 1$), tibia ($n = 1$), femur ($n = 1$), mandible ($n = 1$) and spine ($n = 1$). Pathological diagnoses were osteosarcoma ($n = 4$), Ewing sarcoma ($n = 3$), leiomyosarcoma ($n = 3$), clear cell sarcoma ($n = 1$), chondrosarcoma ($n = 1$), pleomorphic malignant fibrous histiocytoma ($n = 1$), myxoid liposarcoma ($n = 1$), rhabdomyosarcoma ($n = 1$), and alveolar soft part sarcoma ($n = 1$). Histological grade of tumors was grade 1 ($n = 1$), grade 2 ($n = 1$), grade 3 ($n = 11$) and grade 4 ($n = 3$).

All patients of initial staging had increased ^{11}C-choline uptake of the primary lesion (average maximal SUV ± SD: 5.92 ± 3.68 [range, 2.15–15.05]). Pathological T stages available in patients with initial staging are as follows: T1 ($n = 1$), T1a ($n = 1$), T1b ($n = 1$), T2 ($n = 4$) and T2b ($n = 5$). T stages in patients with restaging were T1 ($n = 2$), T1b ($n = 1$) and T2 ($n = 1$). Tumor size of patients for initial staging was 78.5 ± 34.0 mm (mean ± SD [range, 16.0–133.0 mm]). Both ^{11}C-choline PET/CT and conventional imaging classified the T stage correctly in all patients. Twelve (75%) of the 16 patients had N0 disease. Using ^{11}C-choline PET/CT, the N stage was correctly assigned in all patients, whereas the accuracy of conventional imaging in N stage was 63% ($P = 0.041$, Table 2). Understaging occurred in six patients (38%). Three of these patients (19%) had metastasis of inguinal node whose largest diameter was less than 10.0 mm (Fig. 1). The incidence of distant metastases was high in our study population. Both ^{11}C-choline PET/CT and conventional imaging detected bone metastases in seven patients (44%), lung metastases in five (31%) and pleural dissemination in two (18%, Fig. 2). Using ^{11}C-choline PET/CT, the M stage was correctly assigned in 15 patients (94%), whereas the accuracy of conventional imaging in M stage was 81% ($P = 0.617$, Table 2).

The complete stages of all patients were stage IA ($n = 1$), stage IIB ($n = 1$), stage III ($n = 1$) and stage IV ($n = 13$). TNM stage was correctly assessed with ^{11}C-choline PET/CT in 15 of 16 patients (94%) and with conventional imaging in eight of 16 patients (50%, $P = 0.023$, Table 2). ^{11}C-choline PET/CT assigned an incorrect TNM stage in a patient. This patient was understaged due to small metastatic lung tumor which was not clearly visualized by CT part of ^{11}C-choline PET/CT. Eight patients were understaged by conventional imaging (50%). Of these, skip metastases of soft tissues were identified in two (25%) and small nodal metastases in six (75%). ^{11}C-choline PET/CT correctly determined TNM stage in seven patients (44%) in whom stage derived from conventional imaging was incorrect.

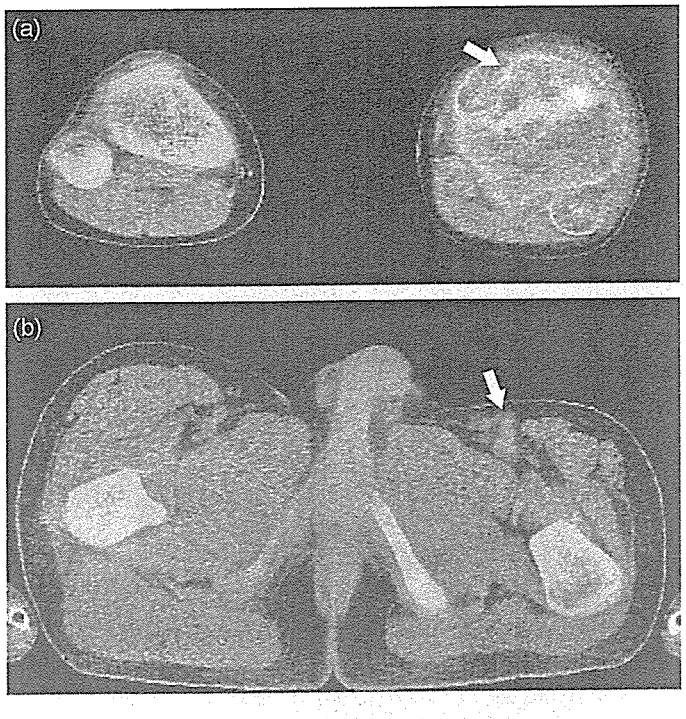

Fig. 1. A 13-year-old boy with osteosarcoma. (a) Transverse ^{11}C-choline positron emission tomography (PET)/computed tomography (CT) image revealed hypermetabolic focus in the proximal portion of the left tibia (arrow). PET/CT findings were verified at histopathological analysis. (b) Abnormal uptake of ^{11}C-choline was also noted in the left inguinal lymph node, which was interpreted as highly suspicious for malignancy (arrow). Subsequent resection revealed metastasis from osteosarcoma.

Discussion

The results of the present study show that ^{11}C-choline PET/CT improves the accuracy of staging in patients with bone and soft tissue sarcomas compared to conventional imaging. Specifically, ^{11}C-choline PET/CT has potentially significant implications for detecting nodal and distant metastases at overall staging. Reports about the efficacy of ^{11}C-choline in the localization and detection of bone and soft tissue sarcomas are still limited.[15] To our knowledge, no study regarding ^{11}C-choline PET/CT for staging bone and soft tissue sarcomas was found. In our study, seven of the 16 patients had skip metastases of soft tissue or nodal metastases detected by ^{11}C-choline PET/CT that were not identified by routine clinical and conventional radiological evaluation.

The ability of PET to depict increased metabolism in malignancies has greatly improved the accuracy in detecting neoplasms.[4] However, compared with conventional imaging studies, use of PET alone results in a lack of substantial detail.[20] The PET/CT device permits sequential acquisition of anatomic CT and functional PET images in a single scanning session. Morphological characterization of scintigraphic lesions by PET/CT resulted in a lower percentage of equivocal interpretations compared with that of conventional imaging. Tumor-detecting PET/CT technology is growing rapidly. However, there are only limited data available on staging of bone and soft tissue sarcomas with PET/CT.

Carbon-11 choline uptake was significantly higher in malignant soft tissue tumors and was due to the high utilization of cell membranes of these lesions. ^{11}C-choline uptake is observed physiologically in the liver, pancreas, kidney and duodenum. ^{11}C-choline is also secreted into phospholipid-rich pancreatic juice in a non-fasting state. A potential advantage of ^{11}C-choline PET/CT might be the assessment of tumors in the skull or retroperitoneum. Blood clearance of ^{11}C-choline is rapid and radioactive distribution

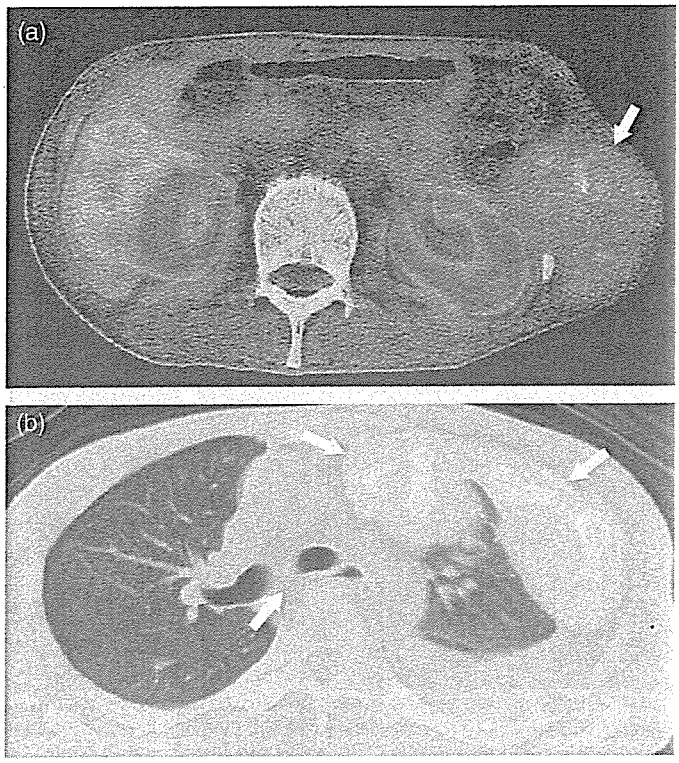

Fig. 2. A 34-year-old man with clear cell sarcoma. (a) Transverse ^{11}C-choline positron emission tomography (PET)/computed tomography (CT) image depicting abnormal uptake in the tumor arising from the left lateral chest wall (arrow). (b) PET/CT image also depicts pleural dissemination and mediastinal lymph node (arrows). Follow-up findings in this patient confirmed the diagnosis.

in tissues is constant in 5 min. The accumulation of ^{11}C-choline in the skull or retroperitoneum is hardly affected by background within the limits of short uptake time. In comparison to ^{18}FDG, physiological background level in the urinary tract is low. This may be due to incomplete tubular reabsorption of the intact tracer, or enhanced excretion of labeled oxidative metabolites like betaine.[12]

Limited resolution of the present generation of ^{11}C-choline PET/CT and the partial volume effect result in failure to detect small lesions. In our study, one patient was understaged due to small metastatic lung tumor, which was not visualized clearly by the CT part of ^{11}C-choline PET/CT. Faint increase in tracer uptake and motion artifact caused by breathing contribute to false negative results. However, the advantage of ^{11}C-choline PET/CT is that the whole-body can be visualized in a single examination. In our study, 50% of patients were understaged by conventional imaging. The inaccuracy of conventional imaging in assessing skip metastases of soft tissues is due to the field of view.

We reported the accurate modality of ^{11}C-choline PET/CT as a non-invasive method for staging in patients with bone and soft tissue sarcomas compared to conventional imaging. Choline is an essential component of the cell membrane, and choline uptake may be via a choline-specific transporter protein. Choline kinase, which catalyzes the phosphorylation of choline, is upregulated in tumor cells.[12] In some types of tumor cells, overexpression of choline-specific transporter protein and choline kinase were identified by *in situ* hybridization.[21] ^{11}C-choline will be phosphorylated by choline kinase as a choline analog and retained in tumor cells.[21] However, the precise pathway of metabolic trapping by tumor cells has not been elucidated, and further studies to clarify the mechanism of imaging by ^{11}C-choline are needed.

Our study has limitations. Most patients in this study had high-grade tumors (88%) and may differ from the patient population of previous studies. Our study was intended to examine the staging prior to treatment; therefore, patient population of high-grade tumors may explain the significant accuracy in overall staging compared to conventional imaging. A study with a larger patient population would clarify the influence of ^{11}C-choline PET/CT on staging. ^{11}C-choline is clearly a sensitive PET tracer for staging patients with bone and soft tissue sarcomas. The short half-life of ^{11}C-choline necessitates the availability of an on-site cyclotron, which causes practical restriction. More specific radiotracers will help overcome this limitation in the future.

In summary, the use of ^{11}C-choline PET/CT in patients with bone and soft tissue sarcomas increases the accuracy of overall staging and N staging compared to conventional staging. Our study suggests that whole-body ^{11}C-choline PET/CT should be the preferred modality for staging in patients with bone and soft tissue sarcomas.

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Radiologic Removal and Replacement of Port-Catheter Systems for Hepatic Arterial Infusion Chemotherapy

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OBJECTIVE. The purpose of our study was to retrospectively evaluate the safety and efficacy of radiologic removal and replacement of port-catheter systems.

MATERIALS AND METHODS. Between January 1999 and December 2004, 532 patients with unresectable advanced liver cancer underwent radiologic placement of port-catheter systems at our institution. Of these, 18 patients (nine men and nine women; age range, 32–83 years; mean age, 53.8 years) underwent removal of an implanted port-catheter system via the right femoral artery and radiographically guided replacement with a new system to allow continuous hepatic arterial infusion chemotherapy; we retrospectively reviewed these 18 cases. The reasons for removal of the previously implanted systems were as follows: catheter dislodgement ($n = 15$), catheter obstruction ($n = 1$), infection related to the implanted port ($n = 1$), and hemodynamic change ($n = 1$). Digital subtraction angiography and CT were performed, usually during injection of contrast medium through the implanted port-catheter system, within a few days after the replacement procedure and every 3 months thereafter.

RESULTS. We successfully performed radiologic removal and replacement of the port-catheter system while the patient was under local anesthesia in all 18 patients without complications requiring treatment. The cumulative patency rates of the hepatic artery after removal of the old port-catheter system and replacement with a new port-catheter system were 87.8% and 64.1% at 6 months and 1 year, respectively. Hepatic arterial infusion chemotherapy after replacement was performed 0–68 times (median, 19 times).

CONCLUSION. When an implanted port-catheter system can no longer be used but the patency of the hepatic artery is confirmed and continuous hepatic arterial infusion chemotherapy is required, removal and replacement of the port-catheter system are recommended.

Keywords: chemotherapy, implantable devices, liver cancer, port-catheter system

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Repeated hepatic arterial infusion chemotherapy using an implanted port-catheter system is reported to be effective for the treatment of patients with unresectable advanced liver malignancies [1–4]. Recent advancements in interventional radiologic techniques have led to nonsurgical placement of port-catheter systems being performed increasingly frequently, and the use of a side-hole catheter with tip fixation is recommended during this procedure to prevent catheter dislodgement and hepatic arterial occlusion [5–8]. Although continuous use of an implanted port-catheter system is the ideal scenario, this generally is not possible even with careful management because of complications such as occlusion, kinking, or dislodgement of the implanted catheter; hepatic artery occlusion; or infection of the implanted port-catheter system [6–12]. In such cases, if the hepatic artery is patent, continued hepatic arterial infusion chemotherapy is possible after the original device has been replaced with a new system. The purpose of this study was to retrospectively evaluate the safety and efficacy of the radiologic removal and replacement of a port-catheter system.

Materials and Methods

This study is a retrospective one, and approval from the institutional review board of our hospital was obtained.

Patients

Between January 1999 and December 2004, 532 patients with unresectable advanced liver cancer underwent radiologically guided placement of port-catheter systems at our institution. Of those patients, 18 (nine men and nine women; age range, 32–83 years; mean age, 53.8 years) received a replacement system after the original device had been

removed to allow continuous hepatic arterial infusion chemotherapy. Seventeen patients had liver metastases that originated from colorectal cancer ($n = 9$), breast cancer ($n = 4$), gastric cancer ($n = 3$), or carcinoma of the papilla of Vater ($n = 1$), and the remaining patient had hepatocellular carcinoma.

The reasons for the removal of the previously implanted systems were as follows: catheter dislodgement ($n = 15$); catheter obstruction ($n = 1$); infection related to the implanted port ($n = 1$); and hemodynamic change ($n = 1$), such as hepatopetal flow of the common hepatic artery that was changed to hepatofugal flow as a result of altered flow in the gastroduodenal artery secondary to stenosis of the celiac artery. All 18 patients had only liver lesions that were well controlled by hepatic arterial infusion chemotherapy, so continuous hepatic arterial infusion chemotherapy was desired if the hepatic artery was patent. That information was obtained from the medical records.

First Placement of Port-Catheter Systems

The placement site of the port-catheter system was originally chosen according to the following method: All patients underwent angiography before catheter placement, which was performed using a 5-French angiographic catheter inserted from the right femoral artery to allow arterial mapping and to prevent extrahepatic influx of anticancer agents. The extrahepatic arteries branching from the hepatic artery, such as the right gastric artery, posterior superior pancreatoduodenal artery, and superior duodenal artery, were embolized with microcoils (Tornado, Cook; or Trufill, Cordis) through a 2.9-French microcatheter (Jamiro, Kaneka; or Sniper, Clinical Supply) inserted coaxially [5, 13]. The left gastric artery and gastroduodenal artery were also embolized when the angiographic catheter tip was inserted into the splenic artery [5].

In patients with more than two hepatic arteries, these arteries were converted into a single arterial supply by microcoil embolization so that drugs could be distributed to the entire liver using a single indwelling catheter [5]. A 5-French angiographic catheter was then inserted from the left subclavian artery ($n = 14$) or the right femoral artery ($n = 4$) and was advanced to the common hepatic artery via the celiac artery.

Subsequently, using the catheter-exchange method, a 5-French indwelling catheter (Anthron P-U catheter, Toray; or W spiral catheter, Piolax) with ($n = 16$) or without ($n = 2$) a side hole was inserted. The tips of these catheters were tapered to 2.7-French and 20 cm in length; the catheters were inserted into the gastroduodenal artery ($n = 9$), the splenic artery ($n = 1$), the peripheral branch of the hepatic artery ($n = 2$), the right hepatic artery ($n = 3$), the common hepatic artery ($n = 2$), or the accessory left gastric artery arising from the left hepatic artery ($n = 1$). In 12 of the 18 patients who had catheters inserted into the gastroduodenal artery ($n = 9$), splenic artery ($n = 1$), and others ($n = 2$), the artery around the tip of indwelling catheter was embolized using microcoils and a mixture (1:1.5) of *n*-butyl cyanoacrylate (Histoacryl, Braun) and iodized oil (Lipiodol Ultrafluide, Laboratoire Guerbet) through a microcatheter inserted coaxially via a 5-French angiographic catheter inserted from the femoral artery. The catheter tip was also fixed in these 12 patients.

In four of the remaining six patients in whom the catheter tip was not fixed, a W spiral catheter was used; the spiral-shaped tip of this catheter has the function of securing it. The side hole of the catheter was placed into the common hepatic artery or the celiac artery. Finally, the proximal end of the indwelling catheter was connected to a port implanted in a subcutaneous pocket created in the left chest wall or the right upper thigh.

Removal and Replacement of Port-Catheter Systems

Written informed consent was obtained from all the patients before these procedures. All the procedures were performed in an angiographic suite by interventional radiologists with the patient under local anesthesia. On the same day as the procedure or the day before the procedure, all patients underwent angiography using a 5-French angiographic catheter inserted from the right femoral artery to confirm patency of the hepatic arteries.

In the four patients in whom the catheter had previously been implanted from the right femoral artery, after opening the subcutaneous space housing the port, the indwelling catheter was directly withdrawn from the right femoral artery with the port.

In the 14 patients in whom the port-catheter system was previously implanted via the left subclavian artery, a 5-French hook-shaped catheter was first inserted from a right femoral artery through a 6-French sheath introducer and was then wrapped around the indwelling catheter. The hook-shaped catheter was then pulled to relocate the indwelling catheter tip to the aorta. After the hook-shaped catheter was withdrawn, a 5-French basket retriever was inserted via the right femoral artery through the sheath introducer to capture the distal tip of the indwelling catheter. After a small incision was made at the insertion site in the left chest wall, the implanted port was withdrawn, the proximal part of the indwelling catheter was cut, and the port was removed from the catheter. The indwelling catheter captured by the basket retriever was then withdrawn from the right femoral artery. Subsequently, replacement with a new port-catheter system was performed using the same methods described earlier.

The total time required for the procedure ranged from 107 to 225 minutes (mean, 155 minutes). Catheters were inserted from the left subclavian artery ($n = 15$), the right femoral artery ($n = 1$), and the left inferior epigastric artery ($n = 2$). In three of four patients in whom the first placement procedure was from the right femoral artery and had been performed at another institution, replacement was from the left subclavian artery. The catheters were advanced via the celiac artery ($n = 16$) or through the pancreaticoduodenal arcade via the superior mesenteric artery in cases of celiac artery stenosis ($n = 2$). Catheter tips were inserted into the gastroduodenal artery ($n = 2$), the splenic artery ($n = 3$), the peripheral branch of the hepatic artery ($n = 6$), the right hepatic artery ($n = 5$), the common hepatic artery ($n = 1$), and the middle hepatic artery ($n = 1$) (Table 1).

In one patient, because selecting a placement site for the catheter was difficult using the method mentioned earlier, placement was performed as follows: We first selected the celiac artery with a 5-French angiographic catheter (inserted via the femoral artery) and then inserted an indwelling catheter (Anthron P-U catheter, Toray) using the catheter-exchange method. A 2.9-French microcatheter (Sniper, Clinical Supply) was inserted coaxially into the right hepatic artery through the indwelling catheter, which was thereby relocated to the aorta. Finally, the proximal end of the microcatheter was connected directly to the implanted port using a connecting device. In six of 18 patients, the tip of the indwelling catheter was fixed using microcoils and a mixture of *n*-butyl cyanoacrylate and iodized oil. In eight of 12 patients in whom the catheter tip was not fixed, a W spiral catheter was used.

Using this system, hepatic arterial infusion chemotherapy was started a few days after the procedure, depending on the clinical circumstances. The details of hepatic arterial infusion chemotherapy and management of this system have been reported previously [7]. Digital subtraction angiography and CT were performed during injection of contrast medium through the implanted port-catheter system within a few days after the procedure and every 3 months thereafter to confirm that the catheter and hepatic artery were patent and that the entire liver was perfused adequately. These investigations were also performed whenever patients reported any symptoms that might be related to hepatic arterial infusion chemotherapy.

Evaluation

Outcome was evaluated in terms of the success rate for removal and replacement of the port-catheter systems, complications of the procedure, and number of sessions of hepatic arterial infusion chemotherapy after replacement with the new systems. The cumulative patency rate of the hepatic artery confirmed by digital subtraction angiography was calculated according to the Kaplan-Meier method.

TABLE 1: Approach Artery and Location of Catheter Tip of Port-Catheter Systems

Removal of Original Port-Catheter System			Placement of New Port-Catheter System		
Approach Artery	Location of Catheter Tip	No. of Patients	Approach Artery	Location of Catheter Tip	No. of Patients
Left subclavian artery	Gastroduodenal artery	9	Left subclavian artery	Gastroduodenal artery	1
				Splenic artery	2
				Right hepatic artery	3
				Peripheral branch of hepatic artery	1
			Left inferior epigastric artery	Splenic artery	1
				Peripheral branch of hepatic artery	1
	Splenic artery	1	Left subclavian artery	Right hepatic artery	1
	Right hepatic artery	1	Left subclavian artery	Right hepatic artery	1
	Peripheral branch of hepatic artery	2	Left subclavian artery	Peripheral branch of hepatic artery	2
	Accessory left gastric artery	1	Left subclavian artery	Common hepatic artery	1
Right femoral artery	Common hepatic artery	2	Left subclavian artery	Peripheral branch of hepatic artery	1
				Gastroduodenal artery	1
	Right hepatic artery	2	Left subclavian artery	Peripheral branch of hepatic artery	1
			Right femoral artery	Middle hepatic artery	1

Results

Patients were followed up for a period ranging from 7 to 1,806 days (median, 373 days) after catheter replacement. We successfully performed removal and replacement of port-catheter systems in all 18 patients (Fig. 1). Although our patients experienced some minor complications requiring no treatment, such as hemorrhage, nausea, and pain, there were no other major complications, such as ischemia or infarction caused by extrahepatic arterial embolization and massive hematoma. Moreover, we have been able to perform hepatic arterial infusion chemotherapy continuously in our department in 16 of these patients.

The progress of one of the remaining two patients is not known because this patient only underwent removal and replacement of the port-catheter system at our institution and was not followed up by us. The other was a 33-year-old woman with multiple liver metastases from breast cancer. The tip of this patient's catheter was originally replaced into a peripheral branch of the hepatic artery; however, because this catheter became dislodged, it was removed 7 days after the original replacement procedure and was replaced with a new port-catheter system on the same day. In this procedure, the catheter tip was also inserted into another peripheral branch of the hepatic artery. In this patient, hepatic arterial infusion chemotherapy could be performed 58 times over 524 days until hepatic arterial occlusion occurred after the second replacement procedure (Fig. 2).

Overall, after replacement of the port-catheter systems, hepatic arterial infusion chemotherapy was performed 0–68 times (median, 19 times). Chemotherapy was continued ($n = 4$) or was terminated because of death ($n = 5$), hepatic arterial occlusion ($n = 4$), catheter dislodgement ($n = 2$), or change to other treatments ($n = 2$). The cumulative patency rates of the hepatic artery at 6 months and 1 year after replacement with new systems were 87.8% and 64.1%, respectively.

Discussion

Repeated hepatic arterial infusion chemotherapy using an implanted port-catheter system is reported to be an effective therapy for patients with unresectable advanced liver malignancies and is used widely as a local approach [1–4]. When placing the catheter radiologically, which is less invasive than placing it using a surgical procedure, use of a side-hole catheter is recommended [5–8] and fixation of the catheter tip is recommended to prevent catheter dislodgement and hepatic arterial occlusion caused by mechanical stimulation resulting from movement of the unfixed catheter tip [5].

Hepatic arterial occlusion and catheter dislodgement are the most common complications that require hepatic arterial infusion chemotherapy to be stopped, with prevalences of 0–17% and 2.2–14.3%, respectively, recently reported during use of nonsurgically inserted port-catheter systems [6–12]. However, placement of a side-hole catheter with tip fixation is reported to be associated less frequently with hepatic arterial occlusion (5.4% [6]) or catheter dislodgement (2.2–2.8% [6, 7]). Accordingly, for the initial placement procedure, we usually insert the tip of a side-hole catheter into the deep portion of the gastroduodenal artery and fix it using microcoils and a mixture of *n*-butyl cyanoacrylate and iodized oil.

Although various complications such as catheter dislodgement can preclude the continued use of an implanted port-catheter system, we aim to continue to treat patients with hepatic arterial infusion chemotherapy if the hepatic artery is patent. A dislodged catheter causes flow into the extrahepatic arteries, resulting in reduced concentrations of drug in the liver. We overcome this complication by embolizing extrahepatic arteries, such as the left gastric artery, splenic artery, or dorsal pancreatic artery [5], if possible. However, in the present study, we removed implanted port-catheter systems and replaced them with new systems because catheter dislodgement was too great to be overcome by embolizing extrahepatic arteries.

We decided to remove the original implanted port-catheter system when replacing it with a new system to minimize the disturbance associated with replacement, the unnecessary stimulation of the artery, and the possibility of infection, and because this was generally the patient's request. Although we anticipated that removal of indwelling catheters with fixed tips would be difficult, it was possible to safely remove the catheter in all nine patients.

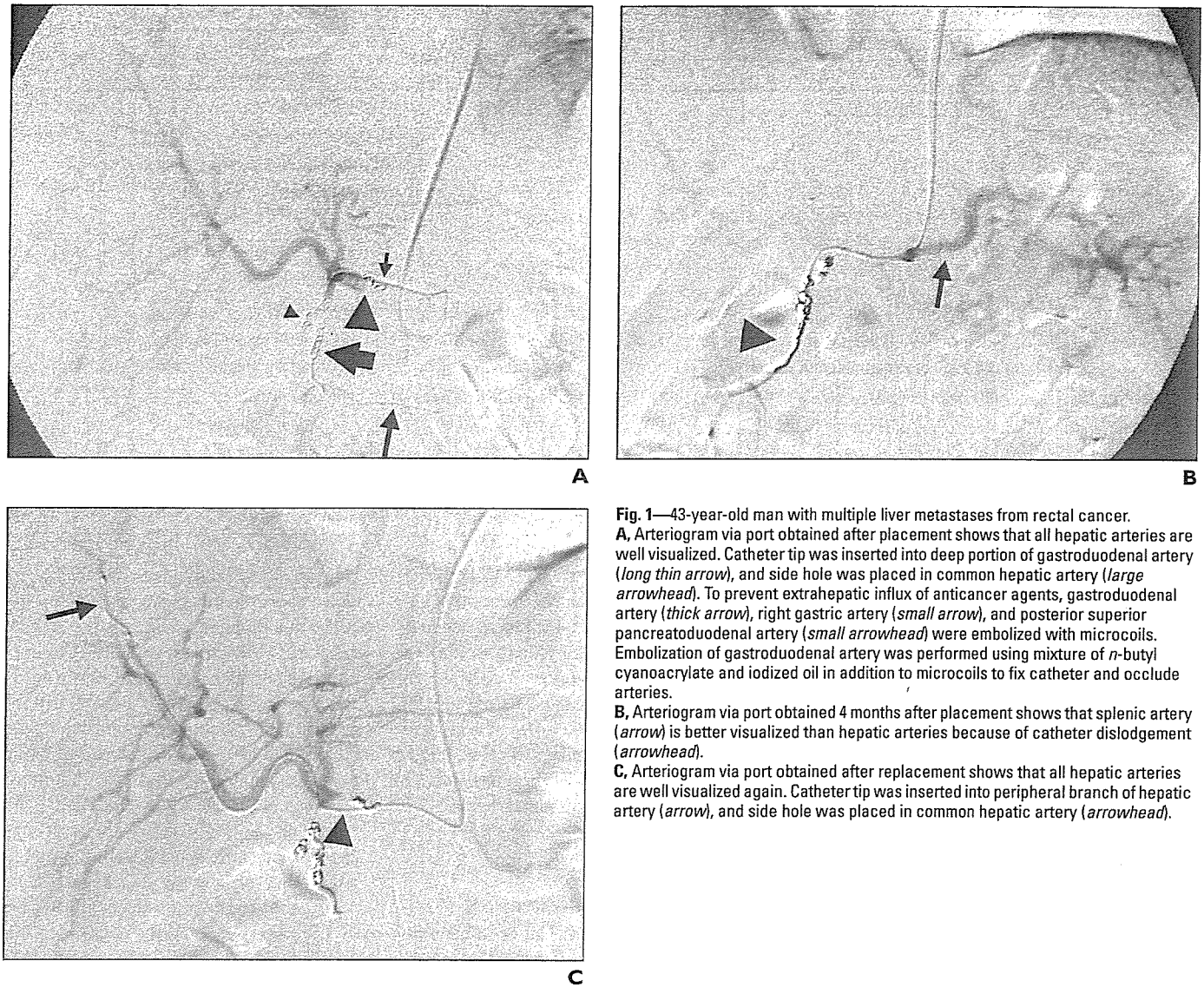

Fig. 1—43-year-old man with multiple liver metastases from rectal cancer.
A, Arteriogram via port obtained after placement shows that all hepatic arteries are well visualized. Catheter tip was inserted into deep portion of gastroduodenal artery (*long thin arrow*), and side hole was placed in common hepatic artery (*large arrowhead*). To prevent extrahepatic influx of anticancer agents, gastroduodenal artery (*thick arrow*), right gastric artery (*small arrow*), and posterior superior pancreatoduodenal artery (*small arrowhead*) were embolized with microcoils. Embolization of gastroduodenal artery was performed using mixture of *n*-butyl cyanoacrylate and iodized oil in addition to microcoils to fix catheter and occlude arteries.
B, Arteriogram via port obtained 4 months after placement shows that splenic artery (*arrow*) is better visualized than hepatic arteries because of catheter dislodgement (*arrowhead*).
C, Arteriogram via port obtained after replacement shows that all hepatic arteries are well visualized again. Catheter tip was inserted into peripheral branch of hepatic artery (*arrow*), and side hole was placed in common hepatic artery (*arrowhead*).

We removed implanted catheters via the right femoral artery in all patients. Particularly when the catheter is originally implanted from the left subclavian artery, removal should be performed via the femoral artery to prevent brain infarction due to release of thrombus around the indwelling catheter and subsequent vertebral arterial embolization [14]. We successfully removed implanted port-catheter systems in all patients without complications (such as brain infarction, hemorrhage, hematoma, infection, or pseudoaneurysm) requiring treatment and with the patient under local anesthesia.

We performed removal and replacement on the same day. After deciding the position of catheter tip insertion based on angiography performed before replacement, we inserted new catheters from the left subclavian artery in many patients because this was the approach artery that had been used previously and patients had therefore previously experienced the procedure. Although the risk of complications such as hemorrhage, hematoma, and pseudoaneurysm is higher if the same route is used, we successfully performed removal and replacement of port-catheter systems using this approach without observing complications requiring treatment.

When an old system was replaced with a new system, the catheter tip was inserted into another artery because we had already embolized the gastroduodenal artery. Replacement of a side-hole catheter with its tip fixed and inserted into another artery was possible in only six of the 18 patients. In one of the remaining 12 patients in whom the tip was inserted into the peripheral branch of the hepatic artery, a second replacement procedure was required because the catheter became dislodged 7 days after the first replacement procedure.

In the present study, at 1 year after replacement, a 64.1% cumulative patency rate for the hepatic artery was achieved. This patency rate is lower than previously reported cumulative patency rates for first placement (81.4% [7] and 86.3% [8]). We think that this discrepancy results from nonfixation of the catheter tip, injury of the hepatic artery caused by prior hepatic arterial infusion chemotherapy, or both. Nonetheless, because we could perform hepatic arterial infusion chemotherapy a median of 19 times after port-catheter system replacement, it seems to be worth continuing

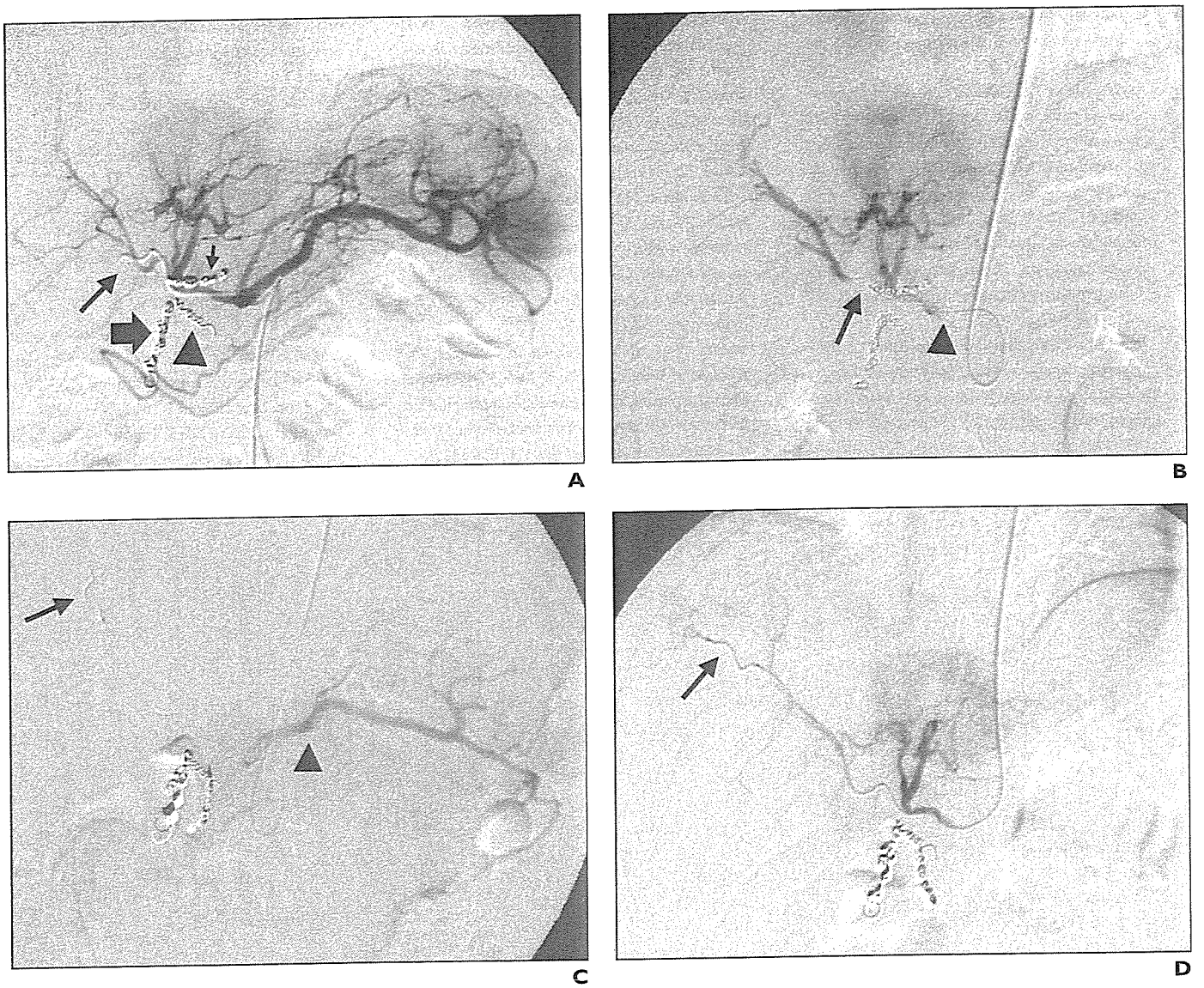

Fig. 2—33-year-old woman with multiple liver metastases from breast cancer.
A, Celiac arteriogram obtained after occlusion of implanted catheter (*long thin arrow*) shows that hepatic arteries are well visualized. Gastroduodenal artery (*thick arrow*), posterior superior pancreatoduodenal artery (*arrowhead*), and right gastric artery (*small thin arrow*) were embolized with microcoils to prevent extrahepatic influx of anticancer agents.
B, Arteriogram via port obtained after replacement shows that all hepatic arteries can be visualized. Catheter tip was inserted into peripheral branch of hepatic artery and side hole was placed in common hepatic artery (*arrowhead*). Origin of right hepatic artery (*arrow*) was not visualized because of stenosis caused by tip of original catheter, but right hepatic artery is well visualized because of blood supply via left hepatic artery through intrahepatic arterial anastomoses.
C, Arteriogram via port obtained 1 week after replacement shows that splenic artery (*arrowhead*) is better visualized than hepatic arteries because of catheter dislodgement (*arrow*).
D, Arteriogram via port obtained after second removal and replacement shows that hepatic arteries are well visualized. Catheter tip (*arrow*) was inserted into another peripheral branch of hepatic artery.

hepatic arterial infusion chemotherapy when this therapy is needed in situations such as absence of extrahepatic lesions or when liver metastases are thought to be the prognosis-limiting factor.

In conclusion, although the retrospective design of this study meant that many limitations exist, it is noteworthy that we could safely remove and replace port-catheter systems so that hepatic arterial infusion chemotherapy could continue. Attempting these procedures appears worthwhile if continuing treatment using an implanted port-catheter system is not possible, the hepatic artery is confirmed patent, and continuous hepatic arterial infusion chemotherapy is required.

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CT-guided needle biopsy of lung lesions: A survey of severe complication based on 9783 biopsies in Japan

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Abstract

Purpose: The aim of our study was to update the rate of severe complications following CT-guided needle biopsy in Japan via a mailed survey.

Materials and methods: Postal questionnaires regarding CT-guided needle biopsy were sent out to multiple hospitals in Japan. The questions regarded: the total number and duration of CT-guided lung biopsies performed at each hospital, and the complication rates and numbers of pneumothorax, hemothorax, air embolism, tumor seeding, tension pneumothorax and other rare complications. Each severe complication was followed with additional questions.

Results: Data from 9783 biopsies was collected from 124 centers. Pneumothorax was the most common complication, and occurred in 2412 (35%) of 6881 cases. A total of 39 (35%) hospitals reported 74 (0.75%) cases with severe complications. There were six cases (0.061%) with air embolism, six cases (0.061%) with tumor seeding at the site of the biopsy route, 10 cases (0.10%) with tension pneumothorax, six cases (0.061%) with severe pulmonary hemorrhage or hemoptysis, nine cases (0.092%) with hemothorax, and 27 cases (0.26%) with others, including heart arrest, shock, and respiratory arrest. From a total of 62 patients with severe complications, 54 patients (0.55%) recovered without sequela, however one patient (0.01%) recovered with hemiplegia due to cerebral infarction, and the remaining seven patients (0.07%) died.

Conclusions: This is the first national study documenting severe complications with respect to CT-guided needle biopsy in Japan. The complication rate in Japan is comparable to internationally published figures. We believe this data will improve both clinicians as well as patients understanding of the risk versus benefit of CT-guided needle biopsy, resulting better decisions.

Keywords: CT-guided needle biopsy; Complication; Lung nodule

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1. Introduction

Transthoracic needle biopsy is a common procedure used mainly to elucidate the nature of pulmonary nodules [1,2]. CT has rapidly become the guidance modality of choice for performing transthoracic needle biopsy due to technical advances in CT and its better detection of pulmonary lesions, which sometimes cannot be identified on chest radiograph [3].

CT-guided needle biopsy is generally regarded as a safe procedure, although pneumothorax and other rare complications can sometimes occur [4]. There have been occasional reports of deaths due to severe complications, such as, air embolism following lung biopsy [5]. Fortunately, these complications are generally very rare; previously published data shows wide variations in complication rates, making them difficult to generalize [5–8].

The aim of our study was to update the rate of severe complications following CT-guided needle biopsy in Japan via a mailed survey.

2. Materials and methods

Postal questionnaires regarding CT-guided needle biopsy were sent out to named radiologists at 101 university hospitals and cancer centers in Japan in August 2001. The radiologists at these hospitals were asked to pass duplications of the questions to other associate hospitals. The questions required information regarding: the total number and duration of CT-guided lung biopsies performed at each hospital, and the complication rates, numbers of pneumothorax, hemothorax, air embolism, tumor seeding, tension pneumothorax, severe pulmonary hemorrhage or hemoptysis which was treated with drugs for hemostasis and other rare complications, and mortalities and morbidities after that.

We defined a case as having a severe complication when one of the following criteria was met: (1) the duration of hospital stay was prolonged due to the biopsy, (2) a special technique or treatment was required to treat the complication, (3) a special procedure was required for resuscitation, and (4) shock or pre-shock developed. Each severe complication was followed with additional questions, including diagnosis of the complication, the position of the pulmonary lesion, the distance of the pulmonary lesion from the peripheral pleura, whether the lesion was located near the hilum or large pulmonary vessel, whether there was any reasonable factor causing the complication such as cough during biopsy, biopsy technique (CT-fluoroscopy or Co-axial method), the number of biopsies for each case, type and size of the needle, and presence of significant sequela from the complication.

Furthermore, the questionnaire included the following enquiries: whether emergency medication was prepared for resuscitation in the operating room, whether the patient was treated by the intravenous route and monitors, such as automatic sphygmomanometer, pulse oximetry, and electrocardiography. Finally, availability of access to other departments in case of emergency was questioned. Postal replies of questionnaire had been received for a year, and these answers were analyzed.

3. Results

A total of 9783 biopsy data were collected from 124 centers. The average number of biopsies performed per center was 79 cases, and that per center per year was 21 cases. The number of institutions in which hyperbaric oxygen recompression can be performed was 41 of 114 (37%) hospitals. Patients were kept on peripheral intravenous drip infusion in 86 of 92 (93%) hospitals, automatic sphygmomanometer in 38 of 92 (41%) hospitals, pulse oximetry in 32 of 92 (35%) hospitals, and electrocardiography in 8 of 92 (9%) hospitals.

Pneumothorax was the most common complication, and occurred in 2412 (35%) of 6881 cases. The number of centers that reported severe complications was 39 (35%) of 114 centers. The total number of overall severe complications was 74 (0.75%) cases. Of these, details of the complications in 64 cases are described in Table 1. There were six cases (0.061%) with air embolism, six cases (0.061%) with tumor seeding at the site of the biopsy route, 10 cases (0.10%) with tension pneumothorax, six cases (0.061%) with severe pulmonary hemorrhage or hemoptysis, 10 cases (0.10%) with hemothorax, and 26 cases (0.26%) with others. The others included 14 cases of pneumothorax requiring temporal drainage of the pneumothorax or chest tube insertion, three cases of heart arrest, and so on. There was no report of coughing during needle placement into the thorax in any of the cases with air embolism. Two of six pulmonary lesions were complicated with air emboli located near the large pulmonary vessel, and one lesion contained a cavity (Table 2). Tumor seeding occurred in two cases following CT-guided biopsy performed

Table 1
Summary of 64 cases of severe complications

Severe complications	No.
Pneumothorax requiring drainage of air	14
Tension pneumothorax	10
Hemothorax	10
Air embolism	6
Tumor seeding	6
Pulmonary hemorrhage of hemoptysis	6
Heart arrest	3
Respiratory arrest	1
Shock	1
Cyanosis	1
Cardiac tamponade	1
Pneumomediastinum	1
Mediastinal hematoma	1
Loss of consciousness	1
Severe pain of biopsied site	1
disseminated intravascular coagulation (DIC)	1
Total	64

Table 2
Summary of cases of air embolism

No.	Age	Sex	Size (mm)	Location (lobe)	Distance from pleura (mm)	Large vessel near the nodule	Cavity	CT-fluoloscopy	Co-axial method	No. of biopsy	Technique of biopsy	Size of the needle	Sequela
1	72	F	20	Left lower	40	Yes	No	Yes	No	2	Core biopsy	18G	Death
2	59	M	10	Left lower	20	No	No	NA[a]	Yes	1	Core biopsy	18G	Totally improved
3	57	F	7	Right middle	25	No	No	Yes	No	1	Core biopsy	18G	Totally improved
4	74	M	20	Right upper	25	Yes	No	Yes	No	2	Core biopsy	20G	Partially improved
5	57	M	12	Right lower	3	No	No	No	Yes	1	Core biopsy	20G	Totally improved
6	75	M	25	Right lower	18	No	Yes	No	No	1	Core biopsy	18G	Totally improved

[a] NA, information was not available.

by the Co-axial method (Table 3). In one of these two cases, the tip of the outer cannula was placed within the chest wall, so that seeding obviously occurred by direct contact of the inner needle with the biopsy route.

From a total of 62 cases with severe complications, 54 cases (0.55%) were recovered without sequela, and one case (0.01%) recovered but with hemiplegia due to cerebral infarction. Unfortunately, four (0.04%) of the remaining seven cases died just after the CT-guided biopsy procedure; these consisted of one case of air embolism, one case of DIC, and two cases of heart arrest. Three cases (0.03%) of the remaining seven cases died several years later due to tumor seeding. Four cases complicated with air embolism, three of which were treated with hyperbaric oxygen recompression, were recovered without sequela out of a total of six cases. In 23 (50%) of 46 centers, an emergency team was able to attend when a severe complication occurred.

4. Discussion

Recently, many small pulmonary lesions, which cannot be detected on chest radiograph, have been easily visualized by CT examination in daily clinical work. These lesions are usually followed with CT, or in some cases these are biopsies using CT-guided technique. CT-guided needle biopsy is a widely accepted technique and is one of the principal methods for evaluating a pulmonary lesion [9]. Although it is not rare to have minor complications due to CT-guided needle biopsy, such as, a small amount of pneumothorax and pulmonary hemorrhage, these complications improve without any treatment [5]. On the other hand, it is well known that potentially life-threatening complications such as air embolism and tumor seeding can occur. Fortunately, the frequency of these complications is considered very rare [5]. However, the number of published reports has shown that the incidence of air embolism has been increasing over the last several years. Only seven cases with air embolism were documented in the 20 years before 1995 [10–16], whereas six cases have already been published in the last 10 years [17–22].

This is the first national research study demonstrating the incidence rate of severe complications with respect to CT-guided needle biopsy based on a large number of biopsy cases using a multi-center survey.

The most common complication of transthoracic percutaneous needle biopsy is pneumothorax, with a frequency rate of 0–61%, whereas the incidence of pneumothorax requiring chest tube drainage ranges from 1.6% to 17% [23]. In the present study, the rate of pneumothorax was 35.1%, which is considered comparable to the previous studies.

Sinner's review of the literature determined that there were two cases suspected of air embolism in 2726 patients [5]. He estimated that the relative risk of air embolism per patient was about 0.07%. In the present study of 9783 biopsies, air embolism occurred in six patients, resulting in an incidence