TABLE II Development of drug resistance by malignancy

Malignancy	*Progressive disease after ...*
Breast cancer	Anthracycline, taxane, or capecitabine
Colorectal cancer	Fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, tyrosine kinase inhibitors with wild-type EGFR
Gastric cancer	Tegafur, gimeracil, and oteracil potassium with or without cisplatin
Pancreatic cancer	Gemcitabine
Lung cancer	Second- or third-line regimens with EGFR mutation
Ovarian cancer	Platinum resistance
Cervical cancer	Cisplatin-containing regimen
Endometrial cancer	Doxorubicin or cisplatin
Sarcoma	Anthracycline- or ifosfamide-containing regimens (excluding Ewing sarcoma and rhabdomyosarcoma)

EGFR = epidermal growth factor receptor.

TABLE III Oncologist and patient characteristics

Characteristic	*Value*
Oncologists (*n*)	14
Career [*n* (%)]	
>10 Years	7 (50)
<10 Years	7 (50)
Patients (n)	75
Age (years)	
Median	60
Range	26–78
Sex [*n* (%)]	
Men	26 (35)
Women	49 (65)
Site of malignancy [*n* (%)]	
Breast	11 (15)
Colorectum	15 (20)
Stomach	4 (5)
Pancreas	15 (20)
Lung	11 (15)
Ovary	5 (7)
Cervix	3 (4)
Endometrium	3 (4)
Sarcoma	8 (11)
Performance status	
0–1	51 (68)
≥2	24 (32)
Oral intake	
Normal	41 (55)
Moderately reduced	25 (33)
Severely reduced	9 (12)

significant correlation between CPS and AS (0.70, $p < 0.001$, Figure 2.).

The survival estimation was accurate (CPS within ±33% of AS) in 36.0% of patients [95% confidence interval (CI): 25.2% to 47.9%], overestimated in another 36.0% of patients (95% CI: 25.2% to 47.9%), and underestimated in 28.0% of patients (95% CI: 18.2% to 39.6%).

3.3 Multivariate Analyses

We examined independent factors correlated with the difference between CPS and AS (Table V). These variables were significant in multivariate regression analysis for inaccurate survival estimations:

- Oncologists with less than 10 years' experience tended to estimate shorter survival times (72.2 days; 95% CI: 8.4 to 136.0 days; $p = 0.027$).
- In patients more than 65 years of age, oncologists tended to underestimate survival times (54.7 days; 95% CI: 6.9 to 102.4 days; $p = 0.025$).
- In patients who did not receive information about PCUS, oncologists overestimated survival times (78.6 days; 95% CI: 15.7 to 141.4 days; $p = 0.014$).

4. DISCUSSION

In the present study, we investigated the accuracy of CPS estimates in patients with advanced cancer who had experienced progressive disease after standard chemotherapy. Survival was accurately predicted in only 36% of cases, although the CPS estimate was highly correlated with AS overall. The professional experience of the oncologist, patient age, and referral to a PCU were independent factors for a difference between CPS and AS.

Giving information as needed to patients, including expected survival, is important even though patients might not ask doctors for that information. In the present study, more than half the patients had a performance status of 0 or 1 at detection of progressive disease after standard chemotherapies. Prediction of survival might have been more difficult for doctors in that setting than in the terminally ill setting. Previous studies reported that only 20%–25% of predictions are accurate in terminally ill cancer patients[8,9]. In our study, 36% of the predictions were in the accurate range, and more than 80% of the predictions were based either on performance status or metastatic lesions (Table IV). As seen in earlier studies, survival predictions for the near future were more accurate than those for more than 6 months into the future (Figure 1 and 2). A report on the association between the professional experience of the oncologist and prediction shows that prognostic accuracy increases with the experience of the doctor[8]; however, another study reported contradictory findings[10]. Of the oncologists who did not disclose

TABLE IV Oncologist decisions about patient factors

Factor	*Responses (n)*	*Decision*	*Value [n (%)]*
Communicate information about CPS	75	No	54 (72)
		Yes (to patients)	13 (17)
		Yes (to family only)	8 (11)
Reason for *not* communicating CPS	54	Uncertainty	31 (57)
		Information not requested	20 (37)
		Apprehensive about communicating CPS	1 (2)
		Other	2 (3)
Main factor in CPS	75	Performance status	29 (39)
		Metastatic lesion	39 (52)
		Dyspnea	2 (2)
		Other	5 (7)
Final treatment	75	Best supportive care	45 (60)
		Chemotherapy	26 (35)
		Clinical trial	3 (4)
		Alternative medicine	1 (1)

CPS = clinical prediction of survival.

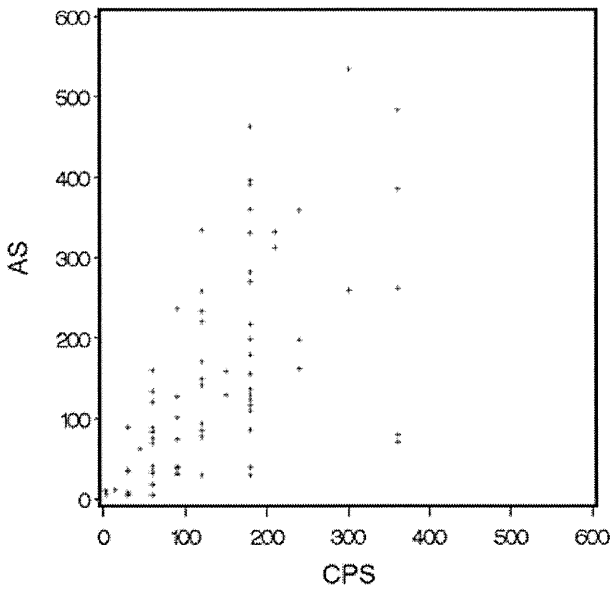

FIGURE 1 The Spearman rank correlation coefficient for clinically predicted survival (CPS) compared with actual survival (AS) was 0.70 ($p < 0.001$), indicating a highly significant association.

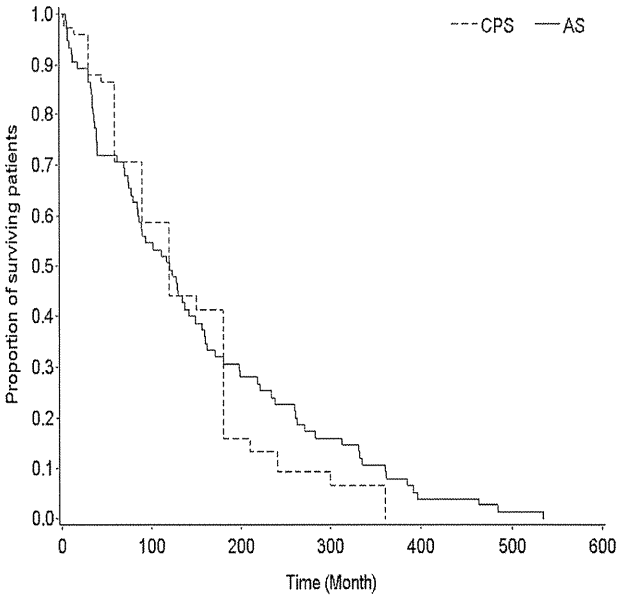

FIGURE 2 Kaplan–Meier curves for clinical predicted survival (CPS) and actual survival (AS). The median difference (CPS – AS) was –5 days (interquartile range: –74 to 43 days).

the CPS to their patients because the patient did not request that information, 80% had been practicing for less than 10 years. Less-experienced oncologists might tend to build strong doctor–patient relationships, and they might therefore be overly optimistic and unwilling to accept the imminent death of their patients. Alternatively, they might be trying not to scare patients[14]. However, an optimistic CPS can result in late referral to a PCU[8]. Indeed, our study findings indicated that patients who were not referred to a PCU had optimistic CPS estimates, although the observed relation between PCU referral and CPS is preliminary because of the small sample size. Patients should be given enough time to prepare for a PCU and should be in appropriate physical and psychological condition for referral. In addition, patients who have no

TABLE V Factors independently correlated with differences between clinical predicted survival (CPS) and actual survival in multivariate analysis

Factor	*Difference in days*		p *Value*
	Estimate	*95% CI*	
Oncologist's professional experience			
>10 Years	Reference		
<10 Years	72.2	8.4 to 136.0	0.027
Site of malignancy			
Breast	Reference		
Colorectum	−92.5	−188.6 to 3.7	0.060
Stomach	−38.0	−149.1 to 73.1	0.503
Pancreas	10.2	−69.9 to 90.3	0.803
Lung	37.5	−52.7 to 127.7	0.415
Ovary	4.5	−96.2 to 105.2	0.930
Cervix	−13.5	−135.9 to 108.9	0.829
Endometrium	57.2	−65.2 to 179.5	0.360
Sarcoma	−14.6	−104.3 to 75.1	0.750
Age (years)			
<65 Years	Reference		
>65 Years	−54.7	−102.4 to −6.9	0.025
Performance status			
0–1	Reference		
≥2	0.5	−69.0 to 70.1	0.988
Oral intake			
Normal	Reference		
Moderately reduced	−30.0	−96.9 to 37.0	0.380
Severely reduced	−72.1	−198.0 to 53.9	0.262
Main factor for CPS			
PS	Reference		
Metastatic lesion	−36.3	−85.3 to 12.7	0.146
Dyspnea	−14.8	−153.5 to 124.0	0.835
Other	−14.6	−103.5 to 74.3	0.748
Final treatment			
Best supportive care	Reference		
Chemotherapy	0.6	−62.9 to 64.0	0.986
Clinical trial	−36.1	−155.6 to 83.3	0.553
Alternative medicine	52.1	−131.6 to 235.7	0.579
Referral to palliative care uni			
Yes	Reference		
No	78.6	15.7 to 141.4	0.014

CI = confidence interval.

information about PCUs tend to receive aggressive chemotherapy near the end of life, which can contribute to poor quality of life[13].

Predicting survival time is difficult, and disclosing the prediction to patients is therefore also difficult. In the present study, the CPS was disclosed in only 28% of cases. Many articles suggest that most patients with incurable cancer are keen on receiving information regarding their prognosis[1–3,15,16]. Most patients would like to know their predicted survival, although physician and patient predictions are largely discordant[17]. Nevertheless, most physicians remain unwilling to disclose prognosis estimates to patients with incurable cancer. In previous studies, physicians favoured providing frank survival estimates in only 37% of cases[18]. Although disclosing the estimated survival time to a patient is not always necessary, doctors should make a considerable effort to communicate with their patients and to help them decide how they wish to live the remainder of their life[19–21].

This study has some limitations. First, because of the small sample size, we might have missed some factors affecting the survival prediction other than experience as an oncologist, patient age, and PCU information given. A larger sample would be required to adequately identify other factors. Second, predictive factors that might improve the accuracy of CPS estimates could not be clarified because of variations in patient characteristics and the professional experience of the oncologists. Third, patients might have been told their CPS after the questionnaire was completed, which might have affected subsequent care choices.

5. CONCLUSIONS

Although it is difficult to accurately estimate survival for patients who acquire resistance to standard chemotherapies, an earnest attempt should be made to provide as accurate a CPS as possible for patients who wish to have this information so that they can improve their quality of life. Well-planned studies to identify predictive factors that can assist in making an accurate assessment of CPS and to determine how best to deliver that information are warranted.

6. ACKNOWLEDGMENTS

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7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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ORIGINAL ARTICLE

Phase II study on hepatic arterial infusion chemotherapy using percutaneous catheter placement techniques for liver metastases from colorectal cancer (JFMC28 study)

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Abstract

***Aim*:** This prospective multicenter study aimed to evaluate the efficacy and adverse events of hepatic arterial infusion chemotherapy (HAIC) using percutaneous catheter placement techniques for liver metastases from colorectal cancer (CRC).

***Methods*:** We administered 5-fluorouracil at 1000 mg/m^2 over 5 h via hepatic arterial infusion on a weekly schedule. The primary endpoint was the overall response rate (RR). The secondary endpoints were the overall survival (OS), progression-free survival (PFS) and toxicities.

***Results*:** Between February 2000 and March 2002, seventy-seven eligible patients were enrolled in this study. After a median of 26 treatment cycles, 4 patients achieved a complete response, 29 achieved a partial response, 28 had stable disease, 15 had progressive disease and the status of one patient was unknown. The overall RR was 42.9% and the disease control rate (DCR) was 79.2%. The median PFS and OS times were 203 and 560 days, respectively. The most common grade 3 or 4 hematological and non-hematological toxicities were total bilirubin level elevation (10.4%) and gamma-glutamyl transferase level elevation (10.4%). With regard to the relationship between the background factors and treatment outcomes, the DCR, RR, PFS and OS were different between patients with and without extrahepatic lesions (DCR: 86.5% *vs* 64%, RR: 46.2% *vs* 36.0%, PFS: 233 days *vs* 99 days, OS: 587 days *vs* 558 days).

***Conclusion*:** The primary endpoint of this study was not met. HAIC using percutaneous catheter placement techniques did not improve the RR for liver metastasis from CRC.

Key words: colorectal cancer, hepatic arterial infusion, liver metastases.

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Conflict of interest: None declared

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INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent malignant disease worldwide.[1,2] Despite screening and early surgery, many patients eventually develop metastatic disease. The liver is the most frequent metastatic site of CRC, and thus managing liver metastasis is critical in the treatment of metastatic CRC.

Hepatic resection is considered the first-line treatment for liver metastasis from CRC.[3] The outcomes of hepatic resection have improved, and previous studies have reported a 5-year overall survival (OS) rate ranging from 43 to 58%. Additionally, the disease-free survival rate has been reported to be approximately 28%.[4,5] However, hepatic resection is only indicated for a limited number of patients, and most patients with liver metastases are treated with chemotherapy.

The efficacy of chemotherapy for CRC was dramatically improved in the 1990s owing to the development of new agents, such as irinotecan (CPT-11), oxaliplatin (L-OHP) and molecular-targeted agents.[6–12] Prior to the existence of these agents, chemotherapy for CRC mainly involved fluoropyrimidines, such as fluorouracil (5-FU), but its efficacy was limited.[13–17] Therefore, hepatic arterial infusion chemotherapy (HAIC), which delivers high drug concentrations to the tumor but results in less systemic toxicity, has been widely employed for the treatment of liver metastases from CRC. However, most randomized controlled trials comparing HAIC and systemic chemotherapy failed to demonstrate a survival benefit with HAIC, and some even reported a lower feasibility with hepatic arterial infusion due to catheter- or pump-related issues.[18,19] In these studies, HAIC was performed using surgical catheter placement techniques via laparotomy under general anesthesia. Accordingly, HAIC has not become a standard treatment for liver metastases from CRC.[19,20]

Percutaneous catheter placement techniques for HAIC were developed in the 1980s, mainly in Japan, and were fully established around 2000.[21–23] The procedure is less invasive than conventional surgical catheter placement because the catheter and port are placed percutaneously using interventional radiology techniques under local anesthesia. Additionally, the drug delivery can be evaluated by digital subtraction angiography (DSA) and computed tomographic angiography (CTA) through the implanted catheter and port system.[24–26] Using this technique for intermittent hepatic arterial infusion of high-dose 5-FU on a weekly schedule, Arai *et al.* reported a response rate (RR) of 78% in 1997.[27] Of note, novel standard systemic chemotherapy regimens such as FOLFIRI and FOLFOX had not been established in Japan at the time of Arai's study.

On the basis of these findings, we conducted a multi-institutional phase II trial to evaluate the efficacy and feasibility of HAIC using percutaneous catheter placement techniques for liver metastases from CRC.

METHODS

Patients

All patients were histologically diagnosed with colorectal adenocarcinoma with liver metastases. The patients' eligibility for surgical resection was determined by imaging studies according to the size and location of the hepatic tumors. Those with extrahepatic metastases were included at the investigators' discretion, provided that the liver was the dominant site of metastasis. The primary colorectal carcinoma had been previously resected in all cases. All patients had bidimensional measurable or assessable disease documented by imaging studies. Adequate hematological (white blood cell [WBC] count > 3000, platelet count > 750 000 and hemoglobin > 8.0 g/dL), liver (serum bilirubin 2 mg/dL) and coagulation (normal prothrombin time and partial thromboplastin time) profiles were required. No patients had received any prior treatment for liver metastasis from CRC before being enrolled in this study. All patients had an Eastern Cooperative Oncology Group performance status of 0–2.

Ethical considerations

The study data and informed consent were obtained in accordance with the Declaration of Helsinki and were approved by the Ethics Review Board of each participating institution. All patients received a written explanation of the study and provided written informed consent before participating.

Procedures and treatment

An indwelling catheter was inserted into the hepatic artery via the subclavian artery using standard interventional radiology techniques. We used the heparinized hydrophilic polymer catheters (Anthron, TORAY, Tokyo, Japan) for 75% of the patients in the present study. The others used another type of catheters. The proximal end of the catheter was connected to an implanted port. The optimal perfusion into the liver was confirmed by CTA, which was performed every 3

months. The details of the treatment procedure have been reported previously.[27] Briefly, patients received HAIC with a 5-h infusion of 1000 mg/m^2 5-FU once a week on an outpatient basis. Such treatment was repeated for as long as possible. Great care was taken to prevent or quickly detect any abnormalities resulting from technical issues such as catheter dislocation, vascular occlusion or inadequate drug distribution, and if necessary, appropriate countermeasures were taken.

Patient follow-up

The patient history was taken and physical and blood examinations were performed before each HAIC cycle. The puncture site was monitored for signs of bleeding, hematoma and infection throughout the procedure and after removal of the indwelling catheter. The National Cancer Institute common toxicity criteria were used to determine whether there was a need for dose modification or treatment discontinuation. In cases with a grade 2 WBC or platelet count decrease, or any grade 3 or 4 toxicity, the treatment was discontinued until full recovery, and the dose was reduced by 25% in the following cycle. If toxicity persisted, an additional 25% dose reduction was made when therapy resumed.

Treatment evaluation

The tumor response was assessed and evaluated according to the World Health Organization criteria.[28] The RR was defined as the combined proportion of complete response (CR) and partial response (PR), whereas the disease control rate (DCR) was the combined proportion of CR, PR and stable disease (SD) among all evaluable patients. Among the responders, relapse was defined as the appearance of new lesions or progression from the response at the time of maximum regression. The duration of the response was defined as the period from the first observation of the response to the time of documented relapse.

Statistical analyses and sample size

The primary endpoint of this study was the RR, whereas the secondary endpoints were the OS, progression-free survival (PFS) and safety. Although the RR for HAIC varied in previous reports, we aimed to achieve a 70% RR after reviewing the previously published data.[27] The required sample size to detect a difference between a threshold overall RR of 50% and a target overall RR of 70% using a one-sided binomial test with an alpha error of 2.5% and a statistical power of 90% was 65 patients.

Table 1 Patient characteristics

	Number (N = 77)	%
Age (years)		
Median	62	
Range	24–81	
Sex		
Male	49	63.6
Female	28	36.4
Primary site		
Colon	53	68.8
Rectum	24	31.2
Liver metastases		
Synchronous	53	68.8
Metachronous	24	31.2
Extrahepatic metastases		
Yes	25	32.5
No	52	67.5
ECOG performance status		
0	57	74.0
1	18	23.4
2	2	2.6
Prior chemotherapy		
Yes	10	13.0
No	67	87.0

ECOG, Eastern Cooperative Oncology Group.

To account for potential dropouts, the number of patients to be accrued was set at 80. The OS and PFS were calculated using the Kaplan–Meier method. A two-sided value of $P < 0.05$ was considered to be statistically significant. The OS was calculated from the date of enrollment to that of death or final follow-up. The PFS was calculated from the date of enrollment to that of disease progression, death or the final follow-up. All analyses were performed using the SAS 9.3. Software program (SAS Institute Japan Ltd., Tokyo, Japan).

RESULTS

Patients

A total of 77 patients were enrolled on the protocol between February 2000 and March 2002. All patients were evaluable regarding the treatment efficacy and safety. The clinical characteristics of all eligible patients are summarized in Table 1. The median age was 62 years (range, 24–81 years), with a male-to-female ratio of 49:28. The primary cancer site was the colon in 53 patients and the rectum in 24. Twenty-four patients presented with metachronous liver metastases, and eight

Table 2 Response to treatment ($n = 77$)

Type of response	No. of patients	Percentage (%, 95% CI)
Complete	4	5.2
Partial	29	37.7
Stable	28	36.4
Progression of disease	15	19.5
Unknown	1	1.3
Response rate	33	42.9 (31.8–53.9)

of these patients had received prior chemotherapy. The remaining 53 patients had synchronous liver disease at the time of their colon cancer diagnosis.

Extrahepatic metastases were present in 25 (32.5%) of the 77 patients, but the liver was the predominant site of metastatic disease in this group. The Eastern Cooperative Oncology Group performance status was 0 in 57 patients (74.0%), 1 in 18 patients (23.4%), and 2 in 2 patients (2.6%).

Treatment response

The overall RR was 42.9% (95% confidence interval [CI], 31.8–53.9%) after a median of 26 (range, 2–84) cycles of treatment. The null hypothesis could not be rejected on the basis of the one-sided binomial test ($P = 0.915$). Four patients achieved a CR, 29 achieved a PR, 28 had SD, 15 had progressive disease, and the status of one patient was unknown (Table 2). The DCR was 79.2%.

With regard to the relationship between the background factors and tumor response, the DCR was significantly different ($P = 0.023$) between the patients without extrahepatic lesions (45 of 52 patients; 86.5%) and those with extrahepatic lesions (16 of 25 patients; 64.0%). Furthermore, although there was no statistically significant difference, the RR was higher in patients without extrahepatic lesions than in those with extrahepatic lesions (46.2% *vs* 36.0%, $P = 0.400$). On the other hand, the RR for the liver metastasis alone was 64.0% (16 of 25) in the patients who had extrahepatic metastasis and 63.5% (33 of 52) in those who did not have extrahepatic metastasis. These values were not significantly different between the two groups ($P = 0.786$).

PFS and OS

The median PFS was 204 days (95% CI, 163–238 days). The median OS was 561 days (95% CI, 493–646 days). The median PFS was significantly different between the patients with and without extrahepatic lesions (99 days *vs* 233 days; log-rank $P = 0.004$, Fig. 1). The median OS was 587 days in patients without extrahepatic lesions and 558 days in those with extrahepatic lesions (log-rank $P = 0.163$, Fig. 2).

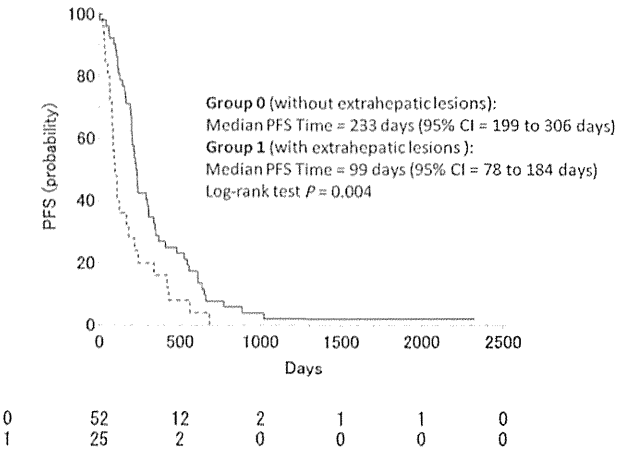

Figure 1 The progression-free survival of patients with and without extrahepatic lesions.

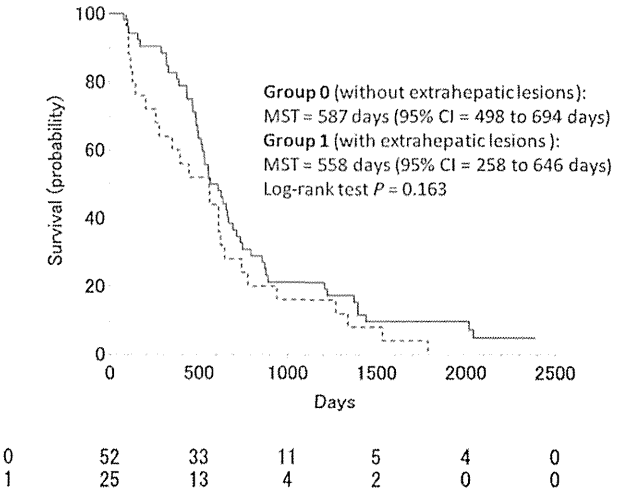

Figure 2 The overall survival of patients with and without extrahepatic lesions.

Treatment exposure and safety

The median number of cycles for hepatic arterial infusion treatment was 26 (range, 2–84). The median 5-FU dose was 37.5 g (range, 3–143 g). All 77 patients were evaluable for the safety of the treatment. To decrease toxicity, the 5-FU dose was reduced at least once in 27 patients. The toxicities observed are summarized in

Table 3 Hematological and biochemical toxicities observed during treatment

	All grades				Grade 3/4 (%)
	1	2	3	4	
Hematological toxicity					
Leucopenia	1	2	2	0	2.6
Neutropenia	1	1	1	0	1.3
Hemoglobin	12	3	0	1	1.3
Platelet	11	5	5	0	6.5
Bilirubin elevation	13	1	7	1	10.4
AST elevation	12	2	2	0	2.6
ALT elevation	6	1	3	0	3.9
γGTP elevation	7	3	8	0	10.4
Non-hematological toxicity					
Anorexia	4	7	1	0	1.3
Nausea	8	7	0	0	0
Vomiting	3	3	0	0	0
Fatigue	3	4	0	0	0
Constipation	0	1	1	0	1.3
Fever	3	5	0	0	0
Gastric ulcer	0	2	1	0	1.3
Duodenal ulcer	0	2	1	0	1.3

ALT, alanine aminotransferase; AST: aspartate aminotransferase; γGTP, γ-glutamyl transpeptidase.

Table 3. The most common grade 3 or 4 hematological toxicities were total bilirubin level elevation (10.4%) and gamma-glutamyl transferase level elevation (10.4%). However, non-hematological toxicities of grade 3 or higher were rare and included anorexia (1.3%) and gastric ulcers (1.3%). No treatment-related death was observed. The overall catheter-related complication rate was 19%. Early complications were more likely to involve inadequate drug distribution, as observed on CTA, and were frequently corrected by additional angiographic interventions. Complications that occurred more than 3 months after catheter and port placement were more likely to be catheter occlusions or arterial thrombosis. The late complications were less likely to be salvaged (30%) compared with those occurring early (70%). We used the heparinized hydrophilic polymer catheters (Anthron, TORAY) for 75% of the patients in the present study. We used another type of catheter in the others. However, there were no significant differences between the two groups in the rate of infusion- and catheter-related complications.

The most common causes of treatment discontinuation were disease progression (39/77 [50.7%]), catheter/procedure-related complications (12/77 [15.6%]) and patient refusal to continue treatment (4/77 [5.2%]).

Clinical course after HAIC treatment

After HAIC treatment failure, six patients underwent liver resection (7.8%). We evaluated their prognosis compared with patients who did not undergo liver resection. Five of these six patients and 69 of the 70 patients died. The median OS was 1418 days in patients who underwent liver resection and 555 days in those who did not (log-rank $P = 0.0023$). However, there were no standard criteria for resectability, and the choice to perform resection was left to the physician's discretion.

Forty-three patients received systemic chemotherapy. Among them, 10 patients received systemic chemotherapy and interventional radiology, 5 patients received systemic chemotherapy and radiation therapy, and 2 patients received systemic chemotherapy, interventional radiology and radiation therapy. Twenty-two patients received interventional radiology, radiation therapy, and combination interventional radiology and radiation therapy. Twelve patients did not receive any treatment after HAIC. When comparing the OS between the patients who received salvage systemic therapy and those who did not, there was a statistically significant difference ($P = 0.424$).

DISCUSSION

To the best of our knowledge, this trial is the first multi-institutional phase II study to evaluate the safety and efficacy of HAIC using percutaneous catheter and port placement techniques for treating liver metastases from CRC. Our primary objective was to confirm a RR of over 70%, which was previously reported in a single-institutional study.[27] However, the RR of HAIC in our study was lower than expected at 42.9%, and our statistical hypothesis in this phase II study was not met.

In this trial, we hypothesized that: (i) catheter-associated complications could be decreased by using percutaneous catheter and port placement techniques; (ii) patients could start HAIC without enduring a performance status decline due to surgical procedures; (iii) adequate HAIC could be repeated, with drug distribution evaluated by DSA and CTA; and (iv) better clinical outcomes of HAIC could therefore be achieved. The first possible explanation for this trial not meeting its primary endpoint is that HAIC might not substantially increase the RR compared with intravenous therapy. Theoretically, HAIC has several advantages over intravenous chemotherapy. For example, chemotherapeutic agents can be delivered more specifically to malignant cells. Normal hepatocytes that mostly rely on the portal venous system are thus exposed to fewer chemothera-

peutic agents. However, many chemotherapy agents used in HAIC have high first-pass hepatic clearance effect, such as 5-FU and floxuridine (FUDR), a prodrug of 5-FU. Over 90% of FUDR and 19–50% of 5-FU are cleared by the liver when they are administered by HAIC.[29] The second possible explanation is the heterogeneity in the level of expertise when performing percutaneous catheter and port placement among the participating institutions. To realize the theoretical benefits of HAIC, optimal drug distribution is critical, which means that the administered drug should be distributed to all intra-hepatic tumors, but not to any extrahepatic organs. Such drug distribution requires various and precise interventional radiology techniques. Furthermore, the procedural skill levels might have differed between this study and the above-mentioned single-institution study that reported better results.[27] In this study, we attempted to evaluate the patency of the hepatic artery and the position of the indwelling catheter every 3 months; however, catheter-related complications were observed in 19% of all patients, and 15.6% of the patients could not continue their treatment due to such complications. Similar rates of catheter-related complications were reported in HAIC performed using surgical procedures.[30–32] Scaife *et al.* reported an overall catheter- and pump-related complication rate of 16% in patients receiving HAIC between 1996 and 2001,[33] whereas Allen *et al.* reported that this rate was 22% in patients treated with a pump between 1986 and 2001.[34] Therefore, the percutaneous catheter and port placement techniques might not have succeeded in reducing catheter-related complications. However, the effects of the operators' skill level on the high incidence of catheter-related complications observed in our study cannot be ruled out. Of note, Campbell *et al.* found that a lack of surgical experience was associated with pump-related complications. The complication rate was 7% for surgeons who had placed more than 10 pumps, whereas it was 37% for surgeons who had placed fewer than 10 pumps.[30] Allen *et al.* also found that the complication rate was lower (19%) for surgeons who had placed more than 25 pumps, whereas this rate was higher (31%) for surgeons who had placed fewer than 25 pumps.[34]

In our study, patients were enrolled from nine different institutions. Arai *et al.* reported a RR of 72% for HAIC combined with systemic CPT-11 by percutaneous catheter placement in a multi-institutional study[35]; however, the above-mentioned study was conducted by well-experienced interventional radiologists at a limited number of institutions. Therefore, various technical factors, such as the operators' skills and/or experience levels, likely contributed to the catheter-associated complications. Moreover, we do not know the learning curve for the generalizability of these technical factors. This is one of the limitations of our study, and further studies should focus on this issue.

Another possible reason for our study's failing to meet its primary endpoint was the patients' background in terms of the presence or absence of extrahepatic lesions on the initial diagnostic images. Similar results were reported in previous studies. Arai *et al.* conducted phase I and II studies to examine the usefulness of HAIC in patients with liver metastasis from CRC, and found that the OS was 25.9 months in patients without extrahepatic lesions compared with 17.3 months in those with extrahepatic lesions.[27] However, the background characteristics between the two patient groups were statistically different in terms of their prior treatment with chemotherapy (20% [10/50] *vs* 0% [0/27], $P = 0.010$), their carcinoembryonic antigen levels (56.5 *vs* 143.6 ng/mL, $P = 0.020$) and their cancer antigen 19-9 levels (93.9 *vs* 409 ng/mL, $P = 0.056$). These background differences might have indicated that the condition of patients with extrahepatic lesions was more severe than that of patients without extrahepatic lesions. In addition, the RR for the liver metastasis only was similar between the patients who had extrahepatic metastasis and those who did not. On the other hand, the relationship between background factors and the tumor response, the DCR, was significantly different between the patients without extrahepatic lesions and those with extrahepatic lesions. Furthermore, although there was no statistically significant difference, the RR was higher in patients without extrahepatic lesions than in those with extrahepatic lesions. Therefore, the inclusion of patients with extrahepatic metastasis might have diluted the overall benefit of HAIC. Thus, it might be possible that HAIC would have been more effective in patients without extrahepatic lesions on diagnostic imaging studies at the time of treatment initiation. However, such a possibility remains unclear based on the present evidence.

Nonetheless, this trial demonstrated that HAIC with a percutaneous approach did not substantially increase the safety of HAIC. The safety profile of percutaneous HAIC in this study was consistent with that of previous reports.[27] No other complications were observed. Therefore, HAIC using percutaneous catheter and port system placement techniques is safe and feasible for liver metastases from CRC, but is not superior to treatment using a catheter placed using conventional surgical techniques.

In conclusion, HAIC using percutaneous catheter placement techniques did not improve the RR for liver metastasis from CRC, probably because these techniques could not reduce catheter-related complications in a multi-institutional setting. However, a difference in treatment outcomes was observed between patients with and without extrahepatic lesions on diagnostic images at the time of treatment initiation. In this regard, HAIC might provide a much better local disease control for patients without initial extrahepatic lesions. Therefore, percutaneous catheter placement techniques were feasible, but future studies on HAIC should focus on liver metastases from CRC in patients without extrahepatic lesions.

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Percutaneous Creation of an Extraanatomic Splenoportal Shunt in a Patient with Bleeding Ectopic Varices

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Editor:

We report percutaneous creation of an extraanatomic splenoportal shunt in combination with a transjugular intrahepatic portosystemic shunt (TIPS) and variceal embolization to treat a patient with bleeding ectopic varices at the site of a previous choledochojejunostomy.

Our hospital's institutional review board did not require approval for this case report. A 74-year-old man with a history of chronic pancreatitis presented with melena and anemia requiring multiple transfusions, resulting in impaired performance status. Computed tomography (CT) and double-balloon endoscopy performed at the referring hospital revealed variceal bleeding in the jejunum, adjacent to the anastomotic site of previous choledochojejunostomy for occlusion of the bile duct caused by pancreatitis. Endoscopy could not control the bleeding, and surgery was deemed unsafe as a result of postsurgical adhesions. The patient was referred to our hospital to seek possible treatment.

On admission, hematologic tests revealed a decrease in hemoglobin level (8.0 g/dL) and platelet count (133,000/μL). Liver function test and coagulation profile results were normal except for decreased albumin level (2.5 g/dL). Contrast-enhanced CT demonstrated occlusion of the portal venous system, involving the intrahepatic bilateral main portal trunks, extrahepatic portal vein, and the confluence of the superior mesenteric and splenic veins. Collateral vessels were identified around the choledochojejunostomy site (Fig 1). On the basis of these findings, recanalization of the portal vein was planned. An angiography/CT system (INFX-8000C/Aquilion 16; Toshiba, Ohtawara, Japan) with a c-arm flat-panel detector combined with a moving multislice CT scanner was used for all procedures, along with an ultrasound (US) system.

First, percutaneous transhepatic and transsplenic recanalization of the portal venous system was attempted. Introducer systems were placed in the right portal vein and splenic vein, and occlusion of the portal and splenic veins with the collateral vessels forming the ectopic varices was demonstrated; however, passage of a guide wire through the occlusion site was not accomplished from either route. A small amount of extravasation was seen, and embolization from a branch of the splenic vein was performed with the use of metallic coils. The percutaneous catheters were removed and tract embolization was performed.

Two days later, a second interventional procedure was performed to create an extraanatomic shunt between the splenic and portal veins. Percutaneous approaches to the right portal vein and splenic vein were established with the same technique as the previous procedure (Fig 2a). A 17-gauge metallic cholangiography needle (PTC needle; Hakko, Chikuma, Japan) was manually bent and cut approximately 3 cm from the tip to allow a 21-gauge metal needle (PTC-D needle; TOP, Tokyo, Japan) to emerge coaxially from the needle. The splenic vein was successfully punctured by using this coaxial needle system, with guidance by the opacified splenic vein (Fig 2b) and confirmation with CT. A guide wire was passed through the transsplenic introducer to establish a through-and-through access. Two covered stents (10 mm × 8 cm and 8 mm × 4 cm; Fluency; Bard, Karlsruhe, Germany), and two bare metal stents (10 mm × 4 cm; Zilver; Cook, Bloomington, Indiana) were deployed, traversing the extraanatomic shunt route between the right portal and splenic veins (Fig 2c). Covered stents were placed to avoid bleeding, and bare stents were placed

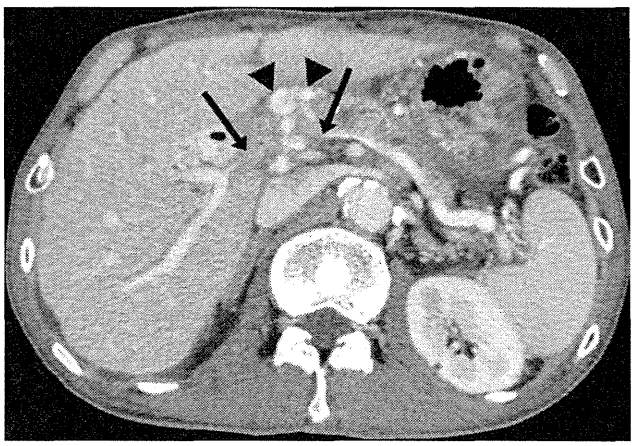

Figure 1. Contrast-enhanced axial CT image before treatment demonstrates portal venous occlusion extending from the right and left intrahepatic portal veins beyond the confluence of the superior mesenteric vein and the splenic vein and into each vessel (arrows). Collateral vessels are identified around the choledochojejunostomy site and porta hepatis (arrowheads).

None of the authors have identified a conflict of interest.

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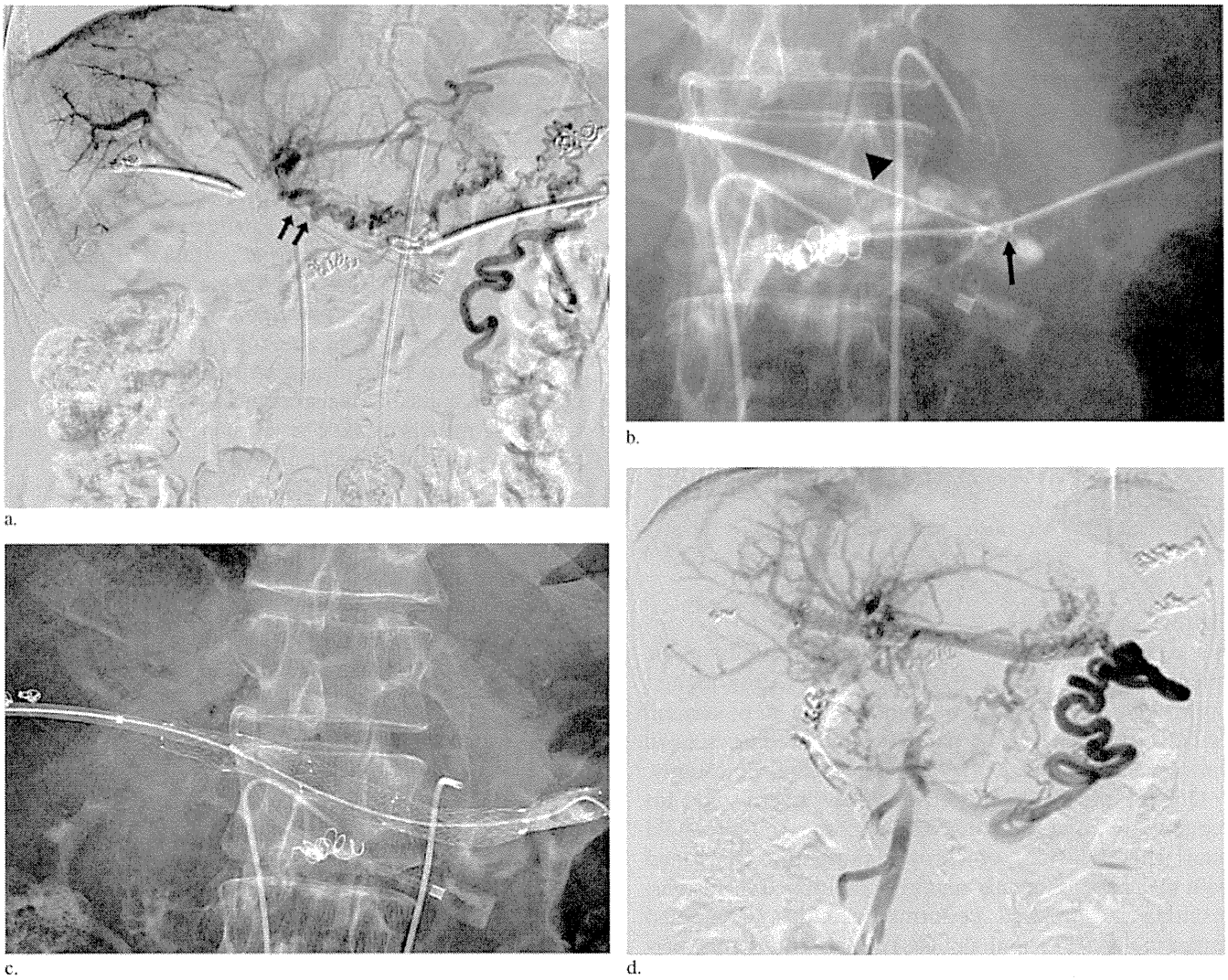

Figure 2. Technical steps of the creation of an extraanatomic splenoportal shunt. **(a)** Transhepatic portography and simultaneous transsplenic splenic venography. Occlusion of splenic vein and portal vein with collateral vessels forming (arrows) are demonstrated. Catheters in the aorta and vena cava, placed in case of massive bleeding, are seen. **(b)** Coaxial technique was employed to puncture the splenic vein from the right portal vein. A 17-gauge needle was advanced to the occlusion point of the portal vein (arrowhead), and the splenic vein was successfully punctured with a 21-gauge needle (arrow) from the 17-gauge needle. **(c)** Two covered stents and two bare metal stents were deployed, traversing the extraanatomic shunt route between the right portal and splenic veins. **(d)** Mesenteric venography after the third procedure. Stents in a TIPS route placed between the right hepatic and right portal veins during the second procedure are seen. Residual varices were embolized. Both bypass route and intrahepatic portal veins are patent.

to maintain the flow in the branch vessels. Balloon angioplasty was performed to dilate the unexpanded stents with a 10-mm × 4-cm balloon catheter (PowerFlex P3; Cordis, Bridgewater, New Jersey). As stagnation in the stents was seen, presumably as a result of insufficient outflow from the splenoportal shunt, a TIPS was created between the right hepatic and right portal veins with the use of a Rösch–Uchida Transjugular Liver Access Set (Cook) and an 8-mm × 4-cm bare metal stent (Zilver). Percutaneous catheters were removed, and tract embolization was performed.

After the procedure, bleeding decreased significantly; however, a small amount of melena with mild anemia was observed and residual varices were seen on CT. Therefore, embolization of the residual varices with n-butyl-2-cyanoacrylate (Histoacryl; B. Braun, Bethlehem, Pennsylvania) and Lipiodol (B. Braun) mixed at a 1:6 ratio was performed from the surgically exposed ileocecal vein 20 days after creation of the splenoportal shunt (Fig 2d). After these procedures, the variceal bleeding was stopped and transfusions were no longer required. Endoscopy and CT demonstrated the shrinkage of varices. Contrast-enhanced CT (Fig 3) and Doppler US at 10 and 12 months demonstrated patent splenoportal and portosystemic shunts. No anticoagulants were administered. The patient has remained well, without episodes of variceal bleeding at 14 months after the procedures.

Ectopic varices arising in the small intestine are often inaccessible by an endoscope. Therefore, the diagnosis and

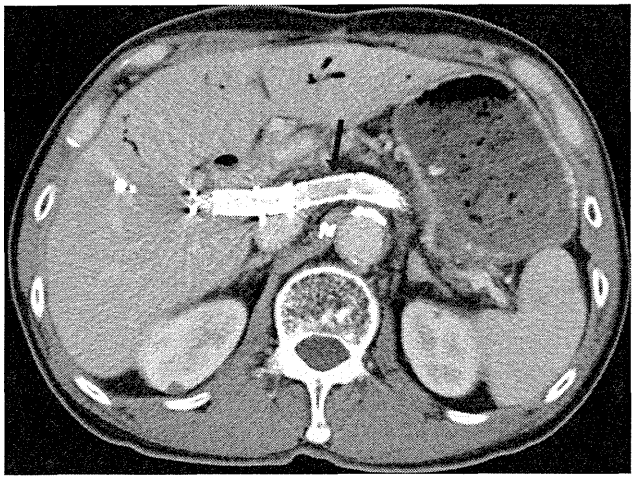

Figure 3. Axial contrast-enhanced CT at 10 months after the procedure. Stents in the splenoportal shunt are patent (arrow) and varices are decreased in size.

treatment methods are determined on a case-by-case basis. A 2013 literature review by Saeki et al (1) identified 13 cases, from 11 reports, of bleeding ectopic varices at the sites of previous choledochojejunostomies. In that series, interventional radiologic techniques were employed in eight patients, including dilation and stent implantation of the portal vein (n = 5) and embolization of varices (n = 3). None of these cases involved percutaneous creation of an extraanatomic shunt as performed in the present case. Decompression of splenic outflow with an extraanatomic shunt was effectively established in the patient described here; however, attempts at recanalization of the portal and splenic veins may have caused fatal complications such as massive abdominal bleeding and should be considered carefully.

Transsplenic access to the splenic vein in patients with an occluded portal vein is a recognized technique (2,3). Because bleeding from the soft and fragile spleen could be a lethal complication, embolization of the puncture tract should be performed. In the present case, both transsplenic approach sessions were uneventful with tract embolization. In addition, successful recanalization of occluded portal veins via a transsplenic approach has been reported (2,3) as in the present case.

In summary, the present case illustrates extraanatomic splenoportal shunt creation in a patient with bleeding jejunal varices after a choledochojejunostomy. This technique may serve as a treatment option for patients with ectopic varices caused by extrahepatic portal venous occlusion associated with difficult portal vein recanalization.

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Imagine IR Symposium: An Approach to Increasing IR Awareness and Understanding among Medical Students

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Editor:

Throughout the past decade, academic literature has repeatedly reported high levels of interest in interventional radiology among medical students; however, it has been shown that students continue to have a limited understanding of interventional radiology concepts and its scope of practice (1). Of 103 responses from 542 medical students surveyed from a Canadian university's medical program, a total of 18% reported being interested in interventional radiology as a career, but 54% of students were unclear about the duties of an interventional radiologist in the hospital (1). Moreover, nearly 75% of students expressed concerns with regard to limited interventional radiology exposure and supported a proposed mandatory interventional radiology rotation (1). Although this supports the notion that new approaches to interventional radiology education are required, current academic literature has not identified effective and practical means of approaching interventional radiology education.

An evening symposium entitled Imagine IR 2.0 was implemented in October 2013 and included small-group workshops and problem-based learning sessions aimed at introducing the subspecialty of interventional radiology to undergraduate medical students. Short lectures and hands-on demonstrations were also elements of the program. The event was a collaborative and interprofessional undertaking by interventional radiologists, a radiological technologist, and a diagnostic imaging

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Two Esophageal Stents in the Abdomen

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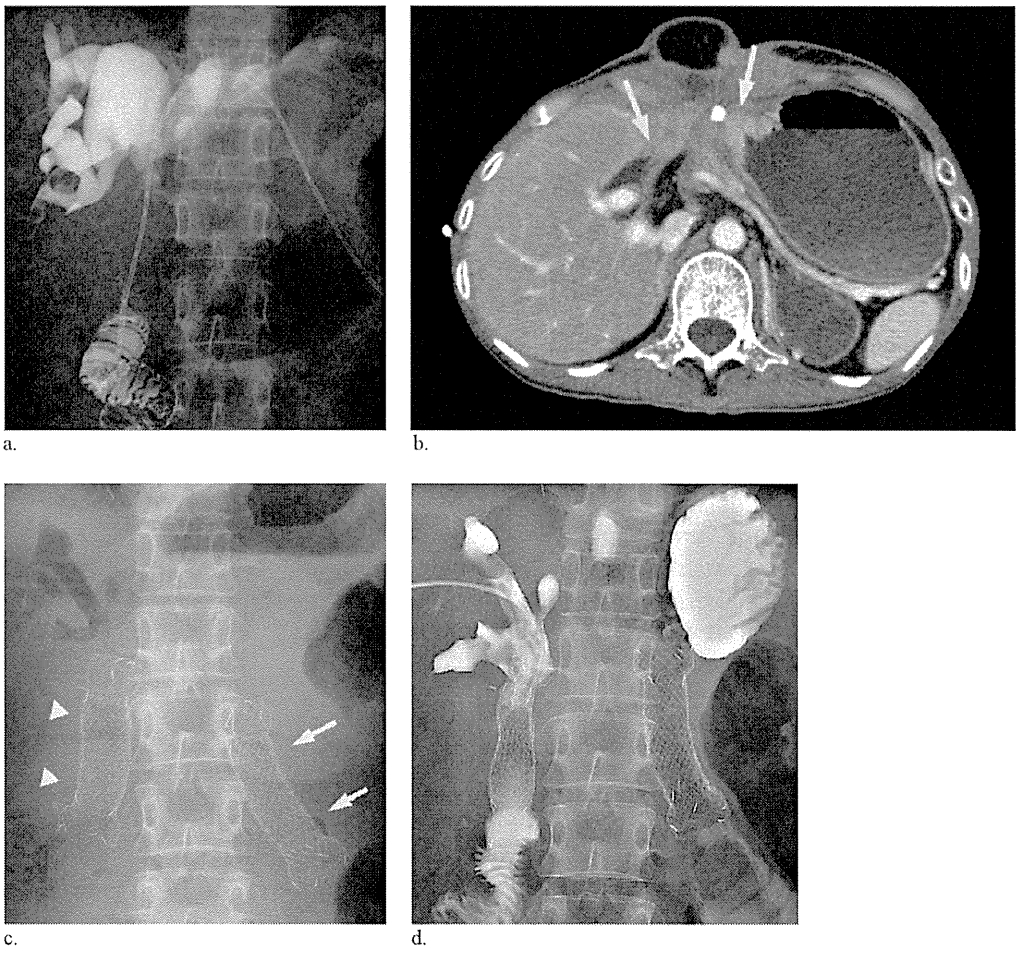

Figure.

A 32-year-old woman presenting with frequent vomiting and jaundice was referred to our hospital. Twelve years previously, she had been diagnosed with cholangiocarcinoma associated with congenital bile duct dilation (Fig a, shows preoperative cholangiography). At that time, the extrahepatic bile duct was resected, and gastrojejunostomy was performed. Computed tomography revealed obstruction of the choledochojejunostomy and gastrojejunostomy anastomotic sites by recurrent tumors (Fig b, arrows). An esophageal self-expandable silicon-covered metallic stent—with a wide aperture and flared structures at both ends to prevent stent migration—was placed percutaneously to relieve biliary obstruction (Fig c, arrowheads). To improve food passage, the same type of stent was placed via her mouth at the gastrojejunostomy stricture (Fig c, arrows). The jaundice and vomiting improved following stent placement (Fig d). Both stents were functioning 10 months later, and she has remained well. Metallic stents are designed for use in multiple anatomic locations. Proper metallic stent selection and placement can dramatically ameliorate symptoms.

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MAGNETIC RESONANCE

Does Gadoxetic acid-enhanced 3.0T MRI in addition to 64-detector-row contrast-enhanced CT provide better diagnostic performance and change the therapeutic strategy for the preoperative evaluation of colorectal liver metastases?

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Abstract
Objectives To compare diagnostic performance in the detection of colorectal liver metastases between 64-detector-row contrast-enhanced CT (CE-CT) alone and the combination of CE-CT and gadoxetic acid-enhanced MRI (EOB-MRI) at 3.0T, and to assess whether EOB-MRI in addition to CE-CT results in a change to initially planned operative strategy.
Methods A total of 39 patients (27 men, mean age 65 years) with 85 histopathologically confirmed liver metastases were included. At EOB-MRI, unenhanced (T1- and T2-weighted), dynamic, and hepatocyte-phase images were obtained. At CE-CT, four-phase dynamic contrast-enhanced images were obtained. One on-site reader and three off-site readers independently reviewed both CE-CT alone and the combination of CE-CT and EOB-MRI. Sensitivity, positive predictive value, and alternative free-response receiver operating characteristic (AFROC) method were calculated. Differences in therapeutic strategy before and after the EOB-MRI examination were also evaluated.
Results Sensitivity and area under the AFROC curve with the combination of CE-CT and EOB-MRI were significantly superior to those with CE-CT alone. Changes in surgical therapy were documented in 13 of 39 patients.
Conclusions The combination of CE-CT and EOB-MRI may provide better diagnostic performance than CE-CT alone for the detection of colorectal liver metastases, and EOB-MRI in addition to CE-CT resulted in changes to the planned operative strategy in one-third of the patients.

Key Points
- *Accurate preoperative imaging is essential for surgical planning and successful hepatic resection.*
- *Combination of CE-CT and EOB-MRI is useful to detect colorectal liver metastases.*
- *EOB-MRI combined with CE-CT contributes to determine the correct therapeutic strategy.*

Keywords Colorectal liver metastases · Gadoxetic acid-enhanced magnetic resonance imaging · Contrast-enhanced computed tomography · Diagnostic performance · Therapeutic strategy

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Introduction

Metastasis to the liver is the most common site of haematogenous spread in patients with colorectal cancer, with 40 % of stage IV patients having only liver metastatic disease [1]. Hepatic resection has emerged as a promising treatment option to improve long-term survival, and resectability criteria include complete resection of metastatic lesions while preserving future liver remnants as much as possible [2, 3]. Therefore, accurate assessment with preoperative imaging,

including the number, size, and location of the lesions as well as the number of involved liver segments, is essential for adequate surgical planning and successful hepatic resection [2, 3].

Multidetector computed tomography (MDCT), using intravenous contrast agents, is routinely employed for the staging of follow-up of patients, and it provides robust and rapid imaging of the chest, abdomen, and pelvis for the detection of liver and extrahepatic metastases. In addition, major advances in liver magnetic resonance imaging (MRI) include the development of high-resolution volumetric imaging approaching the resolution of MDCT, parallel imaging to reduce imaging time, and higher magnetic field strength using a 3.0T system [4].

Gadoxetic acid is a liver-specific MR contrast agent that offers dynamic and static hepatocyte imaging to improve the detection and characterization of focal liver lesions [5], including liver metastases [6–8]. Some studies have compared gadoxetic acid-enhanced MRI (EOB-MRI) and contrast-enhanced MDCT [9, 10], although only two studies have compared EOB-MRI at 3.0T with contrast-enhanced 64-row MDCT for the detection of colorectal liver metastases [11, 12]. And while EOB-MRI has been clinically performed after CT examination for preoperative imaging of colorectal liver metastases, no studies have assessed the diagnostic performance of EOB-MRI combined with contrast-enhanced MDCT to determine the best therapeutic strategy.

The present study compared the diagnostic performance of the 64-detector-row CE-CT alone and in combination with EOB-MRI at 3.0T for the detection of colorectal liver metastases, and assessed whether the combination findings resulted in a change to the initially planned operative strategy.

Materials and methods

Patient populations

Forty-seven consecutive patients suspected of having liver metastases on the basis of their history of colorectal cancer and previous ultrasound findings and/or elevation of carcinoembryonic antigen (CEA) were examined by CE-CT followed by EOB-MRI at our institution in order to acquire additional information prior to surgical liver resection. EOB-MRI was performed within four weeks prior to surgery, and the interval between the CE-CT and EOB-MRI was two weeks or less. All patients had previously undergone surgery at the primary site and had histopathological confirmation of colorectal cancer. Eight of the 47 patients were excluded from our study because they had received previous chemotherapy for liver metastases. The remaining 39 patients (27 men and 12 women) were included. The mean age of the patients was 65 years (range, 45–79 years).

Thirty-seven of these 39 patients had a total of 85 liver metastases, which were diagnosed by histopathological examination of surgical specimens and intraoperative ultrasound (US) in 34 patients and on the basis of tumour growth observed during follow-up examinations in three patients who were not candidates for liver resection. In the remaining two patients, it was confirmed that liver metastases were not evident from imaging examinations and CEA levels during ≥6 months of follow-up. The institutional review board of our institution approved the study, and informed consent was obtained from each patient before enrolment. This study was conducted in accordance with the amended Helsinki Declaration.

CT imaging protocol

CT images were obtained using 64-detector-row MDCT instruments (Aquilion 64; Toshiba Medical System, Tokyo, Japan) with a 0.4-s rotation time and exposure factors of 120 kV and 160 mAs for all images. A total of 100 ml of the contrast material (Iopamiron 300/370; Bayer Schering Pharma, Osaka, Japan) was injected into an antecubital vein at a rate of 3.3 ml/s using an automatic power injector (Mark V ProVis; Medrad, Indianola, PA). An iodine concentration of 300 mg I/ml (Iopamiron 300) was used when the patient's body weight was <50 kg, and 370 mg I/ml (Iopamiron 370) was used when body weight was >50 kg. The examinations were performed in a cephalocaudal direction, starting at the top of the liver, and each examination included non-enhanced and contrast-enhanced imaging.

After non-enhanced imaging was performed in the transverse section, CE-CT was performed for 35 s (arterial phase), 70 s (portal phase), and 120 s (equilibrium phase), after intravenous administration of the contrast material. The following imaging parameters were used: collimation of 32× 1 mm, pitch factor of 0.656, rotation time of 0.5 s, and 5-mm reconstruction interval (slice thickness). A standard algorithm was used for all image displays.

MR imaging protocol

A superconducting magnet system in a 3.0T (Magnetom Trio; Siemens Medical Solutions, Erlangen, Germany) using an eight-channel body phased-array coil was used to perform EOB-MRI. A 45 mT/m gradient field strength and slew rate of 200T/m/s were used to actively shield the magnet. After breath-hold, double-echo T1-weighted gradient-echo (GRE) images (in-phase and opposed-phase images) and navigator-triggered fat-suppressed T2-weighted turbo spin-echo (TSE) images using prospective acquisition correction (PACE) were obtained, and dynamic images using fat-suppressed T1-weighted GRE images with a three-dimensional volumetric interpolated breath-hold examination (3D-VIBE) sequence

were obtained before (pre-contrast) and 14–30 s (arterial phase), 70 s, and 3 min after intravenous administration of gadoxetic acid (Primovist; Bayer Schering Pharma, Osaka, Japan), which was injected as a bolus (2.0 ml/s) at a dose of 0.025 mmol/kg of body weight, followed by 20 ml of a saline flush. Hepatocyte-phase images were obtained 20 min after the injection of gadoxetic acid.

The following parameters were used to acquire breath-hold T1-weighted GRE images: repetition time (TR), 120 ms; echo time (TE), 2.46 m; flip angle, 66°; matrix, 320×180; number of signals acquired, one; section thickness, 7 mm; intersectional gap, 1.4 mm; and acquisition time, 28 s. PACE using the following parameters was used to acquire navigator-triggered fat-suppressed T2-weighted TSE images: TR (effective), 3865–5534 ms; TE (effective), 71 ms; flip angle, 120°; echo train length, 12; matrix, 384×202; number of signals acquired, one; section thickness, 7 mm; intersectional gap, 1.4 mm; and acquisition time, approximately 90 s. A 3D-VIBE sequence with the following parameters was used to acquire fat-suppressed T1-weighted GRE images: TR, 3.68; TE, 1.22; flip angle, 10°; matrix, 256×192; number of signals acquired, one; section thickness, 3 mm; intersectional gap, 0.6 mm; and acquisition time, 21 s.

Standard of reference

In this study, a single radiologist (12 years of experience as a radiologist) and a single surgeon (13 years of experience as a surgeon) determined the presence or absence of liver metastases on the basis of findings obtained at definitive surgery that involved intraoperative US or an increase in size on the imaging examinations over a six-month follow-up period. Hepatic resection and intraoperative US for the non-resected segments were performed by surgeons who were aware of the preoperative MRI findings. The resected specimens at 5-mm intervals in the transverse plane were sectioned by a single pathologist, and the radiologist and pathologist compared the findings with those of EOB-MRI.

Liver metastases were measured on resected specimens and EOB-MRI, and their mean tumour size along the long axis was 2.5 cm (range, 0.5–14.0 cm). Twenty-six of the 85 lesions were <10 mm in diameter (mean, 0.68 mm; range, 0.4–1.0 cm). Seventeen patients had 42 benign hepatic lesions. Of these, 15 patients had a total of 30 cysts (mean size, 1.7 cm; range, 0.8–4.7 cm). Five of these 17 patients had a total of 12 haemangiomas (mean size, 0.9 cm; range, 0.8–2.8 cm). The cysts and haemangiomas were diagnosed on the basis of typical radiological examination findings and by the fact that the lesions demonstrated no change in size on the follow-up examinations performed over a period of ≥12 months (range, 12–31 months).

Image analysis

Image evaluation was performed as an on-site assessment by one clinical investigator (12 years of experience as a radiologist at the institution) and separately as blinded reading by three investigators (19, 13, and 11 years of experience as radiologists) who were not involved in the clinical investigation (off-site readers). In the on-site evaluation, the reader was not blinded to any imaging, pathological or laboratory results relevant to the patient's care. Meanwhile, three off-site readers were aware of the overall goal of the study before the reading session but were unaware of any other information.

Image evaluation in the clinical part of the study (on-site assessment) included a separate assessment of CE-CT images and the combination of CE-CT and EOB-MR images. Image evaluation in the blinded reading of each patient (off-site assessment) was performed in random order. Each reader independently interpreted the CE-CT images, and the readers then viewed EOB-MRI for the patient and re-evaluated and recorded their findings on the combination of CE-CT and EOB-MRI in a similar manner.

In the on-site and off-site evaluations, the readers recorded the presence, location, and size of all focal liver lesions at the segment on schematic drawings of transverse sections of the whole liver to avoid confusion in data analysis. Following this, they assigned a confidence level to each lesion on a four-point scale: 1, probably not liver metastasis; 2, possibly liver metastasis; 3, probably liver metastasis; and 4, definitely liver metastasis. All images were reviewed on a 1536×2048 picture archiving and communication system (PACS) monitor (RadICS, Nihon IBM, Tokyo, Japan).

The criteria for the radiological diagnoses of liver metastasis on CE-CT were described as an ill-defined heterogeneous nodule with higher attenuation than that of bile with some degree of enhancement. The criteria for liver metastasis on EOB-MRI were focal discrete nodular lesions showing high signal intensity relative to the liver parenchyma on T2-weighted FSE images (and lower signal intensity than the gallbladder or cerebrospinal fluid) and low signal intensity relative to the liver parenchyma on T1-weighted GRE images obtained at 70 s and 3 min after gadoxetic acid injection, and more conspicuous on the hepatocyte-phase images. The diagnosis of liver metastases was more definitive when perilesional enhancement was detected on the T1-weighted GRE images obtained 30 s after gadoxetic acid injection.

Change in therapeutic strategy

In the on-site evaluation, the indications for surgical therapy and the planned surgical procedure were provided at two different time points by the clinical radiologist and a surgeon, before and after EOB-MRI examination. The potential planned surgical procedures were hemihepatectomy,

segmentectomy, atypical segmentectomy, and metastasectomy. In addition, watchful waiting was adopted when no liver metastases were evident, and chemotherapy or conservative therapy was performed when surgical intervention was impossible. The planned therapies before and after EOB-MRI examination were compared with the surgical procedure ultimately performed.

Statistical analysis

The sensitivities and positive predictive values (PPVs) of CE-CT alone and the combination of CE-CT and EOB-MRI for the detection of liver metastases were calculated in the on-site evaluation by one reader, and were assessed in the off-site evaluation by each reader using the number of lesions assigned a confidence score of 3 or 4 (i.e., probably liver metastasis or definitely liver metastasis) from the total number of liver metastases. McNemar's test and Fisher's exact test were utilized to compare the sensitivities and PPVs for CE-CT alone and the combination of CE-CT and EOB-MRI among the composite data.

A maximum-likelihood estimation program (ROCKIT 0.9B; C.E. Metz, University of Chicago, Chicago, Ill, 1998) was used to calculate the alternative free-response receiver operating characteristic (AFROC) curve for each reader and each image set in the off-site evaluation. The area under each AFROC curve (Az) indicated the overall diagnostic accuracy of each image set and each reader. A univariate z score test was utilized to test differences between the mean Az values for statistical significance.

Interobserver variability in the off-site evaluation was assessed by calculating the κ statistic for multiple observers using non-weighted κ statistics with binary data defined by the presence or absence of liver metastases. κ values of 0.01–0.20 were considered to indicate poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81–1.0, excellent agreement.

For all tests, a p value <0.05 was considered to indicate statistical significance. A software package (SPSS 12.0 for Windows, SPSS (IBM), Chicago, IL) was used to perform statistical analyses.

Results

Image analysis of on-site data

At the on-site evaluation, the detection sensitivity of liver metastases with the combination of CE-CT and EOB-MRI was significantly higher than that of CE-CT alone, and there was no significant difference in PPVs between CE-CT alone and the combination of CE-CT and EOB-MRI (Table 1).

Table 1 Sensitivity and positive predictive value for the detection of liver metastases on contrast-enhanced CT and gadoxetic acid-enhanced MR imaging by on-site readers

	CECT alone	CECT and EOB-MRI	p value
Mean	Sensitivity (%)		
	78.8 (67/85)	92.9 (79/85)	0.006
Mean	Positive Predictive Value (%)		
	91.8 (67/73)	94.0 (79/84)	0.408

Note: Data in parentheses are numbers used to calculate sensitivity and positive predictive value.

CECT contrast-enhanced CT

EOB-MRI gadoxetic acid-enhanced enhanced MR images

Image analysis of off-site data

In the off-site evaluation, the detection sensitivity of the combination of CE-CT and EOB-MRI was significantly higher than that of the CE-CT alone for each of the three readers (Table 2). No significant differences were found in PPVs between CE-CT alone and the combination of CE-CT and EOB-MRI for any of the three observers.

For the three readers, 16 false-positive lesions were recorded on CE-CT alone and 10 were recorded on the combination of CE-CT and EOB-MRI. On CE-CT alone, six cysts and four haemangiomas were diagnosed as liver metastases (all <1.0 cm), three false-positive findings were attributed to thrombosed vessels (one, 1.2 cm; two, <1.0 cm), two were attributed to partial volume averaging (<1.0 cm), and the remaining one was unexplained. On the combination of CE-CT and EOB-MRI, two cysts and two haemangiomas were misdiagnosed as metastases (all <1.0 cm), four false-positive findings were attributed to intrahepatic vasculature (one, <1.5 cm; five, <1.0 cm), and the remaining two were unexplained sub-centimetre areas on the hepatocyte-phase images.

With regard to the false-negative lesions, none of the readers detected five lesions in three patients on either CE-CT alone or the combination of CE-CT and MRI (all were ≤1.0 cm). Two of these five lesions were detected by intraoperative US, one was detected by surgical palpation, and one was detected only by histopathological inspection. Using CE-CT alone, 11 lesions in eight patients were not detected with a high confidence level by any of the readers. On the other hand, six of these lesions in five patients were detected by at least one reader using the combination of CE-CT and EOB-MRI (Fig. 1).

Statistically significant differences in the Az values for CE-CT alone and the combination of CE-CT and EOB-MRI were demonstrated in the off-site evaluation by each of the three readers (mean Az values for Gd-EOB-DTPA-enhanced MR images, 0.948; mean Az values for CE-CT, 0.859; p=0.034) (Table 3).