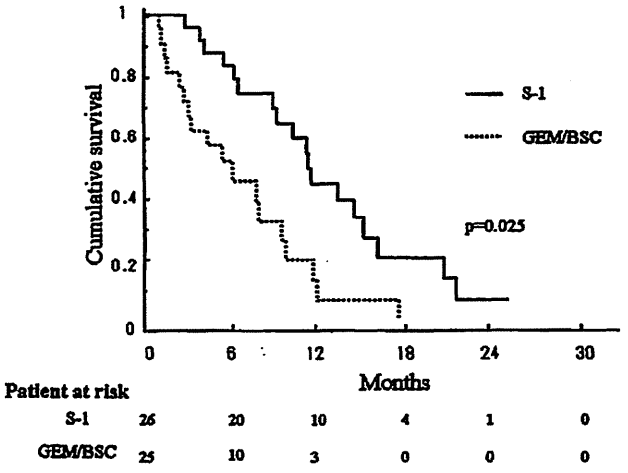

Figure 1. Kaplan-Meier curves for survival periods after recurrence in the S-1 group (solid line) and the GEM/BSC group (dotted line).

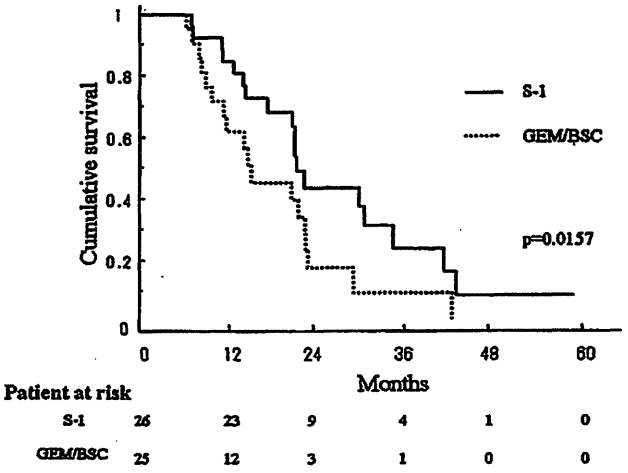

Figure 2. Kaplan-Meier curves for overall survival periods in the S-1 group (solid line) and the GEM/BSC group (dotted line).

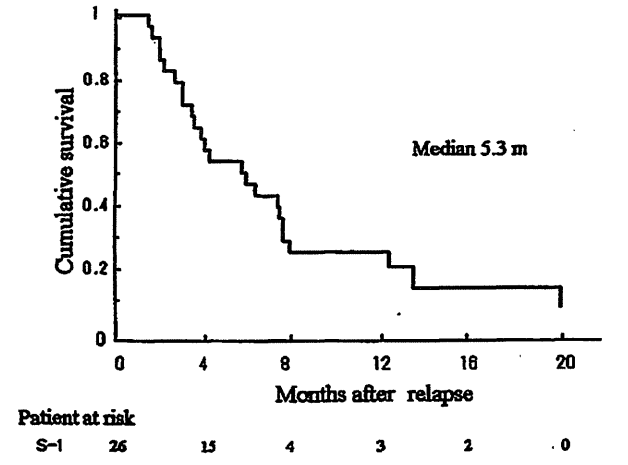

Figure 3. Kaplan-Meier curves for progression-free survival period in the S-1 group. m, months.

Table II. Drug-related adverse effects.

	S1 group (n=26)	
	G1/2 (%)	G3/4 (%)
Hematological toxicity		
Leukopenia	4 (15.4)	1 (3.8)
Neutropenia	3 (11.5)	1 (3.8)
Anemia	1 (0.4)	0 (0.0)
Thrombopenia	0 (0.0)	0 (0.0)
Non-hematological toxicity		
Appetite loss	2 (7.7)	2 (7.7)
Diarrhea	0 (0.0)	0 (0.0)
Nausea	1 (3.8)	0 (0.0)
Vomiting	3 (11.5)	0 (0.0)
Fatigue	3 (11.5)	1 (3.8)

Table III. Efficacy of S-1 in terms of recurrence pattern.

	S-1 MST (months)	GEM/BSC MST (months)	p-value (log-rank)
Liver metastasis	10.5	11.6	0.796
Peritoneal dissemination	13.5	8.7	0.152
Local recurrence	26.9	17.8	0.046

MST, median survival time.

Discussion

In this retrospective study, we investigated the efficacy and feasibility of S-1 as second-line chemotherapy after adjuvant chemotherapy with GEM for patients with pancreatic cancer. Our results show that the administration of S-1 as a second-line chemotherapy was capable of prolonging not only the survival period after relapse (median 11.4 vs. 6.2 months), but also the overall survival period (median 20.9 vs. 13.7 months). Second-line chemotherapy with S-1 combined with adjuvant chemotherapy using GEM may therefore be an efficient and beneficial strategy for pancreatic cancer patients.

Neoptolemos *et al* previously demonstrated that adjuvant chemotherapy was potentially beneficial for patients with pancreatic cancer, whereas adjuvant chemoradiotherapy had a deleterious effect on survival (6). Tani *et al* have reported that adjuvant chemotherapy was an independent factor affecting long-term survival in patients with locally advanced pancreatic cancer who had undergone surgery (10). Oettle *et al* have shown that adjuvant chemotherapy with GEM for pancreatic cancer patients was significantly effective for prolonging disease-free survival (7), and their subsequent study revealed that it was also capable of prolonging OAS (9). In their study, Ueno *et al* have shown that GEM prolonged disease-free survival in patients who had undergone macroscopically curative resection of pancreatic cancer (8). Since these reports

were published, adjuvant chemotherapy with GEM has been the standard treatment in Japan for patients following resection of pancreatic cancer. However, few reports have described the optimal regimens for patients who suffer relapse after adjuvant chemotherapy. In the present study, we retrospectively evaluated the efficacy and safety of S-1, an oral fluoropyrimidine derivative, as second-line chemotherapy for patients suffering disease relapse after adjuvant chemotherapy with GEM.

S-1 is an oral anticancer drug consisting of tegafur, a prodrug of 5-FU, and two biochemical modulators, 5-chloro-2,4-dihydroxypyridine and potassium oxonate (11). S-1 has been shown clinically to exert potent antitumor activity against various solid tumors (12-15). Okusaka *et al* have reported that S-1 is a promising agent for advanced pancreatic cancer, with a response rate of 37.5% and an MST of 9.2 months (16) In our present study, the MST after recurrence was prolonged for up to 11.4 months by S-1 administration. The median progression-free survival time after administration of S-1 was estimated to be 5.4 months. Results show that second-line chemotherapy with S-1 was capable of maintaining progression-free survival for approximately 6 months, but also extended survival for an additional 6 months. This may have been due to the fact that the toxicity of S-1 was sufficiently mild to allow the introduction of third-line chemotherapy.

In general, S-1 should be administered orally for 28 conse-cutive days, followed by a 14-day rest. However, the incidence of adverse reactions tended to be high (83.2%), and 20.3% of all adverse reactions were reported to be of grade 3 or more severe (12,16). Therefore, certain previous reports have proposed that S-1 should be administered for 2 weeks, followed by a 1-week rest, rather than for 4 weeks followed by a 2-week rest. Tsukuda *et al* have reported that, in patients with advanced head and neck cancer, a 2-week administration of S-1 followed by a 1-week rest was safer and more tolerable than 4-week administration followed by a 2-week rest (18). With regard to the administration of S-1 for advanced or recurrent gastric cancer, Kimura *et al* have reported that the rate of adverse reactions was 77% in the 2-week regimen, compared with 93% for the 4-week regimen. They also reported that the total 6-month compliance for S-1 was much more favorable for the 2-week regimen than for the 4-week regimen. These authors concluded that the 2-week regimen may mitigate adverse reactions and prolong the medication period (19). In the present study, S-1 was administered orally for 14 consecutive days, followed by a 7-day rest (2-week regimen). Neither hematological nor non-hematological adverse events were frequent. Severe adverse effects (grade 3/4) were almost not evident, and the medication time was therefore prolonged. This may have contributed to prolonging not only progression-free but also overall survival.

S-1 administration was not capable of prolonging the OAS of patients who had suffered relapse in the form of either peritoneal dissemination or liver or lung metastasis, and was effective only for local recurrence. S-1 administration allowed patients who had suffered local recurrence to survive longer than those who continued with GEM, or received best supportive care. In a phase II study report, Okusaka *et al* stated that S-1 administration was effective against metastatic pancreatic cancer. In their study, although 90% of patients had liver metastasis, a relatively long MST (9.3 months) was observed (16). In the present study, as only a small number of patients developed relapse in the form of liver metastasis, the effectiveness of S-1 may not have reached a significant level.

In conclusion, following not only major surgical treatment, but also cancer relapse, patients experience a relatively severe condition. S-1, an oral anticancer drug, is capable of maintaining a reasonable quality of life under such conditions (20). Since this study revealed a promising anticancer effect of S-1 and a significantly long survival time, S-1 is a potentially beneficial drug for second-line chemotherapy following adjuvant chemotherapy with GEM in patients with pancreatic cancer.

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Results of Hepatic Arterial Infusion Chemotherapy in Patients with Unresectable Liver Metastases

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Keywords
Unresectable liver metastases · Colorectal cancer · Hepatic arterial infusion chemotherapy, HAIC

Summary
Background: Colorectal cancer most commonly metastasizes to the liver. However, in patients with liver metastases precluding radical resection, we still have no other choice but to depend almost completely on anticancer chemotherapy. We report the results of hepatic arterial infusion chemotherapy (HAIC) in patients with multiple unresectable metastases throughout the liver and likely to develop liver failure in the near future. **Patients and Methods:** A total of 284 advanced colorectal cancer patients were treated. Of these patients, 40 and 24 had synchronous and metachronous liver metastases, respectively. Of these liver metastasis patients, 27 had unresectable metastases. 14 of the patients with unresectable liver metastases (likely to develop liver failure in the near future) but without extrahepatic lesions underwent HAIC. The chemotherapy regimen consisted of 5-fluorouracil 600 mg/m^2 and leucovorin 250 mg/m^2. **Results:** HAIC resulted in a complete response, partial response, stable disease, and progressive disease in 2, 7, 3, and 2 patients, respectively. The 1- and 2-year survival rates were 79 and 50%, respectively. **Conclusion:** Colorectal cancer patients with unresectable liver metastases without extrahepatic lesions and likely to develop liver failure in the near future showed relatively good results with no serious side effects. We suggest that HAIC is an effective treatment in selected patients.

Schlüsselwörter
Nicht resektable Lebermetastasen · Kolorektales Karzinom · Hepatisch intraarterielle Chemotherapie, HIC

Zusammenfassung
Hintergrund: Kolorektale Karzinome metastasieren am häufigsten in die Leber. Bei Patienten mit Lebermetastasen, die eine Radikalresektion ausschließen, ist jedoch die Chemotherapie nach wie vor die einzige Therapieoption. Wir berichten hiermit von den Ergebnissen, die mit der hepatisch intraarteriellen Chemotherapie (HIC) bei Patienten mit multiplen, nicht resektablen Metastasen in der gesamten Leber und bevorstehendem Leberversagen erzielt wurden. **Patienten und Methoden:** Insgesamt wurden 284 Patienten mit fortgeschrittenem kolorektalem Karzinom behandelt. Bei 40 Patienten bestanden synchrone und bei 24 Patienten metachrone Lebermetastasen, die in 27 Fällen nicht resektabel waren. 14 Patienten mit nicht rektablen Lebermetastasen (und bevorstehendem Leberversagen), aber ohne extrahepatische Läsionen erhielten HIC. Das chemotherapeutische Regime bestand aus 5-Fluorouracil 600 mg/m^2 und Leucovorin 250 mg/m^2. **Ergebnisse:** HIC führte zu komplettem Ansprechen, partiellem Ansprechen, Krankheitsstabilisierung bzw. Kranksheitsfortschreiten bei 2, 7, 3 bzw. 2 Patienten. Das 1- bzw. 2-Jahres-Überleben waren 79 bzw. 50%. **Schlussfolgerung:** Patienten mit einem kolorektalen Karzinom und nicht resektablen Lebermetastasen, bei denen keine extrahepatischen Läsionen bestehen und baldiges Leberversagen zu erwarten ist, zeigten ein relativ gutes Ansprechen ohne ernsthafte Nebenwirkungen. Wir sind der Ansicht, dass HIC eine effektive Behandlung bei selektierten Patienten ist.

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Introduction

The most commonly involved organ for metastasis and recurrence in colorectal cancer is the liver, which affects the prognosis [1–4]. Surgical removal has the best outcome of all treatments for resectable liver metastases, and chemotherapy is the first-choice therapy for unresectable cases [5–10]. The main administration routes of chemotherapy are systemic administration and hepatic arterial infusion chemotherapy (HAIC). The advantages of HAIC are: i) the concentration of the drug that reaches the tumor is higher; ii) a reduced drug concentration in systemic organs due to drug metabolism in the liver decreases adverse drug reactions, and the maximum dosage can be increased [11–13]. Therefore, it is suggested that the efficacy of HAIC is higher in patients with only liver metastases. We administered HAIC to patients with unresectable liver metastases and no extrahepatic lesions, in whom hepatic failure was likely to occur due to extensive metastases.

Patients and Methods

A total of 284 advanced colorectal cancer patients were treated at the University of Fukui Hospital (Japan) between 2001 and 2005. Of these, 40 and 24 had synchronous and metachronous liver metastases, respectively. Of these liver metastasis patients, 27 had unresectable metastases (synchronous in 20 and metachronous in 7). 14 of the patients with unresectable liver metastases (constituting a prognostic factor) but without extrahepatic lesions underwent HAIC. In these patients, liver metastases had spread to both hepatic lobes and occupied at least 40% of the liver, as evaluated by computed tomography (CT) scan, and liver failure was likely to occur in the near future. All patients were evaluated for performance status (PS) according to the Eastern Cooperative Oncology Group scale. All patients had a PS of 0. This study was retrospectively analyzed.

A hepatic arterial infusion catheter with a side port was inserted through the right femoral artery using the Seldinger technique, and the catheter tip was placed in the gastroduodenal artery to allow drug flow from the side port into the hepatic artery. The gastroduodenal artery was coiled to prevent drug inflow, and the drug was allowed to flow into the hepatic artery under angiography guidance (fig. 1). A 5-french catheter (Sophysa Sa, Orsay, Cedex, France) was inserted intraluminally from the right femoral artery with a subcutaneously implanted reservoir. 14 patients were treated by HAIC via a subcutaneously implanted injection port. There were no complications that were considered to have been caused by surgical procedures. The chemotherapy regimen consisted of 5-fluorouracil (5-FU) 600 mg/m^2 and leucovorin (LV) 250 mg/m^2. A once-weekly infusion for 6 weeks was defined as 1 course. The patients underwent 4 courses of chemotherapy at the end of which response to treatment was evaluated by CT scan. After that, tumor status was assessed every 1–2 courses. All CT scans were reviewed by 2 radiologists. Response rates and adverse events were evaluated according to the RECIST criteria [14, 15] and Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, respectively. Complete response (CR) was defined as the disappearance of all disease. Partial response (PR) was defined as at least a 30% reduction in the sum of the longest diameters of all measured lesions by at least 4 weeks. Progressive disease (PD) was defined as an increase in lesions by 20% or greater, or the appearance of new lesions. Responses not falling into any of these categories were classified as stable disease (SD). When extrahepatic metastases were detected, and their presence was a prognostic factor, patients were converted from HAIC to systemic chemotherapy.

Fig. 1. A hepatic arterial infusion catheter with a side port was inserted in the gastroduodenal artery through the right femoral artery using the Seldinger technique, and the catheter tip was placed in the gastroduodenal artery.

Table 1. Intermittent hepatic arterial infusion of 5-fluorouracil and leucovorin

n	Response	Extrahepatic metastasis	Follow-up, months	Clinical outcome
1	CR	lymph node	52	death
2	PR	lung	16	death
3	CR		69	survival
4	SD	peritoneum	14	death
5	SD	peritoneum	26	death
6	PR	lung, bone	34	survival
7	PR		27	death
8	PR	lung	48	survival
9	PR		38	death
10	PR		17	death
11	PD	lung, lymph node	6	death
12	PR		14	death
13	SD	lung, lymph node	12	death
14	PD		10	death

CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Table 2. Tumor response

Patients, n	Response				Disease control rate, %
	CR	PR	SD	PD	
14	2	7	3	2	86

CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Results

HAIC resulted in CR, PR, SD, and PD in 2, 7, 3, and 2 patients, respectively (tables 1 and 2). Figure 2 shows the CT appearances of the 2 patients who achieved a CR. The first patient was a 55-year-old man with sigmoid colon cancer and multiple hepatic metastases, 5 cm in diameter, in both lobes of the liver (T3, N2, M1 (liver), stage IV). First, we locally controlled the sigmoid colon cancer by sigmoid colectomy, and the patient subsequently underwent HAIC for unresectable liver metastases (fig. 2a). After completion of 4 courses of

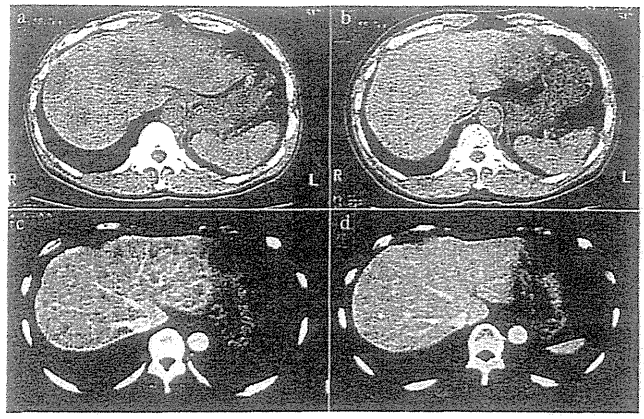

Fig. 2. Abdominal computed tomography of 2 patients. **a,b** Case 1: multiple liver metastases **a** before treatment, and **b** after treatment when no metastases could be detected; **c,d** Case 2: multiple liver metastases **c** before treatment, and **d** after treatment when no metastases could be detected.

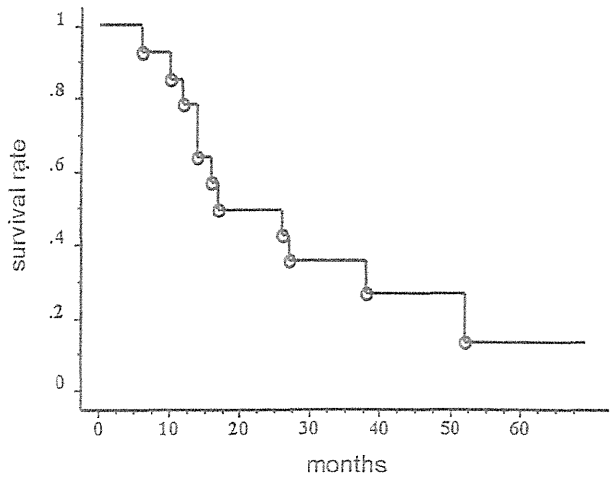

Fig. 3. Overall survival rate for 14 patients.

treatment, no metastases could be detected by CT (fig. 2b). Subsequently, the patient received pyrimidine fluoride anticancer drugs, and has shown no signs of exacerbation for 69 months. No adverse events were observed. The second patient (figs. 2c and d) was a 57-year-old woman with rectal cancer and multiple hepatic metastases, 2.5 cm in diameter, in both lobes of the liver (T3, N1, M1 (liver), stage IV). We locally controlled the rectal colon cancer by low anterior resection before administering HAIC for unresectable liver metastases. After completion of 4 courses of treatment, no metastases could be detected by CT (fig. 2d). No adverse events were observed. Subsequently, the patient received pyrimidine fluoride anticancer drugs, showed recrudescence of liver metastases and lymph node and splenic recurrence after 2 years, and underwent systemic chemotherapy (FOLFIRI: irinotecan/5-FU/LV, followed by FOLFOX: oxaliplatin/5-FU/LV). However, the patient's condition gradually deteriorated, leading to death from cancer 4 years and 6 months after surgery.

Table 3. Toxicity (CTCAE v3.0)

Toxicity	Grade 1–2, n (%)	Grade 3–4, n (%)
Diarrhea	2 (14)	0 (0)
Appetite loss	7 (50)	0 (0)
Pigmentation	6 (43)	0 (0)
Neutropenia	4 (29)	0 (0)

As shown in figure 3, the overall 1- and 2-year survival rates were 79 and 50%, respectively, and the mean survival time (MST) was 21.5 months. Side effects were observed in the form of grade 1–2 diarrhea, appetite loss, pigmentation, and neutropenia, but these were not serious. Quality of life (QoL) remained satisfactory, allowing administration of the scheduled 4 courses of chemotherapy (table 3). Extrahepatic metastases were detected after the start of HAIC and became a prognostic factor in 8 of the 14 patients, who were then converted from HAIC to systemic chemotherapy (table 1).

The 13 patients who developed extrahepatic metastases (lung, peritoneum, bone) but not liver failure, were started on systemic chemotherapy such as FOLFIRI or FOLFOX. The final MST was 18.5 months. No significant difference was noted between the survival time with HAIC and systemic chemotherapy.

Discussion

Liver metastasis is considered to be the decisive prognostic factor for colon cancer. It is thought that liver metastases are already present in approximately 10% of colon cancer patients at the time of the first surgery, and that multiple metastases are present in the liver as a whole in approximately 4% of patients [1–4].

There are currently various opinions regarding the indications for HAIC as a chemotherapeutic approach. Two such opinions are that this therapy is indicated: i) in the case of imminent liver failure due to extensive liver metastases; and ii) when there is metastatic liver cancer for which systemic chemotherapy would be ineffective. It has been reported that in the treatment of unresectable liver metastases HAIC improves the response rate compared to systemic chemotherapy, that hepatic artery infusion therapy maintains QoL, and that both response rate and survival rate are better with HAIC than with systemic chemotherapy [12]. Conversely, it has also been reported that, although HAIC improves the response rate compared to systemic chemotherapy, it does not show any beneficial effects on survival [16]. Outcomes with HAIC have thus been inconsistent.

The present study was carried out in order to investigate HAIC by focusing on 14 patients with unresectable liver

metastases that had spread to both hepatic lobes and occupied at least 40% of the whole liver, and for whom liver failure was considered to be the decisive prognostic factor. All adverse reactions, regardless of the symptoms, were rated as grade 1, with no serious adverse reactions of grade 3 or higher. QoL was maintained well. Both incidence and grade of adverse reactions were low when compared with the FOLFIRI and FOLFOX systemic chemotherapy regimens (table 3) [17, 18].

Among the present patients, the 1-year survival rate was 79%, the 2-year survival rate was 50%, and the MST was 21.5 months (fig. 3). These results were about the same as the 1-year and 2-year survival rates with the FOLFIRI and FOLFOX systemic chemotherapy regimens, and some of the patients survived for a relatively long period of time [17, 18]. Kemeny et al. [12] reported that there are many cases in which extrahepatic lesions appear although HAIC is able to control metastatic foci in the liver itself. We also observed development of extrahepatic lesions in 8 (57%) of the 14 patients, and it can be surmised that there is a limit to how much the survival rate can be increased with HAIC alone. The following scenario can be thought to explain the development of extrahepatic lesions in the case of HAIC. Pharmacologically, HAIC achieves a higher drug concentration in liver lesions when compared with delivery by systemic chemotherapy, resulting in good efficacy in relation to tumors. However, approximately 60% of the anticancer drug administered by HAIC is metabolized in the liver, which reduces the drug concentration delivered to the body as a whole and allows development of extrahepatic lesions. When efficacy was assessed after switching the treatment to systemic chemotherapy in the 8 patients who developed extrahepatic lesions, all were rated as having PD, indicating that treatment efficacy was poor. However, the anticancer drug concentrations that reached the extrahepatic lesions themselves were higher in the case of systemic chemotherapy when compared with HAIC. Accordingly, it is possible that the suppression of tumor progression was fairly good.

Kemeny et al. [19] reported a response rate of 88% and an MST of 22 months or more when patients with resectable liver metastases from colon cancer were treated with a combination of HAIC and systemic chemotherapy. The findings indicate that for patients with recurrence in other organs, which is a risk associated with HAIC alone, addition of systemic chemotherapy to the treatment regimen enables more effective suppression of cancer progression and prolongs survival.

Recently, molecularly targeted drugs such as bevacizumab, cetuximab and panitumumab have been developed, and they have been successful in further extending patient survival [20–22]. The mean survival time has been steadily extended since then, recently reaching approximately 30 months [20, 21]. However, to date, there are no reported large-scale trials showing clear improvements in outcome for HAIC of molecularly targeted drugs. This issue warrants more detailed study in the future.

Based on the study findings presented above, when consideration is given to efficacy against hepatic metastases (in patients likely to develop liver failure in the near future), adverse reactions, and QoL, HAIC is useful; however, when considering the risk of recurrence in organs other than the liver, systemic chemotherapy is necessary. Further study is required in order to effectively implement both of these treatment modalities and to determine whether it is possible to increase treatment efficacy and prolong survival, even in patients with unresectable liver metastases but without extrahepatic lesions.

Disclosure Statement

There were no conflicts of interest to declare.

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^{18}F-fluorodeoxyglucose Positron Tomography is Useful in Evaluating the Efficacy of Multidisciplinary Treatments for So-called Borderline Unresectable Pancreatic Head Cancers

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Abstract : Currently, computed tomography (CT) is widely used to evaluate the efficacy of treatments on tumor regression in unresectable pancreatic head carcinomas. Recently, ^{18}F-fluorodeoxyglucose positron emission tomography (PET) examination has been used for the initial diagnosis of pancreatic tumors, for diagnosis of distant metastasis, and for recurrences of pancreatic carcinomas. PET has also been used for the qualitative diagnosis of existing tumors. The current study was designed to observe if PET examination can be used to gauge the efficacy of multidisciplinary treatments, and to estimate the prognosis for unresectable pancreatic head carcinomas in similar clinical stages and during therapy. This was a prospective cohort study and included 18 cases. All cases were unresectable pancreatic head cancers diagnosed as TNM classification stage 3, and had undergone identical multidisciplinary treatment regimens. The level of tumor markers, tumor-size reduction, and maximum standardized uptake values (SUV_{max}) were correlated with prognosis. Pearson's correlation and Kaplan-Meyer survival rate curves were used for statistical analysis. Tumor-size reduction in CTs and the transition of tumor markers were not related to patient prognosis. Cases in which post-treatment SUV_{max} values were reduced to < 3.0 were correlated with a more favorable prognosis and demonstrated extended survival rates. PET examination can be used to estimate the prognosis of unresectable pancreatic head carcinomas which have undergone multidisciplinary treatments.

Key Words : FDG-PET, unresectable pancreatic cancer, SUV_{max}, multidisciplinary treatments, hyperthermia

Introduction

Excision rates for invasive pancreatic ductal carcinomas remain low, and the disease continues to be treated primarily with chemoradiotherapy. Consequently, the methods used to evaluate therapeutic

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efficacy are important. Using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, evaluation of tumor regression effects on target lesions is recommended. However, in cases of severe infiltrative pancreatic carcinoma which includes multiple non-target lesions (*e.g.* in the surrounding lymph nodes and nervous plexus), examination of an overall tumor response is difficult to evaluate with computed tomography (CT). Even after successful treatments, tumor reduction may appear inadequate due to copious fibrillary elements present in pancreatic carcinomas. In addition to this, changes in tumor marker levels may be inconsistent in pancreatic carcinomas, adding to the difficulty of judging the efficacy of radiotherapy and hyperthermic chemotherapy.

Recently, fluorodeoxyglucose positron emission tomography (PET) has been used in diagnostic imaging for several types of pancreatic carcinomas[1-4]. PET examinations have been used, not only for initial evaluations of differential diagnosis[3-5] and diagnosis of distant metastasis and recurrences, but also for qualitative diagnosis[6]. Several studies have shown that PET is useful for the characterization of pancreatic tumors, as well as for assessments of the efficacy of chemotherapy and outcomes[7,8]. The increased uptake of fluorine-18 fluorodeoxyglucose, due to enhanced glucose metabolism in cancer cells, is a sensitive marker of tumor viability. Because PET examinations evaluate the activity of cancer cells rather than tumor size, the current study was designed to investigate the usefulness of PET examinations in the evaluation of therapeutic effects and prognosis of unresectable pancreatic head carcinomas. This differs from other recent reports because the subject cases examined here were limited to pancreatic head cancers in which excision was difficult and which were accompanied by massive local invasion without distant metastasis[8-11].

Subjects and methods

Characteristics of all the cases are shown in Table I. This study included 18 patients (6 females and

Table I. Response of tumor markers, CT, PET and overall survival times.

Case No.	Age/ Sex	Stage (UICC)	CRT (%)	CA19-9 (u/ml)		DUPAN-2 (U/ml)		SUV_{max}		RRS (%)	ST (months)	Prognosis
				BT	AT	BT	AT	BT	AT			
1	75M	III	6.3	5	5	386	99	5.5	1.3	76.4	38	Deceased
2	63M	III	-4.2	1,760	134	479	224	5.4	2.3	57.4	20	Deceased
3	61F	III	11	968	57	25	25	5.9	2.8	52.5	31	Deceased
4	77M	III	15	63	31	42	39	8.5	3.8	55.3	10	Deceased
5	64M	III	21	12	5	25	25	6.9	2.6	47.8	31	Deceased
6	71M	III	21	501	91	25	25	6.9	3.7	46.4	7	Deceased
7	57F	III	19	342	20	25	31	3.5	2.5	28.6	26	Deceased
8	64M	III	0	1,310	62	150	46	4.9	3.1	36.7	9	Deceased
9	49M	III	3.1	1,350	51	196	64	4.5	2.4	46.7	64	Living
10	79M	III	11	365	104	66	27	8.4	3.9	53.6	30	Deceased
11	72F	III	16	645	45	217	133	4.3	2.1	51.2	27	Deceased
12	74F	III	17	5	5	1,600	575	6.1	3.9	36.1	9	Deceased
13	72F	III	18	125	32	1,120	25	4	2.5	37.5	15	Deceased
14	81M	III	25	4,330	86	25	25	3.2	2.1	34.4	20	Deceased
15	62M	III	26	1,100	20	108	25	11.1	4.6	58.2	13	Deceased
16	66M	III	26	3,570	71	66	27	4.6	2.1	54.3	14	Deceased
17	70M	III	32	2,150	36	42	39	4.1	3.1	24.4	14	Deceased
18	73F	III	17	1,940	994	994	20,000	5.1	4.5	31.4	5	Deceased

CRT: Contraction rate of a tumor; RRS: Reduction rate of SUV_{max}; BT: before treatment; AT: after treatment; ST: survival time.

12 males). The patients' average age was 61 years old (range: 49 to 79 years), and the Karnofsky performance status (PS) at the baseline was ≧ 80%. Subject cases were unresectable pancreatic head cancers diagnosed as TNM classification stage 3 (T4 NX M0) from imaging and operative findings. All cases received the same multidisciplinary treatment and had a measurable pretreatment target lesion evaluated with both CT and PET imaging. Laparotomy was performed on all cases to clarify presence of metastases in the liver and peritoneum. Needle biopsies revealed adenocarcinoma in all cases. For cases with obstructive jaundice (17 cases) and duodenal wall invasion (16 cases), bypass surgery was performed. Blood glucose levels were measured three times per day, and controlled at 150 mg/dl or less with insulin. Outcome parameters in this study were the change in the longest axis of the tumor in multidirectional computed tomography (MDCT) imaging, the change of maximum SUV values (SUV_{max}) in PET imaging, and changes in tumor markers. These examinations were performed both prior to treatments and in the third month after treatments. The longest axis of the target lesion in the pancreatic head was measured using a horizontal section (3 mm slice thickness) in dynamic contrasting MDCT. All patients were examined with a high-resolution, whole-body PET scanner. The patients fasted for more than 4 h before an intravenous injection of ^{18}F-FDG, and the acquisition of whole-body PET images was started 50 min after the injection. Data acquisition was performed in a two-dimensional imaging mode. Cut-off values for SUV_{max} were defined as 3.0. With regard to tumor markers, CA 19-9 (normal < 37 U/ml) was used as the primary marker, and DUPAN-2 (normal < 150 U/ml) was used in cases where no rise of CA 19-9 was observed. Observations were continued for 4.5 years or until the patients died, excluding one example. In addition to the above measurements, the relationship between these variables and disease prognosis was examined using Pearson's coefficient and log-rank test.

Multidisciplinary treatments

Multidisciplinary treatments in this department were as follows: biliary and/or intestinal tract bypass surgery with intra-operative irradiation (8-12 cm in diameter, 20-25 Gy, 15 MeV); postoperative external irradiation (25 times, for a total of 50 Gy); hyperthermia treatments using a Thermotron-RF8 (Yamamoto Vinita Co., Ltd., Osaka, Japan) with CDDP (a total of 100-120 mg) and MMC (a total of 16-20 mg) (50 min, 1 time per week, 4-5 times); and systemic chemotherapy using 5-fluorouracil (5-FU) (a total of 14 g) for 28 days (Fig. 1). Second-line therapies were not initiated until therapeutic efficacies were evaluated at the 3rd month post-treatment.

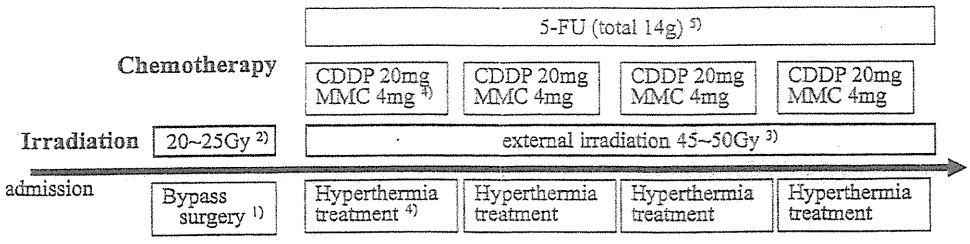

Fig. 1. 1) Biliary and/or gastric bypass surgery. 2) Intra-operative irradiation (20-25 Gy, 15 MeV). 3) Postoperative external irradiation (25 times, total of 50 Gy). 4) Hyperthermia treatment (RF-8) with CDDP (total of 100-120 mg) and MMC (total of 16-20 mg) (1 time per week, 4~5 times). 5) Systemic Chemotherapy using 5 FU (total of 14 g) for 28 days.

Hyperthermia treatments were delivered with an 8 MHz capacitive heating device. An electromagnetic field with power ranging from 1,200 to 1,400 W was used, depending on the patient's condition. This was applied between a pair of electrodes with diameters of 25 cm or 30 cm which were placed on the opposite sides of the target area. A saline solution maintained at 10 degrees Celsius degrees was circulated in boluses to avoid overheating of the skin.

Multidisciplinary treatments in this department appear to provide the following multiple advantages :

(A) Biliary bypass surgery helps prevent the occurrence of acute cholangitis and obstructive jaundice. Serious cholangitis developing during chemotherapy results in the interruption of treatment and adversely affects prognosis.

(B) Gastrointestinal anastomosis can help prevent duodenal stenosis or obstruction due to enterocolitis from radiation and tumor invasion.

(C) Hyperthermia is effective for hypoxic lesions with little effect on radiotherapy, and increases the uptake of anticancer drugs into tumor tissues.

(D) Irradiation (intra-operative and post-operative irradiation ; total 75 Gy) provides not only antitumor effects, but also a reduction of cancer induced pain.

The therapeutic synergism of these multiple and complementary modalities appears to offer good results.

Results

No new metastases were found in any cases until treatment efficacy was evaluated at the 3rd month post-treatment. The average diameter of target lesions was 27 mm (range : 19 to 46 mm). Survival times ranged from 5 to 54 months. After undergoing multidisciplinary treatments, the average regression rate of the tumors was 15.6% (range : −4.2 to 32%) (Table I). A significant correlation between tumor reduction and prognosis was not observed (Pearson's r=-0.290, p-value=0.2636) (Fig. 2). Levels of CA

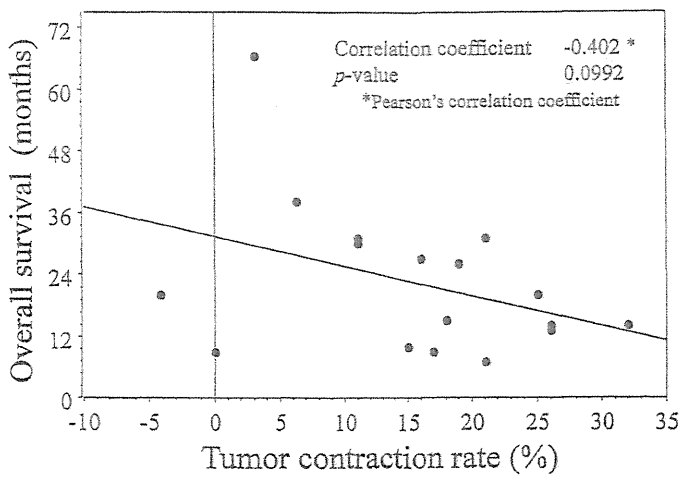

Fig. 2. Correlation of tumor reduction and prognosis. A significant correlation between the contraction rate of the pancreatic head cancer and overall survival was not observed (Pearson's r=-0.402, p-value=0.0992). *Pearson's correlation coefficient.

19-9 decreased in all cases post-treatment, and reached normal values in five cases (Table I). Similarly, no significant correlation was observed between the movement of tumor markers towards normal values and prognosis (Fig. 3). The average SUV_{max} value prior to treatment was 5.2 (Table I). After treatment, the SUV_{max} value decreased in all cases, and decreased to < 3.0 in seven cases. A significant correlation was found between post-treatment SUV_{max} values and a favorable prognosis (Pearson's r= -0.694, p-value=0.0014) (Fig. 4). In contrast, no correlation was found between reduced values of

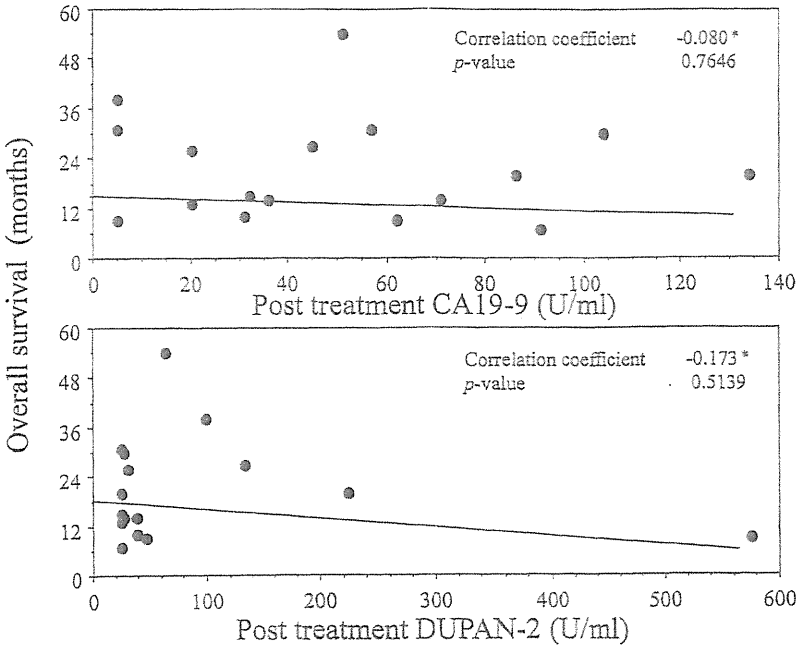

Fig. 3. Correlation of post-treatment tumor markers and prognosis. A significant correlation between post-treatment tumor markers (CA19-9 and DUPAN-2) and overall survival was not observed (Pearson's r=-0.402, p-value=0.0992). *Pearson's correlation coefficient.

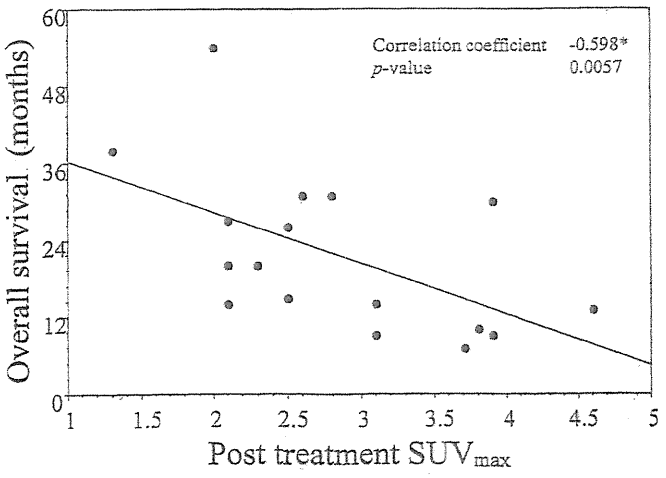

Fig. 4. Correlation of post-treatment SUV_{max} values and prognosis. A significant correlation was found between post-treatment SUV_{max} values and prognosis (Pearson's r=-0.598, p-value= 0.057). *Pearson's correlation coefficient.

SUV_{max} and the overall survival (OS) time (Fig. 5). Fig. 6 shows patient survival curves divided into regions for $SUV_{max} < 3.0$ and $SUV_{max} \geqq 3.0$. There were significant differences between overall survival times for patients with post-treatment values of $SUV_{max} < 3.0$, and for $SUV_{max} \geqq 3.0$ (log-rank test ; p-value=0.032). The median survival time for patients with post-treatment values of $SUV_{max} < 3.0$ increased compared to those with a value of $SUV_{max} \geqq 3.0$ (26 vs. 9 months).

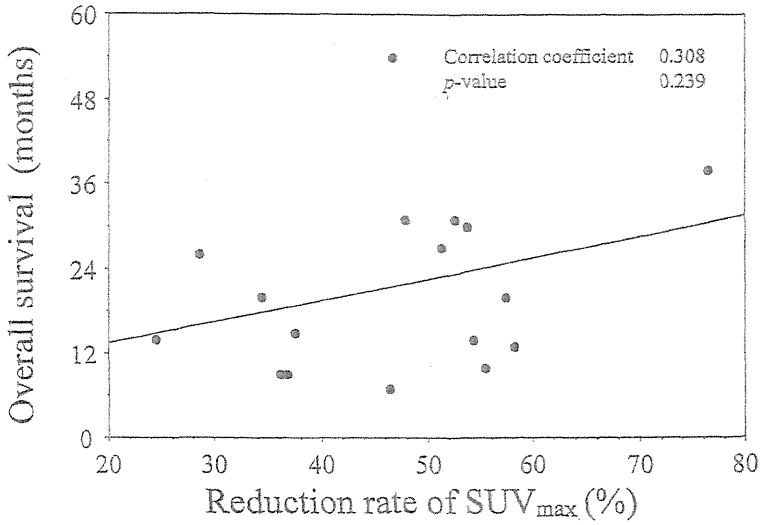

Fig. 5. Correlation of the reduction rate of SUV_{max} and prognosis. No significant correlation was found between the reduction rate of SUV_{max} and prognosis (Pearson's r=0.308, p-value=0.239).

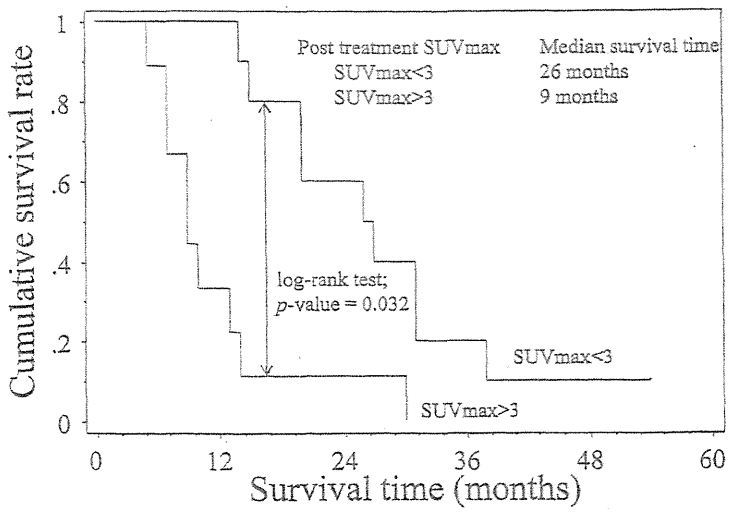

Fig. 6. Kaplan-Meier plot of overall survival times (OS) shows patient survival curves divided into $SUV_{max} < 3.0$ and $SUV_{max} \geqq 3.0$. There were significant differences between overall survival times (OS) for patients with post-treatment $SUV_{max} < 3.0$ and those with $SUV_{max} \geqq 3.0$ (log-rank test ; p-value=0.032). Median survival times of patients with post-treatment $SUV_{max} < 3.0$ increased compared to those with $SUV_{max} \geqq 3.0$ (26 vs. 9 months).

Discussion

Currently, the prognosis for unresectable pancreatic head carcinomas is dependent upon the degree of therapeutic response and the presence of distant metastasis. Following conventional treatment protocols, pancreatic carcinomas with distant metastases require systemic chemotherapy. In this study, multidisciplinary treatments were used for cases of pancreatic head cancer in which excision was difficult and which were accompanied by massive local invasions, including to the para-aortic lymph nodes. In short, these were severe cases for which a total, curative resection was considered impossible. The ultimate goal of this multidisciplinary treatment regimen was not simply tumor reduction with systemic chemotherapy, but rather annihilation of the primary carcinoma tissue itself. A sufficient control of the primary lesion is most important for reducing distant metastases and in obtaining long-term survival times. Currently, it is generally accepted that gemcitabine should be the standard first line chemotherapy drug for pancreatic cancer. However, 5-FU, platinum and MMC were used for these patients because using these drugs as the chemotherapeutic regimen of choice provided better hyperthermic sensitivity. Recently, studies have examined the hyperthermic sensitivity of GEM[12] and the timing of hyperthermia in relation to GEM treatments[13]. The question of whether hyperthermia using GEM provided improvements in tumor regression effect on target lesions was evaluated.

Following RECIST guidelines for solid tumors, tumor regression in the target lesions was evaluated, but in this study, no correlation was found between tumor reduction observed in CT and prognosis. PET examinations may be advantageous when compared to CTs for several reasons. First, retroperitoneal invasion and para-aortic lymph node metastasis often coalesce together in unresectable pancreatic cancer, making CT measurements of nearby target lesions difficult. With PET, this is done more accurately and reliably by measuring the SUV without concern for lesion positions. Second, even if a treatment achieves large-scale tumor cell destruction, because pancreatic carcinomas often have many fibrous components, the tumor may be difficult to shrink. In addition, there is a possibility that edema and inflammation due to irradiation and hyperthermia therapy may increase the tumor size. PET examination can evaluate carcinomatous metabolic activity without regard for potentially misleading issues of size. Finally, PET examinations allow the evaluation of distant metastasis simultaneously, and a more accurate disease localization can be achieved with PET/CT[14,15].

The evaluation method used to measure tumor markers and SUV_{max} is important. When the correlation with overall survival times is evaluated, measured values should be used, in contradiction to a previous study which used the response ratio of tumor markers and SUV_{max} according to European Organization for Research and Treatment of Cancer (EORTC) guidelines[14]. Cancer cells are certain to exist when the post-treatment SUV_{max} value is three or more, even if the response rate of SUV_{max} with treatment is 50%.

Reductions in tumor markers were thought to result from the efficacy of therapy, but CA 19-9 and DUPAN-2 were positive in 83.3% and 55.6% of the cases, respectively. PET examination was useful in cases of pancreatic carcinoma in which tumor markers did not rise. When tumor markers increase along with treatment, there is a high probability of distant metastases being present which were not seen in imaging. In addition, interpretation of a decrease state requires care and attention to the possibility that treatment of bile duct obstructions and acute cholangitis may have reduced tumor marker levels.

Pretreatment values of $SUV_{max} \geqq 3$ in PET imaging is necessary for the optimal evaluation of the therapeutic efficacy of pancreatic cancer treatments. In several studies, correlations between pre-treatment SUV_{max} values and the prognosis are still controversial[1,8], even though a significant correlation was not found in this study. Two studies showed that there was a significant correlation between a prognosis and FDG uptake after treatment, but that there was no relationship between prognosis and FDG uptake before treatment. Oku et al reported that FDG-PET imaging after radiotherapy is a good prognostic indicator for rectal cancer[15], and Brun et al reported the same results for head and neck squamous cell carcinomas[17]. Because PET examinations can simultaneously detect distant metastases (aside from intraperitoneal metastases) which may alter therapeutic strategies, such imaging should be strongly encouraged prior to treatment. With regard to prognostic predictions using SUV values of the primary lesion, SUV values should be evaluated in similar clinical stages and therapies. Even if the SUV_{max} value is less than 3 before treatment, a cancer with distant metastasis or a large size would show a worse prognosis. PET imaging has a sensitivity of 82-100% and a specificity of 67-100% for pancreatic carcinomas[18-22]. Previous several studies reported that the presence of tumors less than 2 cm in diameter and the presence of hyperglycemia may decrease diagnostic accuracy[23,24]. Tumor cellularity is one of factors influencing FDG uptake. Scirrhous tumors have a low cellularity, and thus should show lower accumulations of FDG[25,26]. In general, unresectable pancreatic carcinomas have a large size (in this study, the average tumor diameter was 27 mm) and severe local invasions, and the occurrences of false negatives from PET imaging may be low[27]. Blood glucose levels should be noted in evaluations of PET examinations. The effect of glucose levels in FDG-PET oncology is known, but the management of non-fasting patients or diabetic patients remains controversial. In this study, four subjects had diabetes mellitus, but no false negatives were found, suggesting that pre-examination glucose control may assist in the reduction of false negatives. In particular, in the presence of chronic hyperglycemia (not acute hyperglycemia), the adverse effect caused by high glucose levels was minimal in human adenocarcinoma cell models, except for small lesions (15 mm in size)[28,29]. Friess et al suggested that there was no significant difference between the high blood glucose group and the low one[30]. The only necessity is an instruction to patients to fast, and to check glucose levels immediately prior to FDG injection[31].

In order to avoid the influence of localized inflammation and edema from radiotherapy and hyperthermia treatments, PET imaging was performed during the 3rd month after the final treatment in the protocol. In addition, no additional chemotherapy was given during this period, because it is very likely that chemotherapy decreases carcinomatous carbohydrate metabolism, potentially altering PET accuracy. PET examination in the setting of recent chemotherapy may substantially increase the rate of false negative images.

In conclusion, FDG-PET examinations may be superior to tumor regression measured with CT and measurements of tumor markers after treatments. FDG-PET can be used to evaluate the efficacy and prognosis of unresectable pancreatic carcinoma (TNM classification stage3) cases in the 3rd month after a multidisciplinary treatment protocol. In addition, if post-treatment SUV_{max} values can be reduced to less than 3.0 by multidisciplinary treatments, this may translate to a more favorable prognosis.

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Abstract in Japanese

切除不能膵癌の集学的治療効果判定における ^{18}F-fluorodeoxyglucose positron tomography の有用性

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要　　旨：通常，切除不能膵癌における原発巣の治療効果判定にはCT検査を用いることが多い．最近，^{18}F-fluorodeoxyglucose positron tomography (以下 PET) 検査は膵癌の存在診断だけでなく，腫瘍の質的評価が可能なため，遠隔転移や再発部位の検索にも用いられている．本研究では，集学的治療を受けた切除不能膵癌症例の治療効果と予後の判定にPET検査が有用かを検討した．この研究はprospective cohort studyである．対象の18症例全てが，TNM分類Stage3の切除不能膵頭部癌である．集学的治療としてバイパス手術，放射線療法(術中と術後)，温熱化学療法の全てを施行されている．効果判定の項目として，腫瘍マーカー値，腫瘍の縮小率，SUV_{max} (maximum standardized uptake value) を用い，それらと患者予後との関係を検討した．統計学的解析にはピアソン相関とKaplan-Meyer生存曲線を使用した．CT検査による腫瘍サイズの縮小率と腫瘍マーカーの推移は患者予後と相関しなかった．治療後のSUV_{max}は予後と良く相関し，SUV_{max} 3未満の症例は，特に生存期間が延長した．PET検査は集学的治療を施行された切除不能膵癌の予後評価に有用である．

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and "Exact Test" produced by Prof. S. Aoki (http://aoki2.si.gunma-u.ac.jp/exact/exact.html). The χ^2 test, Fisher exact test probability, and Mann-Whitney U test were used as appropriate. $P \leq 0.05$ was considered as statistically significant.

RESULTS

The incidence of chyle leak was 8.0% (11/138) in all patients. The timing of start for enteral feeding was significantly earlier in the fast-track group (median, day 3; range, days 3–4) compared with the traditional group (median, day 5; range, days 3–16; $P < 0.001$). Incidence of chyle leak was significantly increased in the fast-track group compared to the traditional group (13.3% vs 1.6%, respectively, $P = 0.004$).

In comparison of clinical features, there were no significant differences between the patients with chyle leak and those without chyle leak except for early enteral feeding (timing of enteral feeding start was postoperative day 3 or 4; Table 1).

Five-day fast therapy with total parenteral nutrition was effective for all of our patients with chyle leak. No patients required the use of somatostatin analogs. Overall length of the hospital stay of the patients in the fast-track group without drain infection was significantly longer if there was a chyle leak (median hospital stay, 21 days; range, 15–28 days) compared with the patients without chyle leak (median hospital stay, 11 days; range, 5–23 days; $P < 0.001$).

DISCUSSION

In this study, we showed that the overall incidence of chyle leak in the patients who underwent DP was 8.0%. Only early enteral feeding was associated with the development of chyle leak. Chyle leak was one risk factor for prolonged hospital stay but could be successfully treated with dietary measures.

Several authors suggest lymph node dissection, neoplastic diseases, and chronic pancreatitis as risk factors for the development of chyle leak.[6–8] Malik et al[5] and van der Gaag et al[8] doubt that early enteral feeding affected the incidence of chyle leak in patients who underwent pancreatic resection (PD and DP). Our study showed that early enteral feeding was associated with chyle leak after DP.

Malik et al suggested that the mechanism of action leading to chyle leak may be due to the lipid content of the enteral feed, which may keep the visceral lymphatic channels that have been divided as part of the standard resection open, thus leading to the persistent chyle leak.[5] Chyle leak did occasionally occur despite a period of gut rest; however, it was during this period of early feeding that chyle leak became most problematic. This leads to the recognition that the likely source of this chyle was an early stimulation of the lymphatic drainage of the small intestine. Our results support this hypothesis. Our results also suggest that the visceral lymphatic channels may have remained open at least until 4 days postoperatively because all of our patients with chyle leak were started on enteral feeds on day 3 or 4.

There is little doubt that enteral nutrition carries advantages over total parenteral nutritional support. It is also easier to administer. There may be preservation of gut barrier function with enteral feeding, and it may prevent structural alterations induced by starvation and injury. However, several randomized controlled trials demonstrated that immediate postoperative enteral feeding through a jejunostomy tube is not beneficial in patients undergoing PD and is even associated with impaired respiratory mechanics and postoperative mobility.[10]

We did not deny a clinical benefit of the fast-track program for DP; however, further studies would be needed for establishing the appropriate time to start enteral feeding after pancreatic surgery.

Several authors have also shown that surgical devices such as ultrasound scissors or a vessel sealing system were not useful in preventing chyle leak.[5] In our study, we could not find benefit for using these devices in preventing chyle leak.

In conclusion, the overall incidence of chyle leak in the patients who underwent DP was 8.0% in our institute. Early enteral feeding may be associated with postoperative chyle leak. Further investigation is needed for establishing the appropriate time to start enteral feeding after DP.

The authors declare no conflict of interest.

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Long-Term Results of Surgical Resection After Preoperative Chemoradiation in Patients With Pancreatic Cancer

To the Editor:

We would like to report the long-term results of surgical resection after preoperative chemoradiation therapy (CRT) for patients with pancreatic cancer that extended beyond the pancreas.