Original Paper

Hepatic Arterial Infusion of 5-Fluorouracil and Extrabeam Radiotherapy for Liver Metastases from Pancreatic Carcinoma

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ABSTRACT

Background/Aims: To examine the efficacy and safety of a combined modality therapy consisting of hepatic arterial infusion of 5-fluorouracil and external-beam radiotherapy in patients with advanced pancreatic carcinoma.

Methodology: Hepatic arterial infusion chemotherapy consisted of 5-FU 1000mg/m^2 administrated as a 5-hr continuous infusion once weekly. External-beam radiotherapy (total dose, 50Gy; 2Gy/day) was delivered to the pancreas tumor concurrently for 5-6 weeks. Seventeen patients with no distant metastases except to the liver were enrolled in this study.

Results: Patients received a median of 13 cycles of chemotherapy. Sixteen of 17 patients received a total radiotherapy dose of 50Gy. In one patient, treatment was discontinued after 24Gy of radiotherapy and 2 cycles of chemotherapy because of progressive disease. Nausea and vomiting were the most common types of toxicity. Grade 3 or worse toxicity was observed in 2 patients. Four patients developed gastroduodenal ulcers. Of the 16 patients, 7 (41%) showed a partial response, and 9 (53%) showed no change. The median overall survival was 4.5 months and 1-yr overall survival of 11.8% was observed.

Conclusions: The combined therapy is active and well tolerated, but results in a poorer prognosis, in spite of its high initial response rate.

KEY WORDS: Pancreatic carcinoma; Liver metastasis; Hepatic arterial infusion; 5-fluorouracil; Radiotherapy

ABBREVIATIONS: Hepatic Arterial Infusion (HAI); External-Beam Radiotherapy (EBRT); 5-fluorouracil (5-FU); Partial Response (PR); No Change (NC); Progressive Disease (PD); Carbohydrate Antigen 19-9 (CA19-9); Computed Tomography (CT); World Health Organization (WHO)

INTRODUCTION

Liver metastasis is a common progression of pancreatic carcinoma and the prognosis of patients in whom it occurs is extremely poor. Although gemcitabine has been shown to be an active agent in the treatment of advanced pancreatic carcinoma, it has not been observed to adequately prolong patient survival (1). Hepatic arterial infusion (HAI) of 5-fluorouracil (5-FU) has been performed in several clinical trials in patients with liver metastasis from colorectal cancer and the findings indicate that HAI results in a high response rate (2,3). In addition, with regard to pancreatic carcinoma, recent study of HAI chemotherapy after vascular supply distribution via superselective embolization has also demonstrated promising results (4). At the present time, combined external-beam radiation therapy (EBRT) and 5-FU therapy are considered standard treatment for locally advanced pancreatic carcinoma (5-7). Thus, EBRT combined with HAI therapy using 5-FU is thought to have high clinical applicability and may prove beneficial to patients with pancreatic carcinoma without distant metastases, except to the liver. We therefore conducted a phase 2 study of combined EBRT and HAI using 5-FU to clarify the efficacy and safety of this treatment in patients with pancreatic carcinoma with metastasis restricted to the liver.

METHODOLOGY

Seventeen patients with advanced pancreatic cancer complicated by liver metastasis underwent HAI chemotherapy and EBRT between February 1998 and November 2000 at the National Cancer Center Hospital East. The eligibility criteria for inclusion in this study were: 1) histological proof of adenocarcinoma of the pancreas, 2) no distant metastases on computed tomography (CT) staging, except to the liver, 3) no previous anti-cancer treatment, 4) a performance status of 0, 1, or 2 according to the World Health Organization (WHO) grading system (8), 5) adequate bone marrow functioning (blood cell count of 4,000 or greater, platelet count of 100,000 or greater, and hemoglobin of 10g/dL or greater), adequate renal function (serum creatinine level of less than 1.1mg/dL), and adequate hepatic function (serum bilirubin level of less than 3.0mg/dL, serum alanine and aspartate transaminase levels of less than 200 IU/L), 6) no serious complications, and 7) receipt of written informed consent from the patient. Percutaneous biliary drainage was performed in patients with obstructive jaundice, and patients were required to have a total serum bilirubin level of less than 3.0mg/dL before initiation of treatment. Patient characteristics are summarized in **Table 1**.

Hepatic arteriography was performed prior to

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TABLE 1 Patient Characteristics

Characteristic	No. of patients (%)
Gender	
Male	11 (65%)
Female	6 (35%)
Median age (range)	59 (50-77)
WHO performance status	
0	5 (29%)
1	10 (59%)
2	2 (12%)
Location of primary tumor	
Head	5 (29%)
Body/tail	12 (71%)
Median CEA, ng/mL (range)	8.6 (0.8-185)
Median CA 19-9, U/mL (range)	827 (21-14552)

WHO: World Health Organization;
CEA: carcinoembryonic antigen;
CA 19-9: carbohydrate antigen 19-9.

catheter placement to determine the degree of arterial blood supply to the liver. The gastroduodenal and right gastric arteries of all patients were ligated with steel coils to prevent drug perfusion into the stomach and the duodenum. A catheter was positioned in the gastroduodenal artery. Catheters were placed via the left subclavian artery. The port was connected to the catheter and implanted in the subcutaneous space of the left chest wall.

After implanting the catheter and the port, 5-FU (1,000mg/m^2) mixed with 100mg of hydrocortisone (Solu-Cortef; Pharmacia & Upjohn, New Jersey, USA) and 5,000 U of heparin, was administrated over 5 hours through a battery-operated ambulatory infusion pump. After drug infusion, 20mL of saline and 5,000 U of heparin were infused through the pump. Cycles of intra-arterial infusion were repeated once weekly, unless there was evidence of disease progression or unacceptable toxicity levels.

Radiation therapy was delivered using the conformal, arc rotation technique to deliver a 10-MV X-ray, in order to achieve a total dose of 50Gy, given in 25 fractions over 5 weeks. The radiation field included the primary tumor and a 1- to 3-cm margin which covered the pancreaticoduodenal and celiac axis lymph nodes. This field was defined during treatment-planning CT one or two days before radiation therapy.

The toxicity of treatment was scored weekly according to WHO criteria (8). Both radiotherapy and chemotherapy were suspended if grade 3 toxicity was encountered, and resumed upon recovery to a grade 2 level of toxicity.

Follow-up CT was performed every month for 6 months, and every 2 months thereafter, in order to assess objective tumor responses according to WHO criteria. Local progression was diagnosed when the primary tumor was enlarged on CT, or when obstructive jaundice occurred after treatment. Overall survival was measured from the first day of treatment, and the survival rate was calculated by the Kaplan-Meier method (9). Serum CA 19-9 levels were measured every month by immunoradiometric assay using the Centocor radioimmunoassay kit (Centocor, Inc., Malvern, PA).

Patients received a full explanation about this study and gave written informed consent after approval of the protocols by the Institutional Review Board of the National Cancer Center.

RESULTS

A total of 251+ cycles of HAI chemotherapy were administrated (median 13, range 2-34+). Of 17 patients, 16 received EBRT with a total dose of 50Gy. In the remaining patient, treatment was discontinued after receipt of 24Gy of EBRT and 2 cycles of HAI because of disease progression. Therapy was discontinued due to disease progression in 14 patients, hepatic arterial obstruction in 1, and duodenal ulcer in 1. One patient was still receiving HAI chemotherapy at the time of writing.

Manifestations of treatment-related toxicity are summarized in **Table 2**. No life-threatening toxicity was observed, but 2 patients (12%) encountered Grade 3 toxicity. Nausea and vomiting were the most common types of toxicity. Four patients developed gastroduodenal ulcers after EBRT. Of these patients, one required hospitalization due to bleeding, and another

TABLE 2 Treatment-Related Toxicity according to WHO Criteria

	No. of patients (%)	
	Grade	
Toxicity	2	3
Leucopenia	3 (18%)	0
Anemia	0	0
Thrombocytopenia	3 (18%)	0
Nausea/vomiting	6 (35%)	2 (12%)
Liver dysfunction	0	0
Diarrhea	0	0
Mucositis	0	0

WHO: World Health Organization.

TABLE 3 Changes in the CA 19-9 levels of Patients with Elevated CA 19-9 Levels after Treatment (>100 U/mL)

Case no.	CA 19-9 (U/mL) Before*	After #	Tumor response$	Survival (days)
1	14552		NC	80
2	13216		PD	35
3	9945		PR	84
4	3944	673	PR	402
5	3091	292	NC	86
6	1739	53	PR	349
7	1526		NC	136
8	1428		NC	133
9	827		NC	114
10	318		PR	264
11	212		NC	114
12	170	41	NC	234

CA 19-9: carbohydrate antigen 19-9, NC: no change, PR: partial response, PD: progressive disease. *Maximal levels before treatment are represented; #Minimal levels after treatment are represented where responses were observed; $Assessed by computed tomography.

TABLE 4 Patterns of Initial Disease Progression

	No. of patients
Peritoneum (ascites)	6
Peritoneum and lymph node	1
Liver	2
Liver and lymph node	1
Liver and bone	1
Lymph node	1
Bone	1

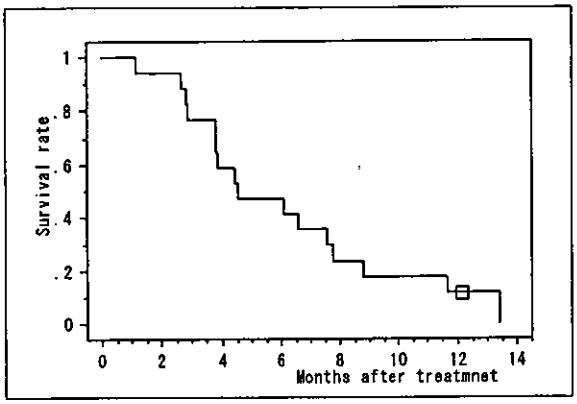

FIGURE 1 Overall survival curve for 17 patients treated with radiation and hepatic arterial 5-fluorouracil infusion. An open square indicates a censored case.

discontinued HAI therapy because of a refractory duodenal ulcer 5 months after initiation of treatment.

Seven (41%) patients had partial responses, 9 (53%) remained stable, and one showed progressive disease. Serum CA 19-9 levels were reduced by more than 50% in 4 of 12 patients (33%) who had pretreatment CA 19-9 levels of 100 U/mL or greater (**Table 3**). Death from cancer was documented in 16 patients at the time of analysis. The initial sites of disease progression were documented in 13 patients (**Table 4**). Peritoneal dissemination was the main cause of progression. Overall survival curves are shown in **Figure 1**. The median overall survival was 4.5 months and 1-yr overall survival was 11.8% observed.

DISCUSSION

Systemic chemotherapy using gemcitabine is considered standard therapy for advanced pancreatic carcinoma. However, a tumor response rate of only 5.4% and a survival time of 5.65 months have been observed with gemcitabine treatment, neither of which are satisfactory outcomes (1). High response rates of liver metastasis to HAI in patients with colorectal carcinoma have been reported (2,3,10). In a previous study (10), we employed continuous HAI of 5-FU for 5 days at a dose of 500mg/m^2/day every 4 weeks in order to treat liver metastasis from pancreatic carcinoma. The treatment was feasible but the overall response rate was only 8% at this dose and schedule. For treatment of liver metastasis from colorectal carcinoma, Arai *et al.* (3) reported a response rate of 78% after intermittent HAI of high-dose 5-FU once a week on an outpatient basis. In accordance with phase 1 and 2 studies, we therefore tried weekly HAI of 5-FU at a dose of 1000mg/m^2 for treatment of isolated liver metastasis from pancreatic carcinoma.

The toxicity associated with this regimen seemed to be mild. In the current study, grade 4 toxicity was not observed and the percentage of patients with grade 3 or worse toxicity was low (12%). Throughout the course of treatment, hematological toxicity was frequent but mild, and gastrointestinal toxicity was the only cause of treatment interruption. In a previous pilot study (11), hepatic artery occlusion was observed in 23% of patients and was the second cause of treatment discontinuation. However, occlusion of the hepatic artery occurred in only one patient (6%) in the current study. The frequency of hepatic artery thrombosis due to 5-FU infusion seemed to be lower with use of the intermittent schedule. On the other hand, gastroduodenal ulcers were frequently observed (24%), compared to a previous study in which HAI was administered continuously (8%) (11).

In the current study, an objective tumor response of 41% was noted following CT assessment. Serum CA 19-9 levels were reduced in 33% of patients with high initial CA 19-9 levels. Nine of the patients (53%) responded to therapy, as evaluated by CT or measurement of CA 19-9 levels. Greater response rates were observed with combination therapy than with any other form of systemic chemotherapy in the treatment of advanced pancreatic carcinoma. However, high response rates did not translate into prolonged survival for the patients in this study. For example, one of the patients who responded to treatment died due to peritoneal dissemination only 2.8 months after the initiation of the treatment. As shown in **Table 4**, peritoneal dissemination was the major cause of treatment failure. Hepatic extraction of 5-FU after HAI was estimated to be between 15-50% (12), thus, we expected a 150-500mg/m^2 weekly dose of 5-FU to produce a systemic anti-tumor effect. However, this dose seemed insufficient to reduce distant metastases, especially peritoneal dissemination. Surgical exploration revealed minute peritoneal metastasis in 12.5% of patients who had no distant metastases but locally unresectable pancreatic carcinoma, as assessed by CT staging (13).

Recently, excellent results have been reported using arterial infusion chemotherapy at the primary site of pancreatic carcinoma (4,14). In these reports, regional chemotherapy for pancreatic carcinoma was repeated for as long as catheters remained patent without occlusion or dislocation. Long-term tumor control might be obtained via this method, provided the tumor is responsive to the agent being infused. With respect to radiotherapy, however, it would be difficult to deliver a dose exceeding 72Gy to the pancreatic region, regardless of whether or not the tumor is responsive to radiotherapy (15). We will not select a higher dose of EBRT in combination with HAI in our next trial because we do not believe intensification of radiotherapy can reduce distant progression in pancreatic cancer patients. We do not know whether regional chemotherapy has the ability to reduce peri-

toneal dissemination from pancreatic carcinoma. However, this might explain the prolonged survival of patients in studies involving regional chemotherapy (4,14).

We conclude that liver metastasis from pancreatic cancer responds well to HAI, but that combination therapy fails to prolong the survival of such patients. Thus, we do not feel that a radiotherapeutic approach can be used to treat patients with pancreatic carcinoma who do not have distant metastases, except to the liver, as evaluated by clinical staging. Therefore, HAI should be used in combination with either systemic chemotherapy or regional chemotherapy at the primary site.

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GASTROENTEROLOGY

Impact of gemcitabine on the treatment of metastatic pancreatic cancer

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Abstract

Background and Aim: A previous randomized trial showed gemcitabine was superior to 5-fluorouracil in overall patient survival. However, the incremental improvement in survival was minimal. It is 2.5 years since gemcitabine has become available for the treatment of pancreatic cancer in clinical practice in Japan. The current study was conducted to examine whether treatment outcomes have changed since the introduction of gemcitabine therapy.

Methods: Ninety-one consecutive patients with metastatic pancreatic cancer treated with systemic chemotherapy at the National Cancer Center Hospital East were surveyed. Patients admitted before April 2001 received 5-fluorouracil, and those admitted subsequently received gemcitabine. The patients were divided into the gemcitabine group ($n = 50$) and the non-gemcitabine group ($n = 41$), and these groups were compared for five outcomes, objective response rate, non-progressive disease rate, carbohydrate antigen (CA)19-9 response rate, actual survival time, and difference between estimated and observed survivals. The estimated survival time was determined using the prognostic index reported in the previous study.

Results: Except for the objective response rate, the four other outcomes in the gemcitabine group were significantly superior to those in the non-gemcitabine group. The frequency of non-progressive disease, CA19-9 response, and favorable prognosis compared with the estimated survival, were 58%, 22%, and 60%, respectively, in the gemcitabine group, and 22%, 6%, 30%, respectively, in the non-gemcitabine group. The median survival time in the gemcitabine and non-gemcitabine group was 5.73 and 2.87 months, respectively.

Conclusion: It is suggested that there was a definite improvement in pancreatic cancer treatment after gemcitabine was introduced.

Key words: carbohydrate antigen 19-9, chemotherapy, gemcitabine, pancreatic neoplasm, prognosis.

INTRODUCTION

Pancreatic cancer (PC) is the fifth leading cause of cancer deaths in Japan, and in 1999, there were 18 654 deaths from this malignancy.[1] Although surgical resection is the only curative modality for this malignancy, most patients have unresectable disease at the time of diagnosis. For a long time, chemotherapy for PC had only limited value in clinical practice, and there had been no regimen superior to 5-fluorouracil (5-FU) therapy alone.[2,3] In the late 1990s, however, gemcitabine (GEM) was introduced as a PC chemotherapy. Gemcitabine therapy showed significantly better results in the clinical benefit response rates and survival in the randomized trial compared with 5-FU.[4,5] Accordingly, GEM has been accepted as first-line chemotherapy for advanced PC in many countries. In Japan, GEM was approved by the Government after a phase 1 trial in Japanese patients[6] and was introduced into hospitals as a practical therapy in April 2000.

In this retrospective study, we surveyed all metastatic PC patients treated with systemic chemotherapy at the

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National Cancer Center Hospital East, to examine whether treatment outcomes have changed since the introduction of GEM therapy.

METHODS

Patients

Between July 1992 and April 2003, 91 consecutive patients with metastatic PC received chemotherapy in the Division of Hepatobiliary and Pancreatic Medical Oncology at the National Cancer Center Hospital East. Among them, 74 received single-agent chemotherapy (5-FU or GEM). The remaining 17 received chemotherapy as part of multicenter clinical trials: phase 2 studies of cisplatin and 5-FU[7] in 10, docetaxel[8] in three, and irinotecan in four.

Histological or cytological confirmation of exocrine PC was obtained from all patients before chemotherapy. In addition, clinical trial patients were required to meet the eligibility criteria determined by each protocol. Briefly, they included: no previous chemotherapy; good performance status (PS); adequate bone marrow, renal, and hepatic function; no serious complications; and receipt of written informed consent.

Chemotherapy

In clinical practice, patients admitted before April 2001 received 5-FU, and those admitted subsequently received GEM. The 5-FU 600 mg/m^2 was administered over 2 h once weekly, or GEM 1000 mg/m^2 was administered over 30 min weekly, three times every 4 weeks. In clinical trials, details of the regimen are shown in the references. In brief: 5-FU 500 mg/m^2 for 5 days and cisplatin 80 mg/m^2 on the first day every 4 weeks;[7] docetaxel 60 mg/m^2 every 3–4 weeks;[8] and irinotecan 100 mg/m^2 weekly, three times every 4 weeks. In each regimen, chemotherapy was continued until evidence of disease progression. Follow-up computed tomography (CT) was performed after every course to objectively assess tumor response according to World Health Organization criteria.[9]

Data collection

We surveyed all case records of the 91 patients and collected each patient's baseline data including potential prognostic value[10–12] and their treatment outcomes. These were: regimen of chemotherapy; age; gender; PS according to the Eastern Cooperative Oncology Group criteria; presence or absence of prior surgery; location of the primary tumor; site of distant metastasis; presence or absence of measurable lesion; serum levels of carcinoembryonic antigen (CEA)[10] and C-reactive protein (CRP)[11] before chemotherapy; serial serum levels of carbohydrate antigen 19–9 (CA19-9) before and after chemotherapy;[12] serial CT reports; the first day of chemotherapy; and the date of death or last contact.

Treatment responses were evaluated using CT and serial change of serum CA19-9.

The CT response criteria were as follows: a complete response (CR) required the disappearance of all measurable disease for more than 28 days, during which time no new lesions could appear; a partial response (PR) required reduction of greater than 50% in the sum of the products of the greatest perpendicular dimensions of all measurable lesions lasting for more than 28 days, during which time no new lesions could appear; stable disease (SD) required reduction of less than 50% or an increase of less than 25% in the sum of the products of the greatest perpendicular dimensions of all measurable lesions lasting for more than 28 days, during which time no new lesions could appear; and progressive disease (PD) was defined as an increase of more than 25% in the sum of the products of the greatest perpendicular dimensions of all measurable lesions or the development of any new lesions. In the current study, we evaluated the primary pancreatic tumor by CT, but did not regard it as the measurable lesion.

When patients had an abnormal serum CA19-9 level of 100 U/mL or greater before chemotherapy, we defined a CA19-9 responder as a patient whose serum CA19-9 level was reduced by greater than 50% within 2 months after the initiation of chemotherapy.[12]

Statistics and analysis

We divided patients into the GEM or non-GEM group according to their regimen, and compared patient backgrounds, treatment responses and survival time between the two groups.

The frequency of each variable of the patient's background was analyzed using the chi-squared test. Continuous variables were grouped by a convenient value near the median value (age) or potential prognostic values (CEA, CA19-9, and CRP).

In the current study, an objective response was reported as a rate of patients with CR + PR divided by all patients in each group. The non-PD rate was also reported as a rate of patients with CR + PR + SD divided by all patients in each group. The CA19-9 response rate was defined as responders divided by all patients with a CA19-9 level of 100 U/mL or greater before chemotherapy in each group. The frequency of each response was analyzed by the chi-squared test.

Overall survival was measured from the first day of chemotherapy to the day of death or the last day of follow up. Survival curves were calculated by the Kaplan–Meier method.[13] Differences in survival were evaluated by log-rank tests. We calculated the prognostic index in each patient using to an equation reported previously.[12] The equation for the index was as follows: 1.144 × (0 for CRP less than 5 mg/dL and 1 for CRP of 5 mg/dL or greater) + 1.029 × (0 for a PS of 0–1 and 1 for a PS of 2–3) + 0.538 × (0 for CA19-9 <10 000 U/mL and 1 for CA19-9 of ≥10 000 U/mL). The pretreatment CA19-9 was not available in one patient so calculations were performed for the remaining 90. We estimated each patient's median survival time in months using this

index: 5.2, 2.6, and 1.4 in the good, intermediate, and poor prognosis groups, respectively, and compared this with his or her observed survival time. When an observed survival time was longer than the estimated one, we regarded it as a favorable prognosis. Censored cases within the estimated median survival time were not regarded as evaluable cases. The frequency of patients with favorable prognosis in each group was analyzed by the chi-squared test.

All analyses were performed using the statistical software SPSS 11.0 J for Windows. Statistical significance was defined as a two-sided *P*-value of 0.05 or less.

RESULTS

Among the 91 patients, 41 were from the non-GEM group and 50 were from the GEM group. Patient characteristics in each group were very similar to each other and are shown in Table 1. Of the nine patients with no measurable lesion, four had ascites with malignant cells other than the primary pancreatic tumor. The remaining five had minute liver metastasis (two patients) and/or peritoneal dissemination (four patients) at the time of laparotomy. Five had recurrent cancer after resection of the primary tumor with curative intent. Of these five, four had distant metastasis with no evidence of local recurrence.

Treatment responses are summarized in Table 2. There was no significant difference in the objective response between the two groups. The non-PD rate in the GEM group (58%) was significantly higher ($P = 0.011$) than that in the non-GEM group (22%). The CA19-9 response rate was evaluated in 72 patients, because pretreatment CA19-9 was not 100 U/mL or greater in the remaining 19. Serial CA19-9 changes after chemotherapy was not available in 17 patients mainly due to their early deterioration. These 17 patients were regarded as non-responders. The CA19-9 response rate in the GEM group was also significantly higher than that in non-GEM group.

Of the 91 patients studied, 81 died and 10 were still alive at the time of writing (December 2003). Six patients (7%) were lost to follow up after observation with a median of 4.3 months. Median survival time in

Table 1 Baseline characteristics of patients in the gemcitabine (GEM) and non-GEM groups

	Non-GEM ($n = 41$)	GEM ($n = 50$)	*P*-value
Age (years)			
Median (range)	60 (28–76)	59 (34–78)	
>60	21 (51%)	29 (58%)	0.534
Sex			
Male	27 (66%)	34 (68%)	1.000
Female	14	16	
Primary tumor			
Head	14 (34%)	10 (20%)	0.153
Body-tail	25	37	
Post-resection	2	3	
Eastern Cooperative Oncology Group performance status			
0, 1	36 (88%)	45 (90%)	0.750
2, 3	5	5	
Site of metastasis			
Liver	36 (88%)	42 (84%)	0.766
Peritoneum	5	10	
Lymph node	5	3	
Lung	5	2	
Bone	1	1	
Soft tissue	1	1	
Measurable lesion			
Present	39 (95%)	43 (86%)	0.177
Absent	2	7	
Carcinoembryonic antigen (ng/mL)			
Median (range)	7.9 (1.5–9082)	12 (1.5–238)	
>10 ng/mL	17 (41%)	32 (64%)	0.056
Carbohydrate antigen 19-9 (U/mL)			
Median (range)	2046 (1–314 070)	1737 (1–38 712)	
>10 000 U/mL	9 (22%)	7 (14%)	0.406
C-reactive protein (mg/dL)			
Median (range)	0.8 (0–13.2)	0.7 (0–29.2)	
>5 mg/dL	5 (12%)	9 (18%)	0.564

Table 2 Treatment responses of patients in the gemcitabine (GEM) and non-GEM groups

	Non-GEM ($n = 41$)	GEM ($n = 50$)	P value
Computed tomography response			
Partial response	1 (2%)	5 (10%)	0.217
Stable disease	8	24	
Progressive disease	18	8	
Not evaluable	14	13	
Serial carbohydrate antigen 19-9			
Pretreatment level >100 U/mL	33	39	
Responder	2 (6%)	11 (22%)	0.029
Non-responder	31	28	

GEM group was 5.73 months with 95% confidence interval (CI) between 3.95 and 7.51. It was significantly longer ($P = 0.0004$) than that in non-GEM group (median; 2.87, 95% CI; 1.72–4.02) (Fig. 1).

According to the calculating prognostic index,[12] we divided the 90 patients into three groups: good ($n = 61$), intermediate ($n = 24$), and poor prognosis groups ($n = 5$). Survival curves in the three prognostic groups showed the index had a good validity ($P = 0.0069$). Because there were three censored cases within the estimated median survival time, we compared each patient's estimated and observed survival time in the remaining 87 (Table 3). Of 47 patients in the GEM group, 28 (60%) showed favorable prognosis, and the frequency was significantly higher than that (12 of 40 patients, 30%) in the non-GEM group ($P = 0.009$).

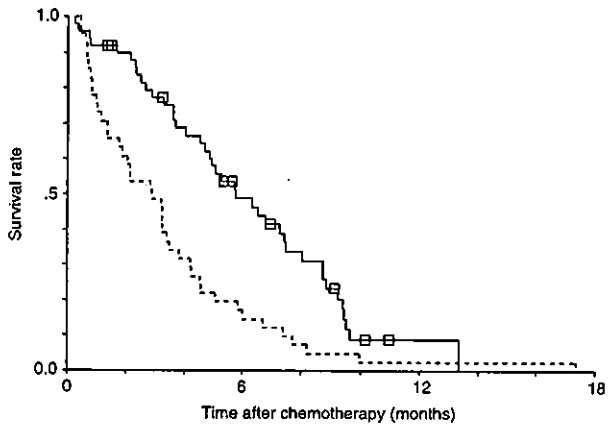

Figure 1 Survival curves of patients in the (—) gemcitabine (GEM) group ($n = 50$) and the (—) non-GEM group ($n = 41$). (□) Censored cases.

DISCUSSION

Gemcitabine was shown to be superior to 5-FU both in the clinical benefit response and in overall patient survival.[5] However, the incremental improvement in overall survival seen with GEM was minimal. In Japan, GEM had been available for the treatment of PC in clinical practice 2.5 years. In the current study, we surveyed PC treatment outcomes to focus on the change before and after the introduction of GEM.

We studied five outcomes: the objective response rate, non-PD rate, CA19-9 response rate, actual survival time, and difference between estimated and observed survivals. The advantage of GEM was demonstrated for four of these outcomes, but was not demonstrated for the objective response rate. The objective response of 8% in the current study was similar to previous findings of GEM monotherapy.[4,5] Despite this poor activity for tumor shrinkage, we favored GEM because of its clinical benefit and manageable toxicity, which were difficult to evaluate in a retrospective analysis. There was a definite antitumor effect in the GEM group, which was indicated by non-PD and CA19-9 response rates, but it was not strong enough to cause evident tumor shrinkage.

We had to make survival comparison analyses carefully because various biases could not be excluded completely in a retrospective study. Although this single institution study warranted all patients to have the same initial staging examinations, monitoring, and approach to supportive care, historical changes of treatment strategy might cause some biases. At first, we compared survival of all (locally advanced and metastatic) patients who received chemotherapy alone. Before the introduction of GEM, we had treated locally advanced patients by intraoperative radiotherapy trials.[14,15] These trials revealed that occult metastases were found in one-third of the patients with CT-staging locally advanced disease at the time of laparotomy. We thereafter selected only good candidates for chemoradiotherapy, whereas 5-FU based concurrent chemoradiotherapy was the standard treatment for locally advanced PC.[16–18] As a result, we treated more CT-staging locally advanced patients with GEM compared with non-GEM chemotherapy. Accordingly, we focused on metastatic PC patients in the current final analysis. The introduction of the prognostic model proposed previously[12] was also used to avoid the biases. The advantage of GEM was significant in the two comparisons. At the initiation of analysis we expected that there would be a subtle difference because the survival advantage of GEM over 5-FU was reported to be only 1 month in a previous randomized trial.[5]

Table 3 Difference between estimated and observed survival time of patients in the gemcitabine (GEM) and non-GEM groups

Prognostic index	Estimated survival time (months)	Non-GEM ($n = 40$) Observed survival time <EST	Non-GEM ($n = 40$) Observed survival time >EST	GEM ($n = 47$) Observed survival time <EST	GEM ($n = 47$) Observed survival time >EST
0	5.2	17	7	15	20
0.538	2.6	4	3	1	2
1.029		2	1	0	0
1.144		3	1	1	2
1.567		1	0	0	1
1.682		0	0	1	0
2.173	1.4	0	0	1	2
2.711		1	0	0	1
		28	12 (30%)	19	28 (60%)

EST, estimated survival time.

There is an evident limitation in the comparison of treatments in such a retrospective study. Various historical changes, such as technical improvement of diagnostic modalities, staging methods, supportive treatments and so on, usually result in better patient survival in addition to anticancer treatment; however, we observed some good responses since the introduction of GEM treatment. From the current analysis, we suggest that there was a definitive improvement of PC treatment following the introduction GEM.

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Needle Tract Implantation of Hepatocellular Carcinoma and Pancreatic Carcinoma after Ultrasound-guided Percutaneous Puncture: Clinical and Pathologic Characteristics and the Treatment of Needle Tract Implantation

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Abstract. Tumor implantation along the needle tract following percutaneous procedures under ultrasonographic guidance for hepatocellular carcinoma (HCC) and pancreatic carcinoma (PC) has been well documented. The purpose of the present study was to investigate the correlation between the procedure, the pathologic differentiation of the primary tumor, and the treatment after implantation. Between July 1992 and March 2000, HCC patients (n = 372) who underwent biopsy, percutaneous ethanol injection (PEI) therapy and percutaneous microwave coagulation therapy (PMCT) and PC (n = 73) patients who underwent biopsy were retrospectively studied. Needle tract implantation was found in six of the HCC patients (1.6%) and one of the PC patients (1.4%). The interval to diagnosis ranged from 5 to 25 months (mean ± SD 11.2 ± 7.6 months) in the HCC patients. The needle tract implantation was evident for all procedure types in these patients (two after PEI alone, two after both biopsy and PEI, and one after PMCT) and for each degree of pathologic differentiation of the primary tumors (well differentiated in one, moderately differentiated in two, and poorly differentiated in one). Each implanted tumor was surgically resected, with no recurrence at the focal lesion. These results suggest that needle tract implantation develops regardless of the procedure or the pathologic differentiation of the primary tumor, and that surgical resection might be effective for controlling these implanted lesions.

For the pathologic diagnosis or treatment of hepatocellular carcinoma (HCC) and pancreatic carcinoma (PC), percutaneous needle biopsy, ethanol injection (PEI), microwave coagulation therapy (PMCT), and radiofrequency (RF) ablation under ultrasonographic (US) guidance have become increasingly common since the late 1980s [1–4]. Complications associated with these procedures have been reported [5, 6], however, with needle tract implantation of cancer cells being particularly well documented [7–16]. To increase the safety of these percutaneous procedures, such complications must be prevented or, at the very least, patients with implantations treated with a minimum load. To date, only a few studies have investigated the relations between such implantation and the procedure, the pathologic differentiation of the primary tumor, and treatment of the implanted tumor. Therefore we retrospectively investigated the clinical and pathologic characteristics and the treatment of needle tract implantation.

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Materials and Methods

The medical records of 372 patients with HCC (484 lesions; 296 men, 76 women; mean age of 62.7 ± 8.5 years) and 73 patients with PC (73 lesions; 48 men, 25 women; mean age of 59.5 ± 10.4 years) who underwent percutaneous biopsy, PEI, PMCT, or a combination of these procedures between July 1992 and March 2000 at the National Cancer Center Hospital East were retrospectively examined. Written informed consent was obtained from all patients prior to needle biopsy, PEI, or PMCT.

At our hospital, needle biopsy for HCC is performed when it is difficult to arrive at a definitive diagnosis of a liver tumor using radiologic examinations, dynamic computed tomography (CT), magnetic resonance imaging (MRI), or hepatic arteriography. In patients who underwent PEI or PMCT for the first time, needle biopsy was also performed immediately prior to treatment to confirm the diagnosis. PEI and PMCT were indicated for HCC lesions 3 cm or less in diameter and three or fewer in number. We performed PEI between July 1992 and March 1998 and PMCT between April 1998 and March 2000 as the treatment of choice for small HCCs. In PC patients, needle biopsy was performed only for those with (1) unresectable advanced disease, (2) locally advanced disease with definite invasion of the celiac artery, the superior mesenteric artery, or the portal vein (or all of them) from both sides of the tumor, or (3) distant metastases.

When needle biopsy, PEI, or PMCT was performed, we used a 3.5 MHz convex probe equipped with a lateral guide attachment. The most appropriate approach was chosen after local sterilization with povidone-iodine, which was also used as the contact medium.

In principle, the intercostal approach was used for lesions located in the right lobe and the medial approach for lesions in the left lobe. The medial approach was always used for pancreatic tumors.

Biopsy of the HCC or PC was performed using a 21-gauge needle (Sonopsy-C1; Hakko, Tokyo, Japan) using one or two punctures. When a needle was introduced for the second time, the needle was thoroughly washed in 10% alcohol prior to puncture. For PEI, one to three needles were introduced percutaneously into the tumor under ultrasonographic guidance. A 22 gauge, 15 cm Chiba needle (Top, Tokyo, Japan) was employed for puncture. A 2- to 5-ml aliquot of absolute ethanol (99.5%) was slowly injected through each needle. The injection was repeated twice a week for two to six sessions. While these needles were being removed, 1 ml of 1% lidocaine was slowly injected through each needle. For PMCT, a microwave tissue coagulator with a microwave frequency of 2450 MHz (Microtaze OT-110M; Azwell, Osaka, Japan) and an electrode needle 1.6 mm in diameter with a 1 cm long monopolar electrode at the tip (Azwell, Osaka, Japan) were used. First, a 14-gauge guide needle (Quickcut-C2; Hakko, Tokyo, Japan) was introduced percutaneously toward the tumor, and the electrode needle was placed into the tumor through this guide needle. Microwave coagulation was performed for 60 seconds at a setting of 60 W as one session, and depolarization was performed for 15 seconds at 20 mA after each session. The coagulation was repeated two to nine times according to tumor size. While the electrode needle and guide needle were being removed, the whole puncture route was exposed to microwave coagulation at 60 W.

Of the 484 HCC nodules in these 372 patients, 99 were diagnosed by clinical examination, including dynamic CT, angiography, and serum α-fetoprotein assay. The remaining 385 HCC nodules were histologically diagnosed by examining specimens obtained by ultrasonically guided needle biopsy using 21-gauge needles. The diagnosis of PC was based on histologic findings of specimens obtained by ultrasonically guided needle biopsy with 21-gauge needles. Based on the degree of pathologic differentiation according to World Health Organization (WHO) criteria, the HCCs and PCs were classified into three classes: well differentiated, moderately differentiated, and poorly differentiated.

For HCC, needle biopsy alone was performed for 31 lesions in 31 patients, and PEI alone was performed for 99 lesions in 69 patients; both biopsy and PEI were performed for 278 lesions in 204 patients, and both biopsy and PMCT were performed for 76 lesions in 68 patients. Among the 31 patients with HCC who underwent needle biopsy alone for diagnosing a hepatic tumor, radiotherapy was performed in 2 patients, hepatectomy in 11, and transcatheter arterial chemoembolization in 18.

Following needle biopsy, PEI, and PMCT, all patients were followed up with US, dynamic CT, or both at least every 3 months. Needle tract implantation was diagnosed when a newly developed tumor was seen by CT and US in the cutaneous or subcutaneous tissue just on the line of needle insertion. Follow-up time ranged from 1 year 6 months to 9 years 3 months.

Statistical analysis was performed using the χ^2 test for independence to compare the pathologic differentiation and some clinical characteristics. Statistical significance was established at the $p < 0.05$ level.

Results

The incidence of needle tract implantation in association with pathologic tumor cell differentiation of primary tumor and procedures is shown in Tables 1 and 2. Needle tract implantation was found in six of the HCC patients (1.6%) and one of the PC patients (1.4%). No other major complications accompanied the needle insertion procedures, except in the abdominal cavity of a patient with HCC treated by PMCT. The patient had severe thrombocytopenia (19,000/mm^3) due to liver cirrhosis, and the bleeding was controlled conservatively. Implantation occurred for each differentiation grade of the HCC tumors and in a PC patient with moderately differentiated adenocarcinoma. No statistical differences were seen between the pathologic differentiation of the primary tumor and implantation for either HCCs or PCs ($p = 0.54$, $p = 0.57$, respectively). Table 2 also shows that there was no statistical difference between the procedures and the needle tract implantation in HCC patients ($p = 0.63$).

Table 1. Incidence of needle tract implantation in association with pathologic tumor cell differentiation of primary tumors.

	HCC		PC	
Parameter	No.	Implantation	No.	Implantation
Pathologic differentiation				
Well	224	1 (0.5%)	6	0
Moderately	110	2 (1.8%)	27	1 (3.7%)
Poorly	51	1 (2.0%)	27	0
Unknown[a]	0	0	13	0
Not examined[b]	99	2 (2.0%)	—	—
Total	484	6 (1.2%)	73	1 (1.4%)

HCC: hepatocellular carcinoma; PC: pancreatic carcinoma.
[a]Unknown: adenocarcinoma was diagnosed by specimen obtained by needle biopsy, but pathologic differentiation was not determined.
[b]Diagnosis of HCC was made by clinical examination, including dynamic computed tomography, angiography, and measurement of serum α-fetoprotein concentration.

Table 2. Incidence of needle tract implantation in association with procedures.

	HCC		PC	
Parameter	No.	Implantation	No.	Implantation
Procedure				
Biopsy	31	1 (3.2%)	73	1 (1.4%)
PEI	99	2 (2.0%)	—	—
Biopsy and PEI	278	2 (0.7%)	—	—
Biopsy and PMCT	76	1 (1.3%)	—	—
Total	484	6 (1.2%)	73	1 (1.4%)

PEI: percutaneous ethanol injection; PMCT: percutaneous microwave coagulation therapy.

Primary tumor and implanted tumor characteristics in patients and the outcomes of these patients are shown in Tables 3 and 4. All implanted tumors were palpable and detected by both US and CT. The interval until the development of the implantation was 2 to 8 months for moderately and poorly differentiated tumors, whereas that for well differentiated tumors was more than 12 months. The interval until the development of the implantation in patients with HCC was 5 to 25 months (11.2 ± 7.6 months, mean ± SD); it was 2 months in the PC patient.

All seven patients with implantation tumors underwent surgical resection. All of these tumors were resected with at least a 1 cm diameter margin. No recurrences in the cutaneous or subcutaneous tissue were detected in five patients with HCC or in the one patient with PC. In the remaining HCC patients (case 5, Table 3), a repeat

Table 3. Clinicopathologic features in patients with needle tract implantation.

Case no.	Primary tumor characteristic				Interval (months)[a]
	Location	Size (mm)	Procedure	Differentiation	
1	S5–8	80	Biopsy	Poorly	5
2	S8	20	Biopsy + PEI	Moderately	5
3	S8	20	Biopsy + PEI	Moderately	8
4	S7	20	PEI	Not examined	10
5	S2	10	PEI	Not examined	14
6	S6	27	Biopsy + PMCT	Well	25
7	Pb[a]	47	Biopsy	Moderately	2

Cases 1 to 6 were hepatocellular carcinoma; case 7 was pancreatic carcinoma.
Pb: pancreas body.
[a]Period between the procedure and the development of needle tract implantation.

Table 4. Outcomes in patients with needle tract implantation.

Case no.	Implanted tumor		Treatment	Survival time (months)[a]	Outcome
	Size (mm)	Differentiation			
1	30	Poorly	Resection	10	Deceased
2	30	Moderately	Resection	13	Living
3	20	Moderately	Resection	6	Living
4	15	Moderately	Resection	64	Deceased
5	25	Well	Resection	44	Living
6	27	Well	Resection	4	Living
7	10	Moderately	Resection	12	Deceased

Cases 1 to 6 were hepatocellular carcinoma; case 7 was pancreatic carcinoma.
[a]Time from the date of resection of the implanted tumor.

operation was required owing to the redevelopment of an implanted tumor in the subcutaneous tissue after the first surgical resection. However, this patient was eventually cleared, with no recurrence of the implanted tumor. Of the six patients with HCC, two died of primary tumor progression and four remain living. The PC patient with the implanted tumor did not experience recurrence of the tumor in the needle tract but later died of primary tumor progression (Tables 3, 4).

Discussion

Percutaneous liver puncture under ultrasonographic guidance, percutaneous liver biopsy, PEI, PMCT, and RF ablation, have been widely performed for the purpose of gaining an exact diagnosis and determining the appropriate treatment. Furthermore, although detection of small pancreatic tumors using US, enhanced CT, and MRI is now possible, an exact diagnosis of some pancreatic tumors is difficult using only diagnostic imaging methods, making a pancreatic biopsy necessary to obtain a definitive diagnosis of a tumor without typical findings on any examination. Several reports of needle tract implantation after biopsy and PEI in patients with HCC [7–12, 16], as well as a few with PC, have been reported [13–15].

Smith [6] reported that the incidence of needle tract implantation was only 0.005% (3/63,108 cases) in 1984. However, that report used results from a review of the literature and the results of a hospital survey, and it included various abdominal tumors, salivary gland adenoma, prostatic carcinoma, and breast carcinoma. Furthermore, the incidence of this complication may have been increasing as the use of US-guided percutaneous puncture has become more widespread. For instance, Ishii et al. [16] reported an incidence of needle tract implantation in HCC patients of 1.1% (4/384 tumors) in 1998, similar to the 1.6% (6/484 tumors) in HCC patients and 1.4% (1/73 tumors) in PC patients in the present study.

In previous reports, the implanted tumor in HCC patients was demonstrated in the early phase as a hyperattenuated lesion, same as the primary tumor in the early phase of enhanced dynamic CT [9, 10]. In the present study, needle tract implantation occurred even in well differentiated HCCs and PCs, which are mostly considered hypovascular tumors on dynamic CT. In some cases, the tumors appear hypovascular on dynamic CT and are subjected to percutaneous needle biopsy or ablation therapy, which also carries the risk of needle tract seeding. In the present study, all implanted tumors were palpable; and at the beginning they were diagnosed by complaints of a mass in the abdominal or chest wall in most patients. Furthermore, all primary lesions also were visible at the same site of the implanted tumors by US and CT, enabling confirmation of needle tract seeding.

The interval between the procedure and the development of needle tract implantation has been reported to be 6 to 46 months after needle biopsy or PEI (or both) [8, 11, 12, 16]. In the present study, this interval was 5 to 25 months for the HCC patients. Furthermore, pathologic differentiation correlated with the interval from puncture to development of the implantation, and there was a tendency for these implanted tumors to develop earlier with moderately or poorly differentiated HCCs than with well differentiated HCCs. With PCs, needle tract implantation tends to develop earlier than with HCCs. Ferrucci et al. [13] reported that needle tract seeding occurred 3 months after biopsy of a pancreatic carcinoma under CT guidance. In the present study, seeding was also observed 2 months after needle biopsy under ultrasonographic guidance in one patient with PC. These findings suggest that follow-up for at least 2 years is required for detection of needle tract implantation in patients who undergo these percutaneous procedures according to the primary tumor, especially well differentiated tumors.

Ishii et al. [16] reported that the risk of needle tract implantation in HCC patients treated by PEI increases when the tumor size is > 2 cm in diameter. However, in the present study, four of the six implanted tumors occurred in primary HCC tumors ≤ 2 cm in diameter, possibly because smaller lesions are increasingly detected by US or CT. Furthermore, the present study has demonstrated that needle tract implantation occurs without regard to pathologic differentiation or procedure. In patients who underwent PMCT, the whole puncture route was coagulated to prevent bleeding by microcoagulation while the needle was being removed. We had thought that needle tract implantation would seldom occur in these patients, but 1 of the 76 patients (1.3%) who underwent PMCT had an implantation. Thus needle tract implantation should be considered during follow-up examinations in all patients who undergo percutaneous needle puncture.

Radiation therapy or surgical resection is generally performed for implanted tumors from an HCC [7–10, 16]. However, there is not yet a consensus on the most suitable treatment for such implanted tumors. Surgical resection is used to treat implanted tumors at our hospital with good results. In the present series, only one HCC patient required another operation owing to significant

invasion of surrounding vessels by the implanted tumor. Surgical resection was, and can be, safely performed for needle tract implantation tumors in all patients. In addition, if the implanted tumor is small and located only in the cutaneous region, surgical resection can be performed under local anesthesia. Thus we believe surgical resection to be the most valuable method for treating implantation tumors.

To avoid needle tract implantation, there are some general points of which physicians should be aware when inserting needles into tumors. (1) Piston-like motion of the needle in the tumor should be avoided, as this procedure can break malignant tissue into smaller pieces. (2) To avoid pieces of malignant tissue falling when a needle is released from a tumor, physicians must constantly absorb debris using negative pressure. (3) After a puncture is performed, there is the danger of cancer cells drifting away from the needle tract into the abdominal cavity and subcutaneous tissue owing to the high pressure of ethanol or normal saline solution injected into the tumor. (4) If an operation on a liver or pancreatic tumor is performed, the route of the needle tract must be resected with the primary tumor.

It is noteworthy that, despite following these guidelines, needle tract implantation still occurred with an incidence of about 1% in the present study. This underlines the importance of performing percutaneous needle biopsy only when absolutely necessary. Furthermore, it is also important that implanted tumors are diagnosed early by follow-up examinations that check for implantation regardless of the pathologic differentiation or the procedures performed. This practice enables surgical resection for the implantation tumor to be safely performed using general or local anesthesia.

Résumé. L'implantation tumorale le long du trajet de la ponction percutanée à l'aiguille sous guidance échographique pour carcinome hépatocellulaire (CHC) et cancer pancréatique (CP) est bien documentée. Il existe quelques études explorant le mode d'implantation tumorale le long de la ponction après ces actes. Le but de cette étude a été d'établir une corrélation entre la ponction, la dédifférentiation anatomopathologique de la tumeur primitive et le traitement de l'ensemencement tumoral. Entre juillet 1992 et mars 2000, tous les patients porteurs de CHC (n = 372) ayant eu, par voie percutanée, soit une biopsie (B), soit une injection d'éthanol (IE) ou un traitement par micro-ondes (MO) et tous les patients porteurs de CP (n = 73) ayant eu une biopsie, ont été étudiés rétrospectivement. On a découvert une dissémination tumorale chez six des patients porteurs de CHC (1.6%) et chez un des patients porteurs de CP (1.4%). L'intervalle entre la ponction et le diagnostic d'ensemencement allait de 5 à 25 mois (moyenne ± ET: 11.2 ± 7.6 mois) chez les patients CHC, l'implantation tumorale ayant été retrouvée après tous les types d'intervention percutanée (deux après IE seule, deux après B et IE et un après MO) et dans tous les types de dédifférentiation histopathologique des tumeurs primitives (bien différenciée dans un, peu différenciée dans deux, et indifférenciée dans un). Dans tous les cas, on a pu exciser chirurgicalement le tissu pathologique, sans aucune récidive locale. Ces résultats suggèrent que la dissémination tumorale se produit quelque soit le procédé employé, le degré de dédifférenciation de la tumeur primitive et que la résection chirurgicale peut être efficace pour contrôler ces lésions de dissémination.

Resumen. Está demostrada la implantación tumoral a lo largo del trayecto de la aguja tras procedimientos de punción percutánea, bajo control ecográfico, en carcinomas hepatocelulares (HCC) y carcinomas de páncreas (PC). Se han efectuado pocas investigaciones de cómo se produce la implantación a lo largo del trayecto de la aguja tras estos procedimientos diagnóstico-terapéuticos. El objetivo del trabajo fue averiguar si existe una correlación entre la técnica, la diferenciación del tumor primario y el tratamiento de los implantes. Se estudiaron retrospectivamente desde julio de 1992 a marzo de 2000 los HCC (n = 372) que fueron biopsiados, sometidos a tratamiento con inyección percutánea de etanol o con coagulación percutánea por microondas. Además, se estudiaron los PC (n = 73) que fueron simplemente biopsiados. Implantación tumoral en el trayecto de la aguja se constató en 6 pacientes con HCC (1.6%) y en 1 con PC (1.4%). En los pacientes portadores de un HCC el tiempo que transcurrió hasta efectuar el diagnóstico osciló entre los 5 y 25 meses (media ± desviación estándar: 11.2 ± 7.6 meses). En estos pacientes la implantación, a lo largo del trayecto de la aguja, se evidenció con todas la diferentes técnicas empleadas [2 tras instilación exclusiva de etanol (PEI), 2 tras biopsia y PEI y uno tras coagulación (PMCT)] y con cualquier grado de diferenciación del tumor primario (bien diferenciado en 1 caso, moderadamente diferenciado en 2 y pobremente diferenciado en uno). Cada implante tumoral fue extirpado quirúrgicamente sin recidiva alguna. Estos resultados demuestran que la implantación a lo largo del trayecto de la aguja no depende, ni de la técnica realizada ni del grado de diferenciación del tumor primario y que la resección quirúrgica del implante constituye el tratamiento de elección.

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Assessment of Portal Vein Invasion in Pancreatic Cancer by Fusion 3-Dimensional Ultrasonography

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Objective. The purpose of this study was to assess the usefulness of a newly developed imaging technique, fusion 3-dimensional ultrasonography (3DUS) in the diagnosis of portal vein (PV) invasion in patients with pancreatic cancer (PC). ***Methods.*** Fourteen patients with proven PC were examined by fusion 3DUS presented as shaded volume-rendering and multiplanar reconstruction images. The surgical findings were obtained in all patients (12 with resection and 2 without). The findings were compared with those of 2-dimensional ultrasonography (2DUS), contrast-enhanced computed tomography (CT), dynamic CT (DCT), angiography, and surgical findings. Portal vein invasion was assessed by 3 independent radiologists for each modality, and objectivity of the assessment was examined by interobserver variability analysis (κ value). ***Results.*** On the basis of surgical findings, the accuracy rates of 2DUS, fusion 3DUS, DCT, and angiography were 78.6%, 92.9%, 85.3%, and 66.7%, respectively. The κ values of 2DUS, fusion 3DUS, DCT, and angiography for PV invasion were 0.57, 0.90, 0.63, and 0.49, respectively, being most objective in fusion 3DUS. ***Conclusions.*** Fusion 3DUS is useful for diagnosis of PV invasion of PC. ***Key words:*** pancreatic cancer; portal vein invasion; 3-dimensional; ultrasonography.

Abbreviations
CT, computed tomography; DCT, dynamic computed tomography; EUS, endoscopic ultrasonography; MPR, multiplanar reconstruction; PC, pancreatic cancer; PD, power Doppler; PV, portal vein; SMV, superior mesenteric vein; SPV, splenic vein; SVR, shaded volume-rendering; 3D, 3-dimensional; 3DUS, 3-dimensional ultrasonography; 2D, 2-dimensional; 2DUS, 2-dimensional ultrasonography

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Pancreatic cancer (PC) is one of the cancers with the worst prognosis among gastrointestinal carcinomas. In this situation, it is important to assess invasion of the vessels surrounding the pancreas before determining the indication for surgery. Now, vascular invasion is assessed by various diagnostic imaging methods, including computed tomography (CT), endoscopic ultrasonography (EUS), and magnetic resonance imaging.[1-7] On ultrasonography, it is reported that 2-dimensional ultrasonography (2DUS) in the Doppler mode provides better diagnosis of vascular invasion than gray scale images.[8-13] However, 2DUS only enables a view of limited sections. In this study, we assessed the diagnostic usefulness of portal vein (PV) invasion in PC by fusion 3-dimensional ultrasonography (3DUS), in which gray scale imaging and vessels surrounding the tumor visualized by the power Doppler (PD) mode were con-

structed 3-dimensionally, synthesized, and displayed on the same screen. The diagnostic performance of fusion 3DUS was compared with that of 2DUS, dynamic CT (DCT), angiography, and surgical findings. In addition, the usefulness of fusion 3DUS regarding objectivity in the assessment of PV invasion was investigated.

Materials and Methods

Patients

The subjects of this study were 14 consecutive patients with PC who were diagnosed and treated in our hospital between July 2002 and June 2004. The study population consisted of 9 men and 5 women with a mean age of 60.2 years (range, 38–72 years). The mean tumor size was 27.0 mm (range, 17–44 mm). Tumors were located in the head of the pancreas in 12 patients and the body and tail in 1 patient, respectively. Two-dimensional ultrasonography, fusion 3DUS, DCT, and angiography were performed in all patients. The presence or absence of PV invasion was confirmed on the basis of surgical findings in all patients (12 with resection and 2 without).

Informed consent was obtained from all the patients, and the study was approved by the Ethical Committee of Chiba University.

Construction of Fusion 3DUS Images

Ultrasonography was performed with an SSA-770A system (Toshiba Co, Ltd, Tokyo, Japan) equipped with 3-dimensional (3D) image processing and a 3.75-MHz convex probe. Two-dimensional ultrasonography was performed in all patients before fusion 3DUS. All ultrasonographic examinations, both 2DUS and fusion 3DUS, were performed by a radiologist with experience in more than 10,000 abdominal scans. He is a certified specialist in abdominal ultrasonography by the Japanese Society of Ultrasound in Medicine. In the PD mode, Doppler frequency, pulse repetition frequency, flow velocity range, and frame rate were 2.5 MHz, 6.0 to 9.0 KHz, 34.6 or 46.2 cm/s, and 6 to 8 frames/s, respectively. Color gain was adjusted for clear tumor imaging. The focus position was just below the bottom of the tumor. In all patients, the portal trunk, splenic vein (SPV), and superior mesenteric vein (SMV) were assessed. To acquire image data, each patient was placed in the supine position, and the probe was adjusted so that the vessels were clearly visualized longitudinally. Next, fan scanning was performed manually and uniformly over the region of the tumor and the surrounding target vessels. The fan angle was set at 60°. To obtain at least 100 sectional images, patients were asked to hold their breath for 15 to 20 seconds, during which time fan scanning was performed at a constant speed.

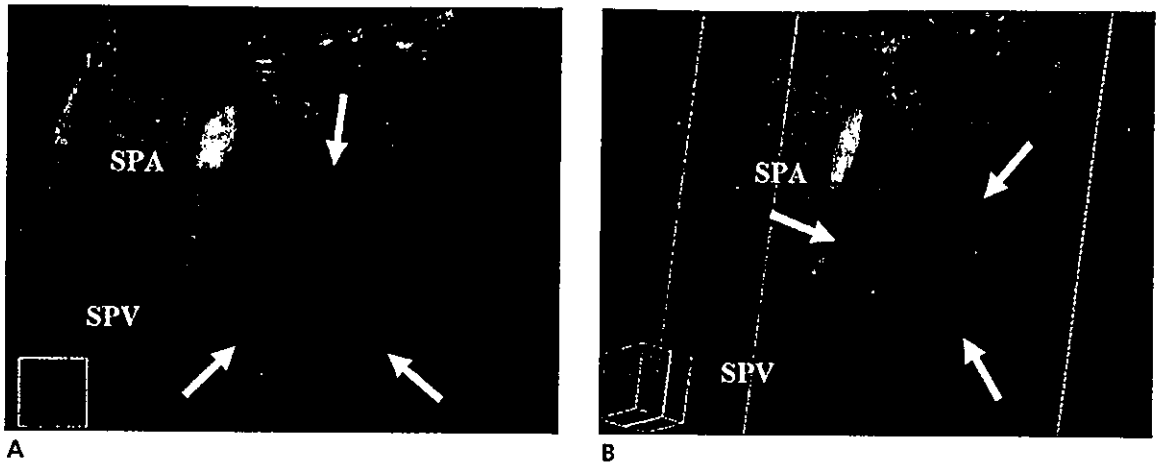
The obtained fusion 3DUS images contained nontarget vascular signals or artifact signals. Therefore, to increase the visibility of images, these signals were eliminated manually by the clipping function, which is built into the ultrasonographic system as an image processor. However, this procedure was not performed on images of the target blood vessels.

Fusion 3DUS images are presented as shaded volume-rendering (SVR) images processed by plain cut and cube cut as well as multiplanar reconstruction (MPR) images. Plain cut is a displaying method by which a cross-sectional 2-dimensional gray scale image is synthesized with a 3D PD image. Cube cut is a displaying method by which a gray scale image and a PD image displayed 3-dimensionally are cut out at an arbitrary cross section with clipping equipment, visualizing a tumor and the surrounding vessels in a lesion (Figure 1). Multiplanar reconstruction is a displaying method by which an image is displayed at an arbitrary cross section based on consecutive volume data. The images comprising 3 cross-sectional (axial, sagittal, and coronal) images were displayed 2-dimensionally for the assessment.

The obtained data were saved on the hard disk of the ultrasonographic equipment and a magneto-optical disk. Ultrasonographic examinations, including reconstruction of the images, were performed by 1 radiologist before DCT or angiography was performed, and then 3D images were interpreted by 3 reviewers for the assessment of PV invasion of the tumor without any information about the patients, including the results of 2DUS.

Computed Tomography and Angiography

Dynamic CT was performed with a helical CT scanner (LightSpeed Ultra 8 and 16; GE Healthcare, Milwaukee, WI). After injection of 100 mL of a contrast medium at 350 mgI/mL via a 20-gauge needle inserted into the forearm vein at a rate of 3 mL/s, arterial, portal, and late phases were captured with delays of 30, 90, and 180 seconds, respectively. All images were obtained



A B

Figure 1. Plain cut (A) and cube cut (B) of an SVR image. The SPV is in contact with the tumor (arrows), and SPV invasion was confirmed in a resected specimen. In the other modalities, this was not able to be diagnosed as invasion positivity. SPA indicates splenic artery.

with 1.25 mm collimation at the site of the pancreatic tumor including surrounding vessels.

On angiography, the PV was assessed by superior mesenteric and celiac arteriography from a right femoral artery approach. The contrast medium (25 mL) was administered at a constant rate of 5 mL/s with an automatic injector.

Assessment of PV Invasion

To assess vascular invasion by 2DUS, fusion 3DUS, and DCT, the degree of contact between the tumor and the vessel was determined. Portal vein invasion was divided into 2 categories: invasion-negative (the tumor and the vessel did not contact each other, or less than one third of the circumference of the vessel contacted the tumor) and invasion-positive (at least one third of the circumference of the vessel contacted the tumor, the vessel was lost, or the vessel was contained in the tumor). This criterion of vascular invasion was based on a previous report.[13] On angiography, invasion-positive was defined as a vessel that was irregularly narrowed or lost at the tumor site.

Assessment for Reproducibility of Imaging Diagnosis

In all patients, PV invasion was assessed by 2DUS, fusion 3DUS, DCT, and angiography in a double-blinded method by 3 independent radiologists who had not been informed of the clinicopathologic findings. The assessment of PV invasion by each modality was divided into positive, equivocal, and negative findings to assess the sensitivity, specificity, and accuracy. The radiologists selected equivocal when they could not assess PV invasion as either positive or negative, and we categorized the assessment of equivocal as a result of misdiagnosis. The objectivity of the assessment in each modality by the 3 radiologists was investigated with the use of surgical findings as the criterion standard.

Statistical Analysis

Statistical analysis was performed with StatView 5.0 statistical software (Abacus Concepts Inc, Berkeley, CA). The accuracy of these modalities was compared by Fisher analysis. $P < .05$ was considered statistically significant. For the analysis of interobserver variability in the assessment of vascular invasion with each modality, κ statistics were used to measure the degree of agreement between 2 observers. κ values of up to 0.40 were considered to indicate poor correlation; 0.41 to 0.60, moderate correlation; 0.61 to 0.80, good correlation; and greater than 0.81, excellent correlation.

Results

Assessment of PV Invasion by Each Imaging Modality

Six patients had a presence of PV invasion, and 8 patients had an absence of invasion that was confirmed on the basis of surgical findings. The average sensitivity values of 2DUS, fusion 3DUS, DCT, and angiography for detection of PV invasion were 55.5% (range, 50.0%–66.7%), 83.3%, 61.1% (50.0%–66.7%), and 61.1% (50.0%–83.3%), respectively; the specificity was

95.8% (87.5%–100%), 100%, 100%, and 75.0%, respectively; and the accuracy was 78.6% (71.4%–85.7%), 92.9%, 83.3% (78.6%–85.7%), and 66.7% (64.3%–71.4%), respectively (Table 1).

Objectivity of the Diagnosis in Each Imaging Modality Attained

With regard to the assessment of PV invasion, the κ values of 2DUS, fusion 3DUS, DCT, and angiography were 0.57, 0.90, 0.63, and 0.49, respectively (Table 1). Two-dimensional ultrasonography and angiography achieved a moderate correlation, and DCT achieved a good correlation, whereas fusion 3DUS achieved an excellent correlation. This result indicated that the assessment of vascular invasion made by fusion 3DUS was subject to less variation among the 3 radiologists.

Discussion

In the assessment of PV invasion, fusion 3DUS was found to be more accurate than the other modalities; thus, its diagnostic performance was better than that of 2DUS. It seemed that observation of multiple sections by MPR imaging (Figure 2) or observation of stereoscopic images of an arbitrary section obtained by SVR imaging enabled a more objective and easier assessment of vascular invasion than when using limited sections obtained by 2DUS, DCT, and angiography. This seemed to be a factor that increased the accuracy of assessment of vascular invasion. In the patient shown in Figure 3, it was possible to predict SMV invasion noninvasively before the operation with the use of MPR images, which is impossible to visualize by 2DUS; thus, observation of multiple sections from MPR images contributed to a better diagnostic performance. In other reports on PV invasion assessed on the basis of surgical findings as the criterion standard, accuracy was reported to be 75% to 95% by CT,[2,5,8,10] 85% to 92% by angiography,[5,10,12] and 83% to 95% by 2DUS.[10,12,13] Although there are many criteria for venous invasion on imaging diagnosis, including CT, no absolute criterion has been determined yet. The criterion we adopted, dividing PV invasion into negative and positive categories as described in "Materials and Methods," was one of these, and we investigated venous invasion of the tumor by this criterion. The utility of the criterion was reported previously by Kaneko et al.[13]

In this study, the usefulness of fusion 3DUS was evaluated regarding objectivity in the assessment of images. In the assessment of PV invasion, only fusion 3DUS showed an excellent correlation, and the variation in the assessment of findings by fusion 3DUS was the smallest among the modalities used here. Observation of MPR and SVR imaging enables a more objective assessment of

Table 1. Assessment of PV Invasion and Objectivity of the Diagnosis by Each Imaging Modality

Modality	Sensitivity, n (%)	Specificity, n (%)	Accuracy, n (%)	κ
2DUS				
Radiologist A	4/6 (66.7)	8/8 (100)	12/14 (85.7)	
Radiologist B	3/6 (50.0)	8/8 (100)	11/14 (78.6)	
Radiologist C	3/6 (50.0)	7/8 (87.5)	10/14 (71.4)	
Average	(55.5)	(95.8)	(78.6)	0.57
Fusion 3DUS				
Radiologist A	5/6 (83.3)	8/8 (100)	13/14 (92.9)	
Radiologist B	5/6 (83.3)	8/8 (100)	13/14 (92.9)	
Radiologist C	5/6 (83.3)	8/8 (100)	13/14 (92.9)	
Average	(83.3)	(100)	(92.9)	0.90
DCT				
Radiologist A	4/6 (66.7)	8/8 (100)	12/14 (85.7)	
Radiologist B	3/6 (50.0)	8/8 (100)	11/14 (78.6)	
Radiologist C	4/6 (66.7)	8/8 (100)	12/14 (85.7)	
Average	(61.1)	(100)	(83.3)	0.63
Angiography				
Radiologist A	5/6 (83.3)	6/8 (75.0)	10/14 (71.4)	
Radiologist B	3/6 (50.0)	6/8 (75.0)	9/14 (64.3)	
Radiologist C	3/6 (50.0)	6/8 (75.0)	9/14 (64.3)	
Average	(61.1)	(75.0)	(66.7)	0.49

The denominator of sensitivity is the number of invasion positivity with surgical proof, and that of specificity is the number of invasion negativity with surgical proof.

vascular invasion; thus, the variation in the assessment by radiologists is smaller than in other modalities.

Fusion 3DUS is a noninvasive method that does not require any contrast agent; it may be repeated; and images are processed in a short period (about 15 minutes per patient). In addition, fusion 3DUS has advantages in that it has good spatial resolution, and one can obtain images of arbitrary sections.

There were several limitations in this study. The images may have been distorted because they were acquired by manual fan scanning. Therefore, patients were required to hold their breath enough for good images to be obtained. The number of cases in which pathologic findings were obtained was small. The 3DUS examination and construction of the 3D images were performed by a single radiologist. That 3DUS preceded 2DUS may cause a bias against scanning and construction of the 3D images; however, 3DUS scanning performed as uniformly as possible, and construction of the 3D images was conducted without any information about the diagnosis, including the findings of 2DUS; therefore, possible bias is thought to be a little. We did not assess arterial invasion, liver metastasis, or nodal involvement of the tumors in this study, but they are important factors in determining the indication for resection. The actual usefulness of 3DUS in the diagnosis of PC would be elucidated after assessment of all of these factors, and we must accomplish that in the next step.

In this study, we did not perform multidetector CT, which could create 3D images. Three-dimensional CT angiography is a very promising technique for the assessment of vascular invasion in PC.[6,14] The diagnostic ability of fusion 3DUS should be compared with that of 3D CT angiography in the future. Furthermore, EUS has an important role in diagnosis of PC.[5,15,16] By using EUS with a high resolution, it is possible to observe the tumor and surrounding vessels in

Figure 2. Multiplanar reconstruction image by fusion 3DUS shows the PV in contact with more than one third of the tumor (arrows). This variety of imaging section can never be obtained by 2DUS. In this case, PV invasion was confirmed in a resected specimen.

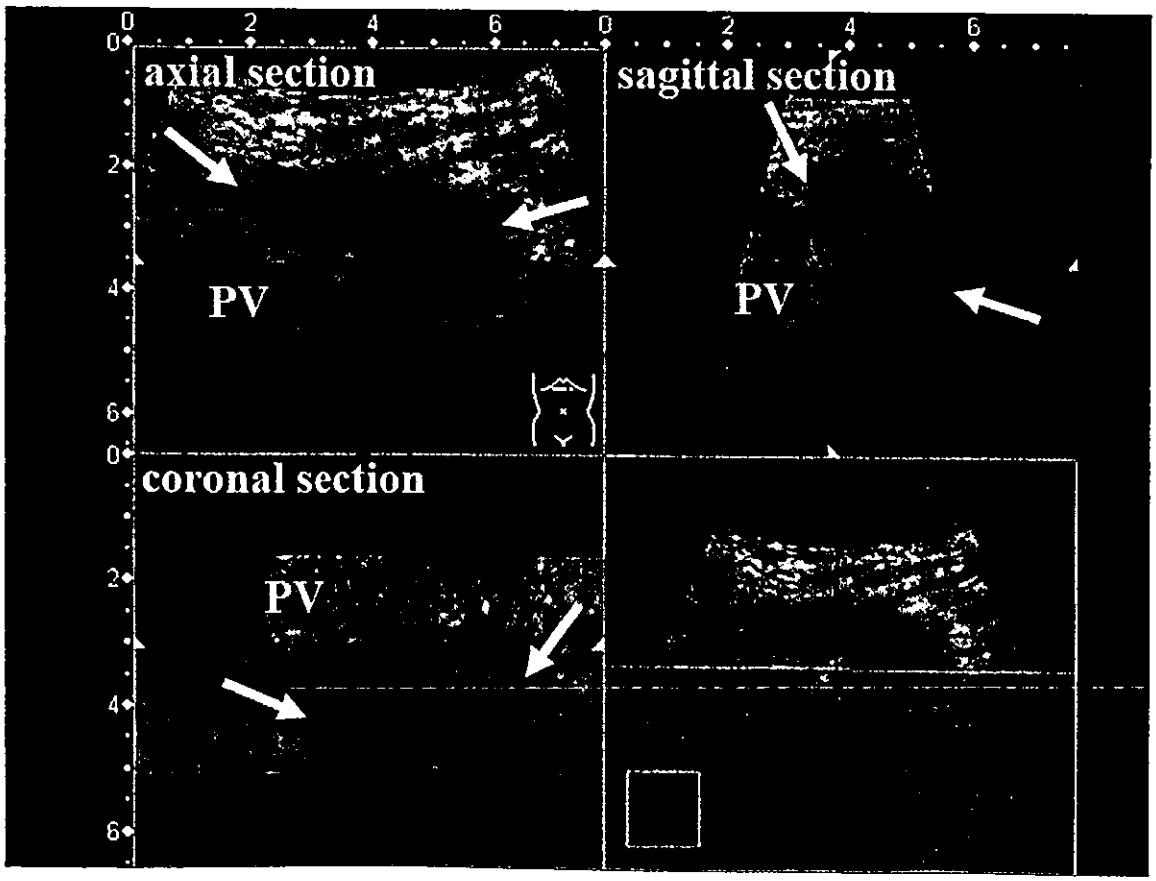
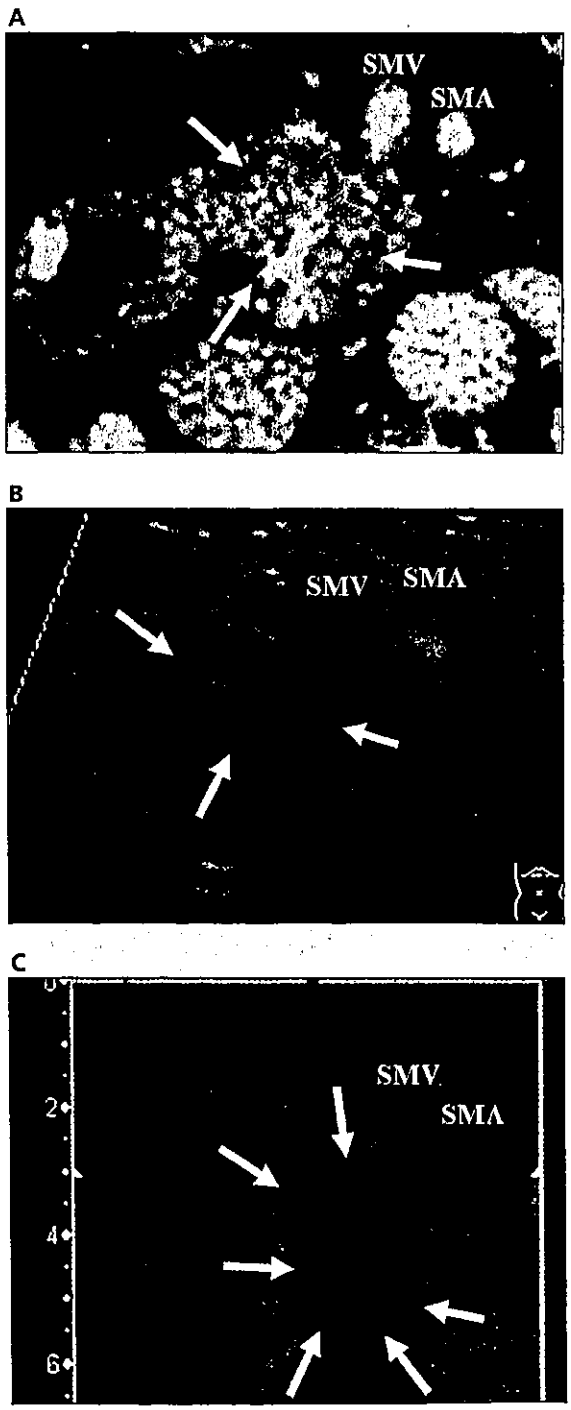


Figure 3. A, Dynamic CT shows the tumor (arrows) in the head of the pancreas, and the SMV is considered to be not in contact with the tumor. B, Two-dimensional ultrasonography shows the tumor (arrows) in the head of the pancreas. The SMV is in contact with less than one third of the tumor, judged negative for vascular invasion. C, Coronal section of the MPR image by fusion 3DUS shows the SMV contained by the tumor (arrows), indicating SMV invasion. In this case, SMV invasion was confirmed in a resected specimen. SMA indicates superior mesenteric artery.



detail, and it is useful for detection and staging of the PC. Moreover, it is also possible to perform fine-needle biopsy for diagnosis.

To obtain good images by fusion 3DUS, it was reported that 2D image data of 24 to 60 sections are required.[17] However, it seems that data from about 100 sections are required to assess PV invasion, as in this study.

Fusion 3DUS is being investigated in many fields. The usefulness of MPR images and 3D PD images has been reported. Specifically, it was reported that observation of images of various sections by 3DUS enables an easy determination of the physical relationship between an applicator and a tumor in the treatment of liver tumors by ablation.[18] It was also reported that 3DUS was useful for visualizing the continuity of intratumoral vessels in patients with hepatocellular carcinoma, producing images similar to those produced by angiography.[19]

In conclusion, fusion 3DUS is useful for diagnosis of PV invasion in patients with PC. Furthermore, fusion 3DUS may enable us to assess vascular invasion objectively. It is expected that, in the future, ultrasonographic equipment will be further improved technologically; for example, acquisition of volume-rendering images by automatic scanning at a high frame rate and improvement of image-processing speed.

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