Noninvasive Assessment of Tumor Vascularity by Contrast-Enhanced Ultrasonography and the Prognosis of Patients with Nonresectable Pancreatic Carcinoma

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BACKGROUND. Studies have shown that angiogenesis is one of the factors that influences the prognosis of patients with solid tumors, including pancreatic carcinomas. However, none have assessed noninvasively the relation between angiogenesis and prognosis in patients with pancreatic carcinoma. Contrast-enhanced ultrasonography (US) not only is a convenient, harmless, and noninvasive imaging modality, but it also provides detailed information on tumor vascularity. The objectives of this study were to assess the vascularity of pancreatic carcinoma noninvasively by contrast-enhanced US and to clarify the prognostic value of tumor vascularity in patients with nonresectable pancreatic carcinoma.

METHODS. Thirty-five consecutive patients with pathologically confirmed, nonresectable pancreatic carcinoma were examined with contrast-enhanced US before systemic chemotherapy. The correlations among tumor vascularity, clinicopathologic factors, and clinical outcomes then were analyzed statistically to investigate prognostic indicators.

RESULTS. The median time to progression (TTP) was longer in patients who had avascular tumors compared with patients who had vascular tumors (110 days vs. 28 days, respectively; $P = 0.0072$; log-rank test). The median survival also was longer in patients who had avascular tumors (267 days vs. 115 days, respectively; $P = 0.0034$; log-rank test). A multivariate analysis using a Cox proportional hazards model revealed that tumor vascularity was a significant, independent factor that influenced TTP ($P < 0.001$) and survival ($P = 0.022$) along with primary tumor size and serum lactate dehydrogenase (LDH) level, which are well known as prognostic factors in patients with pancreatic carcinoma.

CONCLUSIONS. The current results indicated that contrast-enhanced US may be useful in assessing the prognosis of patients with nonresectable pancreatic carcinoma who receive systemic chemotherapy. *Cancer* **2005;103:1026–35.**
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KEYWORDS: pancreatic carcinoma, contrast-enhanced ultrasonography, tumor vascularity, noninvasive assessment, prognostic factor, survival, time to progression, chemotherapy.

The incidence of pancreatic carcinoma has increased steadily over the last 4 decades, and this tumor now ranks as the fifth leading cause of cancer death in Japan. Despite an increased understanding of the biology of pancreatic carcinoma, the 5-year survival rate is < 5%, the worst in the Surveillance, Epidemiology, and End Results data base. This poor survival rate is attributed to the high incidence of metastatic disease at diagnosis and the relative chemoresistance of

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this tumor. Therefore, improvement in the outcome of patients with pancreatic carcinoma depends on the development of effective systemic therapies. Gemcitabine is the most common cytotoxic agent used for this disease. However, the objective response rate of patients with pancreatic carcinoma who are treated with this drug is $< 10\%$.[1,2] Thus, numerous clinical trials of systemic chemotherapy that include combinations of gemcitabine and other antitumor agents have been introduced in an attempt to improve the response rate and survival of patients with advanced pancreatic carcinoma.[3–7] However, we have found that even identical chemotherapy regimens bring about different outcomes in different patients. That is, some patients show improvements in survival and tumor response, whereas others only suffer from inconvenience and increased toxicity. It has been suggested that the burden of treatment should not be added to the suffering of those with advanced pancreatic carcinoma. Therefore, the identification of prognostic factors before treatment would be helpful in selecting the subgroups of patients for which chemotherapy improves survival and in determining efficient treatment strategies with reference to expected survival.

Recently, several studies have shown that angiogenesis is an important factor in the growth, progression, and metastasis of solid tumors, including pancreatic carcinomas,[8–11] and increases in tumor vessel count and in the expression of angiogenic factors, such as vascular endothelial growth factor (VEGF), have been associated with a poor prognosis in patients with pancreatic carcinoma.[12–14] However, all of those studies were conducted on patients who had undergone surgery, and no reports assessing noninvasively the association of angiogenesis with the prognosis of patients with pancreatic carcinoma have been published.

Contrast-enhanced ultrasonography (US) with the contrast agent Levovist (Schering AG, Berlin, Germany) can offer detailed information on tumor vascularity[15–17] and recently has been used to assess the vascularity of pancreatic tumors for differential diagnosis.[18–22] Therefore, the objectives of the current study were to assess the vascularity of pancreatic carcinoma noninvasively with contrast-enhanced US and to clarify the prognostic value of tumor vascularity in patients with nonresectable pancreatic carcinoma.

MATERIALS AND METHODS

Patients

The study included 35 consecutive patients with metastatic or locally advanced, inoperable pancreatic carcinoma and a baseline Karnofsky performance status $\geq 60\%$. These patients were treated by systemic chemotherapy at the Kanagawa Cancer Center Hospital, Kanagawa, Japan, between August, 2001 and February, 2004. US images, computed tomography (CT) scans, and chest X-rays were obtained as pretreatment staging studies to assess the local extension of the tumor and the presence of distant metastasis. Patients who had received previous chemotherapy or radiotherapy were excluded from the analysis. Pathologic confirmation of adenocarcinoma was obtained in all patients by surgical procedures or by fine-needle aspiration biopsy (Sonopsy; Hakko, Tokyo, Japan). All patients with obstructive jaundice underwent percutaneous transhepatic or endoscopic retrograde biliary drainage before chemotherapy.

Contrast Agent

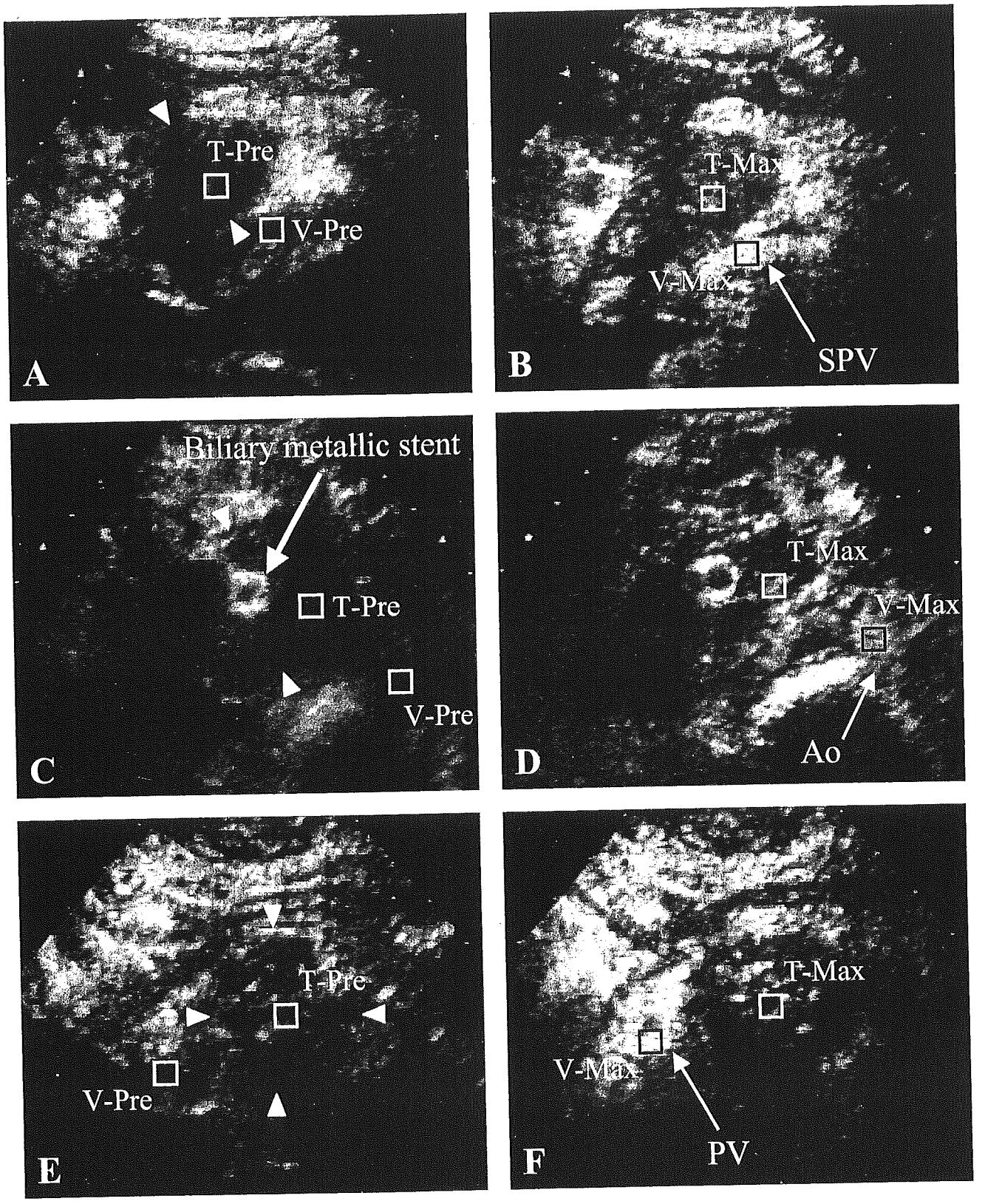
All patients were injected with the US contrast agent, Levovist, which is composed of 99.9% galactose and 0.1% palmitic acid. The agent (2.5 g) was shaken for about 10 seconds with 7 mL of sterile water to yield an opalescent suspension of air microbubbles. The suspension was equilibrated for a few minutes and then was injected manually through a 20-gauge cannula placed into the antecubital vein as a bolus infusion (300 mg/mL of contrast agent; approximately 7 mL in total). After the bolus injection of Levovist, a 0.9% saline solution was infused continuously at 5.0 mL per minute.

US Examination

We used a sonographic scanner (Sequoia 512; Acuson Corporation, Mountain View, CA) with a 4C1 curvilinear array transducer in the harmonic imaging mode, which transmits 2 MHz and receives 4 MHz of sound. We observed the pancreatic tumors from 5 seconds before to 60 seconds after the administration of Levovist, with a frame rate of 1–2 Hz at a mechanical index of 1.5. While imaging tumors, we fixed the transducer at the position where the tumor was drawn initially. US images were recorded continuously on videotape.

US Image Analysis

The US images were analyzed macroscopically for the presence and distribution of tumor vascularity. Patterns of tumor vascularity were described as diffuse enhancement if a vascular signal was identified throughout the lesion, as spotty enhancement if a microbubble signal was observed in part of the tumor, and as no enhancement if parenchymal flow was absent or was detectable only minimally (Fig. 1). In the next step, all images recorded on videotape were changed into digital data by Power Director software (version 2.0; CyberLink Corporation, Tokyo, Japan) in


T-Pre
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A
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Biliary metallic stent
T-Pre
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C
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V-Pre
E
T-Max
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PV
F

FIGURE 1

a Microsoft Windows 98 environment (Microsoft Corporation, Redmond, WA), and the effect of enhancement by Levovist was quantified in Photoshop (version 5.0; Adobe Systems Corporation, San Jose, CA). Transverse images of the tumor that were obtained before enhancement and at maximal enhancement were selected. Five-millimeter square regions of interest (ROIs) containing 324 pixels were placed in the most enhanced portion within the tumor (avoiding large vessels involved in the tumor) and in the surrounding vessel (aorta, celiac trunk, superior mesenteric artery, portal vein, or splenic vein) on the US image obtained at maximal enhancement. The mean signal intensity in each of the ROIs, which represented tumor intensity (TI) or vessel intensity (VI), was measured by using the histogram function. TI and VI before enhancement also were measured in the ROIs corresponding to those at maximal enhancement, and then the relative tumor enhancement (RTE) to the surrounding vessel enhancement was calculated as the percentage of the increase in TI compared with the increase in VI between preenhancement and maximal enhancement with the following formula: RTE (%) $= (TI_{max} - TI_{pre}) \times 100/(VI_{max} - VI_{pre})$, in which max is maximal enhancement and pre is preenhancement (Fig. 1). That is, RTE was used as an index of tumor vascularity.

Chemotherapeutic Regimens

All patients were treated with either gemcitabine, S-1, or a combination of both. Twenty-eight patients received chemotherapy with gemcitabine (1000 mg/m^2), which was administered once weekly for 3 weeks followed by 1 week of rest. Four patients were treated with S-1 (80–120 mg/body), which was given twice daily for 28 days followed by 2 weeks of rest. Based on previous studies,[23,24] body surface area (BSA) was used to determine the dose of S-1 administered, as follows: BSA $<$ 1.25 m^2, 80 mg; BSA = 1.25–1.5 m^2, 100 mg; BSA $>$ 1.5 m^2, 120 mg. The remaining 3 patients received combination chemotherapy with gemcitabine (400–1000 mg/m^2) and S-1 (40–100 mg/body) conducted as a Phase I trial at our hospital. Dose escalation was performed in a stepwise manner in which the dose of one drug was escalated while the dose of the other drug was kept constant. Chemotherapy was continued until disease progression, death, or unacceptable toxicity.

Factors Analyzed

Along with RTE, 12 other variables were selected in the current study based on previous investigations[25–33] and our own clinical experience. All data were obtained just before the beginning of systemic chemotherapy. The variables were as follows: age, gender (male or female), primary tumor location (pancreatic head or pancreatic body and tail), primary tumor size, tumor status (metastatic or locally advanced), histologic grade (differentiated [Grade 1 and 2] or undifferentiated [Grade 3]), serum albumin level, serum lactate dehydrogenase (LDH) level, serum C-reactive protein (CRP) level, serum carcinoembryonic antigen (CEA) level, serum carbohydrate antigen 19-9 (CA 19-9) level, and prior biliary drainage (presence or absence). The size of the primary tumor was estimated carefully using enhanced CT and US studies.

Statistical Analysis

The time to progression (TTP) and survival were measured from the first day of chemotherapy to the date of progressive disease and death, respectively. Patients who did not die were censored at the time they were last known alive. The statistical significance of the correlation between RTE and clinicopathologic parameters was assessed with the Mann–Whitney U test, the Kruskal–Wallis test, or the Spearman rank correlation test. TTP and survival were estimated using the Kaplan–Meier method, and statistical comparisons were made with the log-rank test. Univariate and multivariate analyses were performed to determine significant variables related to prognosis with a Cox proportional hazards model. All P values were obtained with a 2-tailed statistical analysis, and P values < 0.05 were considered statistically significant. Statistical analyses

FIGURE 1. The patterns of tumor vascularity and the relative tumor enhancement in pancreatic carcinomas. (A, C, and E) These ultrasonographic (US) images were obtained before administration of the contrast agent. (B, D, and F) These US images were captured at maximal enhancement after administration of the contrast agent. Five-millimeter square regions of interest (ROIs) are placed in the tumors and surrounding vessels on the unenhanced and enhanced US images. (A and B) Typical type of diffuse enhancement. (A) Poorly differentiated adenocarcinoma (arrowheads) measuring 2.9 cm in the pancreatic head. (B) Strong vascular signals are present throughout the lesion. The relative tumor enhancement in this image is 20.07%. (C and D) Typical type of spotty enhancement. (C) Moderately differentiated adenocarcinoma (arrowheads) measuring 3.9 cm in the pancreatic head. (D) Mild vascular signals are observed in part of the tumor. The relative tumor enhancement in this image is 16.90%. (E and F) Typical type of no enhancement. (E) Poorly differentiated adenocarcinoma (arrowheads) measuring 3.2 cm in the pancreatic body. Hyperechoic spots are seen before enhancement. (F) Hardly any vascular signals are detected in the tumor. The relative tumor enhancement in this image is 9.56%. Squares indicate ROIs. T: tumor; V: vessel; Pre: preenhancement; Max: maximal enhancement; SPV: splenic vein; Ao: aorta; PV: portal vein.

were performed using the Statistical Package for Social Sciences (version 11.0; SPSS Inc., Chicago, IL).

RESULTS

Patient Follow-Up

Tumor assessment with US, CT, or magnetic resonance imaging (MRI) was performed every 4 weeks after the first course of systemic chemotherapy, and tumor response was evaluated according to World Health Organization criteria.[34] Five patients achieved an objective partial response. Objective stable disease (≥ 58 days) was documented in 12 patients, and objective progressive disease was documented in 18 patients. No patients achieved an objective complete response. The sites of disease recurrence and causes of death were investigated carefully. At the time of this analysis, the median follow-up for the 9 survivors was 183 days (range, 58–603 days), whereas the remaining 26 patients died between 28 days and 549 days (median, 123 days). All deaths occurred as a result of disease progression. There were no significant differences in TTP or survival among the groups that received different chemotherapeutic regimens.

Quantitative Analysis of Vascular Signal Assessed by Contrast-Enhanced US

After administration of the contrast agent, the increase in TI at maximal enhancement, compared with the TI before enhancement, ranged from 0.66 to 39.48 (median, 9.40; mean ± standard deviation, 11.47 ± 8.88). The intensity of the surrounding vessels also increased in all patients, with the elevation of intensity ranging from 26.55 to 106.27 (median, 55.09; mean ± standard deviation, 62.19 ± 21.95). In all 35 patients, the RTE to the surrounding vessel enhancement ranged from 1.12% to 53.23% (median, 16.50%; mean ± standard deviation, 18.07% ± 13.09%). None of the patients experienced complications such as allergic reactions or renal dysfunction.

We divided all patients into 2 groups (a group with vascular tumors and a group with avascular tumors) according to the cut-off value, which represented the median of the RTE in all pancreatic carcinomas (16.50%). Vascular tumors were defined as tumors in which the RTE value was > 16.5%, whereas avascular tumors were defined as tumors in which the RTE value was ≤ 16.5%.

Patterns of Tumor Vascularity Assessed by Contrast-Enhanced US

Three patterns of tumor vascularity were identified by contrast-enhanced US: diffuse enhancement (2 of 35 patients; 5.71%), spotty enhancement (18 of 35 patients; 51.43%), and no enhancement (15 of 35 patients; 42.86%) (Fig. 1). The RTE in the 3 patterns of tumor vascularity ranged from 20.07% to 50.75% (median, 35.41%; mean ± standard deviation, 35.41% ± 21.69%) in tumors with diffuse enhancement, from 12.25% to 53.23% (median, 20.16%; mean ± standard deviation, 24.50% ± 10.72%) in tumors with spotty enhancement, and from 1.12% to 23.08% (median 6.10%; mean ± standard deviation, 8.05% ± 6.25%) in tumors with no enhancement (Table 1). Among 17 vascular tumors, 2 tumors showed diffuse enhancement, 14 tumors showed spotty enhancement, and 1 tumor showed no enhancement; whereas, among 18 avascular tumors, 4 tumors showed spotty enhancement, and 14 tumors showed no enhancement.

Patient Characteristics and Relation between RTE and Clinicopathologic Factors

The patient characteristics are listed in Table 1. The median age was 61 years (range, 43–76 years), 21 patients were male, and 14 patients were female. The primary tumor location was the pancreatic head in 13 patients and the pancreatic body or tail in 22 patients. The primary tumor size ranged from 2.62 cm to 7.56 cm (median, 4.31 cm). Twenty-four patients had evidence of metastatic disease, and 11 patients had evidence of locally advanced disease. The histologic grade was differentiated in 23 patients and undifferentiated in 12 patients. Prior to chemotherapy, eight patients with obstructive jaundice underwent percutaneous transhepatic or endoscopic retrograde biliary drainage. RTE was associated closely with the patterns of tumor vascularity. There were no significant correlations between RTE and the other clinicopathologic factors.

Prognostic Value of Tumor Vascularity

The median TTP was 28 days for patients with vascular tumors and 110 days for patients with avascular tumors. The TTP curves are shown in Figure 2A. There was a significant difference in TTP between the 2 groups ($P = 0.0072$).

RTE ($P = 0.001$), primary tumor size ($P = 0.013$), tumor status ($P = 0.015$), histologic grade ($P = 0.026$), and serum LDH level ($P = 0.028$) all showed a significant relation with TTP in the univariate analysis. However, none of the other variables (age, gender, primary tumor location, serum albumin level, CRP level, CEA level, CA 19-9 level, and prior biliary drainage) reached a level of significance. Multivariate analysis using a Cox proportional hazards model showed that RTE ($P < 0.001$), primary tumor size ($P = 0.006$), tumor status ($P = 0.022$), and serum LDH level ($P = 0.007$) were significant independent factors influencing TTP (Table 2).

TABLE 1
Relation between Relative Tumor Enhancement and Clinicopathologic Factors

Characteristics	Relative tumor enhancement (%)		
	No. of patients	Median (range)	*P* value
Patterns of tumor vascularity			
Diffuse enhancement	2	35.41 (20.07–50.75)	< 0.001[a]
Spotty enhancement	18	20.16 (12.25–53.23)	
No enhancement	15	6.10 (1.12–23.08)	
Age (yrs)			
Median	61	rs = −0.013	0.940[b]
Range	43–76		
Gender			
Male	21	16.23 (1.12–53.23)	0.522[c]
Female	14	16.60 (2.29–50.75)	
Tumor location			
Head	13	16.91 (1.28–42.97)	0.539[c]
Body-tail	22	15.04 (1.12–53.23)	
Tumor size (cm)			
Median	4.31	rs = 0.333	0.050[b]
Range	2.62–7.56		
Tumor status			
Metastatic	24	15.51 (1.12–53.23)	0.749[c]
Locally advanced	11	18.37 (2.29–36.35)	
Histologic grade			
Differentiated	23	16.47 (1.28–36.35)	0.224[c]
Undifferentiated	12	18.29 (1.12–53.23)	
Albumin (g/dL)			
Median	3.80	rs = −0.251	0.147[b]
Range	3.00–4.50		
LDH (U/L)			
Median	335	rs = −0.242	0.161[b]
Range	205–861		
CRP (mg/dL)			
Median	1.0	rs = 0.128	0.464[b]
Range	0.0–23.5		
CEA (ng/mL)			
Median	6.0	rs = 0.051	0.770[b]
Range	1.0–650.0		
CA 19-9 (U/mL)			
Median	845	rs = −0.192	0.269[b]
Range	11–425,000		
Prior biliary drainage			
Present	8	16.69 (12.24–42.97)	0.724[c]
Absent	27	16.50 (1.12–53.23)	
Anticancer agent			
Gemcitabine	28	16.48 (1.12–53.23)	0.949[a]
S-1	4	16.31 (9.56–23.08)	
Gemcitabine and S-1	3	16.91 (6.15–28.37)	

LDH: lactate dehydrogenase; CRP: C-reactive protein; CEA: carcinoembryonic antigen; CA 19-9: carbohydrate antigen 19-9; rs: Spearman rank correlation coefficient.
[a] Kruskal–Wallis test.
[b] Spearman rank correlation test.
[c] Mann–Whitney *U* test.

The median survival was 115 days for patients with vascular tumors and 267 days for patients with avascular tumors. The survival curves are shown in Figure 2B. The survival of patients with avascular tumors was significantly better ($P = 0.0034$).

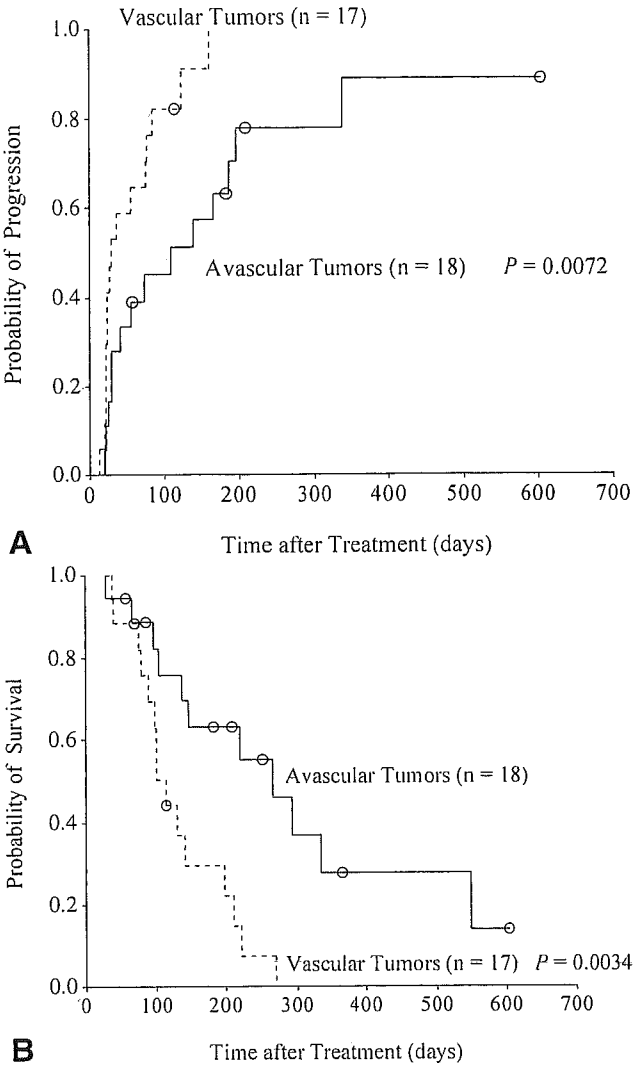

FIGURE 2. Progression and survival curves for 35 patients with nonresectable pancreatic carcinoma according to vascular and avascular tumors. The cut-off value of relative tumor enhancement (RTE) is the median in all pancreatic carcinomas (16.5%). (A) Patients who had avascular tumors (RTE ≤ 16.5%) had a significantly lower incidence of disease progression compared with patients who had vascular tumors (RTE > 16.5%; $P = 0.0072$; log-rank test). (B) The survival of patients who had avascular tumors was significantly better compared with patients who had vascular tumors ($P = 0.0034$; log-rank test). Open circles indicate censored patients.

RTE ($P = 0.003$), primary tumor size ($P = 0.002$), and serum levels of LDH ($P = 0.001$), CRP ($P = 0.001$), and CEA ($P = 0.025$), but not age, gender, primary tumor location, tumor status, histologic grade, serum albumin level, CA 19-9 level, or prior biliary drainage, showed a significant association with survival in the univariate analysis. Multivariate analysis using a Cox proportional hazards model showed that RTE (*P*

TABLE 2
Univariate and Multivariate Analyses of Prognostic Factors Associated with the Time to Disease Progression in Patients with Nonresectable Pancreatic Carcinoma

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Relative tumor enhancement	1.051 (1.021–1.081)	0.001	1.081 (1.035–1.128)	< 0.001
Age	1.028 (0.990–1.067)	0.149	1.027 (0.967–1.090)	0.390
Gender				
Male	0.987 (0.464–2.098)	0.973	0.646 (0.219–1.903)	0.428
Female				
Tumor location				
Head	1.046 (0.474–2.309)	0.912	1.108 (0.322–3.805)	0.871
Body-tail				
Primary tumor size	1.541 (1.095–2.169)	0.013	2.130 (1.242–3.653)	0.006
Tumor status				
Metastatic	2.916 (1.229–6.917)	0.015	4.847 (1.255–18.717)	0.022
Locally advanced				
Histologic grade				
Differentiated	0.421 (0.197–0.903)	0.026	0.992 (0.309–3.190)	0.990
Undifferentiated				
Albumin	0.730 (0.361–1.478)	0.382	0.365 (0.076–1.760)	0.209
LDH	1.003 (1.000–1.006)	0.028	1.007 (1.002–1.012)	0.007
CRP	1.061 (1.000–1.126)	0.050	0.842 (0.686–1.034)	0.100
CEA	1.001 (0.998–1.004)	0.429	1.000 (0.994–1.006)	0.978
Log of CA 19-9	1.171 (0.847–1.619)	0.339	0.647 (0.370–1.131)	0.127
Prior biliary drainage				
Present	0.663 (0.250–1.763)	0.411	0.134 (0.018–0.996)	0.050
Absent				

HR: hazard ratio; 95% CI: 95% confidence interval; LDH: lactate dehydrogenase; CRP: C-reactive protein; CEA: carcinoembryonic antigen; CA 19-9: carbohydrate antigen 19-9.

= 0.022), primary tumor size ($P = 0.039$), and serum LDH level ($P = 0.001$) had significant influence on survival as an independent factor (Table 3).

DISCUSSION

In the current study, TTP and survival were significantly longer in patients who had low tumor vascularity compared with patients who had high tumor vascularity. Furthermore, tumor vascularity was a significant independent factor that influenced TTP and survival along with primary tumor size and serum LDH level. Thus, we believe that contrast-enhanced US may be a valuable tool for prognostic evaluation and treatment planning in patients with nonresectable pancreatic carcinoma.

Pancreatic adenocarcinomas usually show hypovascular patterns on radiographic images obtained using contrast media, such as dynamic CT and angiography.[35,36] However, previous investigators have reported that adenocarcinoma itself showed some enhancement in a quantitative analysis of pancreatic enhancement during dual-phase helical CT.[37–39] Furthermore, several reports of pancreatic adenocarcinomas showed hypervascular findings.[40,41]

Contrast-enhanced US reportedly facilitates the detailed evaluation of tumor vascularity in hepatocellular carcinoma.[17,42] More recently, improved sensitivity to the contrast agent due to technical developments, such as harmonic imaging, has allowed better assessment of the vascularity of pancreatic tumors as well as hepatocellular carcinomas.[18–22,43] For example, Oshikawa et al.[18] reported that, after administration of the contrast agent, the change in TI of pancreatic carcinomas ranged from 0.1 dB to 18.6 dB. Nagase et al.[21] observed positive Doppler signals and intratumoral blood flow in 10.8% and 56.6%, respectively, of pancreatic ductal carcinomas. Ohshima et al.[43] found that the number of pancreatic carcinomas with definite vascular signal was greater than the number with almost no vascular signal (65% vs. 35%, respectively). Similarly, in the current study, we were able to detect tumor vascularity (diffuse and spotty enhancement) macroscopically in > 50% of the number of pancreatic carcinomas investigated with contrast-enhanced US (20 of 35 patients; 57.14%).

Oshikawa et al.[18] reported that, in 93% of tumors, any enhancement on dynamic sonography using Levovist was correlated closely with the grade of en-

TABLE 3
Univariate and Multivariate Analyses of Prognostic Factors Associated with Survival in Patients with Nonresectable Pancreatic Carcinoma

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Relative tumor enhancement	1.042 (1.014–1.072)	0.003	1.060 (1.008–1.113)	0.022
Age	1.019 (0.978–1.062)	0.364	1.005 (0.948–1.064)	0.874
Gender				
Male Female	1.054 (0.462–2.404)	0.900	1.207 (0.416–3.507)	0.729
Tumor location				
Head Body-tail	2.103 (0.856–5.170)	0.105	1.915 (0.492–7.458)	0.349
Primary tumor size	1.835 (1.242–2.710)	0.002	1.774 (1.030–3.054)	0.039
Tumor status				
Metastatic Locally advanced	2.061 (0.820–5.177)	0.124	1.648 (0.410–6.632)	0.482
Histologic grade				
Differentiated Undifferentiated	0.625 (0.274–1.424)	0.264	0.967 (0.285–3.286)	0.957
Albumin	0.556 (0.249–1.241)	0.152	0.441 (0.083–2.359)	0.339
LDH	1.005 (1.002–1.008)	0.001	1.010 (1.004–1.016)	0.001
CRP	1.146 (1.060–1.240)	0.001	0.970 (0.798–1.179)	0.759
CEA	1.004 (1.000–1.007)	0.025	1.000 (0.994–1.006)	0.994
Log of CA 19-9	1.260 (0.877–1.810)	0.211	0.565 (0.308–1.035)	0.064
Prior biliary drainage				
Present Absent	1.390 (0.496–3.898)	0.531	0.472 (0.072–3.100)	0.434

HR: hazard ratio; 95% CI: 95% confidence interval; LDH: lactate dehydrogenase; CRP: C-reactive protein; CEA: carcinoembryonic antigen; CA 19-9: carbohydrate antigen 19-9.

hancement on dynamic CT scans. Nagase et al.[21] examined tissue specimens obtained by surgical resection to assess the patterns of vascularity in pancreatic adenocarcinoma and showed that the ratio of patent vessels to total vessels was related to the degree of enhancement. Ohshima et al.[43] investigated the relation between contrast-enhanced Doppler signals and VEGF expression in pancreatic carcinomas and reported that VEGF expression was significantly higher in vascular tumors than in avascular tumors. In the current study, we could not compare tumor vascularity assessed by contrast-enhanced US with that assessed by histologic examination, because all lesions were nonresectable pancreatic carcinomas. However, reports indicate that contrast-enhanced US provides precise information on the vascularity of pancreatic carcinomas.

Angiogenesis is an important factor in the growth, progression, and metastasis of solid tumors, including pancreatic carcinomas.[8–11] Recently, it has been shown that the histologic assessment of intratumoral microvessel density and expression of angiogenic factors are important prognostic factors in pancreatic carcinomas.[12–14] However, all of those studies were conducted on patients who had undergone surgery, and no reports regarding the relation between angiogenesis and prognosis in patients with nonresectable pancreatic carcinoma have been published. The results of our current study provide evidence that contrast-enhanced US can be used to predict the outcome of patients with pancreatic carcinoma before treatment.

Patients with nonresectable pancreatic carcinomas have an especially poor prognosis and have many severe symptoms.[44] The analysis of prognostic factors before treatment may be helpful in selecting appropriate candidates for chemotherapy and determining treatment strategies. For example, patients who have a poor prognosis may be treated best with only supportive care because of their short survival. Alternatively, these patients may be treated with more aggressive treatment schedules, such as a more intensive multiagent chemotherapy or arterial infusion chemotherapy.[45] In the current study, we examined prognostic factors in patients with nonresectable pancreatic carcinoma. Among the variables investigated, RTE, primary tumor size, and serum LDH level were significant independent predictors of both TTP and survival, and tumor status was associated independently only with TTP in the multivariate analysis. Not only pri-

mary tumor size, serum LDH level, and tumor status but also age, histologic grade, and serum albumin, CRP, CEA, and CA 19-9 levels are well known prognostic factors in patients with resectable or nonresectable pancreatic carcinoma.[25–33] However, in the current study, multivariate analysis did not show that the latter six variables had significant predictive value for TTP or survival.

US examinations are essential to making a differential diagnosis of pancreatic masses, evaluating the extent of pancreatic lesions, and determining adequate treatments.[46,47] Furthermore, the results of our study lead us to conclude that the addition of contrast-enhanced US to conventional US may provide useful information more accurate than or equal to other prognostic factors in evaluating the malignant phenotype of pancreatic carcinomas or predicting chemotherapeutic effect. Contrast-enhanced US also has the advantage of not requiring exposure to X-rays and iodic contrast media, to which patients occasionally are allergic.[48] In fact, the contrast agent for US did not cause an allergic reaction and did not influence renal function in the current study.

However, contrast-enhanced US also has several flaws.[49,50] One major problem is that the method occasionally has limitations, such as a restricted image resolution of deep regions and poor visualization of the pancreas due to overlying abdominal gas. Another major problem is that contrast-enhanced US is not very precise in the evaluation of tumor vascularity, because it is dependent on the visual interpretations of the observer. In our past investigations, only 1 pancreatic lesion among > 100 pancreatic masses could not be detected using contrast-enhanced US. Moreover, the quantitative analysis of tumor vascularity enabled us to assess objectively the vascular information from pancreatic carcinomas. With regard to the quantitative analysis of tumor vascularity, two different types of analytic methods have been reported: One is the method for assessing the intensity of tumor enhancement, such as the contrast index[18,22] (contrast index = elevation of intensity in the tumor/elevation of intensity in the pancreatic parenchyma) and the RTE to the vessel enhancement used in this study, and the other is the method for assessing the area of tumor enhancement, such as the signal ratio[43] (signal ratio = vascular signal area/tumor area). However, the intensity of tumor enhancement was associated highly with the area of tumor enhancement according to the results from our study and from a previous report.[22] Oshikawa et al.[18] found that the contrast index was applicable only to patients in whom the pancreatic tumor and parenchyma can be scanned clearly in a single attempt. Therefore, in the current study on nonresectable, large pancreatic carcinomas, the RTE was more suitable for the quantitative analysis of tumor vascularity than the contrast index, because we could scan the tumor and surrounding vessels, but not the tumor and parenchyma, in a single attempt for all patients.

In conclusion, contrast-enhanced US ensures the assessability of tumor vascularity in pancreatic carcinomas. Patients who have avascular tumors have significantly longer TTP and survival compared with patients who have vascular tumors. Findings of contrast-enhanced US may be helpful in assessing the prognosis of patients with nonresectable pancreatic carcinoma who are receiving systemic chemotherapy.

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A. 膵　癌　VII. 膵癌の治療
進行・再発膵癌の治療／化学療法

Gemcitabine

大川伸一

Key words　gemcitabine，膵癌，化学療法

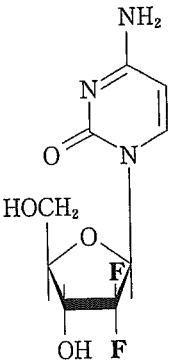
はじめに

各画像診断が進歩し続ける現在においてもなお，膵癌は早期診断が困難であり病院を訪れる膵癌患者の約80％は初診時に既に切除不能な進行膵癌である．したがって膵癌の治療において過去も現在も化学療法は極めて重要であるが，過去長きにわたって5-FU系の薬剤がその主流であった[1-3]．5-FUの進行膵癌に対する奏効率は6-26％であり，他剤と組み合わせてもこれを上回る奏効率は得られなかった．しかし1997年にBurrisら[4]が進行膵癌に対してgemcitabineと5-FUの成績を比較した研究を発表して以来，欧米ではgemcitabineが膵癌化学療法における標準薬となり，遅れて日本でも2001年から膵癌に認可された．

本稿ではgemcitabineについてその作用機序，膵癌に対する治療成績，最近の知見および今後の展望などについて述べる．

1. 作用機序[5]

gemcitabine(塩酸ゲムシタビン：dFdC)はデオキシシチジン(dCyd)の糖鎖の2′の水素をフッ素に置換したヌクレオシド誘導体で，DNA合成が主に行われているS期に特異的な作用を示す(**図1**)．gemcitabineは，細胞内で三リン酸化物(dFdCTP)に代謝された後，デオキシシチジン三リン酸(dCTP)と競合してDNA鎖に取り込まれ，DNAの合成を阻害する．



2′,2′-ジフルオロデオキシシチジン，dFdC

図1　Gemcitabineの構造

通常，DNA鎖に誤って取り込まれたヌクレオチドはDNAポリメラーゼにより除去されてDNA鎖が修復されるが，gemcitabineによるDNA鎖の伸長停止は，dFdCTPがDNA鎖に取り込まれた後，別のヌクレオチドが1つ付加されたときに起こる．そのため，DNAポリメラーゼにより除去されず，DNA鎖の修復が阻止され('マスクされたDNA鎖修復')，DNA合成が不可逆的に阻害される．

更にgemcitabineは，'自己増強'と呼ばれる

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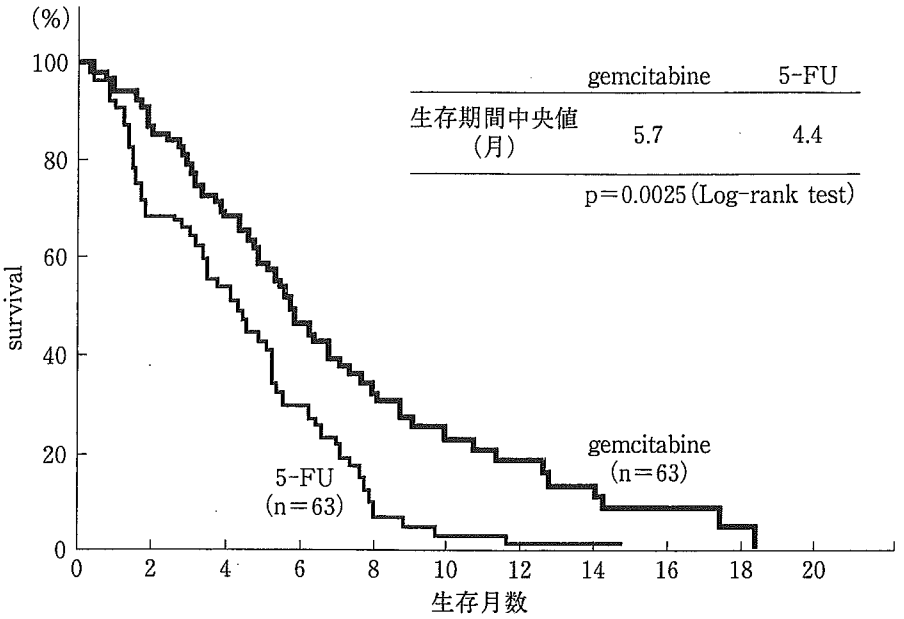

図2　生存期間の比較（gemcitabine 対 5-FU）（Burris HA ら[4]より引用）

代謝特性を有し，活性代謝物が効果的に作用して自己のリン酸化を促進し，gemcitabine の活性代謝物（dFdCTP）が正常な DNA 合成経路の dCTP 産生にかかわるリボヌクレオチドリダクターゼを抑制し，細胞内の dCTP 濃度を低下させる．またデオキシシチジンキナーゼは dCTP による負の制御を受けているため，細胞内の dCTP 濃度が低下するとデオキシシチジンキナーゼが活性化されて gemcitabine のリン酸化が促進され，かつ不活性化酵素を阻害するため，細胞内濃度が高濃度に維持され，dFCTP との競合過程において，DNA 鎖に有利に取り込まれ，強い抗腫瘍効果を示すと考えられている．

2. 治療成績

1997 年に Burris ら[4]は，切除不能の進行膵癌患者を無作為に 2 群に分け，一方に gemcitabine を，もう一方に 5-FU を投与し成績を比較し報告した．生存期間中央値（median survival time: MST）は 5-FU が約 4.4 カ月に対して gemcitabine が約 5.7 カ月と有意に延長していた（**図 2**）．更に 1 年生存率は 5-FU の 2％に対して gemcitabine は 18％であった．この研究の優れた点は症状緩和効果（clinical benefit response: CBR）を評価項目としたことである（**図 3**）．すなわち，化学療法により performance status（PS）と疼痛の改善を有意に認めたものを CBR 陽性とし評価したところ，5-FU では 4.8％の改善しか認めなかったが gemcitabine では 23.8％の症状緩和効果を認めた．有害事象も gemcitabine には生命を脅かすものはほとんど認められず，十分忍容性があった．また 5-FU に抵抗性の膵癌に対しても gemcitabine は CBR を 27％に認めた[6]．膵癌は疼痛や食欲低下など多くの症状を有する疾患であり，抗癌剤によりこの点が改善でき患者の QOL の向上を可能にしたことはそれまでの薬剤には認められなかったため画期的なものとして評価された．gemcitabine はこのようにそれまでの標準的薬剤であった 5-FU との比較試験を経た初めての薬として評価され膵癌に対する第一選択薬となっている．

3. 投与方法と注意点

最も標準的な投与方法は，体表面積を算出し 100 m*l* の生理食塩水に 1,000 mg/m^2 を溶解し，30 分以内の時間で点滴にて投与する．30 分以上時間をかけると毒性が強くなるため投与時間には注意が必要である．このとき制吐剤として 5-HT_3 製剤を同時に投与してもよい．また皮疹が出現した患者にはステロイド剤を併用するこ

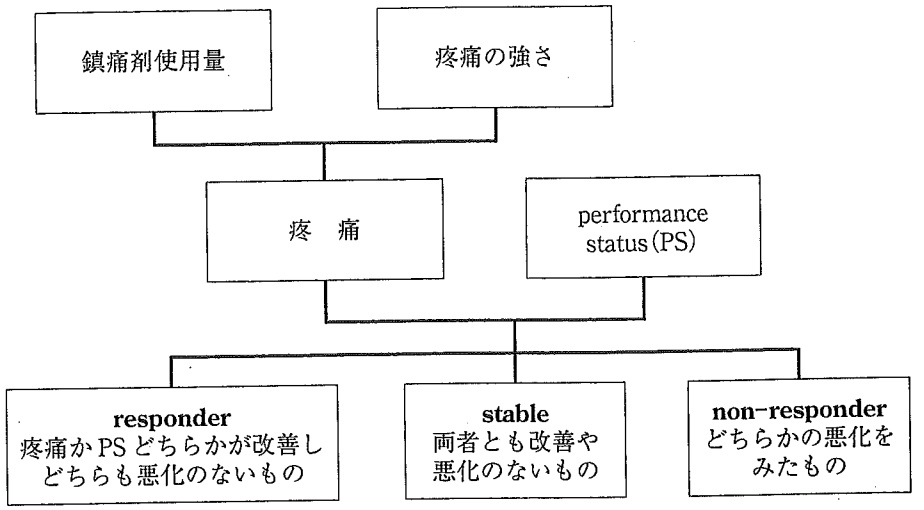

図3　症状緩和効果（clinical benefit response: CBR）アルゴリズム
（Rothenberg ML ら[6]より引用）

ともある．このようにしてgemcitabineをday 1, 8, 15に投与しday 22は休薬，28日間を1コースとし，これを繰り返す．有害事象は主として骨髄抑制，嘔気などであるが，骨髄抑制は投与日または前日に採血して白血球数や血小板数をチェックし，減量や休薬規準を厳守することにより危険は避けられる．嘔気なども制吐剤などにてコントロールが可能である．このような標準的な投与方法は外来治療が十分可能であり，外来にて治療を開始するcaseも増加している．

4. Gemcitabineの投与法変法および他剤との併用療法

a. 投与法の変法

gemcitabineの1回の投与に時間をかけることにより治療効果の改善をはかった研究が幾つか報告されている[7,8]．毒性は増強するが抗腫瘍効果も増強する場合がある．

b. 併用療法

様々な薬剤とgemcitabineの併用療法が試みられている（**表1**）．

1）Cytotoxicな薬剤

cisplatin, irinotecan, exatecan, oxaliplatinなどが報告されている．cisplatinについては早くから研究報告があり抗腫瘍効果がある程度増すことは認められている[9]．gemcitabineとこれらの薬剤との併用療法がgemcitabine単独療法に比べて優れているか否かを調べる比較試験が行われている．irinotecan[10]やexatecan[11]については米国にて比較試験が行われた．またcisplatin[9]やoxaliplatin[12]については欧州にて比較試験が行われ効果が期待された．しかしこれらの主立った薬剤については現在までのところgemcitabine単独療法に比べて抗腫瘍効果の改善はみられることがあるものの，生存期間の有意な延長は認められていない．

2）分子標的薬

欧米では種々試みられている．metalloprotease inhibitorであるmarimastat[13]，farnesyl transferase inhibitorであるtipifarnib[14]，epidermal growth factor receptor inhibitorであるerlotinib[15]などについてgemcitabineとの併用療法がgemcitabine単独療法より優れているかどうかの比較試験が行われた．marimastatおよびtipifarnibはgemcitabineと併用しても単独療法に比べて抗腫瘍効果やMSTの有意な延長は認められなかった．またerlotinibとの併用試験については生存期間の有意な延長は認めたが，その差はごくわずかであり（6.37カ月対5.91カ月），gemcitabineの単独療法に代わる標準治療とは成り得ていない（**表1**）．以上の結果，現段階では欧米にてもgemcitabineの単独療法がいまだに標準治療とされている．

表1 Gemcitabineの併用療法と単独療法の比較試験

drug	例数	奏効率	MST(月)	1年生存率
Gem+cisplatin	53	26%	6.9	—
Gem	54	9%	4.6	—
Gem+irinotecan	180	16%	6.3	～20%
Gem	180	4%	6.4	～20%
Gem+exatecan	175	8%	6.7	23%
Gem	174	7%	6.2	21%
Gem+oxaliplatin	157	26%	9.0	34.7%
Gem	156	16%	7.1	27.8%
Gem+marimastat	120	11%	5.4	18%
Gem	119	16%	5.4	17%
Gem+tipifarnib	341	6%	6.3	27%
Gem	347	8%	5.98	24%
Gem+erlotinib	285	8.6%	6.37	24%
Gem	284	8%	5.91	17%

5. Gemcitabineによる治療の問題点と将来の展望

gemcitabineは膵癌治療に初めて明確なevidenceとして有効性が示された薬剤であり，様々な苦痛を伴う膵癌に対して症状緩和効果を発揮する優れた薬剤である．しかし，gemcitabine治療後のsecond line therapyについてはほとんど選択すべき有効な薬剤がなく，実際の臨床上大きな問題である．またgemcitabineは抗腫瘍効果の点ではそれまでの薬剤と同等であり，他の薬剤との併用療法にて更に治療効果の改善が切に望まれるところである．現段階では単独療法を明らかに凌駕する併用療法はないが，例えば治療対象を更に細分化し，PSの良い患者にはcytotoxicな薬剤の併用療法を選択したり，また分子標的薬は特定の人種や性などを選んで効率的に使用されることになるかもしれない．

おわりに

前述のように世界中の多くの研究者がgemcitabineと新たな薬剤との有効な併用療法を開発すべく努力しているが，今後も当分はgemcitabineが膵癌化学療法のkey-drugであると考えられる．

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Editorial

Complications of endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) for pancreatic lesions

Article on page 907
Usefulness of endoscopic ultrasound-guided fine-needle aspiration biopsy for the diagnosis of pancreatic cancer
Ryozawa S, Kitoh H, Gondo T, et al.

Conventional endoscopic ultrasound (EUS) with radial scanning echoendoscopes has been used for more than 20 years. It has widespread application as a useful diagnostic tool for local cancer staging and for the detection of small lesions near the gastrointestinal tract. EUS is highly sensitive and capable of delineating even small lesions, but because it has relatively low specificity, differentiating between benign and malignant lesions can be difficult.[1] An endoscopic-ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) enables a tissue diagnosis to be made when a definitive diagnosis cannot be obtained with EUS alone.[2–5] Pancreatic mass lesions have been reported to be among the best indications for EUS-FNAB since it was developed.[6] The sensitivity, and specificity of EUS-FNAB for pancreatic neoplasms in different series are 64%–85%, and 90%–100%, respectively.[7] In this issue, Ryozawa et al.[8] reported that the diagnostic accuracy, sensitivity, and specificity of EUS-FNAB for pancreatic neoplasm are 89.4%, 82.1%, and 100%, respectively. Their results concur with findings reported so far. Thus EUS-FNAB shows high diagnostic accuracy, but it has not been widely accepted in Japan because of technical difficulties, the cost of the equipment, and the complications. Ryozawa et al.[8] pointed out these same three reasons to explain why EUS-FNAB is not widely used in Japan. They also stressed in their article that physicians in Japan are concerned about tissue samplings by EUS-FNAB because of the risk of procedural complications, including the peritoneal dissemination of tumor cells. Then, my editorial comments here make special reference to the complications of EUS-FNAB.

The overall complication rate of EUS-FNAB appears to be 1% to 2%.[7] The major EUS-FNAB complications reported are infections, bleeding, pancreatitis, and duodenal perforation.[9] In a large multicenter trial involving 554 consecutive mass or lymph node biopsies, only five complications (two perforations, three febrile episodes, and one hemorrhage) were observed, and all were nonfatal.[10] Cystic pancreatic lesions were reported to have a greater risk of infectious complications than solid pancreatic masses. Two deaths as a result of EUS-FNAB have been reported. One patient developed fulminate cholangitis associated with EUS-FNAB of a liver metastasis, and the other developed uncontrolled bleeding from a pseudoaneurysm after undergoing EUS-FNAB of the pancreas.[11] Ryozawa et al. reported no complications related to EUS-FNAB.[8] We have experienced EUS-FNAB-related complications in 0.79% (6/760) of cases.[12] They involved three peritumoral hematomas (two asymptomatic and one symptomatic), one massive bleeding in a case of gastric submucosal tumor using a trucut needle, one acute portal vein thrombosis in a case of advanced pancreatic cancer, and one rupture of a pancreatic pseudoaneurysm followed by massive gastrointestinal bleeding in a case of advanced pancreatic cancer. A case of acute portal vein thrombosis was treated with conservative therapy, and one of a rupture of a pancreatic pseudoaneurysm was treated with interventional radiology. These two cases might possibly have been caused by acute focal pancreatitis. The risk of acute pancreatitis after an EUS-FNAB of pancreatic masses was estimated in 19 centers and was found to have a frequency of 0.29% in a retrospective analysis and 0.64% in a prospective study.[13] Thus, although EUS-FNAB for pancreatic lesions has been evaluated as a good indicator for further treatments, largely because of the high technical reliability of pancreatic tissue sampling, the possibility of acute pancreatitis needs to be well considered.

The risk of tumor seeding caused by EUS-FNAB is strongly stressed in the dissenting opinions against this indication, especially in Japan. Although whether tumor seeding by EUS-FNAB occurs has not been fully determined, there have been some reports concerning

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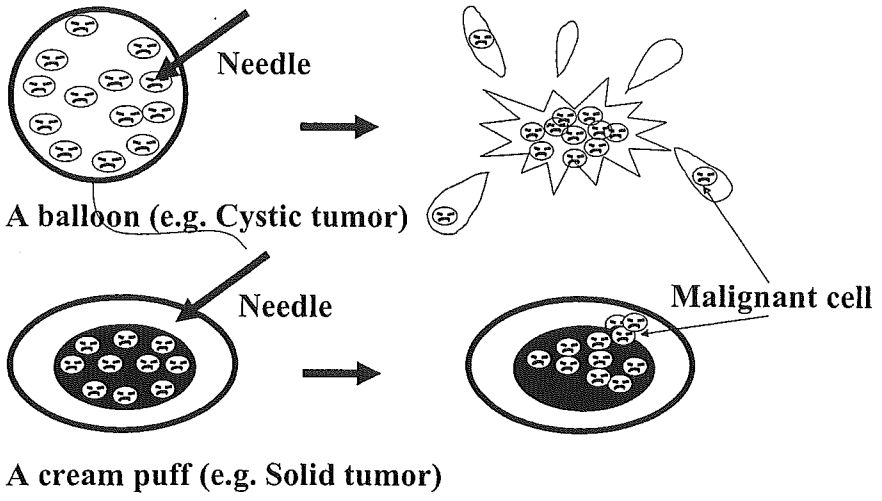

Fig. 1. The relationship between tumor seeding by endoscopic-ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) and histological type of pancreatic cancer. Theoretically, tumor seeding may occur more frequently in cystic malignancy like a balloon than in solid cancer like a cream puff

the needle tract seeding[14,15] by ultrasound-guided or CT-guided fine needle biopsy. According to these reports, the frequencies of needle tract seeding ranged from 0.003 to 0.009. The frequencies of needle tract seeding were extremely low by transabdominal biopsy, but a biopsy of pancreatic carcinoma was reported to be more dangerous with needle tract seeding (five of eight reported cases).[15] There have been only three reports of seeding possibly caused by EUS-FNAB. A case of intraductal papillary mucinous tumor in which EUS-FNAB caused dissemination has been reported.[16] In that report, tumor cells were clearly observed on peritoneal lavage cytology, and the patient finally died of carcinomatous peritonitis 20 months after surgery. Needle tract seeding has been reported in a case of melanoma[17] and one of pancreatic adenocarcinoma.[18] On the other hand, Micames et al.[19] reported that only one of the patients who had undergone neoadjuvant chemoradiation in the EUS-FNAB group had developed peritoneal carcinomatosis compared with seven in the percutanous FNA group (2.2% vs 16.3%; $P < 0.025$). They also reported that no patients with a potentially resectable tumor in the EUS-FNAB group had developed peritoneal carcinomatosis. The present authors[20] reported no significant difference between patients who had undergone EUS-FNAB and those who had not, with regard to the incidence of ascites in locally advanced or metastatic pancreatic cancer. Ishikawa et al.[21] reported several patients with a positive postoperative cytology for drained fluid from the pancreatic bed after a curative resection of pancreatic cancers had developed peritoneal carcinomatosis. Therefore disseminating cancer cells by FNAB seems not necessarily to cause peritoneal carcinomatosis. Theoretically, tumor seeding may occur more frequently in cystic lesions than in solid ones (Fig. 1) and in the body or tail lesions by the transgastric approach than in the head lesion by the transduodenal approach. In consideration of these data and ideas, EUS-FNAB should be carefully performed or not performed by the transgastric approach on a pancreatic body or tail lesions suspected of intraductal papillary mucinous neoplasm or mucinous cystic neoplasm of the pancreas.

It is my conclusion that EUS-FNAB is a method to acquire the tissue diagnosis of pancreatic mass lesions that is safe, efficient, and indispensable. However, it should be carefully performed with special reference to complications peculiar to a pancreatic biopsy, such as acute pancreatitis and tumor seeding.

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Editorial

Treatment strategy of intraductal papillary-mucinous tumor of the pancreas

Article on page 744

Mode of progression of intraductal papillary-mucinous tumor of the pancreas: analysis of patients with follow-up by EUS

KOBAYASHI G, FUJITA N, NODA Y, et al.

Intraductal papillary-mucinous neoplasm (IPMN) is closely related to mucous-secreting pancreatic cancer, first proposed by Ohashi et al. in 1982.[1] Because they established clinical criteria for this cancer, much information concerning this type of cancer has accumulated, mainly in Japan[2,3] and the definition of the tumor has been revised. This definition was based on clinical concepts and, more specifically, on the characteristic features of the papilla of Vater and pancreatic duct (excretion of mucin through the patulous orifice and accumulation of mucin in the dilated pancreatic duct). Since that time, a lot of new basic and clinical information about this unique tumor has been reported.[2,3] However, there has been some confusion, especially between intraductal mucin-hypersecreting tumor and mucinous cystic neoplasm, because mucus-secreting pancreatic cancer or mucin-producing pancreatic tumor was the clinical term. Recently, the disease criteria for IPMN and mucinous cystic neoplasm (MCN) have been largely established.[4–9] According to AFIP criteria,[5] IPMN is defined as an intraductal tumor formed of papillary proliferations of mucin-producing epithelial cells that have some gastroenteric differentiation. MCN is defined as a cystic pancreatic tumor formed of epitherial cells producing mucin; there is evidence of gastroenteropancreatic differentiation and "ovarian-type stroma." Most confusion was solved after the definition of IPMN and MCN, e.g., regarding the definite differences in clinicopathological aspects between the two. However, some debate still remains about the most effective treatment methods in cases of IPMN. Like MCN, the adenoma–carcinoma sequence applies to IPMN,[2,10] and distinguishing benign from malignant tumors is difficult even when using diagnostic imaging techniques. As a result, a strategy in which early recognition and resection are cornerstones has been widely accepted.[7] However, when considering surgery, the following characteristics of IPMN should be taken into account: the incidence of IPMN is highest among the elderly (high-risk patients); biologically, IPMN is a slow-growing tumor; and in about half of surgical cases, IPMN is histopathologically diagnosed as a benign tumor, hyperplasia, or ductal ectasia with a favourable prognosis.[11,12] Therefore, recent investigations to evaluate the abilities of various diagnostic imaging techniques to predict the degree of malignancy and to assist in determining the necessity of surgery,[13–15] and also understanding the natural history of IPMN are supposed to be helpful for planning appropriate initial and follow-up therapies.

The present study by Kobayashi et al.[16] and several long-term follow-up studies[17,18] on IPMN seem to indicate that IPMN grows very slowly when compared with conventional pancreatic cancer. Following excision of IPMN, the biological malignancy greatly differs from that of conventional pancreatic cancer.[11,12] Recent advances in diagnostic imaging have also increased the number of asymptomatic IPMN cases. Furthermore, because the incidence of cancer of pancreatic remnant or other organs has been reported to be high, it may be advisable to examine postoperative or follow-up patients with IPMN at regular intervals.[17]

Surgery is indicated when diagnostic imaging clearly reveals fistula formation or infiltration into the surrounding tissue, but therapeutic strategies for IPMN in this study varied greatly between physicians. While some performed surgery on all IPMN patients, some planned therapy based on such information as the diameter of the main pancreatic duct, cyst diameter, and the presence of a mural nodule.[13–15] Unfortunately, neither cytological examination of pancreatic fluids nor brushing cytological examination was able to accurately assess the malignancy of IPMN.[6] The results of the present study showed that the large branch duct with

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thick septum-like structures is one of the recommended signs for surgery.[16]

The results of long-term follow-up observations of IPMN patients showed that IPMN is a remarkably slow-growing tumor with a favorable prognosis. Treatment plans for IPMN should be based on the following diagnostic imaging findings, which indicate malignancy: infiltration into the surrounding tissue; main duct type; the presence of a nodule; and a largely dilated branch duct with thick septum-like structures (TSS). Furthermore, it may be advisable to examine postoperative or follow-up patients with IPMN at regular intervals. However, further prospective studies should be performed to clarify whether this treatment plan is appropriate or not.

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