Table 4 Nonhaematological toxicity during first cycle (in all cycles)

		No. of patients (cycles) with grade of toxicity						
		Anorexia		Nausea and vomiting		Rash		
Dose level	Total no. of patients (cycles)	1–2	3–4	1–2	3–4	1–2	3–4	DLT
1	3 (27)	1 (2)	0 (0)	1 (1)	0 (0)	3 (6)	0 (0)	
2a	6 (66)	1 (4)	1 (2)	1 (5)	1 (2)	3 (7)	1 (1)	1
2b	12 (61)	2 (5)	1 (1)	5 (8)	0 (0)	11 (12)	0 (0)	

Table 5 Duration of administration and dose intensity

			No. of cycles		Cycles with dose reduction in gemcitabine	
Dose level	S-1/gemcitabine ($mg\,m^{-2}$)	No. of patients	Total	Median (range)	No.	%
1	60/800	3	27	10 (3–14)	5	19
2a	80/800	6	66	7 (2–20)	31	47
2b	60/1000	12	61	4 (2–10)	6	10

Table 6 Objective tumour response

		Response				
Dose level	No. of patients	CR	PR	SD	PD	Response rate (%)
Level 1	3	0	1	2	0	33
Level 2a	6	1	3	1	1	67
Level 2b	12	0	5	3	4	42
Total	21	1	9	6	5	48

months (range, 2.2–16.1 months), the median survival time was 9.3 months (95% CI, 6.3–12.3%) and the 1-year survival rate was 35% (95% CI, 12–58%).

DISCUSSION

The primary end point of this trial was to define a chemotherapy regimen with an acceptable toxicity profile that could potentially improve the therapeutic efficacy of gemcitabine in patients with pancreatic cancer. S-1 has been selected as a candidate to be investigated in combination with gemcitabine in patients with pancreatic cancer because of its consistent activity as a single agent in this disease and because of the lack of cross-resistance between gemcitabine and 5-FU derived from S-1, as suggested by the observed activity of gemcitabine in patients refractory to 5-FU (Rothenberg *et al*, 1996). Also, gemcitabine combined with infusional 5-FU has been noted to possess synergy in *in vitro* cytotoxicity in a variety of malignant cell lines, including pancreatic cancer (Bruckner *et al*, 1998). Therefore, we expected additive and synergistic efficacy by combining gemcitabine with S-1, hoping that it would mimic the continuous infusion of 5-FU and also have DPD inhibition, leading to enhancement of antitumour activity (Takechi *et al*, 2002).

When considering this study regimen, the authors considered the possibility that this combination of gemcitabine with S-1 might produce more severe toxicities than those generated by gemcitabine alone. Thus, we tried to lessen the frequency of gemcitabine in this regimen, administering it twice every 3 weeks. S-1 has already undergone phase I and II testing in several solid tumours in Japan and western countries. The DLT was myelosuppression in a Japanese phase I study (Taguchi *et al*, 1997), and diarrhoea in a European and a North-American phase I study (van Groeningen *et al*, 2000; Hoff *et al*, 2003). In Japan, the standard single-agent dose is $80\,mg\,m^{-2}\,day^{-1}$ for 28 consecutive days, every 5–6 weeks, although the RD of S-1 was $70–80\,mg\,m^{-2}$ for 28 consecutive days, every 5 weeks in Europe, and $60\,mg\,m^{-2}$ for 28 consecutive days, every 5 weeks in the US, divided into twice-daily doses. Consequently, we conducted this study in an attempt to maintain the same dose intensity as that used in the standard S-1 administration, but in combination with gemcitabine. Both of the phase II trials in Japan revealed that low grades of gastrointestinal toxicities, including nausea, vomiting and anorexia, and of myelotoxocities such as neutropenia, occurred frequently during the third week of S-1 administration. Therefore, we adopted the regimen of S-1 administration for 14 consecutive days repeated every 3 weeks to avoid severe toxicity. The dose intensity of S-1 in this regimen amounts to almost the same level as that in Japanese standard regimen: S-1 for 28 consecutive days, every 5–6 weeks. Also, given that an *in vitro* study of pancreatic cancer cells has also demonstrated maximum synergy for gemcitabine when exposure to a thymidylate synthase inhibitor such as 5-FU precedes exposure to gemcitabine (Rauchwerger *et al*, 2000), we adopted the regimen of gemcitabine administration on days 8 and 15 after S-1 administration of each cycle.

Myelosuppression, especially neutropenia, frequently seen in the combination of continuous infusion 5-FU and gemcitabine, was predicted as the main toxicity of this study. In this study, the incidence of grade 3 or 4 neutropenia during the first cycle was higher than that of other toxicities, with four of six patients at dose

level 2a and three of 12 patients at dose level 2b having grade 3 or 4 neutropenia. On the other hand, the incidence of gastrointestinal toxicity during the first cycle and all cycles was low. Only one patient at dose level 2a had grade 4 anorexia and grade 3 nausea, one patient at dose level 2b had grade 3 anorexia.

A median number of 10 cycles were administered at dose level 1, seven cycles at dose level 2a and four cycles at dose level 2b. However, there was no significant difference among the median number of administered cycles at every dose level. During all treatment cycles in this study, the incidence of grade 3 or 4 neutropenia at dose level 2b was 10%, at dose level 1 it was 19%, and at dose level 2a it was 33%. Consequently, only six of 61 cycles at dose level 2b needed a dose reduction of gemcitabine compared to 31 of 66 cycles at dose level 2a, which required that.

The first course of chemotherapy was conducted by hospitalisation for all patients, but the second or subsequent courses could be performed at an outpatient clinic for 19 of 21 patients. The other two patients showed early progression of the disease. Moreover, oral administration of S-1, which eliminates the cost and inconveniences of infusion pumps and catheters with their potential risks of infection and thrombosis, also contributes to fewer hospital visits during this outpatient treatment. Anticancer treatment for APC would be preferable on an outpatient rather than an inpatient basis, given the short life expectancy and quality of life considerations. In treatment for patients with APC, it is important to not only improve the prognosis of APC but also create a feasible regimen of chemotherapy that does not require hospitalization. These results indicated that the combination at the RDs selected in this study is quite feasible in the outpatient treatment setting.

In conclusion, this combination chemotherapy with gemcitabine and S-1 was well tolerated. Although this trial was only a phase I study to determine the RD and feasibility of such combination, an encouragingly high response rate has been observed. This result is very promising, but the survival benefit in comparison with gemcitabine monotherapy needs to be confirmed in future studies.

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Phase II trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer

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We conducted a phase II trial of gemcitabine with S-1, oral fluorouracil (5-FU) prodrug tegafur combined with two modulators, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate, to evaluate the activity and toxicity of such a combination in metastatic pancreatic cancer (MPC) patients. Patients who had pathologically proven pancreatic cancer with metastatic lesions were eligible candidates for entry into the study. S-1 was given orally (30 mg m^{-2}) b.i.d. for 14 consecutive days and gemcitabine (1000 mg m^{-2}) was given on days 8 and 15. The cycle was repeated every 21 days. We enrolled 33 MPC patients. The median number of cycles was eight (range 1–20). Grade 3–4 toxicities were leucopenia (33%), neutropenia (55%), anaemia (9%), thrombocytopenia (15%), anorexia (6%), fever (9%), and interstitial pneumonia (6%). Objective responses were obtained in 16 patients (one complete response and 15 partial responses; response rate, 48%; 95% confidence interval (CI), 33–65). Median survival and 1-year survival rate were 12.5 months (95% CI, 5.9–19.1) and 54% (95% CI, 36–72), respectively. Combination chemotherapy with GEM and S-1 was well tolerated and yielded a significantly high response rate.
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Pancreatic cancer is one of the most frequently observed gastrointestinal cancers and its prognosis remains extremely dismal. It is the fifth leading cause of cancer death in Japan, as well as in the US and European countries (Matsuno *et al*, 2004). The 5-year survival rate is still poor, at less than 10%, which is commonly considered to be linked to the high incidence of metastatic disease even on initial diagnosis, as well as the relative chemoresistance of this tumour. Therefore, innovations in systemic chemotherapy are needed to improve the survival of patients with advanced pancreatic cancer (APC) (Glimelius *et al*, 1996; Evans *et al*, 1997).

Over the past few years, gemcitabine has been the most widely used chemotherapeutic agent in APC and was reported to yield significantly better symptom control of APC than 5-FU in a randomised phase III clinical study (Burris *et al*, 1997). However, the activity of gemcitabine in pancreatic cancer remains modest and there is a clear need to improve its efficacy by combining it with other anticancer drugs.

Chemotherapy combinations for the treatment of pancreatic cancer could involve prolonged or continuous infusion of 5-FU, because the combination of gemcitabine and 5-FU is shown to have a marked synergistic cytotoxic effect against pancreatic cancer cells in *in vitro* assay (Bruckner *et al*, 1998). Oral administration of 5-FU is not effective, owing to the inability to achieve plasma concentration of sufficient magnitude. An interesting way to increase the efficacy of 5-FU is through the inhibition of the degrading enzyme, dihydropyrimidine dehydrogenase (DPD).

S-1 is a new oral fluorinated pyrimidine developed by Taiho Pharmaceutical Co Ltd (Tokyo, Japan). The agent contains tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) in a molar ratio of FT : CDHP: Oxo = 1 : 0.4 : 1, based on the biochemical modulation of 5-FU (Shirasaka *et al*, 1996a, b). Tegafur, a prodrug of 5-FU, is gradually converted to 5-FU and is rapidly catabolised by DPD in the liver. 5-chloro-2, 4-dihydroxypyridine is a competitive inhibitor of 5-FU catabolism, being about 180 times more potent than uracil in inhibiting DPD (Tatsumi *et al*, 1987). When combined with 5-FU, this results in the prolonged maintenance of 5-FU concentrations, both in plasma and in tumours. In addition, it has been suggested that CDHP has the potential to enhance the antitumour activity of 5-FU against subcutaneous tumours in nude mice, using human pancreas carcinoma cells with a high tumoural DPD activity (Takechi *et al*, 2002). Oxo is an agent that decreases the phosphorylation of 5-FU in the gastrointestinal tract by inhibiting the enzyme pyrimidine phosphoribosyl transferase. Oxo preferentially localises in the gut rather than in the tumour and has a potential biochemical effect on the enzyme pyrimidine phosphoribosyl transferase, thereby selectively inhibiting the formation of 5-FU nucleotides in the gut and theoretically reducing gastrointestinal side effects (Takechi *et al*, 1997).

S-1 has undergone phase I evaluation in Japan, as well as extensive phase II studies in gastric, colon, head and neck and breast cancers, leading to registration in this country for gastric

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cancer. In phase II studies for advanced gastric cancer conducted in Japan, S-1 showed high response rates of 44–49% (Sakata *et al*, 1998; Koizumi *et al*, 2000). In studies outside of Japan, the phase II studies of S-1 against gastric (Chollet *et al*, 2003) and colorectal cancer (Van den Brande *et al*, 2003) in Europe by the EORTC-Early Clinical Study Group revealed moderate activity. The antitumour activity of S-1 in patients with pancreatic cancer has not yet been investigated outside Japan, but favourable results of S-1 monotherapy have been reported in Japanese early phase II and late phase II studies of patients with APC (Furuse *et al*, 2005; Ueno *et al*, 2005).

The administration of oral S-1 is more convenient and simulates the effect of continuous infusion of 5-FU. The combination of gemcitabine and 5-FU is shown to have a marked synergistic cytotoxic effect against pancreatic cancer cells in *in vitro* assay (Bruckner *et al*, 1998). We anticipated that combination chemotherapy of gemcitabine and S-1 would be effective through the synergistic activity of gemcitabine and 5-FU derived from S-1. Thus, we performed a phase I study to evaluate the safety of treatment combining GEM with S-1 and to determine the MTD of each drug in patients with APC (Nakamura *et al*, 2005). This combination chemotherapy was well tolerated and showed outstanding antitumour activity.

Therefore we conducted a phase II study of this combination chemotherapy in patients with metastatic pancreatic cancer (MPC) and assessed the efficacy and toxicity of this regimen.

PATIENTS AND METHODS

End point

The primary end point of this study was to determine the efficacy of a combination of gemcitabine and S-1 in MPC. The secondary end points were to assess toxicity, time to progression, and survival.

Patient selection

Patients with histopathologically proven APC with distant metastasis were eligible for the study. Other eligibility criteria included: 20–74 years of age, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less (ambulatory and capable of self-care), estimated life expectancy of more than 2 months, adequate renal function (normal serum creatinine and blood urea nitrogen levels), liver function (total bilirubin level $\leqslant$2.5 times upper normal limit (UNL) or $\leqslant$3 times UNL after biliary drainage if the patient had obstructive jaundice and serum transaminases (GOT, GPT) levels $\leqslant$2.5 times UNL or $\leqslant$3 times UNL), bone marrow reserve (white blood cell count between 4000 and 12 000 mm^{-3}, neutrophil count $\geqslant$2000 mm^{-3}, platelet count $\geqslant$100 000 mm^{-3} and haemoglobin level $\geqslant$9.5 $g\,dl^{-1}$) and pulmonary function (PaO_2 $\geqslant$70 mmHg). If the patients had a previous history of cancer treatment, that treatment (tumour resection, chemotherapy, immunotherapy, or radiotherapy) had to have been discontinued for at least 4 weeks before entry into the study. All subjects provided written informed consent.

The exclusion criteria were as follows: pulmonary fibrosis or interstitial pneumonia, marked pericardial effusion, severe heart disease, difficult to control diabetes mellitus, active infection, pregnant or lactating women, women of childbearing age unless using effective contraception, severe drug hypersensitivity, metastases to the central nervous system, severe neurological impairment or mental disorder, active concomitant malignancy, and other serious medical conditions. The patients that have pancreatic cancer with neuroendocrine characteristics were excluded.

This study was approved by the institutional review board of Chiba University Graduate School of Medicine.

Treatment plan

We gave orally 30 $mg\,m^{-2}$ S-1 twice daily, after breakfast and dinner for 14 consecutive days (from the evening of day 1 to the morning of day 15) followed by a 1-week break. Each capsule of S-1 contained 20 or 25 mg of FT. Individual doses were rounded down to the nearest pill size less than the calculated dose, given the available formulation. We administered 1000 $mg\,m^{-2}$ gemcitabine in a 30-min intravenous infusion on days 8 and 15 of each cycle. The cycle was repeated every 21 days.

The dose of S-1 was not adjusted for toxicity, because reducing dose of 30 $mg\,m^{-2}$ twice daily S-1 could not maintain effective blood concentration as 5-FU and the synergistic activity of gemcitabine and 5-FU derived from S-1 was weakened. Similarly, the dose of infusional 5-FU was fixed, and the dose of gemcitabine was adjusted for toxicity in the report of phase I/II study of gemcitabine combined infusional 5-FU (Hidalgo *et al*, 1999).

Full doses of both drugs were given in cases with grade 0–1 toxicity. If grade 2 toxicity was observed the gemcitabine dose was reduced to 800 $mg\,m^{-2}$ on days 8 or 15. In cases of grade 3 toxicity, gemcitabine administration was omitted. In cases of grade 4 toxicity, both drugs were stopped and adjourned for 1 week.

When grade 3 toxicity was observed in two consecutive cycles, or when grade 4 toxicity was observed even once, 800 $mg\,m^{-2}$ gemcitabine and 30 $mg\,m^{-2}$ twice daily S-1 were administered for subsequent cycles. When grade 3 or 4 toxicity was observed even at those doses, further reduction to 600 $mg\,m^{-2}$ gemcitabine and 30 $mg\,m^{-2}$ twice daily S-1 were administered for subsequent cycles. We abandoned this treatment when grade 3 or 4 toxicity was observed at that dose.

Pretreatment and follow-up studies

Pretreatment evaluation consisted of baseline studies including medical history, physical examination, WHO performance status assessment, blood chemistries, urine analysis, electrocardiograms, CA19-9 serum levels. Chest X-ray and abdominal computed tomography (CT) were performed within the period of 2 weeks before starting chemotherapy in order to accurately define the extent of the disease and the target lesions. Measurable disease was defined as a bidimensionally measurable lesion 10 mm or more in size on spiral CT scan. Patients were re-evaluated every two cycles (i.e. every 6 weeks) and then every 2 months after the withdrawal of the protocol. Blood cell counts were performed weekly during treatment and serum chemistry before every new cycle.

The National Cancer Institute (NCI) Common Toxicity Criteria (CTC) scale (version 2.0) was used to evaluate treatment-related side effects.

Assessment of efficacy

All patients were included in efficacy measurements on an intent-to-treat basis. Tumour responses were evaluated according to the World Health Organization's criteria (World Health Organization, 1979). A complete response (CR) was defined as the disappearance of all clinical evidence of the tumour for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or greater reduction in the sum of the products of two perpendicular diameters of all measurable lesions for 4 weeks or longer without any evidence of new lesions. Stable disease (SD) was defined as less than a 50% reduction or less than a 25% increase in the sum of the products of the two perpendicular diameters of all lesions for 4 weeks or longer without any evidence of new lesions. Progressive disease (PD) was defined as an increase of 25% or more in the sum of the products of two perpendicular diameters of all lesions, the appearance of any new lesion, or deterioration in clinical status that was consistent with disease progression. To assess objective response,

patients were evaluated every two cycles (i.e. every 6 weeks) by three independent radiologists

The time to progression was measured from entry into the trial up to the time when progression or death without evidence of progression was observed.

Overall survival was estimated from the date of first treatment to death or last follow-up visit.

Statistics

The number of patients required for the study was determined according to the optimal two-stage design. Threshold response rate and expected response rate were 10 and 30%, respectively. The sample size of this trial was 29 patients (α- and β-error probabilities 0.05 and 0.2, respectively). Time-related parameters were analysed using Kaplan–Meier on an intention-to-treat analysis.

RESULTS

All 33 patients with APC were registered between September 2003 and February 2005. Of 33 patients, 28 had liver metastasis, six had lung metastasis and one presented with peritoneal carcinomatosis and massive ascites only (Table 1). Although eligibility criteria included patients who had a previous history of cancer treatment (tumour resection, chemotherapy, immunotherapy, or radiotherapy) before entry into the study, in actuality no patients had previously received such treatment.

A total of 278 cycles (median 8, range 1–20) were administered. Eleven patients (33%) received full dose intensity (Table 2).

A total of 22 patients (67%) observed grade 2 or more toxicity needed dose reductions of administration of gemcitabine at least once. However, 13 out of these patients could continue this combination regimen at preplanned dose of 1000 mg m^{-2} of gemcitabine from the subsequent cycles. The other nine (27%) patients still continued at reduced dose of gemcitabine for the subsequent cycles. Thus, 24 (73%) of all 33 patients did not require one or more step of dose reduction of administration of gemcitabine for all cycles.

Table 1 Patient characteristics

Median age (range)	**61 (45–73)**
Gender	No. of patients (%)
Male	21 (64)
Female	12 (36)
ECOG PS	
0	11 (33)
1	20 (61)
2	2 (6)
Stage	
Locally advanced	0
Metastatic	33 (100)
Prior therapy	
Tumour resection	0
Radiotherapy	0
Chemotherapy	0
Sites of metastatic disease[a]	
Liver	28 (85)
Lung	6 (18)
Peritoneum	1 (3)

[a]Some were overlapping. ECOG = Eastern Cooperative Oncology Group.

Table 2 Duration of administration and dose intensity of gemcitabine

No. of patients	**33**
No. of cycles	
Total	278
Median	8
Range	1–20
Relative dose intensity of gemcitabine	
Average	0.81
Median	0.90
Range	0.43–1.0

Table 3 Tumour response

	Response				
No. of patients	**CR**	**PR**	**SD**	**PD**	**Response rate (%)**
33	1	15	9	8	48 (95% CI: 33–65%)

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

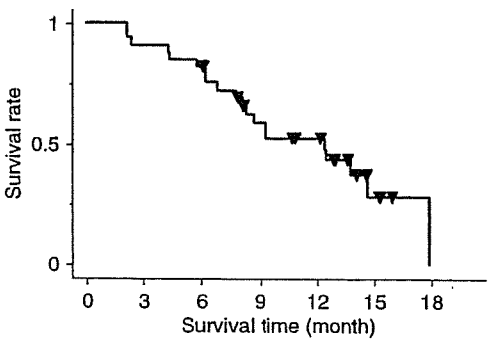

Figure 1 Overall survival curve for all 33 patients. Of 33 patients, 13 are still alive. Median survival time was 12.5 months (95% CI, 5.9–19.1 months). One-year survival rate was 54% (95% CI, 36–72%).

Efficacy and survival

Results are shown in Table 3. An overall objective response was observed in 16: one CR and 15 PR, and the overall response rate was thus 48% (95% confidence interval (CI), 33–65%). Although early discontinuation of treatment before the first evaluation was caused by early progression in two patients, all responses were confirmed 1 month later. Progressive disease was observed in eight patients (24%) including the two patients.

Median time to progression was 5.4 months (95% CI, 2.5–8.4 months). Overall survival was 12.5 months (95% CI, 5.9–19.1 months). The Kaplan–Meier estimate of survival is shown in Figure 1. The 1-year survival rate was 54% (95% CI, 36–72%). Overall, at the time of the last analysis, 20 patients had died, all of them due to progression of disease.

Toxicity

Maximum toxicity data for the 33 patients during all cycles of this chemotherapy are listed in Table 4. The National Cancer Institute/Common Toxicity Criteria grade 3 or 4 neutropenia, thrombocytopenia and anaemia were observed in 55, 15 and 9% of the patients, respectively, including two cases of febrile neutropenia; relevant grade 3 or 4 nonhaematological toxicities consisted of anorexia, nausea, vomiting and diarrhoea but were very limited.

Table 4 Maximum toxicity per patient during all cycles

	Grade 1		Grade 2		Grade 3		Grade 4	
	Per patient (%)	Per cycle (%)	Per patient (%)	Per cycle (%)	Per patient (%)	Per cycle (%)	Per patient (%)	Per cycle (%)
Leucopenia	5 (15)	78 (28)	14 (42)	66 (24)	11 (33)	16 (5.8)	0	0
Neutropenia	4 (12)	61 (22)	7 (21)	48 (17)	12 (36)	37 (13)	6 (18)	14 (5.1)
Anaemia	5 (15)	24 (8.7)	13 (39)	38 (14)	3 (9.1)	4 (1.5)	0	0
Thrombocytopenia	10 (30)	38 (14)	13 (39)	22 (8.0)	5 (15)	8 (2.9)	0	0
Anorexia	12 (36)	30 (11)	2 (6.1)	5 (1.8)	2 (6.1)	2 (0.7)	0	0
Nausea	14 (42)	26 (9.5)	2 (6.1)	4 (1.5)	0	0	0	0
Vomiting	4 (12)	6 (2.2)	0	0	0	0	0	0
Diarrhoea	1 (3.0)	2 (0.7)	0	0	0	0	0	0
Rash	14 (42)	15 (5.5)	12 (36)	12 (4.4)	0	0	0	0
Fever	5 (15)	10 (3.6)	0	0	3 (9.1)	3 (1.1)	0	0
Stomatitis	4 (12)	4 (1.5)	1 (3.0)	1 (0.4)	0	0	0	0
Interstitial pneumonia	0	0	0	0	2 (6.1)	2 (0.7)	0	0

The total number of cycles was 278, in a total of 33 patients.

Although a reduction of administration of gemcitabine was needed in two-thirds of the patients in this study because of grade 3 or 4 neutropenia, it was possible to limit grade 3 or 4 neutropenia during all cycles to 18% by reducing the quantity of administration of gemcitabine in subsequent cycles. There was no patient who gave up treatment because of neutropenia. There were two patients who stopped treatment because of interstitial pneumonia. Although grade 1 or 2 rash was observed in 79% of the patients for the first cycle, it had improved by the preventive administration of 4 or 8 mg dexamethasone before administration of gemcitabine for subsequent cycles.

DISCUSSION

Although the current standard regimen for patients with APC consists of single-agent gemcitabine, the objective responses are low and the median survival benefit is modest in comparison with 5-FU alone. Owing to the activity of gemcitabine, a variety of studies have now assessed its activity in combination with other chemotherapy or novel agents. These studies have shown varying degrees of success, with no combination showing clear evidence of significantly superior activity.

Preliminary favourable results of S-1 in patients with APC have been reported in Japanese early phase II study and late phase II study (Furuse *et al*, 2005; Ueno *et al*, 2005). As yet, the combination regimen of S-1 and gemcitabine for patients with APC has not been investigated. We previously performed a phase I study to evaluate the safety of treatment combining gemcitabine with S-1 to determine the MTD of each drug in patients with APC (Nakamura *et al*, 2005). That study indicated that the recommended dose was 30 mg m^{-2} twice daily of S-1 given orally for 14 consecutive days and 1000 mg m^{-2} gemcitabine given on day 8 and 15, and that the cycle should be repeated every 21 days. The main grade 3–4 toxicities observed during first cycle were neutropenia (33%), anaemia (10%), thrombocytopenia (14%) and anorexia (10%). Responses were one CR (5%) and nine PR (43%) among 21 patients. This combination was well tolerated and showed outstanding antitumuor activity. Therefore, we chose to use this regimen in a phase II study in patients with MPC.

This treatment administration as well as the tolerance profile can be considered as satisfactory regarding the toxicities observed although a reduction of administration of gemcitabine was required in two-thirds of the patients. Myelosuppression, especially neutropenia, frequently seen in the combination of continuous infusion 5-FU and gemcitabine, was predicted as the main toxicity of this study. The incidence of grade 3 or 4 neutropenia was greater than that of other toxicities, but, the incidence of gastrointestinal toxicity during all cycles was low.

Our efficacy results compare well with the other combination regimen in pancreatic cancer although it is difficult to compare phase II studies. Our response rate (48%) was much higher than that observed in gemcitabine combined with infusional 5-FU (19%) (Hidalgo *et al*, 1999) and in gemcitabine combined with capecitabine (19%) (Hess *et al*, 2003) or UFT (16%) (Feliu *et al*, 2000), which is also an oral prodrug of 5-FU, like S-1. Moreover, the median survival (12.5 months) and 1-year survival rate (54%) were favourable notwithstanding all patients in this study having distant metastatic disease.

Moreover, oral administration of S-1, which eliminates the cost and inconvenience of continuous infusion of 5-FU, requiring special pumps and catheters, with their potential risks of infection and thrombosis, also contributes to fewer hospital visits during this outpatient treatment. In fact, 31 of all 33 patients were treated at outpatient clinics. These results indicated that the combination at the recommended doses selected in this study is quite feasible in the outpatient treatment setting.

In conclusion, the results of this study demonstrate the tolerability and effectiveness of gemcitabine combined with oral S-1 in patients with APC. The toxicities observed in this study were mainly haematologic, with mild nonhaematologic toxicity. An encouragingly high response rate was observed. This result is very promising, but the survival benefit in comparison with gemcitabine monotherapy needs to be confirmed in a future randomised clinical trial.

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2. 膵癌

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動　向

膵癌は最も予後不良な悪性腫瘍の1つであり，その5年生存率は5～10%程度にすぎない．しかも近年，膵癌の死亡者数は漸増傾向にあり，その病態の解明と治療法の確立は21世紀における大きな課題である．

膵癌予防，早期発見にはリスクファクターの同定と高危険群の絞り込みが重要である．これまで多くの疫学的研究が行われているが，主たる病因はいまだ不明である．近年，分子生物学的手法を用い，膵癌の病態解明に向けて精力的に研究が行われている．またPanIN分類が提唱され膵癌前駆病変，発癌過程について新たな知見が集積されつつあり，早期診断への応用も期待される．

高率に遠隔転移を認める膵癌の治療において，有効なsystemic therapyの確立が重要である．現在，gemcitabine（GEM）をkey drugとした多くの併用化学療法が無作為化比較試験により検討されているが，GEM単剤を凌ぐ治療成績は示されていない．近年，分子標的治療薬を用いた臨床試験の報告がみられるが，無作為化比較試験にて検証していく必要がある．今後，さらなる分子生物学的な病態の解明とそれに基づいた新しい治療薬の開発，治療の個別化などが求められていく．

A. 疫学

これまでの疫学的研究により，喫煙が主たる膵癌発症の危険因子として認知されるが，この他にも糖尿病，慢性膵炎，家族歴，遺伝因子，性別（男性），人種（黒人），胃切除，職業，食生活，肥満などの因子が検討されている．

喫煙は25%～29%の膵癌発症に寄与し，そのodds ratioは1.6～5.4とされる[1]．喫煙による膵癌発症の機序は明らかではないが，N-Nitroso化合物との関連が想定されている[2]．また，近年Duellらは喫煙と膵癌発症におけるCYP1A1およびGSTT1（glutathione S-transferase）などの発癌関連酵素の遺伝子多型の関与につき検討し，GSTT1-null型において喫煙者の膵癌リスクが上昇することを示した[3]．

膵癌の家族歴は膵癌発症の危険因子の1つと考えられ，遺伝性膵炎，家族性黒色腫，家族性乳癌Peutz-Jugher 症候群，末梢血管拡張性運動失調症，遺伝性非腺腫症性大腸癌などいくつかの遺伝性疾患と膵癌の関連も報告されている[1]．Kleinらは一親等間で膵癌を有する家族性膵癌370家系を含む838家系5179人につき検討を行い，家族性膵癌の家系では膵癌発症のリスクが9.0［95%

confidence interval (CI) 4.5～16.1] と有意に高いことを示した．また，一親等の膵癌が1人の場合，膵癌リスクは 4.6 [95%CI 0.5～16.4]，2人の場合6.4 [95%CI 1.8～16.4]，3人の場合32.0 [95%CI 10.2～74.7] と一親等の膵癌罹患数が増加するに従い膵癌発症のリスクは増加した[4]．これまで複数の case-control study に基づき膵癌全体の約10%に家族因子が関与するとされてきたが，最近の大規模な研究報告ではBartschらの3.5%およびHemminkiらの1.1%とこれまでより低い結果が示されている[5,6]．

肥満と膵癌の関連については近年，これを指示する報告がなされた．Calleらは900,000人を対象としたprospective study においてBMI (body mass index) が30以上では膵癌リスクが男性で1.4倍，女性で1.3倍と上昇することを示した[7]．また，14件の疫学的研究を検討したメタアナリシスでは膵癌リスクはBMIの上昇とともに軽度上昇すると報告された[8]．

一方，膵癌発症の予防因子としてビタミンCや食物繊維の摂取などがあげられている[9]．また，アスピリンが膵癌リスクを低下させると報告されたが，最近大規模な前向き研究により否定的な見解が示された．JacobsらはCancer Prevention Study IIに登録された987,590人のコホートにつき1982年から2000年の期間経過観察を行い，膵癌による死亡とアスピリン投与歴の関連について検討した．観察期間中4577人が膵癌にて死亡したがアスピリン30回/月以上の投与例と未投与例の膵癌死亡の rate ratio は0.97 [95%CI 0.86～1.09] と両者に差を認めなかった[10]．また，Schernhammerらは88,378人の女性の集団を18年間経過観察し，161人に膵癌発症を認めたが，アスピリン投与歴と膵癌死亡との関連は認めなかった．(rate ratio 1.20 [95%CI 0.87～1.65]) [11]

B. 分子生物学

近年，膵管上皮内腫瘍性病変をpancreatic intraepithelial neoplasia (PanIN) とよび，平坦過形成 (PanIN-1A)，乳頭状過形成 (PanIN-1B)，異型乳頭状過形成 (PanIN-2)，高度異型乳頭状過形成/上皮内癌 (PanIN-3) の4段階に分類され，遺伝子異常や蛋白発現の解析が行われている[12,13]．PanIN分類の発表以来，膵癌前駆病変および発癌過程に関する新たな知見が集積されつつある．

膵癌の発生にはK-rasなどの癌遺伝子およびp16，p53，Smad4などの癌抑制遺伝子の関連が指摘される．K-rasの点突然変異は膵管腫瘍化の早期に起こり，膵癌の約75～90%以上にみられる．p16の不活化も比較的早期に起こるとされ膵癌の95%にみられる．p53，Smad4の不活化はそれぞれ50～75%，55%にみられ癌化の後期に起こるとされる[14]．この他，survivin[15] やsynuclein-γ [16] の過剰発現は膵癌の浸潤性発育や転移などに関与している可能性が示されている．また，Peutz-Jeghers症候群とSTK11[17]，家族性乳癌とBRCA1，BRCA2[18]，家族性黒色腫とp16[19] など，ある種の遺伝性疾患では膵癌発生と遺伝子異常の関連が指摘されている．

膵癌における染色体異常はこれまで18，13，12，17，6番染色体の欠失が報告されている．最近の報告では，9p，17p，18qの欠失が高頻度 (＞60%) にみられ，3p，6q，8p，17q，18p，21q，22qの欠失が40～60%にみられる[20]．なお，9pには前述の癌抑制遺伝子であるp16が，17pにはp53が，18qにはSmad 4がそれぞれ存在する．

膵癌発生およびその進展にはこれら遺伝子の異常に加え，低酸素やアシドーシス，フリーラジカルなど腫瘍細胞を取り巻く環境的因子やインターロイキン8，VEGFなどの細胞増殖，血管新生をつかさどる種々のgrowth factorの統制機構の破綻などが関与するものと考えられる[1]．新たな診

断および治療法の開発に膵癌発生の分子生物学的メカニズムの解明は不可欠であり，現在精力的に研究が行われている．

低酸素環境はVEGF産生の主要な促進因子であり，腫瘍の進展に関与している可能性が指摘される[21]．Okamiらは膵癌において，低酸素状態でアポトーシスを誘導するBNIP3の不活化が認められ，このBNIP3が膵癌発育を抑制する可能性を示唆している[22]．

また，Diazらはtissue-type plasminogen activator (t-PA) が腫瘍細胞外膜のannexin II蛋白に結合しplasminの産生を通じ腫瘍の発育を促進することを示し，この経路を阻害する薬剤が膵癌の治療薬となりうると述べている[23]．

TGFβは組織のhomeostasisを維持し，腫瘍化を抑制する働きを有する．しかし，その一方で腫瘍の浸潤，転移との関連も指摘されている[24,25]．Subramanianらは Smad4の欠失がTGF-βによる腫瘍進展に促進的に働く可能性を示唆し，TGF-β受容体シグナルを標的とした治療の可能性について報告している[26]．

C. 画像診断

近年，multidetector-row CT (MDCT) の登場により空間分解能，時間分解能が飛躍的に向上し，より精密な診断が可能となっている．MDCTでは薄いスライス厚で全膵の高速な撮像が可能であり，造影剤注入後のタイミングにあわせた全膵の経時的な評価が可能である．Fletcherらは膵癌においてMDCTを用いたtriple phase studyを行い，各時相における腫瘍描出能などにつき検討を行っている[27]．同報告ではarterial phase（造影剤注入開始より20～30秒後），pancreatic phase (40～50秒後)，hepatic phase (60～70秒後) に撮像を行い腫瘍描出はpancreatic phaseおよびhepatic phaseで優れ，血管侵襲の評価はhepatic phaseで良好であった．またBronsteinらは2cm以下の小膵癌18例に対しtriple phase helical CTを行い（MDCTは7例），スライス厚を薄くしpancreatic phaseで評価することにより以前と比べ診断能が向上したと報告している[28]．またMDCTでは得られたvolume dataを利用しmultiplanar reformation (MPR)，curved planar reformation (CPR) などの画像再構成により，任意の断面での評価が可能となり脈管浸潤などの膵癌進展度診断，resectabilityの評価に応用されている[29-33]．この他，これまで報告されたvolume renderingやmaximum intensity projection (MIP) によるCT angiographyもMDCTの登場により大いに進展する可能性がある[34,35]．

その一方，single cletecta CTを用いた膵癌切除例のprospectiveな検討においてリンパ節転移の正確な評価はCTでは困難と報告される[36]．また，Sorianoらは膵癌のresectabilityの評価のためEUS，CT，MRI，angiographyの有用性をprospectiveに検討し，局所進展，血管浸潤，転移巣，TNM stage，resectabilityのいずれにおいてもCTが優れたが，腫瘍径，リンパ節転移の評価ではEUSが有用であったと報告している[37]．

また，近年膵腫瘍の診断における造影超音波の有用性を示す報告が散見される．Kitanoらは膵癌49例を含む膵疾患65例に対しcoded phase inversion harmonic imagingを用いた造影超音波を行い膵癌の67%で腫瘍血管を描出可能であり微細な血流パターンの解析により膵腫瘍を鑑別しうると報告した[38]．Ohshimaらは膵癌69例にdynamic flowを用いた造影超音波を行い血流信号を認めた65%（A群）と認めなかった35%（B群）について比較検討を行い，A群ではB群に比べ肝転移は高率であり，VEGF発現量も有意に高値であった[39]．

D. 治療

1. 手術療法

以前より，切除可能な膵癌の術式として標準的なリンパ節郭清を行う標準切除か拡大リンパ節郭清を行う拡大切除かの議論がなされてきた．2002年，Yeoらは膵癌167例を含む膵頭部領域癌299例に対しradical group（膵頭十二指腸切除術＋遠位胃切除＋後腹膜拡大郭清）とstandard group（膵頭十二指腸切除術）の無作為化比較試験を報告した．同報告では術後合併症はradical groupで有意に多く（43% vs 29% p = 0.01），1年，3年，5年生存率は両者に有意差を認めなかった[40]．

一方，術後のadjuvant therapyとして，1980年代にGastrointestinal Tumor Study Group（GITSG）より放射線化学療法（CRT）およびその後の維持化学療法（CT）の有用性が報告された[41]が，その後も複数の無作為化比較試験が報告され議論が続いている．近年，European Study Group for Pancreatic Cancer-1（ESPAC-1）は膵癌治癒切除後の289人をCRT群（5FU + RT20Gy），CT群（5FU + Leucovorin），CRT＋CT群（5FU + RT20Gy→5FU + Leucovorin），無治療群の4群に無作為に振り分け比較試験を行った．その結果，術後維持化学療法を受けた場合（CRT + CT群，CT群）では5年生存率21%であり，受けなかった場合（CRT群，無治療群）の8%と比し有意に良好であった．（p = 0.009）[42] この報告では化学療法として5FU + Leucovorinを行っているが，現在GEMを使用した臨床試験が進行中である[43]．

2. 全身化学療法

1997年Burrisらの報告以後，切除不能進行膵癌に対する標準的治療はgemcitabine（GEM）による全身化学療法とされる[44]．しかし，その生存期間中央値（MST）は5～7カ月といまだ不良であり現在新たな治療法が検討されている．これまでGEM＋5FU vs GEM[45]，GEM + cisplain（CDDP）vs GEM[46]，GEM + irinotecan vs GEM[47]などの無作為化比較試験が行われたが，いずれもGEM単剤の治療成績を凌駕することはできなかった．

oxaliplatin（Ox）は新しいプラチナ系抗癌剤でありin vitroにおいてCDDPやcarboplatinに抵抗性の腫瘍細胞に対しても有効性が示されている[48]．2004年のASCOではGERCOR/GISCAD IntergroupによるGEM + Ox（GemOx）vs GEMの無作為化比較試験の最終報告が発表された[49]．GemOx療法はday1にGEM 1000mg/m^2 100分点滴静注（10mg/m^2/min），day 2にOx 100mg/m^2 2時間点滴静注としこれを2週間毎に繰り返した．GEM単独群はGEM 1000mg/m^2 30分点滴静注を週1回×7週/8週間→週1回×3回/4週間毎に投与した．切除不能局所進行および転移性膵癌326例が登録され，奏効率においてGemOx群が26.8%とGEM群の17.3%に比し有意に良好であったが（p = 0.04），MSTはGemOx群9.0カ月，GEM群7.1カ月（p = 0.13）と有意差はみられなかった．

一方，ReniらはPEFG療法 vs GEMの第III相試験を行いその有用性を報告している[50]．PEFG療法はCDDP 40mg/m^2 day1，epirubicin（epi）40mg/m^2 day1，5FU 200mg/m^2 day 1～28，GEM 600mg/m^2（10mg/m^2/min）day1，8の併用治療であり，GEM群は1000mg/m^2 30分点滴静注を週1回×7週/8週間→週1回×3回/4週間毎の投与とした．局所進行および転移性膵癌104例が登録されprimary endpointである4カ月無増悪生存率はPEFG群62%［95%CI 46～72%］，GEM群28%［95%CI 17～42%］とPEFG群で有意に良好であった．また奏効率はPEFG群40%とGEM群8.4%に比し良好であった．（p = 0.0003）しかしその一方，1年生存率はPEFG群38.5%［95%CI 26～52%］，GEM群21.3%［95%CI 12～35%］であり，overall survivalで有意差が得られ

ておらず大規模試験での検討が必要である．

この他，新しいトポイソメラーゼI阻害剤であるexatecan（DX-8951f）vs GEM[51]，GEM + exatecan vs GEM[52]，葉酸代謝拮抗剤であるpemetrexed + GEM vs GEM[53]，また近年，分子標的治療としてMMP阻害剤のMarimastatstat + GEM vs GEM[54]，BAY（12-9566）vs GEM[55]，farnesyltransferase阻害剤のtipifarnib + GEM vs GEM[56]などの無作為化比較試験が報告されたがいずれにおいてもGEM単剤が標準治療であることが確認された．この他分子標的治療として抗EGFRモノクローナル抗体（cetuximab）[57] + GEM，抗VEGFモノクロール抗体（bevacizumab）[58] + GEMなどが報告されており，今後の展開に期待される．

3. 放射線化学療法

過去の複数の無作為化比較試験の結果に基づき，遠隔転移のない外科的切除不能な局所進行膵癌の標準的治療は5FU併用放射線療法とされる．そのMSTは7～10カ月程度であり治療成績の向上を目指して，GEM併用放射線療法をはじめ種々の治療法が新たに検討されている．

OkusakaらはGEM 250mg/m^{2}の週1回投与と放射線療法（RT）1.8Gy × 28回の第II相試験を行いMST 9.5カ月，1年生存率28%であったと報告している[59]．主たる有害事象は白血球減少と食欲不振であり，1例が十二指腸出血および敗血症にて死亡した．また，MooreらはGEM 600 mg/m^{2}の週1回投与とRT 1.8Gy × 28回の第II相試験を行いMST 7.9カ月［95%CI 6.6～10.9カ月］，1年生存率31.1%［95%CI 7.4～54.8%］との成績を示した．しかし，有害事象としてgrade 3の血液毒性を12例（42.8%），非血液毒性を10例（35.7%），grade 4の非血液毒性を3例（10.7%）に認めた[60]．いずれの治療成績も5FU併用放射線療法の治療成績を凌ぐことはできず，ときに重篤な合併症を認めている．

これに対しMcGinnらはGEM併用放射線療法における有害事象と照射体積との関連を示唆し，予防的リンパ節照射を行わずmarginを1cmとして照射体積を縮小させ，GEMを通常投与量の1000mg/m^{2}に固定しradiation dose escalation studyを行った．同報告によれば，照射野縮小による局所制御の悪化はなく，推奨線量は1回2.4Gy，総線量36Gy，MSTは11.6カ月であった[61]．

この他にもGEM + CDDP併用放射線療法[62-64]，GEM + paclitaxel併用放射線療法[65]などGEMをkey drugとした放射線化学療法が検討されている．しかし，その一方，ときに重篤な有害事象が経験されたことから5FU併用放射線療法との比較において，GEM併用放射線療法に対し否定的な見解も少なくない[66]．現在，ECOGにてGEM併用放射線療法 vs GEMの無作為化比較試験が進行中であり結果が待たれる．

また，GEM以外の薬剤を増感剤とした放射線療法としてRadiation Therapy Oncology Group（RTOG）よりpaclitaxel併用放射線療法第II相試験が報告され，MST 11.2カ月，1年生存率43%との結果が示された[67]．一方，Goldsteinらは5FU 200mg/m^2/dayとRT 1.8Gy × 25～30回の同時併用療法の前治療および後治療にGEMによる全身化学療法を行うcombined modality therapyを報告した[68]．中間報告ながら局所進行膵癌においてMST 13.4カ月との成績が示されている．

また，近年新たな照射法としてintensity modulate radiotherapy（IMRT）についての報告がみられる．IMRTは照射野内のビーム強度を変化させることで腫瘍の三次元形状への線量集中度を格段に向上させる放射線治療法であり，原体照射に代わる照射法として高い注目を集めている．膵癌における報告では従来の照射法と比し肝，腎，胃，小腸など周囲組織への線量が抑えられ，有害事象が軽減される可能性が示された[69,70]．

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2. 膵　癌

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動　向

膵癌は最も予後不良な悪性疾患の1つであり，5年生存率はわずか5～10%に過ぎない．しかも近年，膵癌死亡者数は漸増傾向にあり有効な診断法および治療法の確立は21世紀における重要な課題である．

近年，検査機器や手技の発達に伴い，膵癌の発癌過程に対する分子生物学的な知見が多数報告される．またPanIN分類が提唱され，通常型膵管癌の発育，進展モデルとして遺伝子異常や蛋白発現の解析が行われている．さらに，従来の遺伝子レベルの解析に加え，新たにプロテオミクス技術を用いた蛋白質レベルの解析も始まっている．これら基礎的研究によって得られた新たな知見は，診断・治療の両面において徐々に臨床へフィードバックされつつある．

一方，高率に遠隔転移を認める膵癌の治療において，有効なsystemic therapyの確立が急務である．これまで全生存期間においてgemcitabine (GEM) を凌ぐ治療法はみられなかったが，ASCO (American Society of Clinical Oncology) において，GEMと上皮増殖因子受容体 (EGFR) チロシンキナーゼ阻害剤であるerlotinibの併用療法の治療成績が初めてGEM単独の成績を上回ったことは2005年の大きなトピックスである．標準的治療としてGEM + erlotinibが認知されるかについては議論の余地があるが，分子標的治療薬の有用性を示した研究としてその意義は大きい．

膵癌の予後改善にはさらなる病態解明が不可欠であり，それに基づいた新しい診断法や治療法の開発，治療の個別化などが求められていく．

A. 疫　学

現在，膵癌は米国における癌死の第4位を占める．また罹患者数 (32,180人) と死亡者数 (31,800人) の比率は近接しており，その差は約1.2%とあらゆる固形癌の中で最も予後不良である[1]．根治手術例における5年生存率は10～20%程度と報告されるが，いわゆる通常型膵管癌において長期生存例はまれである．Carpelan-Holmstromらは1990～1996年にフィンランドにおけるcancer registry and statisticsに膵癌として登録された4,922人のうち，5年生存例89人 (1.8%) の診断を病理学的に再検討したところ，実際に膵管癌であることが確認できたのはわずか10人のみであった[2]．この89人の中には内分泌腫瘍，乳頭部癌，intraductal papillary mucinous neoplasm,

膵炎，solid pseudopapillary neoplasm，serous cystadenomaなどが含まれていた．この報告において筆者らは膵管癌における長期生存の最も多い原因は誤った診断であると結論している．

これまでの疫学的研究により，喫煙が主たる膵癌発症の危険因子として認知されており，そのodds ratioは1.6～5.4と報告される[3]．この他にも糖尿病，慢性膵炎，家族歴，遺伝因子，性別(男性)，人種（黒人），胃切除，職業，食生活，肥満などの因子が検討されている[3]．

糖尿病を膵癌のリスクファクターとする疫学的研究は多くみられるが，膵癌のスクリーニング対象としての意義は確立されていない．糖尿病の罹患期間と膵癌の相対危険度の相関を指摘する報告があるが，罹患期間の長い高齢の糖尿病患者の絶対数は多く，膵癌診断のスクリーニング対象としての意義は限られる．一方，Chariらは新規発症の糖尿病が膵癌診断のマーカーになる可能性について報告している[4]．彼らは50歳以上で初めて糖尿病と診断された2,122人を対象とし，3年以内に膵癌を発症した患者の割合について検討した．全対象中，18人（0.85%）が膵癌を発症し，リスク比は7.94であった．なお，この18人中10人（56%）が糖尿病診断から6カ月未満に膵癌と診断されている．本研究の結果は50歳以上の新規発症の糖尿病患者100人につき約1人の割合で3年以内に膵癌が発症するということを意味しており，膵癌のスクリーニングという観点から興味深い検討である．

食事と膵癌の関係についても多くの疫学研究が実施されているが，一致した見解が得られていない[5]．主として症例対照研究により野菜や果物の摂取は膵癌発症と逆相関の関係にあると報告されるが，一方，過去に行われた前向きコホート研究ではこれらの関連について否定的な見解も示されている．また肉食と膵癌の関係についても研究者により異なった見解が示されている．近年，Michaudらは果物や野菜中心の食生活と，肉や脂肪中心の食生活について，膵癌発症の相対危険度を検討した結果，食事パターンと膵癌には相関はみられなかった[5]．

膵癌の家族歴は膵癌発症の危険因子の1つであり，遺伝性膵炎，Peutz-Jugher症候群，末梢血管拡張性運動失調症，家族性黒色腫，家族性乳癌，遺伝性非腺腫症性大腸癌などの遺伝性疾患と膵癌の関連も報告される[3]．Kleinらは一親等間で膵癌を有する家族性膵癌370家系を含む838家系5,179人につき検討を行い，家族性膵癌の家系では膵癌発症のリスクが9.0［95% confidence interval (CI) 4.5～16.1］と有意に高いことを示した．また，一親等の膵癌罹患数が増加するに従い膵癌発症のリスクは増加した[6]．

以前よりアスピリンが膵癌リスクを低下させる可能性について報告されているが，最近2つの大規模な前向き研究により否定的な見解が示された．Jacobsらは987,590人のコホートを対象として1982年から2000年の期間経過観察を行い，4,577人が膵癌にて死亡したがアスピリン30回/月以上の投与例と未投与例の膵癌死亡のrate ratioは0.97［95%CI 0.86～1.09］と両者に差を認めなかった[7]．また，Schernhammerらは88,378人を対象として18年間経過観察し161人に膵癌発症を認めたが，アスピリン投与歴と膵癌死亡と関連はみられなかった（rate ratio 1.20［95%CI 0.87～1.65］)[8]．

B. 分子生物学

近年，検査機器や手技の発達に伴い，膵癌の発癌過程に対する分子生物学的な知見が多数報告される．また，膵管上皮内腫瘍性病変をpancreatic intraepithelial neoplasia (PanIN) とよび，通常型膵管癌の発育，進展モデルとして遺伝子異常や蛋白発現の解析が行われている[9]．膵癌の発生に

はK-rasなどの癌遺伝子およびp16, p53, Smad4などの癌抑制遺伝子の異常に加え，プロモーター領域の異常メチル化などepigeneticな変化の関与が指摘される．また，これら遺伝子の異常に加え，低酸素やアシドーシス，フリーラジカルなど腫瘍細胞を取り巻く環境的因子やインターロイキン8, VEGFなどの細胞増殖，血管新生をつかさどる種々のgrowth factorの統制機構の破綻などが関連する．新たな診断および治療法の開発に膵癌発生の分子生物学的メカニズムの解明は不可欠であり，現在精力的に研究が行われている[3,10-12]．

K-rasの点突然変異は膵管腫瘍化の早期に起こり，膵癌の約90%以上にみられる．しかし，K-ras遺伝子変異は膵癌に特異的なものではなく，膵液や便中のK-ras遺伝子変異の検討では慢性膵炎や喫煙者などでも認められる．また，血液中のK-ras遺伝子変異の検討では，進行癌での陽性率は高いものの早期診断における有用性は否定的である[10]．近年，血液や膵液中のK-ras遺伝子変異を従来よりも高精度に定量可能なLigAmp法が報告され，今後の展開に期待される．本法ではK-ras遺伝子の変異型，野生型を同時に測定可能であり，膵癌と他疾患の鑑別に有用となる可能性がある[13]．

膵癌の発癌過程において多くの遺伝子メチル化異常の関与が報告されるが，これらの変化は正常膵組織において認められることはまれであり，膵癌診断への応用が期待される．現在，P16, ppENK, SPARC, Cyclin D2, SOCS1, TSLC1などの遺伝子において異常メチル化の関与が知られるが，プロモーター領域の異常メチル化は癌関連遺伝子の不活化の一因と考えられ重要な意義を有する[10]．最近ではBNIP3, CDH13, TFPI2などの異常メチル化による不活化が報告される[14-16]．BNIP3は低酸素状態で細胞にアポトーシスを誘導するregulatorであり，膵癌ではBNIP3の不活化によって低酸素環境においても細胞死に至らない可能性が示唆される[14]．また，TFPI2は広いspectrumを有するセリンプロテアーゼ阻害作用を有し，TFPI2の不活化と膵癌の発育，浸潤性の関連が指摘されている[16]．

現在，これら遺伝子レベルの解析に加え膵液や血液を利用した蛋白質レベルでの検討も始まっている．遺伝子のコードする最終産物は蛋白質であり，膵癌に特異的な蛋白質や蛋白発現のパターンを発見できれば診断に有用となる可能性がある．最近の報告では膵液や血液を対象としてSELDI (surface enhanced laser desorption ionization) やMALDI (matrix associated laser desorption ionization) などの新しいプロテオミクスの技法を用いた研究が試みられており，今後の展開に期待される[17-19]．

また，膵癌診断の新たなマーカーとして血清中のMIC-1やosteopontinなどの有用性が報告される[20-22]．Koopmannらは膵癌切除群，慢性膵炎群，健常コントロール群のおのおの50人につきMIC-1とCA19-9の比較検討を行ったが，膵癌切除群と健常コントロール群の鑑別においてMIC-1が有意に良好な成績であった（area under the curve 0.99 vs 0.78, $p = 0.003$）[21]．

C. 治　療

1. 局所進行膵癌に対する治療

明らかな遠隔転移はないが膵周囲への強い浸潤により切除不能と判断される場合，これを局所進行膵癌とよぶ．しかし，この定義は非常に曖昧であり施設により異なるのが現状である．従来，欧米では上腸管膜静脈や門脈への浸潤，または，上腸管膜動脈，腹腔動脈への浸潤などを有する場合，切除不能とされてきた[23]．しかし最近は手術手技の進歩により，門脈や上腸管膜静脈への浸潤については切除可能とする施設もみられる．局所進展により切除不能と判断された場合，5FUを使