Table 5. Clinical trials involving patients with locally advanced pancreatic cancer

Author	Chemotherapy	RT	Response rate (CR + PR)	Disease control rate (CR + PR + SD)	CA 19-9 response	MST (months)	1-year survival
Ishii (4)	5-FU	50.4 Gy	10%	90%	83%	10.3	41.8%
Saif (18)	Capecitabine	50.4 Gy	20%	85%	No data	17.2	58%
Moureau-Zabotto (20)	5-FU+oxaliplatin	55 Gy	26%	62%	No data	12.2	52.1%
Okusaka (16)	GEM 250 mg/m^2/w	50.4 Gy	21%	83%	76%	9.5	28%
Small (17)	GEM 1,000 mg/m^2/w	36 Gy	5.1%	84.6%	No data	No data	73%

Abbreviations: CR = complete response; GEM = gemcitabine; MST = median survival time; PR = partial response; RT = radiation therapy; SD = stable disease; w = week.

as modified radiotherapy approaches such as hyperfractionated (24) or intensity-modulated radiation therapy (25) have been conducted. Especially, gemcitabine-based chemoradiotherapy has been investigated in many studies because this agent has shown significant survival benefit compared with 5-FU in patients with metastatic pancreatic cancer. However, the combination of gemcitabine and radiotherapy is often related with severe toxicity, and therefore, Phase I studies have indicated the need to reduce the dose of gemcitabine when combined with standard-dose radiotherapy (26, 27). No regimens have achieved survival benefit over conventional chemoradiotherapy with 5-FU infusion.

On the other hand, in recent clinical trials, the feasibility of chemoradiotherapy using oral fluoropyrimidines such as UFT or capecitabine instead of 5-FU infusion has been reported for various solid tumors, including pancreatic cancer (18, 28). Capecitabine is an oral fluoropyrimidine carbamate that was designed to generate 5-FU preferentially at the tumor site. Tumor-selective generation of 5-FU could potentially improve the therapeutic ratio for capecitabine. To achieve tumor selectivity, capecitabine was designed to exploit the high concentrations of thymidine phosphorylase in the tumor compared with normal tissues (29, 30). Saif et al. (18) conducted a Phase II study of capecitabine and radiotherapy in patients with locally advanced pancreatic cancer. Twenty patients were treated with 50.4 Gy of radiotherapy and capecitabine, with a response rate of 20% and a 1-year survival rate of 58%. The authors emphasized the convenience and safety of oral administration. Oral administration is more convenient for patients than infusion regimens, and it avoids the risks of complications associated with intravenous administration. Considering the poor prognosis of patients with locally advanced pancreatic cancer, this approach seems to be an important option in terms of patients' quality of life.

In this treatment strategy, S-1 is an attractive candidate because it showed favorable antitumor effect in metastatic pancreatic cancer. To date, three Phase I studies of S-1 and concurrent radiotherapy in locally advanced pancreatic cancer have been reported including our regimen (15, 31, 32). Ikeda *et al.* (31) reported that the recommended dose of S-1 with concurrent radiotherapy (50.4 Gy in 28 fractions) was 80 mg/m^2/day on the day of irradiation. Shinchi *et al.* (32) investigated a regimen of S-1 and concurrent radiotherapy at a total dose of 50 Gy per 40 fractions for 4 weeks, and the recommended dose of S-1 was 80 mg/m^2/day given on Days 1–21. However, the efficacy and safety of this combination have not been fully evaluated in Phase II trials. Although the current Phase II study involved a small number of patients, the safety and efficacy results are promising. Recently, Kim *et al.* conducted a Phase II study, in which 25 patients were treated with S-1 and concurrent radiotherapy using a similar dose and schedule to those recommended in our Phase I study. In that study, this combination had a low toxicity profile and showed favorable efficacy with a response rate of 24% and a median survival of 12.9 months. The main difference between Kim's study and our Phase II study lies in maintenance chemotherapy. In Kim's study, 75% of the patients received gemcitabine-based chemotherapy after completion of radiotherapy, whereas most patients received maintenance chemotherapy using S-1 (97%) and salvage chemotherapy using gemcitabine (90%) in our study.

In summary, this study showed that oral S-1 at the dose recommended for systemic chemotherapy plus concurrent radiotherapy exerted a promising antitumor activity with acceptable toxicity in patients with locally advanced pancreatic cancer. S-1 has a great clinical advantage of oral administration, and thus this combination therapy is attractive alternative to conventional chemoradiotherapy using 5-FU infusion. This regimen should be further studied and its survival benefit in comparison with gemcitabine monotherapy or conventional chemoradiotherapy using 5FU infusion needs to be confirmed in a randomized controlled trial.

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ORIGINAL ARTICLE

Borderline resectable pancreatic cancer: rationale for multidisciplinary treatment

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Abstract
Background Borderline resectable pancreatic cancer (BRPC) appears to be most frequently related to a positive surgical margin and has a poor prognosis after resection. However, few reports are available on differences in tumor characteristics and prognoses among resectable pancreatic cancer (PC), BRPC, and unresectable PC.
Methods Records of 133 patients resected for pancreatic ductal adenocarcinoma and 185 patients treated as locally advanced PC (LAPC) were reviewed.
Results Twenty-four patients who initially underwent resection (BRPC-s) and 10 patients who were initially treated as LAPC (BRPC-n) met the criteria for BRPC. Prognosis of BRPC was significantly better than that of unresectable PC, but was significantly worse than that of resectable PC. BRPC-s showed more frequent nerve plexus invasion ($P < 0.01$), portal vein invasion ($P < 0.01$), and loco-regional recurrence ($P = 0.03$) than resectable PC. The positive surgical margin rate was not significantly higher in BRPC-s (29%) than in resectable PC (19%) ($P = 0.41$).
Conclusions BRPC had a poorer prognosis with more local failure than resectable PC although prognosis of BRPC was significantly better than that of unresectable PC. Considering the tumor and treatment characteristics, multidisciplinary treatment including resection is required for BRPC.

Keywords Pancreatic cancer · Resection · Borderline resectable pancreatic cancer

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Introduction

Borderline resectable pancreatic cancer (BRPC) is a newly proposed category that is now being established [1–4]. BRPC tumors can be understood radiologically and technically as an intermediate stage between resectable tumor and locally advanced tumor. These tumors are often treated as resectable in some specialized centers, but are more likely to be removed with positive surgical margins, with positive margins generally being predictive of decreased survival [5, 6]. Multidisciplinary treatment for BRPC aiming to improve surgical resectability and prognosis is thought to be a promising strategy [7]. The surgical oncology group of the MD Anderson Cancer Center proposed neoadjuvant chemotherapy and chemoradiation for BRPC patients, and they reported favorable outcomes, with a low positive surgical margin rate and relatively long survival after the combined modality treatment [1, 2]. In the report of the AHPBA/SSO/SSAT Consensus Conference, it was recommended that BRPC patients should be studied separately from those with resectable PC or unresectable PC [7].

However, little information is available on the differences in patient demographics and surgical results,

including prognosis and positive surgical margin rate, between resectable PC and BRPC that might support a rationale for selective neoadjuvant therapy for BRPC patients. Furthermore, prognosis of BRPC patients initially treated with nonsurgical treatment such as chemotherapy or chemoradiotherapy has not been well documented.

The objective of this paper was to investigate clinicopathological factors and prognosis in patients with resected BRPC and to compare the above factors between patients with resected BRPC and those with resectable PC. We also compared outcomes between BRPC and unresectable PC to assess prognostic significance of surgical resectability in PC patients initially treated with nonsurgical treatment for local development of the tumor.

Methods

Definition of BRPC

BRPC was defined in this study according to the criteria for resectability status in the "NCCN Practice Guidelines in Oncology" [4]. Namely, the criteria for BRPC were as follows: (1) severe superior mesenteric vein (SMV)/portal impingement; (2) <180° tumor abutment on the superior mesenteric artery (SMA); (3) abutment or encasement of the hepatic artery, if reconstructible; and (4) SMV occlusion, if of a short segment, and reconstructible. In this study, in terms of SMV/portal impingement, only patients with bilateral SMV/portal impingement were included.

Patient population

A total of 133 patients who had undergone surgical resection for pancreatic ductal adenocarcinoma at the National Cancer Center Hospital East between January 2002 and December 2008 were examined retrospectively. No patients received neoadjuvant chemotherapy or chemoradiation. According to staging by multidetector-row computed tomography (MDCT) findings, 24 patients met the criteria for BRPC, and the remaining 109 patients had resectable pancreatic cancer. The 24 BRPC patients who were initially treated with resection were classified as BRPC-s.

In order to find BRPC patients who had been initially treated with nonsurgical therapy, resectability status of a total of 185 patients who were treated as locally advanced pancreatic cancer (LAPC) between January 2002 and December 2008 was examined. According to staging by MDCT findings, 10 patients met the criteria for BRPC, and the remaining 175 patients had unresectable pancreatic cancer. The 10 BRPC patients who were initially treated with nonsurgical therapy were classified as BRPC-n. For treatment of the 10 BRPC-n patients, chemotherapy was performed in 7 and concurrent or sequential chemoradiotherapy in 3. For treatment of the 175 unresectable PC patients, chemotherapy was performed in 120 patients, radiotherapy in 2, and concurrent or sequential chemoradiotherapy in 53. After initial therapy, surgical resection was performed in 2 patients out of the 10 BRPC-n patients, and 3 out of the 175 unresectable patients.

All patients had a confirmed pathological diagnosis as pancreatic ductal adenocarcinoma.

Operative procedure

Patients with ductal adenocarcinoma of the head of the pancreas typically underwent subtotal stomach-preserving pancreaticoduodenectomy, and those with ductal adenocarcinoma of the body or tail underwent distal pancreatectomy. All patients underwent dissection of lymph nodes, including nodes along the common hepatic artery (CHA) and SMA and the regional lymph nodes around the pancreas, while patients with pancreatic head cancer underwent dissection of the lymph nodes in the hepatoduodenal ligament in addition. Dissection of para-aortic lymph nodes was not routinely performed. The operative procedure generally included resection of the nerve plexus around the SMA (half on the tumor side), the nerve plexus around the CHA, and the celiac plexus. When the portal vein (PV) or SMV was involved, PV/SMV resection was performed if reconstructible. However, when the SMA, CHA, or celiac axis was definitively involved at operation, the tumor was considered unresectable, unless distal pancreatectomy with celiac axis resection for pancreatic body cancer that involved the celiac axis or the proximal part of the CHA could be performed for curative intent. Intraoperative pathological assessment of the pancreatic cut end margin was performed using frozen tissue sections. If the cut end margin was positive for adenocarcinoma, further resection of the pancreas was performed.

CT examination

All images were viewed on soft-tissue windows of MDCT. Two-phase abdominal contrast-enhanced CT (arterial and portal venous phase) was performed with 16-slice MDCT scanner in all patients before initial treatment. Images were reconstructed at 2-mm intervals using a standard soft-tissue algorithm. For interpretation of CT images, axial images were mainly assessed, but oblique-coronal MPR images

were assessed concurrently whenever available. All interpretations in terms of resectability were made by experienced surgeons and a radiologist according to the aforementioned criteria for BRPC.

Pathology investigations

Each resected pancreatic specimen was examined histologically for the histological type, tumor size, arterial invasion, PV invasion, nerve plexus invasion, bile duct invasion, duodenal invasion, serosal invasion, retroperitoneal invasion, nodal status, and margin status. Histological diagnosis was performed according to the TNM classification system of malignant tumors published by the International Union Against Cancer (UICC), 6th edition [8].

Postoperative adjuvant chemotherapy

No patients received postoperative adjuvant chemotherapy until 2007. Since 2007, 35 patients have received adjuvant chemotherapy consisting of three weekly intravenous infusions of gemcitabine 1,000 mg/m^2 followed by a 1-week pause for 6 months. Alternatively, 80 mg/m^2 of oral S-1 was given for 4 weeks, followed by a 2-week pause, for 6 months in 10 patients on a protocol designed for patients after resection of pancreatic adenocarcinoma.

Survival

Patients were followed regularly at 3-month intervals with blood testing and MDCT. Survival and follow-up were calculated from the time of the operation to the date of death or last available follow-up, and for LAPC patients, from the time of beginning first treatment. Cause of death and recurrence status were recorded. The survivors' median follow-up time after surgery was 26.4 months.

Statistical analysis

The χ^2 test and Student t test were used for univariate comparisons of clinicopathological factors except preoperative CA 19-9 level between subgroups based on resectability status. Mann-Whitney's U test was used to compare preoperative CA 19-9 level between subgroups. Analyses of survival were performed using the Kaplan–Meier method [9], and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model [10]. A P value of <0.05 was considered significant. Statistical analysis was performed using SPSS version 17.0 software (SPSS, Chicago, IL, USA).

Results

MDCT findings for BRPC

During the period of this study, 24 of the 133 patients who initially underwent surgical resection for pancreatic ductal adenocarcinoma (i.e., BRPC-s) and 10 of the 185 patients who were initially treated as LAPC (i.e., BRPC-n) met the criteria for BRPC. Bilateral SMV/portal impingement was recognized in 11 patients (Fig. 1a, b), tumor abutment on the CHA in 7 (Fig. 1c), tumor abutment on the SMA in 16 (Fig. 1d), and tumor abutment on the celiac axis in 7.

Clinicopathological features of patients with BRPC

Table 1 summarizes the clinicopathological features of patients with resectable PC, BRPC, and unresectable PC. Tumor located in the head of the pancreas was significantly more frequent in patients with resectable PC than in those with BRPC ($P < 0.01$). Tumor size of BRPC was significantly greater than that of resectable PC ($P < 0.01$) and was significantly smaller than that of unresectable PC ($P < 0.01$). Preoperative CA 19-9 value seemed to increase as tumor resectability status progressed, but the differences were not significant.

Moreover, detailed pathological analyses were performed between resectable PC and BRPC-s. Tumor size of BRPC-s was 3.3 cm and tended to be greater than that of resectable PC ($P = 0.16$). Invasion of the artery, the PV, and the nerve plexus was seen in 14, 32, and 33 out of 109 resectable PC patients, and in 4, 14, and 18 out of 24 BRPC-s patients. Invasion of the PV and the nerve plexus was observed more frequently in BRPC-s than in resectable PC ($P < 0.01$). There was no significant difference in status of arterial invasion and invasion to other organs between the two subgroups. Patients with N1 were more frequently seen in BRPC-s patients ($n = 21$) than in resectable PC patients ($n = 81$), but the difference was not significant ($P = 0.19$). According to the TNM system [8], 1, 22, and 1 patients were diagnosed with stage IIA, IIB, and III disease, respectively, in BRPC-s patients, while 3, 25, 80, and 1 patients were diagnosed with IB, IIA, IIB, and III disease, respectively, in resectable PC patients.

Surgical resections of BRPC

In the BRPC-s group, subtotal stomach-preserving pancreaticoduodenectomy was performed in 15 patients, distal pancreatectomy in 4, distal pancreatectomy with celiac axis resection in 4, and total pancreatectomy in 1. In the 24 BRPC-s patients, 14 underwent SMV/PV resection, and 4 underwent celiac axis/CHA resection without reconstruction. The colon, jejunum, left adrenal gland, and left kidney

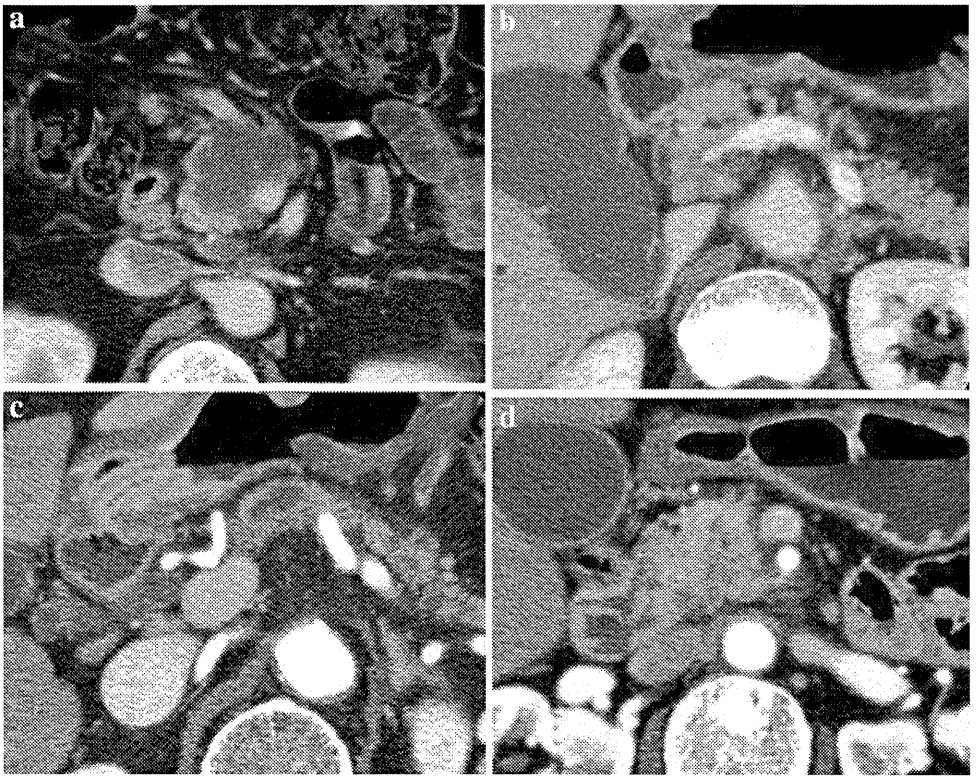

Fig. 1 Axial images from contrast-enhanced MDCT in patients with BRPCs. **a** Bilateral impingement of the SMV by the tumor located in the uncus. **b** Occlusion of a short segment at the confluence of the SMV and splenic vein. **c** Tumor abutment on the CHA. **d** Tumor abutment on the SMA with involvement of the root of the first jejunal artery

Table 1 Clinicopathological characteristics of patients with resectable PC, BRPC, and unresectable PC

Factor	Status of resectability			*P* value
	Resectable PC ($n = 109$)	BRPC ($n = 34$)	Unresectable PC ($n = 175$)	
Age, median (range) (years)	65 (34–85)	64 (40–84)	65 (34–85)	NS
Sex (*n*)				
Male	72	19	84	NS
Female	37	15	91	
Location of tumor (*n*)				
Head	77	17	90	<0.01*
Body or tail	32	17	85	
Histological type of tumor (*n*)				
Well	15	8	24	NS
Moderate/poor or others	94	26	84	
Not classified	0	0	67	
Tumor size, median (range) (cm)	2.8 (1.0–8.0)	3.5 (1.5–10.0)	4.1 (1.8–12.0)	<0.01**
CA 19-9, median (range) (U/ml)	106.0 (0.6–53,820)	191.5 (0.5–35,380.0)	339 (0.1–24,365.0)	NS

* Difference between resectable PC and BRPC

** Difference between resectable PC and BRPC, and between BRPC and unresectable PC

were also resected with pancreatic tumor in 2, 1, 1, and 1 patients, respectively. Positive microscopic surgical margins were more frequently seen in BRPC-s (7 of 24, 29%) than in resectable PC (21 of 109, 19%). However, the difference between the two groups was not significant ($P = 0.41$). There was no mortality. Eight postoperative complications were observed: five cases of pancreatic fistula, two cases of diarrhea, and one case of pleural effusion.

In the BRPC-n group, two patients underwent subtotal stomach-preserving pancreaticoduodenectomy for pancreas head cancer after systemic chemotherapy. One patient was alive with disease 35 months, and the other patient was alive without recurrence 21 months after beginning of the first treatment. Surgical resection was performed significantly more frequently in BRPC-n patients than in unresectable patients ($P < 0.01$).

Survival after resection of BRPC

The 2-year survival rates [estimated median survival time (MST)] of 109 patients with resectable PC, 34 patients with BRPC, and 175 patients with unresectable PC were 50.4% (24.6 months), 33% (15.7 months), and 13.5% (10.3 months), respectively (Fig. 2a). The prognosis of BRPC patients was significantly better than that of unresectable PC patients ($P < 0.01$), but was significantly worse than that of resectable PC patients ($P = 0.04$). In patients who initially underwent surgical resection for PC, survival was significantly shorter after resection of BRPC-s than after resection of resectable PC ($P = 0.03$) (Fig. 2b). On the other hand, in patients who were initially treated with nonsurgical therapy, the prognosis of BRPC-n was significantly better than that of unresectable PC patients ($P = 0.03$) (Fig. 2b).

Correlation between clinicopathological factors and overall survival in 133 PC patients who initially underwent resection

To identify prognostic factors for survival after resection of pancreatic ductal adenocarcinoma, clinicopathological factors and overall survival were analyzed in the 133 patients (Table 2). Maximum size above 3 cm ($P = 0.03$), nerve plexus invasion ($P < 0.01$), N1 ($P = 0.03$), SMV/portal impingement ($P = 0.02$), resectability ($P = 0.03$), and no adjuvant chemotherapy ($P < 0.01$) were significantly correlated with overall survival. The aforementioned factors were entered into multivariate analysis with a Cox proportional hazards model. Resectability was excluded from the analyses because it was strongly correlated with SMV/portal impingement. Nerve plexus invasion ($P < 0.01$), N1 ($P = 0.03$), and no adjuvant chemotherapy ($P = 0.02$) were predictors for decreased overall survival.

Recurrences after resection of BRPC

After surgical resection, 22 patients (92%) in the BRPC-s group and 75 (69%) in the resectable PC group developed recurrences. The locations of the initial recurrences in BRPC-s and resectable PC, respectively, were as follows: liver in 7 (29%) and 34 (31%); local recurrence in 10 (42%) and 23 (21%); lymph node in 4 (17%) and 13 (12%); peritoneum in 9 (38%) and 21 (19%); and other organs in 3 (13%) and 10 (9%). Local recurrence was more frequent in the BRPC-s group than in the resectable PC group ($P = 0.03$).

Postoperative adjuvant chemotherapy

Seven (29%) of 24 BRPC-s patients and 28 (26%) of 109 resectable PC patients received postoperative adjuvant chemotherapy. Gemcitabine was administered to 6 BRPC-s patients and 19 resectable PC patients, while S-1 was administered to 1 BRPC-s patient and 9 resectable PC patients. The median duration from operation to the start of adjuvant chemotherapy was 64 days in the BRPC-s patients and 56 days in the resectable patients (NS). Six (86%) BRPC-s patients and 19 (68%) resectable PC patients completed the 6-month course of adjuvant chemotherapy. Relative dose intensity of adjuvant chemotherapy was 85% in BRPC-s patients and 78% in resectable PC patients (NS).

Survival by postoperative adjuvant chemotherapy

In the resectable PC group, survival in patients with adjuvant chemotherapy (MST: not reached) was significantly better than that in patients without adjuvant chemotherapy (MST: 20.5 months) ($P < 0.01$). However, in

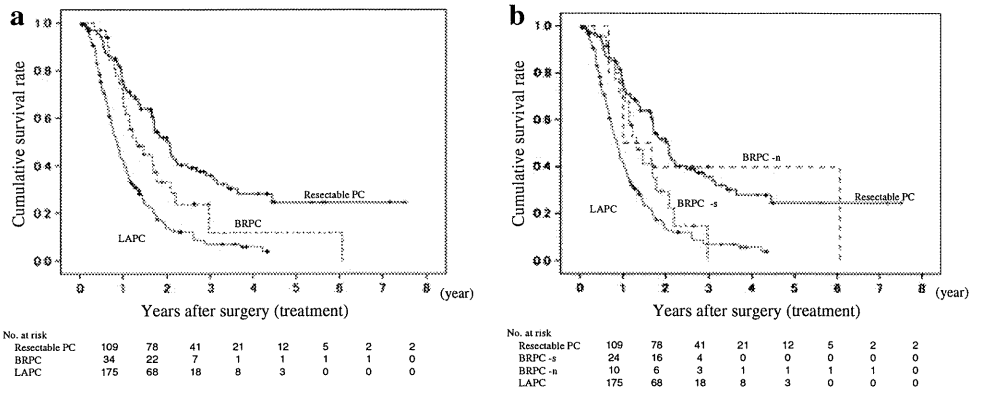

Fig. 2 **a** Comparison of survival in patients with resectable PC, BRPC, and unresectable PC. Both the differences between the resectable PC group and the BRPC group ($P = 0.04$) and between the BRPC group and the unresectable PC group ($P < 0.01$) were significant. **b** Cumulative survival curves according to detailed resectability status. Prognosis of BRPC-s was significantly worse than that of resectable PC ($P = 0.03$). Prognosis of BRPC-n was significantly better than that of unresectable PC ($P = 0.03$). *BRPC-s* BRPC treated with resection initially, *BRPC-n* BRPC treated with nonsurgical therapy initially

Table 2 Associations between overall median survival time (MST) and patient, tumor, and treatment characteristics in PC patients who were initially treated with surgical resection

Factor	MST (months)	Univariate analysis	Multivariate analysis	
		P value	Hazard ratio (95% CI)	*P* value
Age (years)				
<70	22.1	0.97		
≥70	20.8			
Tumor size				
≥3 cm	20.6	0.03	1.31 (0.84–2.05)	0.23
<3 cm	25.5			
CA 19-9				
≥200 U/ml	20.8	0.89		
<200 U/ml	25.0			
Portal vein invasion				
Present	21.6	0.196		
Absent	22.1			
Nerve plexus invasion				
Present	16.4	<0.01	2.33 (1.48–3.67)	<0.01
Absent	30.1			
Nodal status				
N1	20.5	0.03	1.89 (1.08–3.31)	0.03
N0	34.7			
SMV/portal impingement				
Present	12.8	0.02	1.72 (0.83–3.55)	0.15
Absent	25.0			
Tumor abutment on SMA, CE, or CHA				
Present	17.8	0.62		
Absent	22.1			
Status of resectability				
Borderline resectable	16.0	0.03	–	–
Resectable	25.0			
Resection status				
R0	22.4	0.09		
R1	21.6			
Adjuvant chemotherapy				
Yes	–	<0.01	0.49 (0.26–0.91)	0.02
No	20.8			

the BRPC-s group, the difference in survival between patients with adjuvant chemotherapy (MST: 20.3 months) and those without adjuvant chemotherapy (MST: 13.7 months) was not significant ($P = 0.54$).

Discussion

Borderline resectable pancreatic cancer is a newly proposed subset that shows interactions with the PV, SMV, SMA, celiac axis, and hepatic artery, and may have a high possibility of a positive surgical margin and worse prognosis after resection [1–3]. In the report of the AHPBA/SSO/SSAT Consensus Conference, it was recommended that patients with BRPC receive neoadjuvant therapy to increase the possibility of R0 resection in a clinical trial setting specific for BRPC patients [7]. As the rationale for the recommendation, the MD Anderson Cancer Center group demonstrated that neoadjuvant therapy enabled margin-negative resection in 37%, with median survival after resection of 40 months in the 84 patients with anatomical BRPC as defined on CT [2]. Chun et al. [11] also reported significantly better survival (23 vs. 15 months) and a higher R0 resection rate (59 vs. 11%) in 74 BRPC patients with preoperative chemoradiation than in 35 BRPC patients without preoperative therapy. However, little has been reported on the difference in surgical results, including prognosis and positive surgical margin rate,

between resectable PC and BRPC that might support the use of neoadjuvant therapy specific for BRPC patients. Furthermore, prognosis of BRPC patients initially treated with nonsurgical treatment such as chemotherapy or chemoradiotherapy has not been well documented.

In the present study, MDCT findings before initial treatment of all resected PC patients and all patients treated for LAPC were assessed for the possibility of BRPC because BRPC should be diagnosed before initial treatment to determine the treatment plan. BRPC was sub-classified into two types: BRPC-s, which was initially treated with resection, and BRPC-n, which was initially treated with nonsurgical therapy. Prognosis of all 34 BRPC patients was significantly worse than that of resectable PC patients and significantly better than that of unresectable PC patients. Moreover, in patients who initially underwent resection, prognosis of patients with BRPC-s was significantly worse than that of resectable PC patients, and in patients who were initially treated with nonsurgical therapy, prognosis of BRPC-n was significantly better than that of unresectable PC patients.

As possible reasons for the worse prognosis of BRPC-s than that of resectable PC, BRPC-s had a high rate of positive PV invasion and nerve plexus invasion compared to resectable PC ($P < 0.01$). Moreover, BRPC-s tended to show a more advanced stage in nodal status ($P = 0.19$) and tumor size ($P = 0.16$) than resectable PC. Nerve plexus invasion and lymph node metastasis were the independent poor prognostic factors in all 133 resected PC patients. The poor prognosis of BRPC-s patients was primarily attributable to these advanced characteristics. In terms of resection status, patients with BRPC-s had a positive surgical margin rate 10% higher than that of resectable PC patients, but the difference was not significant ($P = 0.41$). Interpretation of the 10% difference in the R0 rate between BRPC-s and resectable PC was difficult when evaluating how much the poor prognosis of BRPC-s patients was due to the difference in the R0 rate, considering both the lesser prognostic value of margin status and the frequent recurrence at locoregional sites in the BRPC-s patients. With respect to the surgical margin, there are no international standardized protocols for processing pancreatic specimens or criteria for positive margins [12, 13], and the relevance of margin status for prognosis is not clear in resected PC patients [6, 14–18]. An international standardized protocol for the histological examination of the surgical margins of pancreatic specimens is needed to prepare comparable data.

Nerve plexus invasion is a distinctive type of tumor spread in pancreatic ductal carcinoma, and it is also known to be a poor prognostic factor after tumor resection [19–21]. The nerve plexus of the pancreatic head runs from the pancreas to the celiac or superior mesenteric plexus along the celiac axis and SMA [22, 23]. Considering the anatomy, it is understandable that BRPC invades the nerve plexus quite frequently. Mochizuki et al. [24] reported that the mass and strand pattern and the coarse reticular pattern continuous with tumor on MDCT images are highly suggestive of nerve plexus invasion. Taking these results into account, tumor abutment on the arteries in BRPC could represent mostly nerve plexus invasion along those arteries. The higher R1 rate and frequent local recurrence in BRPC-s patients could be partly due to nerve plexus invasion.

Curiously, the prognosis of BRPC-n was significantly better than that of unresectable PC in patients who were initially treated with nonsurgical therapy. Less tumor burden as shown in tumor size and CA 19-9 value could mostly account for the better prognosis of patients with BRPC-n than that of patients with unresectable PC. In addition, surgical resection after down-staging by nonsurgical therapy was performed significantly more frequently in the BRPC-n group than in the unresectable PC group. Frequent conversion from nonsurgical therapy to surgical resection might also be one of the possible reasons for better survival of patients with BRPC-n. However, assessment of tumor resectability during nonsurgical treatment was not performed systematically or thoroughly for BRPC-n patients or unresectable PC patients in this study. Thus, the resectability rate of BRPC patients and unresectable PC patients was not definitive in the present study. In order to investigate conversion rate from nonsurgical therapy to surgical resection, systematic assessment for resectability during nonsurgical treatment is required although criteria of resectability after treatment have not been clarified. Owing to the different backgrounds and prognoses between BRPC and unresectable PC, they should be regarded as different categories.

Similar to the AHPBA/SSO/SSAT Consensus Conference recommendation [7], we reached the conclusion that neoadjuvant therapy such as chemoradiation for BRPC should be evaluated separately from those for resectable PC or unresectable PC for several reasons. First, patients with BRPC-s had poorer survival and more frequent recurrence at the local site than patients with resectable PC. Thus, patients with BRPC should be treated with more intensive therapy with strong local effect rather than the existing treatment for resectable PC. Second, neoadjuvant therapy could benefit patients with BRPC by providing early treatment for those with advanced disease at high risk of early systemic and local failure [2, 7]. Several phase II studies showed the possibility of neoadjuvant chemotherapy [25] or chemoradiation [26] for BRPC. Furthermore, adjuvant chemotherapy might not be as effective in BRPC patients as in resectable PC patients according to the results of the present study, although multi-institutional randomized controlled study is needed to clarify the effectiveness of adjuvant treatment for BRPC. Adjuvant chemotherapy

with gemcitabine or S-1 was a favorable prognostic factor for all 133 resected PC patients. However, in BRPC-s, the prognosis of patients with adjuvant chemotherapy was as poor as that of patients without adjuvant chemotherapy, while the duration from surgery to start of adjuvant treatment and relative dose intensity of adjuvant treatment did not differ between BRPC-s patients and resectable PC patients. Third, BRPC should be studied separately from unresectable PC because of the different tumor characteristics and prognoses. BRPC is more often resectable than unresectable PC, thus resectability status should be assessed systematically and thoroughly.

The limitations of our study are its retrospective design and the relatively small number of patients studied.

In conclusion, patients with BRPC showed more advanced tumor characteristics, including frequent nerve plexus invasion, frequent loco-regional recurrence, and poorer prognosis than patients with resectable PC although BRPC had less tumor burden and better prognosis than patients with unresectable PC. Neoadjuvant treatment with intensive local and systemic effect that is specific for BRPC is required. A multi-institutional phase II trial of neoadjuvant chemoradiation for BRPC is now in the planning stage.

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Original Contribution

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Biweekly gemcitabine with S-1 combination chemotherapy in locally advanced or metastatic pancreatic cancer

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Objective: Gemcitabine (GEM)-based combination chemotherapy has been studied to determine whether or not it improves outcomes, but results have generally been disappointing. We retrospectively compared chemotherapy with biweekly GEM plus a novel form of an oral 5-fluorouracil derivative (S-1) (GEM+S-1) with GEM alone in locally advanced or metastatic pancreatic cancer.

Patients and Methods: We studied patients with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic pancreatic cancer with measurable lesions. Ninety-six patients received GEM+S-1 (GEM 800-1,000 mg/m^2 intravenously on days 1 and 15 plus S-1 40 mg/m^2 twice daily orally on days 1-7 and days 15-21 of a 28-day cycle), and 66 patients received GEM alone (GEM alone, 1,000 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle). Treatment was repeated every 4 weeks.

Results: The overall response rate was 36.5% in the GEM+S-1 group and 7.6% in the GEM-alone group (P = 0.0028). The median survival time was 16.2 months in the GEM+S-1 group and 7.8 months in the GEM-alone group (P = 0.008).

Conclusions: This regimen for GEM+S-1 combination chemotherapy is feasible, well tolerated, and more effective than GEM alone in patients with locally advanced or metastatic pancreatic cancer.

Key words: pancreatic cancer, gemcitabine, oral 5-fluorouracil derivative (S-1)

Introduction

Pancreatic cancer has one of the poorest prognoses among all neoplasms because it is difficult to detect it in an early stage, has a very high rate of postoperative recurrence, and is relatively insensitive to chemotherapy and radiotherapy. Surgery is the only curative treatment for pancreatic cancer, but few tumors are resectable at the time of the diagnosis.

Gemcitabine (GEM) has been the standard chemotherapeutic agent for unresectable pancreatic cancer since the time that Burris et al. reported that GEM is more effective than 5-fluorouracil (5-FU) for alleviating some disease-related symptoms in patients with advanced, symptomatic pancreatic cancer.[1] GEM was also reported to confer a modest survival advantage over 5-FU.[2] However, the benefits were limited, with an objective response rate of less than 15% and a median survival of less than 6 months. GEM-based combined chemotherapy has been studied to improve outcomes,[3-8] but it is insufficient to merely prolong survival as compared with that in patients given GEM monotherapy.

Recently, the National Cancer Institute of Canada Clinical Trials Group reported that erlotinib plus GEM significantly prolonged overall survival as compared with GEM alone in patients with advanced pancreatic cancer (P = 0.038, median 6.24 months vs. 5.91 months).[9] However, the overall survival benefit was only 2 weeks. Phase III randomized studies of GEM alone vs. GEM plus capecitabine have demonstrated a significant survival benefit, but a worldwide consensus has yet to be reached.[10,11]

The oral 5-FU derivative (S-1) is a fluorinated pyrimidine preparation, combining tegafur, 5-chloro-2, 4-dihydroxypyridine (CDHP), and potassium oxonate in a 1:0.4:1 molar concentration ratio. Tegafur is a prodrug of 5-FU that is gradually converted to 5-FU but rapidly metabolized by dihydropyrimidine dehydrogenase (DPD) in the liver. CDHP is a competitive inhibitor of 5-FU metabolism that is about 180 times more potent than

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uracil in inhibiting DPD. Inhibition of 5-FU metabolism by CDHP results in prolonged active concentrations of 5-FU in both plasma and tumors. Potassium oxonate, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract and reduces gastrointestinal toxicity associated with 5-FU.[12-15]

Since 2001, we have used the single-agent GEM to treat locally advanced or metastatic pancreatic cancer. After 2003, we started to use GEM biweekly in combination with S-1 (GEM+S-1) for this indication. In the present study, we retrospectively evaluated and compared the safety and effectiveness of GEM+S-1 with those of GEM alone.

Patients and Methods

Patients

The study group was comprised of patients with a histologically or cytologically confirmed diagnosis of inoperable, locally advanced or metastatic pancreatic cancer with measurable lesions. None of the patients had previously received chemotherapy or radiotherapy. All of the patients were 20 to 83 years of age and had a Karnofsky performance status of 70% to 100%, an adequate hematologic profile (white cell count >3,000/mm^3, neutrophil count >2,000/mm^3, hemoglobin concentration >10.0 g/dl, platelet count >100,000/mm^3), adequate liver function (transaminase levels <5 times the upper limit of normal), adequate renal function (normal serum creatinine level), and a life expectancy of more than 2 months. Patients were excluded if they were receiving treatment with phenytoin, warfarin potassium, or flucytosine or had active infections, severe heart disease, mental disorders, or uncontrolled diabetes mellitus.

Treatments

Patients received either GEM+S-1 or GEM alone. In the GEM+S-1 group, GEM 1,000 mg/m^2 (under 75 years old) or 800 mg/m^2 (over 75 years old) was administered as a 30-minute intravenous infusion on days 1 and 15 (biweekly) and S-1 40 mg/m^2 twice daily was administered on days 1 to 7 and days 15 to 21 of a 28-day cycle. In the GEM-alone group, GEM 1,000 mg/m^2 was given on days 1, 8, and 15 of a 28-day cycle. Treatment was repeated every 4 weeks and continued until disease progression, unacceptable adverse events, or withdrawal of informed consent by the patient.

Complete blood cell counts and serum chemical analyses, including serum total bilirubin, transaminases, and alkaline phosphatase, were performed before each dose of GEM. If leukopenia (<2,000/mm^3), neutropenia (<1,000/mm^3), thrombocytopenia (<50,000/mm^3), total bilirubin >2.0 mg/ml, or transaminase levels higher than 5 times the upper limit of normal developed, chemotherapy was withheld until recovery. In patients who had grades 3 or 4 hematologic or nonhematologic toxicity, the GEM dose was reduced by 20% for all subsequent courses.

Assessments

All patients underwent computed tomography after every 2 cycles of chemotherapy, and tumor response was evaluated according to the RECIST (Response Evaluation Criteria in Solid Tumors). Toxicity was evaluated with the National Cancer Institute - Common Toxicity Criteria (CTC ver. 3.0). Patients were regularly interviewed to assess signs and symptoms such as pain, nausea, vomiting, mucositis, general fatigue, diarrhea, asthenia, and body weight loss.

Statistical analysis

Overall survival and median survival time were estimated by the Kaplan-Meier method and compared using the log-rank test. Patients' characteristics, toxic effects, and laboratory values were compared between patients receiving GEM+S-1 and those receiving GEM alone using the χ^2 and Fisher's *t*-tests.

P values of <0.05 were considered as statistically significant.

Results

Patient characteristics

A total of 96 patients with locally advanced or metastatic pancreatic cancer received GEM+S-1 from 2003 through 2009, and 66 patients received GEM alone from 2001 through 2007. Their clinical characteristics are shown in Table 1. In the GEM+S-1 group, 29 patients had locally advanced cancer and 67 had metastatic cancer. In the GEM-alone group, 19 patients had locally advanced cancer and 47 had metastatic cancer. Sites of metastases (GEM+S-1 vs. GEM alone) were the liver (46 cases vs. 26 cases), lymph nodes (24 cases vs. 22 cases), ascites (11 cases vs. 9 cases), lung (11 cases vs. 2 cases), and bone (3 cases vs. 2 cases) (Sites were overlapping). Most patients had a Karnofsky performance status of 80% to 100% in both groups, indicating good general condition. There were no significant differences in clinical characteristics between the GEM+S-1 group and the GEM-alone group.

Table 1. Patient characteristics

Characteristics	GEM+S-1 (n = 96)		GEM alone (n = 66)		P
	No.	%	No.	%	
Sex					NS
Male	44	45.8	35	53.0	
Female	52	54.2	31	47.0	
Age (years)					NS
Mean	65.6		66.7		
SD	8.7		8.8		
Range	41-83		42-83		
Karnofsky performance status					NS
100	37	38.5	14	21.2	
90	48	50.0	37	56.1	
80	11	11.5	13	19.7	
70	0	0.0	2	3.0	
Disease extent					NS
Locally advanced	29	30.2	19	28.8	
Metastatic	67	69.8	47	71.2	
Site of metastatic disease					NS
Liver	46	48.0	26	39.4	
Lymphnode	24	25.0	22	33.3	
Ascites	11	11.5	9	13.6	
Lung	11	11.5	2	3.0	
Bone	3	3.1	2	3.0	

Table 2. Treatment and efficacy results

	GEM+S-1 (n = 96)	GEM alone (n = 66)
No. of cycles		
median	12.0	7.0
range	2-22	2-22
Tumor response, %		
CR	0	0
PR	36.5	7.6
SD	47.9	53.0
PD	15.6	39.4
Overall survival time		
median, month	16.2	7.8
Survival rate, %		
6-month	80.2	66.3
1-year	56.8	29.7
2-year	25.2	8.1

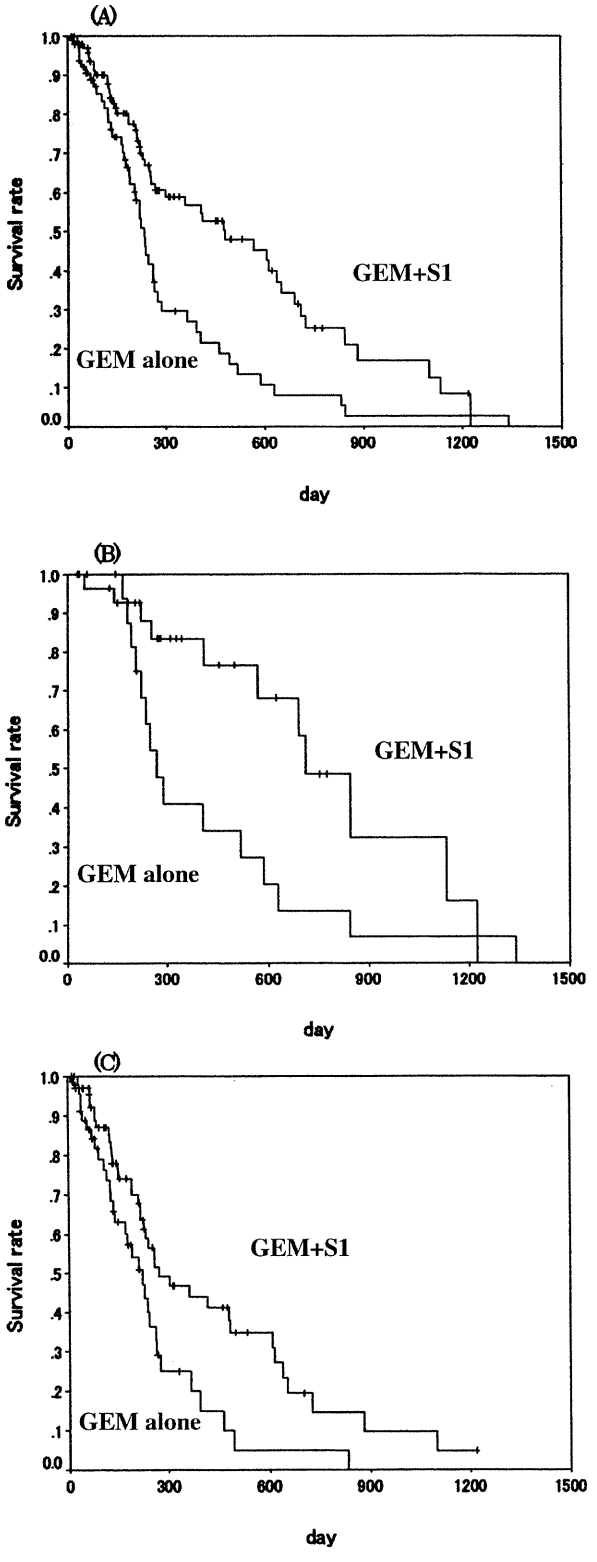

Figure 1. (A) Kaplan-Meier survival curves for the overall study group, (B) Patients with locally advanced pancreatic cancer, (C) Patients with metastatic pancreatic cancer. There were statistical significances (**A**, P = 0.008; **B**, P = 0.003; **C**, P = 0.008).

Treatments and efficacy

The median number of treatment cycles was 12.0 in the GEM+S-1 group (range, 2-22) and 7.0 in the GEM-alone group (range, 2-22). The responses of the patients are shown in Table 2. The overall response rate was 36.5% in the GEM+S-1 group and 7.6% in the GEM-alone group (P = 0.00028), and there were no complete responses in either group. Kaplan-Meier survival curves are shown in Figure 1A. The median survival time was 16.2 months in the GEM+S-1 group and 7.8 months in the GEM-alone group, and the 1-year survival rate was 56.8% in the GEM+S-1 group and 29.7% in the GEM-alone group (both, P = 0.008).

Kaplan-Meier survival curves for the patients with locally advanced pancreatic cancer are shown in Figure 1B. In the patients with locally advanced pancreatic cancer, the median survival time was 23.7 months (95% confidence interval [CI], 18.1-29.3) in the GEM+S-1 group and 8.9 months (95% CI, 7.2-10.7) in the GEM-alone group, and the 1-year survival rate was 83.5% in the GEM+S-1 group and 34.2% in the GEM-alone group (both groups, P = 0.003). In the patients with metastatic pancreatic cancer, the median survival time was 9.0 months (95% CI, 4.3-13.7) in the GEM+S-1 group and 8.2 months (95% CI, 5.9-10.5) in the GEM-alone group, and the 1-year survival rate was 44.0% in the GEM+S-1 group and 24.9% in the GEM-alone group (both groups, P = 0.008) (Figure 1C). There were cases of discontinued treatment because of cerebrovascular infarction in 1 patient in the GEM+S-1 group and in 2 patients in the GEM-alone group.

Toxicity

Treatment-related adverse events are summarized in Table 3. The incidences of grades 3 or 4 leukopenia, neutropenia, anemia, and thrombocytopenia were, respectively, 25.0%, 26.0%, 15.6%, and 7.3% in the GEM+S-1 group, and 22.7%, 39.4%, 4.5%, and 15.2% in the GEM-alone group (anemia, P < 0.05; others, P > 0.05). Most of these events were well tolerated, and there were no severe complications. Grades 3 or 4 nonhematologic toxicities (GEM+S-1 vs. GEM alone) were nausea (1.0% vs. 4.5%), vomiting (0.0% vs. 3.0%), anorexia (3.1% vs. 10.6%), and general fatigue (13.5% vs. 0.0%). These effects were tolerable and reversible. Treatment was discontinued because of cerebrovascular infarction in 1 patient in the GEM+S-1 group and 2 patients in the GEM-alone group.

Table 3. Treatment related toxicity (grades 3 and 4)

Adverse Event	GEM+S-1 (n = 96)		GEM alone (n = 66)		P
	No.	%	No.	%	
Leucopenia	24	25.0	15	22.7	NS
Neutropenia	25	26.0	26	39.4	NS
Anemia	15	15.6	3	4.5	<0.05
Thrombocytepenia	7	7.3	10	15.2	NS
Nausea	1	1.0	3	4.5	NS
Vomitting	0	0	2	3.0	NS
Anorexia	3	3.0	7	10.6	NS
General fatigue	13	13.5	0	0	<0.05

Discussion

Until the 1990s, chemotherapy was largely ineffective against locally advanced or metastatic pancreatic cancer. Since the introduction of GEM, however, chemotherapy was confirmed to prolong survival. The standard regimen for locally advanced or metastatic pancreatic cancer has been single-agent GEM. However, the overall response remained unsatisfactory, with low survival rates and short median survival times. Various regimens for GEM-based combination chemotherapy have, therefore, been studied in an effort to improve response and outcomes.

5-FU had been the mainstay of chemotherapy for pancreatic cancer until GEM became available, but 5-FU in combination with GEM did not improve the median survival of patients with advanced pancreatic cancer as compared with single-agent GEM.[2] Erlotinib is the only agent that was statistically shown to provide an additional survival benefit as compared with GEM alone in patients with advanced pancreatic cancer.[9] However, the benefit in terms of overall survival was only 2 weeks. Therefore, new GEM-based combination regimens are being investigated to improve clinical benefits for patients with pancreatic cancer.

S-1 is an oral fluorinated pyrimidine preparation that has produced moderate-to-high response rates in patients with gastric cancer, colorectal cancer, and biliary cancer.[12,13] An early phase II study of S-1 in patients with metastatic pancreatic cancer reported a response rate of 21.1% with a median survival time of 5.6 months.[16] In a late phase II study, the response rate was 37.5% with a median survival of 9.2 months.[17]

Recently, several studies have assessed combinations of GEM and S-1 in patients with locally advanced or metastatic pancreatic cancer.[18-23] One phase II trial of oral S-1 combined with GEM in metastatic pancreatic cancer obtained a median survival time of 12.5 months (95% CI, 5.9-19.1) and a 1-year survival rate of 54%

(95% CI, 36-72). In that study, S-1 (30 mg/m^2 twice daily) was given orally for 14 consecutive days, and GEM (1,000 mg/m^2) was given on days 8 and 15 of a 21-day cycle.[18] Grades 3 or 4 toxic effects were leukopenia (33%), neutropenia (55%), anemia (9%), thrombocytopenia (15%), anorexia (6%), fever (9%), and interstitial pneumonia (6%). Another phase II trial reported a median survival time of 7.89 months (95% CI, 5.96-9.82) in patients with locally advanced or metastatic pancreatic cancer who received S-1 (40 mg/m^2 orally twice daily on days 1-14 of a 21-day cycle) plus GEM (1,250 mg/m^2 on days 1 and 8), repeated every 3 weeks.[20] The major toxicities were grades 3 or 4 neutropenia (28.1%), grades 3 or 4 thrombocytopenia (15.6%), and grade 3 diarrhea (15.6%). Oh et al. performed a multicenter phase II study of GEM+S-1 combination chemotherapy in patients with unresectable pancreatic cancer.[23] The median survival time was 8.4 months (95% CI, 5.7-11.1), and the 1-year survival rate was 34% (95% CI, 19%-49%). The regimen used was GEM 1,000 mg/m^2 on days 1 and 8 plus S-1 40 mg/m^2 given orally twice daily on days 1 to 14 of a 21-day repeated cycle. The major grades 3 or 4 hematologic toxicities were neutropenia (39.5%), leukopenia (15.8%), thrombocytopenia (2.6%), and anemia (7.9%), and the major grades 3 or 4 nonhematologic toxicities included anorexia (10.5%), stomatitis (2.6%), rash (7.9%), fatigue (7.9%), and hyperbilirubinemia (5.3%). These studies used similar regimens and obtained comparable median survival times and 1-year survival rates. Toxicities were consistently mild and tolerable.

In the present study, the overall median survival time was 16.2 months (95% CI, 8.7-23.6), and the 1-year survival rate was 56.8% in the GEM+S-1 group, which were significantly better than the results in the GEM-alone group (P = 0.008). The incidences of grades 3 or 4 leukopenia, neutropenia, anemia, and thrombocytopenia were 25.0%, 26.0%, 15.6%, and 7.3%, respectively; and most of these events were tolerable, with no severe complications. Grades 3 or 4 nonhematologic toxicities were nausea (1.0%), anorexia (3.1%), and general fatigue (13.5%). These adverse effects were also tolerable and reversible.

Our regimen in the GEM+S-1 group differed from those used in previous studies, i.e., regimens in previous studies were that GEM 1,000-1,250 mg/m^2 was given intravenously on days 1 and 8 or on days 8 and 15, and S-1 30-40 mg/m^2 twice daily was given orally on days 1 to 14 of a 21-day cycle.[19,20-23] On the other hand, our regimen was that GEM 1,000 mg/m^2 was given intravenously on days 1 and 15 and S-1 40 mg/m^2 twice daily was given orally on days 1 to 7 and days 15 to 21 of a 28-day cycle. In this regimen, GEM was given biweekly, not weekly, and patients had S-1 free time for 1 week after S-1 was given. We therefore considered our regimen was more eligible and tolerable for patients, and they could receive the chemotherapy continuously and achieved a higher level of efficacy as a result.

This cycle can be broken down into two, 2-week cycles, during which the same treatment is given. These 2-week cycles are easy for patients to understand and facilitate the design of the treatment plans.

In conclusion, the survival of patients who received the regimen described in the present study of GEM+S-1 combination chemotherapy was significantly longer than that of patients who received GEM alone. Further randomized controlled studies are warranted to confirm these results showing that the GEM+S-1 regimen was feasible and well tolerated in patients with locally advanced or metastatic pancreatic cancer.

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ORIGINAL ARTICLE

Xenon-Inhalation Computed Tomography for Noninvasive Quantitative Measurement of Tissue Blood Flow in Pancreatic Tumor

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Abstract
Background and Aims The purpose of this prospective study was to demonstrate the ability to measure pancreatic tumor tissue blood flow (TBF) with a noninvasive method using xenon inhalation computed tomography (xenon-CT) and to correlate TBF with histological features, particularly microvascular density (MVD).
Methods TBFs of pancreatic tumors in 14 consecutive patients were measured by means of xenon-CT at diagnosis and following therapy. Serial abdominal CT scans were obtained before and after inhalation of nonradioactive xenon gas. TBF was calculated using the Fick principle. Furthermore, intratumoral microvessels were stained with anti-CD34 monoclonal antibodies before being quantified by light microscopy (×200). We evaluated MVD based on CD34 expression and correlated it with TBF.
Results The quantitative TBF of pancreatic tumors measured by xenon CT ranged from 22.3 to 111.4 ml/min/100 g (mean ± SD, 59.6 ± 43.9 ml/min/100 g). High correlation ($r = 0.885$, $P < 0.001$) was observed between TBF and intratumoral MVD.
Conclusion Xenon-CT is feasible in patients with pancreatic tumors and is able to accurately estimate MVD noninvasively.

Keywords Tomography · X-ray computed · Perfusion imaging · Pancreatic neoplasms · Microvessel density

Introduction

Pancreatic cancer is responsible for 227,000 deaths per year, and despite being only the 13th in incidence, is the 8th most common cause of death from cancer in both sexes combined due to the very poor associated prognosis with a mortality-to-incidence ratio of 0.98 [1]. The 5-year survival rate for pancreatic cancer is one of the lowest at 5% [2]. Although surgical resection is the most effective method, early detection is difficult and many cases present as advanced, non-resectable tumors, characterized by invasive growth, and metastases to the liver and lymph nodes, sometimes even when the primary itself is small [3].

Currently, gemcitabine is the most standard chemotherapeutic agent in use, [4] but the response rate is poor, less than 10% [5]. The reason for relative treatment resistance could be from the poor perfusion found in pancreatic malignant lesions compared with normal pancreatic tissue, as indicated by early angiographic studies [6]. Therefore, noninvasive evaluation of the perfusion of malignant pancreatic lesions would potentially be helpful for pretreatment estimation of perfusion prior to undergoing chemotherapy. Due to the inaccessibility of the organ deep within the abdominal cavity and the lack of an established noninvasive method, quantification of pancreatic tissue blood flow

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presents a challenge in routine clinical practice. Several attempts to solve this problem have been tried with the help of different imaging techniques, including angiography [6], dynamic contrast-enhanced computed tomography (CT) [7, 8], contrast-enhanced ultrasound [9], contrast-enhanced magnetic resonance (MR) imaging [10], and positron emission tomography (PET) [11, 12].

Xenon-inhalation CT (xenon-CT) has been reported to be useful for the evaluation of regional cerebral blood flow [13, 14]. With this technique, xenon gas is inhaled and the temporal changes in radiographic enhancement produced by the inhaled xenon gas are measured by a series of CT scans. The sequential changes in CT values in the various tissue segments are then computed to derive regional blood flow maps [15]. Previous studies have measured tissue blood flow (TBF) of the liver using Xenon CT [15–17], but none have evaluated pancreatic TBF noninvasively using Xenon CT.

In the study presented here, we sought to measure the TBF of pancreatic tumors in patients using xenon-CT, and to correlate TBFs with the tumor microvessel density (MVD).

Materials and Methods

Patients

This prospective study included 11 consecutive patients with histologically proven pancreatic ductal carcinoma and 3 patients with pancreatic neuroendocrine tumor who had undergone surgical resection at our institute. This study complied with the Declaration of Helsinki principles [18]. Signed informed consent was obtained from all participants in this study, which was designed as a prospective study.

Xenon-CT Technique

Xenon-CT was performed within a month before surgery except in case 5 (Table 1). The xenon-CT technique was used to assess regional TBF by using a wash-in/wash-out protocol, which has been previously used for measurement of regional cerebral blood flow [19]. The Kety–Schmidt equation, based on the Fick principle used for cerebral blood flow evaluation, was used to calculate TBF [20]. Nonradioactive xenon gas (XENON COLD®; Anzai Medical, Tokyo, Japan) was administered via a closed gas circuit inhalation system (AZ-725; Anzai Medical). The xenon concentration in the respiratory circuit (end-tidal peak xenon values) was continuously measured during the examination by a xenon monitor incorporated in the AZ-725 circuit. End-tidal peak xenon values were recognized automatically and fitted to a monoexponential curve (end-tidal xenon curve) [21]. Changes in arterial blood xenon concentrations were estimated based on the end-tidal xenon curve [13].

Changes in CT values of the pancreatic tumor were measured by a helical CT (LightSpeed Ultra; GE Healthcare, WI, USA). Following identification of the pancreatic tumor by plain CT scan, four axial images with a 10-mm slice thickness including the pancreatic tumor were obtained incrementally as baseline CT images prior to xenon inhalation. In the next step, the patient inhaled 25% (vol/vol) xenon gas for 4 min (wash-in), followed by breathing room air for 5 min (wash-out) [19]. In the meantime, CT scans were acquired at each level at 1-min intervals. As many as ten CT images per patient were obtained in total including the baseline image at each level. Exposure factors were selected at 100 kVp, 200 mA, and 1 s, and patients were required to hold their breath for 7 s during a series of scans at four levels. Smoothing with a 9 × 9 pixel filter was used to reduce noise on the CT

Table 1 Values of tissue blood flow (TBF) measured by xenon-CT and MVD

Case	Pathology	Histological grade	Mean MVD	Tumor TBF (ml/min/100 g)	Days between CT and surgery
1	Gastrinoma	N/A	143.25	173.6	24
2	Adenocarcinoma	Moderate	22.5	29.82	22
3	Adenocarcinoma	Poor	68.75	63.11	16
4	Adenocarcinoma	Well	38.5	23.33	6
5	Islet cell carcinoma	N/A	93.5	78.58	75
6	Adenocarcinoma	Moderate	27	13.1	1
7	Adenocarcinoma	Moderate	33	48.4	6
8	Adenocarcinoma	Well	36.5	29.64	4
9	Adenocarcinoma	Moderate	37.25	23.8	6
10	Adenocarcinoma	Moderate	49	43.6	3
11	Adenocarcinoma	Well	80.5	100.6	4
12	Adenocarcinoma	Moderate	47.5	41	11
13	Adenocarcinoma	Moderate	45.75	54	27
14	Islet cell carcinoma	N/A	131	111.43	1

N/A Not available

images. Body movement related to respiration was taken into account, and changes in pancreatic position on each enhanced CT image were digitally corrected relative to the baseline image on the screen of a blood flow imaging analysis computer system (AZ-7000W; Anzai Medical).

The AZ-7000W was also used to create color maps for TBF from images obtained by xenon-CT as well as confidence images, which showed the variance in values for each pixel based on the least-squares method. High TBF appeared as red regions and low TBF as blue regions. The confidence images were used to evaluate the reliability of the TBF value for each pixel of the image [16, 17]. TBF was determined by placing regions of interest (ROI) on the pancreatic tumor on the color maps. When the tumor was small, we carefully selected the ROI (Fig. 1), but would otherwise use the largest ROI possible for any given tumor area seen on CT.

Assessment of Immunohistochemical Staining and MVD

For all 14 cases, immunohistochemical staining was performed by an immunoperoxidase technique using a mouse monoclonal IgG antibody for CD34 (NU-4A1; Nichirei, Japan) at a 1:2 dilution, as described in detail elsewhere. [22] Microvessels were counted from the three separate, most highly vascularized areas (hot spots), which were identified by scanning the entire immunostained tumor at $\times 100$ magnification. All vascular structures within those areas were counted at $\times 200$ magnification, and an average value was computed from the three areas to determine the mean MVD (Fig. 2) [23].

Statistical Analysis

Correlation between mean MVD with the TBF measured by xenon-CT was examined by the Spearman rank correlation coefficient. All analyses were performed using the SAS statistical package (SAS Institute, Cary, NC, USA) with significance defined as $P < 0.05$ for two-tailed tests.

Results

The quantitative TBF of pancreatic tumors measured by xenon-CT ranged from 22.3 to 111.4 ml/min/100 g (mean ± SD, ml/min/100 g). A comparison of the quantitative values obtained by xenon-CT and mean MVD in each pancreatic tumor is shown in Table 1.

There was high linear correlation between xenon CT and mean MVD ($y = 0.8155x + 12.421$, $R^2 = 0.88503$, $P < 0.05$) (Fig. 3). There was a tendency that TBF of pancreatic carcinoma was relatively lower than that of islet cell tumor.

Discussion

Tumor angiogenesis is characterized by the rapid growth of new microvessels and associated change in permeability. MVD evaluated by counting vessels on tissue specimens is considered the gold standard for quantifying angiogenesis in histologic studies, but this requires tissue, which can be

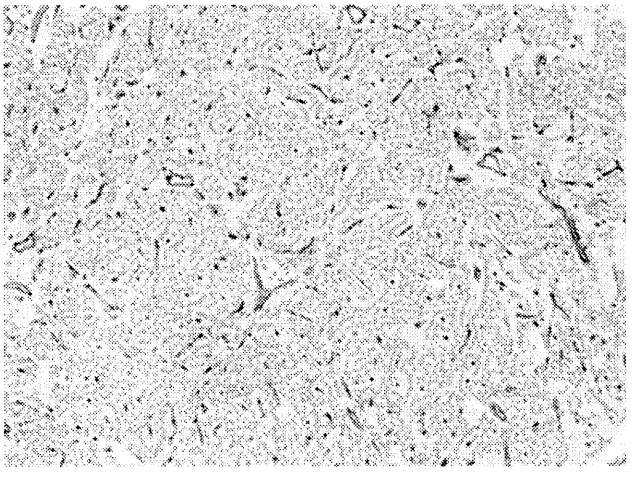

Fig. 2 Immunohistochemical staining of tumor microvessels (CD34-positive cells) in pancreatic cancer specimens. Original magnification $\times 200$

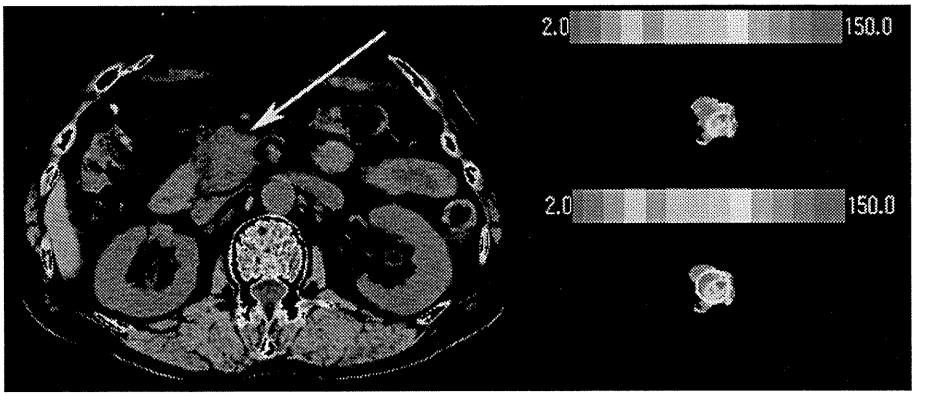

Fig. 1 A 63-year-old male with a pancreatic head cancer. The CT image shows a pancreatic head tumor (*arrow*) that appears on xenon-CT and xenon-CT with ROI (TBF = 39.3 ml/mg/100 g)

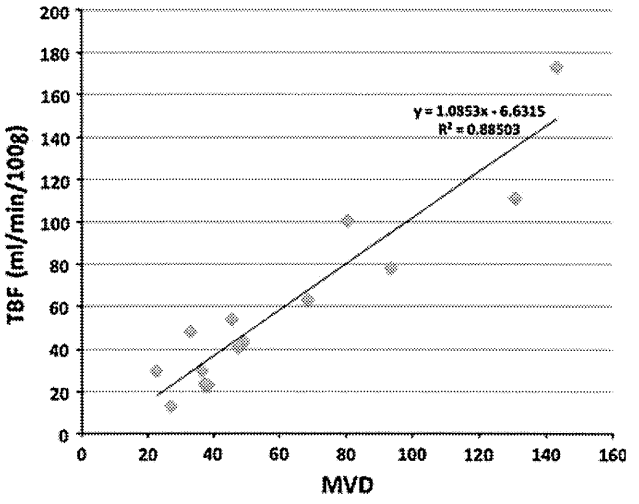

Fig. 3 The quantitative values of TBF and mean MVD are plotted on this graph. A high linear correlation is shown ($y = 1.0853x - 6.6315$, $R^2 = 0.88503$)

invasive and difficult to obtain [24]. On the other hand, CT enhancement is noninvasive and can indirectly reflect the state of intra-tumor angiogenesis because the degree of tumor enhancement is dependent upon the number of blood vessels within the tumor [25–27], particularly with xenon-CT which can allow quantitative measurements of TBF.

To our knowledge, this is the first prospective study in which TBF measured by xenon-CT has been compared to MVD in patients presenting with pancreatic cancer. We found that TBF was significantly lower in pancreatic adenocarcinoma than pancreatic neuroendocrine tumors, which is consistent with previous studies that demonstrated that pancreatic carcinomas are less vascular than neuroendocrine tumors [28.] Murakami et al. [15] also reported a correlation between TBF and pathologic features of liver tumors, which suggested that xenon-CT could be used to differentiate relatively hypovascular, well-differentiated hepatocellular carcinoma (HCC) from hypervascular, moderately and poorly-differentiated HCC.

Our study showed that the pancreatic tumor MVD and TBF obtained using xenon-CT were significantly correlated, with a high correlation coefficient ($R^2 = 0.88503$, $P < 0.05$).

Recently, several studies have suggested that a high histologic MVD is a significant predictor of metastatic disease and a poorer overall survival in patients with solid tumors [29], particularly in pancreatic carcinomas where several studies have reported a positive correlation between a high MVD and mortality [30–32]. This was observed in patients with pancreatic carcinoma who underwent contrast-enhanced ultrasonography where ultrasonographic enhancement classes were positively correlated with histologic MVD, predicting a worse prognosis for patients with markedly hypovascular tumors at contrast-enhanced ultrasonography [33]. Conversely, patients with high MVDs who underwent resection or systemic chemotherapy have been correlated with better prognoses, possibly because a high tumor MVD may indicate hyperperfusion and greater sensitivity of the tumor to anticancer agents.However, in pancreatic endocrine tumors, three studies [34–36] with 37, 45, and 82 patients have shown that a low MVD could be an unfavorable histoprognostic factor, which suggests that different kinds of pancreatic tumors may respond differently to treatment and that clinicians should pay particular attention to tumor type when interpreting MVD values.

MVD count is typically unavailable prior to initiating treatment unless the patient undergoes a biopsy, which is invasive and not commonly performed in clinical practice. Thus, TBF measured by xenon CT might be helpful in estimating MVD and potentially risk stratifying patients to predict the effect of chemotherapy on the malignant pancreatic tumor and impact prognosis.

Conclusions

Xenon-CT is feasible in patients with pancreatic tumors and is able to estimate mean MVD without an invasive procedure.

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