The QOL was assessed at 6, 12, and 24 months after surgery using the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) questionnaire. The FACT-Ga questionnaire consists of the 27-item FACT-Ga, which assesses physical, social, emotional, and functional well-being using a series of subscale scores, and a newly validated 19-item portion, which assesses gastric cancer-specific domains of postoperative gastrointestinal symptoms including dumping syndrome, gastric fullness, appetite loss, weight loss, diarrhea, and bile reflux gastritis [19].

Late postoperative complications

Late postoperative complications such as weight loss, dumping syndrome, peptic ulcer, and diarrhea were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [20]. Weight loss is defined by CTCAE version 4.03 as follows: grade 1, weight reduction of 5 to <10 % from baseline, intervention not indicated; grade 2, weight reduction of 10 to <20 % from baseline, nutritional support indicated; grade 3, weight reduction of >20 % from baseline, tube feeding and total parenteral nutrition (TPN) indicated [20]. Symptoms of dumping syndrome included abdominal pain, nausea, dizziness, exhaustion, flushing, diarrhea, or sweating, with onset within 30 min to 1 h of eating or within 2–3 h of eating [21, 22]. Dumping syndrome and peptic ulcer were defined by CTCAE version 4.03 as follows: grade 1, clinical or diagnostic observation only; grade 2, medical intervention indicated; grade 3, TPN indicated, elected operative or endoscopic intervention indicated; grade 4, urgent operative intervention indicated; and grade 5, death [20]. Diarrhea was defined by CTCAE version 4.03 as follows: grade 1, increase of fewer than four stools per day over baseline; grade 2, increase of four to six stools per day over baseline; grade 3, increase of seven or more stools per day over baseline; grade 4, urgent intervention indicated; and grade 5, death [20]. Diabetes associated with endocrine insufficiency was defined as either new diabetes (requiring new medical treatment such as dietary treatment, oral drugs, or insulin) or worsening diabetes (requiring a modification of the medical treatment for deterioration of previously diagnosed diabetes).

Statistical analysis

Data are expressed as mean ± SD. Patient characteristics and perioperative and postoperative factors between the two groups were compared using χ^2 statistics, Fisher's exact test, and the Mann–Whitney *U*-test. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed with SPSS software, version 20 (SPSS, Chicago, IL, USA).

Table 1 Demographic characteristics of 130 enrolled patients

	PpPD ($n = 64$)	PrPD ($n = 66$)	p
Age (years)	68 ± 9	67 ± 9	0.5776
Sex (male/female)	33/31	38/28	0.6084
Diabetes (yes/no)	18/46	19/47	0.9999
Preoperative biliary drainage (yes/no)	34/30	26/40	0.1161
Serum hemoglobin level (g/dl)[a]	13.0 ± 1.5	12.5 ± 1.3	0.2184
Serum creatinine (mg/dl)[b]	0.68 ± 0.2	0.72 ± 0.2	0.1903
Serum total bilirubin level (mg/dl)[c]	3.8 ± 4.0	4.0 ± 6.0	0.7965
Serum amylase level (IU/L)[d]	124 ± 134	111 ± 104	0.5232
Benign/malignant tumors	12/52	14/52	0.8953
Pancreatic adenocarcinoma	17	23	
Bile duct carcinoma	18	15	
Ampullary adenocarcinoma	6	3	
Duodenal adenocarcinoma	0	1	
Intraductal papillary neoplasms	15	15	
Pancreatic endocrine tumor	1	2	
Tumor-forming pancreatitis	3	5	
Other disease	4	2	

PpPD pylorus-preserving pancreaticoduodenectomy; *PrPD* pylorus-resecting pancreaticoduodenectomy

[a] Normal range 12–17.5 g/dl

[b] Normal range 0.53–1.02 mg/dl

[c] Normal range 0.2–1.2 mg/dl

[d] Normal range 15–150 IU/L

Results

Follow-up

Median follow-up for patients in this study was 37.5 months (3–78 months) in the PpPD group and 41.5 months (1–76 months) in the PrPD group. During follow-up, 45 of 130 enrolled patients died due to cancer recurrence (19 after PpPD versus 26 after PrPD). Complete data for body weight and nutritional assessment at the 2-year follow-up were obtained from 85 of the 130 eligible patients (52.7 %).

There was no significant difference between groups regarding the number of malignant (PpPD: $n = 52$, PrPD: $n = 52$) and benign (PpPD: $n = 12$, PrPD: $n = 14$) tumors (Table 1).

Late postoperative complications and long-term outcomes

Table 2 compares late postoperative complications of PpPD and PrPD. Dumping syndrome, which was classified as grade 2 assessed by CTCAE 4.03, was diagnosed in one

Table 2 Late postoperative complications and long-term follow up

	PpPD ($n = 64$)	PrPD ($n = 66$)	p
Follow-up (months)	37.5 (3–78)	41.5 (1–76)	0.992
Late postop. complications[a]			
Dumping syndrome (grade 2)	0	1 (1.6 %)	0.999
Peptic ulcer (grade 2)	1 (1.6 %)	3 (4.5 %)	0.619
Diarrhea (grade 2)	0	1 (1.6 %)	0.999
New-onset or worsening diabetes[b]	3 (4.7 %)	2 (3.0 %)	0.678
New diabetes	2	1	
Worsening diabetes	1	1	
Use of pancreatic enzyme supplement	24 (37.5 %)	28 (42.4 %)	0.567
Use of antiulcer agent	16 (25.0 %)	13 (19.7 %)	0.468
Postop. adjuvant chemotherapy	43 (67.1 %)	41 (62.1 %)	0.546
Nutritional status			
Albumin[c] (g/dl)			
Preoperation	4.1 ± 0.5	4.0 ± 0.5	0.649
6 months postop.	4.0 ± 0.4[e]	3.9 ± 0.4[e]	0.415
12 months postop.	4.1 ± 0.5[e]	4.0 ± 0.5[e]	0.645
18 months postop.	4.0 ± 0.5[e]	4.1 ± 0.4[e]	0.339
24 months postop.	4.0 ± 0.5[e]	4.2 ± 0.3[e]	0.105
Prealbumin[d] (g/dl)			
Preoperation	22.2 ± 7.1	21.0 ± 6.3	0.319
6 months postop.	21.0 ± 5.0[e]	19.4 ± 5.7[e]	0.094
12 months postop.	21.6 ± 5.9[e]	22.3 ± 4.6[e]	0.167
18 months postop.	21.2 ± 5.0[e]	22.6 ± 3.5[e]	0.238
24 months postop.	22.3 ± 5.6[e]	23.5 ± 4.4[e]	0.293

PpPD pylorus-preserving pancreaticoduodenectomy, *PrPD* pylorus-resecting pancreaticoduodenectomy, *Postop.* postoperatively

Results are expressed as the median and range, the number and percent, or the median ± SD

[a] Dumping syndrome, peptic ulcer, and diarrhea were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Dumping syndrome has onset of symptoms with feeling unwell, such as stomach pain, nausea, dizziness, exhaustion, flushing, diarrhea, or sweating within 30 min–1 h of eating or within 2–3 h of eating

[b] New diabetes is defined as diabetes that requires new medical treatment, such as dietary treatment, oral drug(s), or insulin. Worsening diabetes is defined as diabetes that requires modification of the medical treatment because of deterioration of previously diagnosed diabetes

[c] Normal range 3.8–5.1 g/dl

[d] Normal range 22–40 mg/dl

[e] Recovery to baseline or higher than the preoperative level

patient after PrPD—resolved by dietary treatment alone (altered meal size and meal frequency). Dumping did not occur at all after PpPD. Four patients had endoscopically documented peptic ulcer with symptoms of new-onset epigastric pain or tarry stool. Although peptic ulcer classified as grade 2 based on CTCAE 4.03 was diagnosed in one patient after PpPD and three patients after PrPD, there was no significant difference in the incidence between the two procedures. Peptic ulcers in the four patients was completely cured with proton pump inhibitors without requiring an interventional approach. There were no significant differences between the two procedures with regard to diarrhea. The frequency of administration of pancreatic enzyme supplement was similar between the two procedures; 37.5 % for PpPD and 42.4 % for PrPD.

There were no significant differences between the two procedures concerning the incidence of new-onset or worsening diabetes. Serum rapid turnover proteins, such as albumin and prealbumin, at 6, 12, 18, and 24 months after each procedure recovered to preoperative levels. The two procedures were also shown to be equivalent with regard to nutritional status.

Long-term outcomes of body weight after PpPD and PrPD

Long-term outcomes of body weight change during 24 months after surgery are shown in Table 3. Mean body weight preoperatively and 24 months postoperatively were not significantly different between the PpPD and PrPD groups. The incidences of weight loss > grade 2 at 6 and 12 months after surgery were 41.1 and 43.0 % in the PpPD patients and 45.3 and 27.3 % in the PrPD patients, respectively. There was no significant difference between PpPD and PrPD regarding the incidence of weight loss > grade 2 at 6 and 12 months after surgery. However, the incidences of weight loss > grade 2 at 18 and 24 months after surgery were 39.1 and 42.2 % in the PpPD group and 15.8 and 16.2 % in the PrPD group. Weight loss > grade 2 at 18 and 24 months after surgery improved significantly in the PrPD group compared with that in the PpPD group ($p = 0.018$ and 0.011, respectively).

Long-term outcomes of gastric emptying and quality of life

The results of T_{max} are shown in Table 4. T_{max} at 6, 12, and 24 months after surgery in the PpPD group was significantly delayed compared with that in the PrPD group: 27.8 ± 19.8 versus 15.2 ± 6.3 min, 23.4 ± 16.9 versus 14.2 ± 4.5 min, 20.9 ± 15.6 versus 14.0 ± 5.5 min, respectively.

Of the 130 patients in this study, those available for QOL assessment at 6, 12, 18, and 24 months numbered 109 (83.0 %), 95 (73.0 %), 84 (63.9 %), and 82 (63.1 %), respectively. The return rate for questionnaires at each time point was 100 %. The overall QOL scores based on the FACT-Ga scales are presented in Table 4. The highest possible total FACT-Ga score is 184. The highest possible score for the 19-item FACT-Ga subscale assessing gastric cancer-specific domains of postoperative gastrointestinal symptoms is 76. There were no significant differences

Table 3 Long-term outcomes regarding body weight between PpPD and PrPD

Outcome	PpPD	PrPD	*p*
Change in BW (kg)			
Preoperative BW (kg)	54.9 ± 10	55.0 ± 9	0.934
Change in BW 6 months postop.			
Available for follow-up	56	53	
Body weight (kg)	50.9 ± 11	50.0 ± 8	0.471
Weight loss > grade 2[a], *n* (%)	23 (41.1 %)	24 (45.3 %)	0.657
Change in BW 12 months postop.			
Available for follow-up	51	44	
Body weight (kg)	51.0 ± 11	50.7 ± 8.9	0.891
Weight loss > grade 2[a], *n* (%)	22 (43.0 %)	12 (27.3 %)	0.108
Change in BW 18 months postop.			
Available for follow-up	46	38	
Body weight (kg)	51.2 ± 11	52.0 ± 9.1	0.700
Weight loss > grade 2[a], *n* (%)	18 (39.1 %)	6 (15.8 %)	0.018
Change in BW 24 months postop.			
Available for follow-up	45	37	
Body weight (kg)	51.1 ± 11	53.0 ± 9.5	0.417
Weight loss > grade 2[a], *n* (%)	19 (42.2 %)	6 (16.2 %)	0.011

BW body weight, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PrPD* pylorus-resecting pancreaticoduodenectomy

[a] Weight loss greater than grade 2 here is a loss that is >10 % from baseline. Weight loss has been defined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 as follows: grade 1, reduction of 5 % to <10 % from baseline, intervention not indicated; grade 2, reduction of 10 % to <20 % from baseline, nutritional support indicated; grade 3, reduction of >20 % from baseline, tube feeding and total parenteral nutrition indicated

Table 4 Long-term outcomes of gastric emptying and quality of life after PpPD or PrPD

	PpPD ($n = 64$)	PrPD ($n = 66$)	*p*
Gastric emptying by ^{13}C-acetate breath test (T_{max}) (min)[a]			
6 months postop.	26.7 ± 18.8	17.4 ± 13.2	0.020
12 months postop.	23.4 ± 16.9	14.2 ± 4.5	0.011
24 months postop.	20.9 ± 15.6	14.0 ± 5.5	0.036
Quality of life			
Total FACT-Ga score (range 0–184)			
6 months postop.	139.1 ± 22.9	139.6 ± 21.4	0.914
12 months postop.	144.7 ± 20.0	145.9 ± 24.8	0.831
24 months postop.	149.5 ± 20.1	148.8 ± 23.2	0.886
FACT-Ga subscale (range 0–76)			
6 months postop.	59.6 ± 11.0	60.1 ± 11.3	0.814
12 months postop.	61.3 ± 10.0	60.8 ± 11.6	0.812
24 months postop.	63.5 ± 10.5	62.7 ± 10.9	0.766

FACT-Ga functional assessment of cancer therapy–gastric cancer survey, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PrPD* pylorus-resecting pancreaticoduodenectomy

[a] Gastric emptying was evaluated by T_{max} (the time to peak $^{13}CO_2$ content) using the ^{13}C-acetate breath test at 1, 3, 6, 12, and 24 months after surgery

between the PpPD and PrPD groups regarding the results of any subscale score or the total FACT-Ga scores at 1, 3, 6, 12, and 24 months after surgery. The QOL scores after PpPD and PrPD increased smoothly.

Short-term and long-term outcomes after early postoperative DGE

Regarding short-term outcomes, there was no significant difference between patients with and without DGE concerning the incidence of pancreatic fistula: 42.9 and 27.6 % in patients with and without DGE, respectively ($p = 0.381$). Concerning an association between DGE and intraabdominal abscess, there was no significant difference between patients with and without DGE. The incidences of intraabdominal abscess were 21.4 and 10.3 % in patients with and without DGE, respectively ($p = 0.206$). Body weight and nutritional status were assessed between patients with and without early postoperative DGE during the 24 months after surgery (Table 5). The incidence of weight loss > grade 2 at 24 months after surgery was 63.6 % in the patients with DGE and 25.3 % in those without DGE. Body weight at 24 months after surgery improved significantly in patients without DGE compared to that in patients with DGE ($p = 0.010$). Serum albumin at 24 months after surgery was higher in patients without DGE than those with DGE: 3.7 ± 0.6 versus 4.1 ± 0.4 g/dl ($p = 0.013$). T_{max} at 24 months after surgery in patients who had early postoperative DGE was significantly delayed compared to that in patients without early postoperative DGE: 27.9 ± 22.7 versus 16.5 ± 10.1 min ($p = 0.023$). There were no significant differences in the results of any subscale scores or the total FACT-Ga scores at 24 months after surgery for patients with and without DGE.

Discussion

Recent advances in surgical techniques and perioperative management have led to increased length of survival after PD [21–23]. Therefore, long-term outcomes for survivors have become a great concern. We clearly demonstrated in an RCT that PrPD significantly reduces the incidence of DGE compared with PpPD at the short-term follow-up [1]. However, long-term outcomes after PrPD remained

Table 5 Short-term and long-term outcomes for patients who had early postoperative DGE

Parameter	With DGE	Without DGE	*p*
Short-term outcome			
Available no.	14	116	
Pancreatic fistula[a]	6 (42.9 %)	32 (27.6 %)	0.381
Intraabdominal abscess	3 (21.4 %)	12 (10.3 %)	0.206
Long-term outcome (24 months postop.)			
Available no.	11	71	
Preoperative BW (kg)	55.8 ± 9.2	55.1 ± 9.2	0.804
Change in BW 24 months postop.			
Body weight (kg)	49.8 ± 11.4	52.3 ± 10.5	0.477
Weight loss > grade 2[b] *n* (%)	7 (63.6 %)	18 (25.3 %)	0.010
Nutritional status			
Albumin[c] (g/dl)			
Preoperation	3.9 ± 0.7	4.1 ± 0.5	0.110
24 months postop.	3.7 ± 0.6	4.1 ± 0.4	0.013
Prealbumin[d] (g/dl)			
Preoperation	20.3 ± 7.6	21.8 ± 6.7	0.454
24 months postop.	21.3 ± 5.1	23.1 ± 5.0	0.272
Gastric emptying by ^{13}C-acetate breath test (T_{max}) (min)[e]	27.9 ± 22.7	16.5 ± 10.1	0.023
Quality of life			
Total FACT-Ga score (range 0–184)	143.2 ± 25.9	150.1 ± 20.7	0.886
FACT-Ga subscale (range 0–76)	58.3 ± 14.8	63.8 ± 9.8	0.766

DGE delayed gastric emptying, *FACT-Ga* functional assessment of cancer therapy-gastric cancer survey

[a] Pancreatic fistula was defined by the International Study Group on Pancreatic Fistula (ISGPF)

[b] Weight loss greater than grade 2: weight loss more than 10 % from preoperative body weight

[c] Normal range of albumin level: 3.8–5.1 g/dl

[d] Normal range of prealbumin level: 22–40 mg/dl

[e] Gastric emptying was evaluated by T_{max} (the time to peak $^{13}CO_2$ content) in ^{13}C-acetate breath test at 1, 3, 6, 12, and 24 months after surgery

unknown. Therefore, this report focused on long-term outcomes after PrPD compared with PpPD.

Some authors have proposed that postoperative body weight change should be assessed as a percentage of preoperative body weight because the assessment by body weight change based on one time point during the postoperative period may be misleading [24, 25]. Our study has shown that patients who underwent PrPD had a more favorable recovery than those with PpPD at 18 and 24 months after surgery concerning weight loss of >10 % from their preoperative weight. One reason for weight loss may be associated with dietary intake based on the gastric emptying function. The ^{13}C-acetate breath test is a useful marker of gastric emptying [22]. T_{max} in the ^{13}C-acetate breath test was significantly more delayed in the PpPD patients than in the PrPD patients. After PpPD, pyloric dysfunction caused by denervation may be responsible. It was also reported that there was a significant correlation between the ^{13}C-acetate breath test and dietary intake [26]. Favorable gastric emptying may have contributed to increased dietary intake and led to subsequent improved body weight in the PrPD patients. Concerning nutritional status, serum albumin and prealbumin after PrPD (which preserves almost the entire stomach) was similar to that after PpPD for a long time after surgery. The serum albumin level is well established as one of the markers for nutritional assessment [27]. Nutritional status is a good indicator when estimating QOL [28].

Rapid gastric emptying caused by resection of the pylorus ring during PrPD may result in more frequent occurrence of dumping syndrome than after PpPD. Dumping syndrome is a serious late postoperative complication affecting QOL, body weight change, and nutritional status [7]. Several studies have reported that PpPD reduces postgastrectomy syndrome, including dumping, compared with its occurrence after PD with antrectomy [6–8, 24]. Previous studies have also reported that dumping syndrome after PpPD is rare, although its incidence after PD is 0–10 % in the literature [6, 7, 29–31]. In our study, only 1 of 66 patients (1.6 %) with PrPD had dumping syndrome (grade 2) during follow-up, and the patients could be treated with dietary management alone. PrPD patients may not have severe dumping syndrome because its pooling ability in the stomach is similar to that after PpPD. FACT-Ga was designed specifically to assess gastrointestinal disorders such as dumping syndrome [19]. Therefore, the FACT-Ga questionnaire was chosen in this study to focus on postgastrectomy syndrome or the postoperative gastric emptying function. FACT-Ga results indicated that PrPD had QOL outcomes similar to those achieved with PpPD.

As another important result of this study, we clarified short- and long-term outcomes in patients with DGE for the first time. DGE is a persistent, frustrating complication and decreases QOL [6–10]. Many pancreatic surgeons believe that DGE after PD is a secondary phenomenon caused by postoperative complications such as pancreatic fistula or intraabdominal abscess. However, our study demonstrated that pancreatic fistula or intraabdominal abscess is not associated with the incidence of DGE. It has been reported that factors such as nutritional status and dehydration related to DGE are the common reasons for readmission

after PD in the short term [32]. However, there have been no reports to evaluate how DGE affects long-term outcomes after PD. In this study, the patients with DGE had significantly lower serum albumin and prealbumin levels than those without DGE at 24 months. Moreover, the patients with DGE had significantly poorer body weight recovery than those without DGE at 24 months after surgery. Interestingly, T_{max} in the ^{13}C-acetate breath test was significantly more delayed in patients who had early postoperative DGE than those who did not—even 24 months after surgery. In patients who did not have early postoperative DGE, favorable gastric emptying may have contributed to increased dietary intake over the long term, leading to their subsequent recovery of body weight.

Malignant disease, administration of a pancreatic enzyme supplement, or postoperative adjuvant chemotherapy may affect body weight loss after PD over the long term. The frequency of postoperative adjuvant chemotherapy may cause poor oral intake tolerance. Two studies have reported that weight loss after PD is associated with diarrhea or exocrine insufficiency [17, 27]. In the present study, the incidences of DGE were similar for patients with malignant and benign disease (8.7 % in malignant disease patients vs. 19.2 % in benign disease patients, $p = 0.120$). Also, neither malignant disease nor postoperative adjuvant chemotherapy for malignant disease affected the incidence of body weight loss at 24 months after surgery (29.8 % in those with malignant disease vs. 32.0 % in those with benign disease, $p = 0.844$ and 29.5 % in patients with adjuvant chemotherapy vs. 31.6 % in patients without adjuvant chemotherapy, $p = 0.842$).

The present study has an important methodologic limitation arising from missing data due to death or disease progression during follow-up. Missing data may have biased the results and overestimated any positive effect of treatment. Also, follow-up is needed to clarify how the incidence of DGE or type of procedure affects body weight change in the long term.

Conclusions

Our previous study suggested that PrPD has a significant impact on reducing the incidence of DGE (compared with PpPD) in the short term [1]. In the present study, we clarified that PrPD was associated with more favorable recovery of body weight. Long-term outcomes were shown to be similar with PpPD and PrPD concerning QOL, nutritional status, and gastrointestinal symptoms. Moreover, DGE may be associated with weight loss and poor nutritional status after surgery, affecting long-term outcomes. Therefore, PrPD is one of the procedures that may be recommended for treatment of periampullary neoplasms, including pancreatic adenocarcinoma.

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Phase II clinical study of alternate-day oral therapy with S-1 as first-line chemotherapy for locally advanced and metastatic pancreatic cancer

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Abstract
Purpose Based on the results of first-line chemotherapy for advanced pancreatic cancer, S-1 was confirmed to be non-inferior to gemcitabine. However, the recommended regimen of 4 weeks of administration followed by 2 weeks of drug withdrawal frequently causes adverse effects. On the other hand, we experienced in clinical practice that alternate-day administration of S-1 reduced adverse effects and were tolerable for advanced pancreatic cancer patients unwilling to continue the standard daily administration. We therefore conducted a multicenter cooperative prospective study to compare daily with alternate-day administration of S-1 for advanced pancreatic cancer.
Methods Patients with advanced pancreatic cancer were eligible for enrollment in this trial. S-1 was administered at a dose of 40–60 mg twice daily, calculated according to body surface area, on Monday, Wednesday, Friday, and Sunday. Each treatment cycle was 42 days. The primary end point was overall survival (OS). Secondary end points were safety, response rate (RR), progression-free survival (PFS), and time to treatment failure (TTF).
Results Forty-eight patients were evaluable for response. OS as the primary end point was 8.4 months (95 % CI 5.4–10.8), and the 1-year survival rate was 29.2 %. PFS was 5.5 months, and TTF was 3.9 months. RR was 10.4 %, and the disease control rate was 79.2 %. Grade 3/4 hematological and non-hematological toxicities were minor. All of these adverse reactions were tolerable and reversible.
Conclusions The current data demonstrate the mitigation of adverse effects with alternate-day administration of

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S-1, and this appears to be a more sustainable option for advanced pancreatic cancer.

Keywords Alternate-day · Oral therapy · S-1 · Chemotherapy · Pancreatic cancer

Introduction

Pancreatic cancer is known for its most unfavorable prognosis, with a 5-year survival rate of approximately 9 % [1]. Surgery is the only treatment expected to completely eradicate the condition, but 80 % of patients are diagnosed with the cancer when they have already reached an inoperable status. For unresectable patients, chemotherapy is commonly used, and since Burris et al. [2] demonstrated the significant efficacy of gemcitabine (GEM) in prolonging life expectancy over 5-fluorouracil (5-FU) in a comparative study conducted in 1997, GEM has become the major chemotherapeutic agent; yet the median survival time (MST) of unresectable patients treated with GEM remains 5–7 months, suggesting that its effect on survival is inadequate. In Japan, a tegafur/gimeracil/oteracil combination capsule (S-1) is used to treat various types of cancers, and a domestic late phase II trial to evaluate S-1 in patients with pancreatic cancer showed that the response rate (RR) was 37.5 %, and the median progression-free survival time (PFS) was 3.7 months [3]. Furthermore, phase III studies (GEST study) of GEM + S-1 combination therapy (GS therapy), GEM, and S-1 were conducted in Japan and Taiwan in patients with unresectable advanced pancreatic cancer, and a controlled trial of the effects of GEM versus S-1 on survival showed that the hazard ratio (HR) was 0.96 (97.5 % confidence interval [CI] 0.78–1.18), demonstrating the non-inferiority of S-1 to GEM [4]. The standard regimen of S-1 treatment used in the GEST study, a 4-week daily administration followed by a 2-week rest period, has frequently been associated with digestive symptoms such as anorexia, diarrhea, and stomatitis, which can result in a need to discontinue treatment altogether. It is still unclear, however, whether the therapeutic efficacy of modified regimens with reduced overall dosage or of shortened treatment cycles is as effective as the standard dosage regimens in patients reporting adverse events with S-1. In recent years, an alternate-day administration of S-1 has been reported to alleviate adverse reactions without reducing the efficacy of treatment. Arai et al. [5] started treatment for 92 patients with advanced recurrent gastric cancer with a schedule of administration for 4 consecutive weeks followed by a 2-week rest period, but later switched to an alternate-day regimen for 72 patients, upon their own request, in whom the therapy had to be interrupted due to grade 1 or higher non-hematological toxicities (31.5 %). As a result, the number of patients with grade 2 or higher non-hematological toxicities dropped remarkably to 2 (2.8 %), and the average duration of therapy for the alternate-day regimen was extended to 272 days, as opposed to 47 days with daily administration. In the study, time to progression (TTP) was 170 days, MST was 11 months, and the disease control rate in the evaluable patients was reported to be 53 % (31/58). Since we have observed the reduction in adverse events and the long-term administration rendered possible by replacing the S-1 regimen with an alternate-day administration, we also conducted a clinical phase II study of alternate-day S-1 administration for the treatment of advanced recurrent pancreatic cancer in an attempt to alleviate adverse reactions and to achieve long-term administration.

Patients and methods

Eligibility

The eligibility criteria for patients were as follows: pancreatic cancer with adenocarcinoma or adenosquamous cancer confirmed by histological testing; locally advanced and metastatic pancreatic cancer; a measurable lesion; ultrasonography examination taken 28 days prior to enrollment; no prior treatments (radiotherapy, chemotherapy, or immune therapy) other than resection of pancreatic cancer; patients in whom pre- and postoperative adjuvant chemotherapy had been administered were eligible if recurrence was confirmed 24 weeks after the final administration (or after day 169 counting from the day following the termination of treatment); patient age between 20 and 80 years; 0 or 1 ECOG performance status (PS); patients with the principal organ functions sufficiently maintained (see criteria below); orally administrable; no abnormal findings leading to clinical complications confirmed by electrocardiogram (ECG) taken within 28 days (4 weeks) of enrollment; and cases in which a patient's written consent had been obtained. The following criteria were used to define whether principal organ functions were sufficiently maintained, from laboratory data taken within 14 days of enrollment (tests conducted on the same day as the enrollment day 2 weeks prior were acceptable): white cell count >3,500/mm^3; neutrophil count >2,000/mm^3; hemoglobin >9.0 g/dL; blood platelet count >100,000/mm^3; total bilirubin <2.0 mg/dL; AST/ALT <150 IU/L; serum creatinine <1.2 mg/dL; and creatinine clearance >60 mL/min.

Treatment

The appropriate dose of S-1 was calculated as follows: patients with a body surface area of <1.25, 1.25–1.50, and >1.5 m^2 received daily doses of 80, 100, and 120 mg/day,

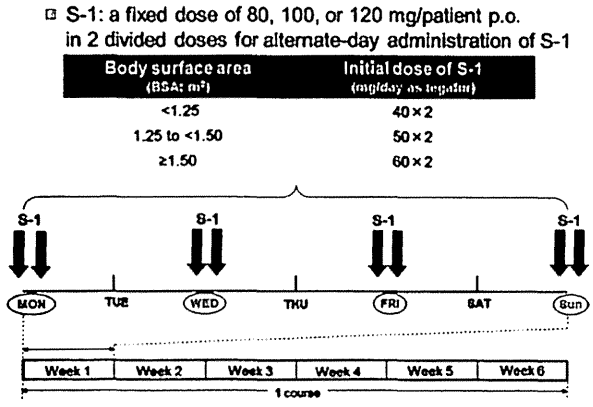

Fig. 1 Treatment schedule for alternate-day with S-1

respectively, administered orally in two equal amounts, after breakfast and after the evening meal. The initial dose of S-1 was administered either on a Monday, Wednesday, Friday, or Sunday (the specified days). S-1 was then administered according to the schedule for the alternate-day regimen for a cycle of 6 weeks. The first day of S-1 treatment was defined as day 1. The first dose of S-1 was taken after the evening meal if it could not be taken after breakfast. The day on which the first dose was administered was designated as day 1 even if the initial dose was taken after the evening meal. The second dose was then taken on the following specified day (e.g., if the initial dose was administered on Friday evening, the next dose would be taken on the following Sunday morning). S-1 administration was continued on Mondays, Wednesdays, Fridays, and Sundays until any one of the criteria for terminating the regimen was satisfied (Fig. 1). The days specified for administering S-1 could not be altered. No missed doses could be taken on days other than those initially prescribed. A dose reduction of 20 mg/day was recommended if grade 3 or higher hematological or non-hematological toxicity occurred in the previous cycle; dose re-escalation was not allowed. Patients who required more than 4 weeks of rest for recovery from any toxicity other than nausea, vomiting, or anemia, or who required a dose reduction of >20 mg/day, were withdrawn from the study.

Evaluation

Assessment of the response rate (RR) was carried out using the sum of complete (CR) and partial response (PR) rates. The antitumor efficacy was interpreted in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and evaluated according to the following criteria: The maximum response rate obtained for each patient by the final course was designated as the response rate of the patient, thereby making the confirmation of 4-week sustained efficacy unnecessary. The efficacy evaluation was carried out for all eligible cases. The number of non-evaluable cases was added only to the denominator of the efficacy evaluation. Stable disease (SD) referred to a stable condition in which none of the other conditions, that is, progressive disease (PD) confirmed CR, and confirmed PR, applied throughout the 6-week cycle. Adverse event nomenclature, grades, and dates of onset were recorded in the follow-up report forms by the participating physicians. The evaluation of adverse event grades and nomenclature were recorded according to the CTCAE v4.0. Overall survival (OS) and the secondary end points, progression-free survival (PFS), and time to treatment failure (TTF) were calculated using the Kaplan–Meier method.

Statistics

The primary end point was OS, and the secondary end points were PFS, TTF, RR, and the frequency and severity of adverse events. Forty-five patients were required, based on the assumption of an expected OS of 6 months and a threshold of 4 months, with an α-error of 0.05 and a β-error of 0.2. In order to allow for patients who were ineligible or who subsequently dropped out, it was planned that 50 patients would be included in this study.

Results

Patients

During the period from August 2009 to May 2011, a total of 50 patients were enrolled from 13 different institutions. Two of these patients did not meet the eligibility criteria: One was excluded due to the patient's refusal and the other on the grounds of inadequate renal function. The baseline characteristics of the patients are shown in Table 1.

Treatment

The 48 patients received a total of 99 cycles of chemotherapy, with a median number of cycles of 2.6 (range 1–12). The dose of S-1 was reduced in one patient because of grade 3 anorexia and fatigue. The median relative dose intensity for the population was 98.9 %, indicating that patient compliance with S-1 chemotherapy was good. Reasons for withdrawal of treatment were progressive disease (79.2 %), patient's refusal (10.4 %), and adverse events (8.3 %). After discontinuation of alternate-day therapy, 14 patients (29.2 %) received GEM-based chemotherapy, 3 patients (6.2 %) received S-1-based chemotherapy, 3 patients (6.2 %) received GEM + S-1 chemotherapy, and 28 patients (58.3 %) received supportive care.

Table 1 Patient characteristics

Characteristic	Number (%)
Age (year)	
Median	67
Range	34–75
Sex	
Male	21 (44)
Female	27 (56)
Performance status	
0	40 (83)
1	8 (17)
Extent disease	
Locally advanced	11 (23)
Metastatic	37 (77)
Metastatic sites	
Liver	21 (44)
Peritoneum	10 (21)
Distant lymph nodes	6 (13)
Lung	1 (2)

Toxicity

The most common adverse events are listed in Tables 2 and 3. The only grade 3 or higher hematotoxicities reported were neutropenia (4.2 %) and cholecystitis (2.0 %), and most other instances remained below grade 2 (<30 %). Furthermore, the only grade 3 or higher non-hematotoxicities reported were anorexia and general malaise (2.0 %), and most of these adverse events were also below grade 2 (<20 %). Although gastrointestinal toxicities and myelosuppression were frequently observed with standard treatment, alternate-day treatment was manageable with appropriate medical care. There was no incidence of treatment-related death.

Table 4 Patient characteristics in relation to the response

Variable	Number (%)
Complete response	0 (0.0)
Partial response	5 (10.4)
Stable disease	33 (68.8)
Progressive disease	10 (16.6)
Objective response rate (%)	5 (10.4)
95 % CI	(3.5–22.7)
Disease control rate (%)	38 (79.2)
95 % CI	(65.0–89.5)

Response and survival

The antitumor effect is shown in Table 4. The objective response rate was 10.4 % (95 % CI 3.5–22.7 %), and the disease control rate was 79.2 % (95 % CI 65.0–89.5 %). At the median follow-up interval of 24 months, 3 patients were still alive and censored. The median overall survival time was calculated for all 48 patients: OS was 8.4 months (95 % CI 5.4–10.8), the one-year survival rate was 29.2 %, and PFS was 5.5 months. Time to treatment failure (TTF) was 3.9 months (95 % CI 2.6–7.3). The Kaplan–Meier survival curve is shown in Figs. 2, 3, and 4.

Discussion

While the results obtained in GEST showed that S-1 monotherapy was one of the standard therapeutic modalities

Table 2 Hematological toxicities

Event	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	≧Grade 3 (%)
Leukopenia	7 (14.6)	5 (10.4)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	4 (8.3)	1 (2.0)	2 (4.2)	0 (0.0)	2 (4.2)
Thrombocytopenia	6 (12.5)	8 (16.6)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	5 (10.5)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total bilirubin increased	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increased	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 3 Non-hematological toxicities

Event	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	≧Grade 3 (%)
Anorexia/fatigue	4 (8.3)	5 (10.4)	1 (2.0)	0 (0.0)	1 (2.0)
Mucositis	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	2 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (2.0)

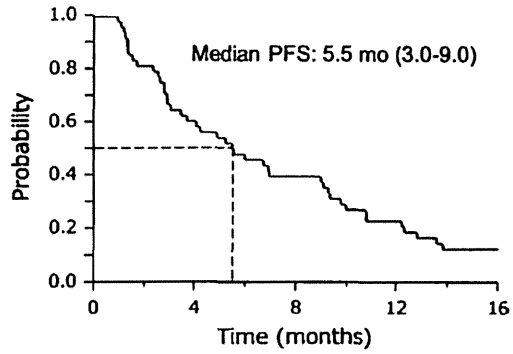

Fig. 2 Kaplan–Meier estimate of progression-free survival according to treatment of S-1

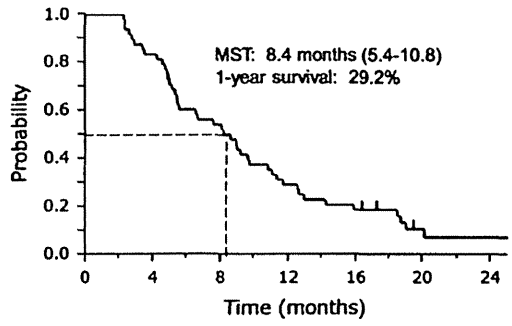

Fig. 3 Kaplan–Meier estimate of overall survival according to treatment of S-1

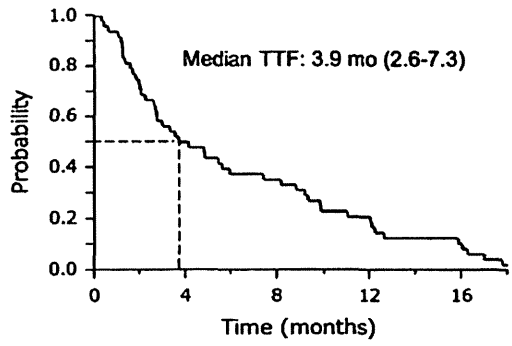

Fig. 4 Kaplan–Meier estimate of time to treatment failure according to treatment of S-1

against advanced pancreatic cancer, there still was room for improvement with respect to the administration schedule, in order to reduce adverse events. At the same time, Lipkin et al. and Clarkson and Ota et al. [6, 7] demonstrated a significant difference between the cell cycles of a host's normal cells and cancer cells. The cell cycle of the normal cells was determined to be half to 1 day, and the length of S phase in which 5-FU was activated was 12 h. In contrast, the cell cycle of cancer cells was 4–5 days, and their S phase lasted for more than 24 h. Thus, by taking advantage of the difference in the cell cycles, a clinically optimum dosage regimen for 5-FU could be ascertained. If a reasonable number of normal cells were to avoid exposure to 5-FU (by means of a 1 day cessation of 5-FU treatment), it could be possible to avoid some of the toxic effects of 5-FU on the normal cells of the intestinal mucosa. In addition, because not only was the cell cycle of cancer cells longer (4–5 days), but also their S phase lasted for more than 24 h, Shirakawa et al. [8] argued that the alternate-day regimen for S-1 would not diminish the cytotoxic effects against cancer cells even if 5-FU were repeatedly activated every other day with a drug cessation period in between. Moreover, Arai et al. [9] treated gastric cancer cell lines with the same total dose of S-1 on alternate or consecutive days to compare these regimens. Although it was a basic study, the results demonstrated that alternate-day treatment with S-1 was equivalent to consecutive-day treatment in terms of the relative inhibition of tumor growth, but with lower toxicity. Furthermore, Sakuma et al. conducted a retrospective examination of the alternate-day regimen in 266 patients with gastric cancer (including advanced recurrent cancer and postoperative adjuvant chemotherapy). The results obtained in the study showed that the efficacy of the regimen was by no means inferior to that of the standard regimen, and with respect to the incidence of adverse events for each grade, extremely favorable results were obtained as follows: 0 % grade 3 or higher, 6 % grade 2, and 7.5 % grade 1 [10].

In this phase II study, the MST was 8.4 months, 1-year overall survival rate was 29.2 %, PFS was 5.5 months, and TTF was 3.9 months. Seven cases of grade 2 or higher non-hematotoxicities (14.6 %), and two cases of grade 3 or higher hematotoxicities (4.2 %) were reported; therefore, the efficacy and safety of the regimen have been confirmed. Although a high response rate was not obtained with S-1 alternate-day administration in this study, the disease control rate was approximately 80 %, and the frequency of adverse events was noticeably less compared to that of the 4-week S-1 regimen followed by a 2-week rest period [3, 4]. The transition to a second-line therapy was not specified in this study; however, these data were recorded as follows. The percentage of patients who underwent transition to GEM, S-1, or GEM + S-1 therapy, or to no further treatment was 29.2, 6.2, 6.2, and 58.3 %, respectively; in total, the percentage of patients undergoing transition to second-line treatment in this study was lower than the percentage undergoing transition to second-line treatment with GEM or GEM + S-1 in the GEST study (approximately 70 %). The fact that in 60 % of patients given the S-1 alternate-day regimen, the second-line treatment could not be

administered due to worsening of the overall health status induced by the first-line treatment has suggested that there is still room for improvement in the treatment efficacy/route of administration of first-line treatment for pancreatic cancer.

Therefore, by comparison with the standard regimen, the S-1 alternate-day regimen may have superior tolerability as well as continuity in the treatment for advanced recurrent gastric cancer or unresectable advanced pancreatic cancer. Compared to other types of carcinoma, unresectable advanced pancreatic cancer has been associated with a higher frequency of serious adverse events when treated with S-1; the alternate-day administration schedule of S-1 therefore has promising potential for not only making treatment more patient-friendly by alleviating side effects, but also achieving improvements in compliance and treatment outcomes [4, 11, 12].

In conclusion, from the results obtained in this study, we have designed and are conducting a randomized phase II study confirming non-inferiority, in terms of overall survival, of the alternate-day regimen for S-1, which has been suggested to result in superior safety and continuity and comparing safety and health-related quality of life in the standard and alternate-day regimens (PAN-01, UMIN000008604). The objective is to determine a standard treatment method necessary to conduct a superiority analysis for developing novel treatment approaches in the future. Furthermore, this research will facilitate the much-awaited development of combination chemotherapy maintaining the efficacy of each individual drug, by applying the alternate-day regimen, which promises fewer side effects, as a basic treatment.

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ORIGINAL ARTICLE

Predicting factors for unresectability in patients with pancreatic ductal adenocarcinoma

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Abstract
Background The aim of the present study was to identify the predicting factors for unresectability and to clarify who should receive precise evaluations for distant metastasis and locally advanced unresectability in patients with pancreatic ductal adenocarcinoma (PDAC).
Methods A total of 200 consecutive patients with PDAC who presented to the outpatient clinic between June 2009 and October 2012 were analyzed retrospectively. Clinical factors and the serum levels of carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, DUPAN-2 (pancreatic cancer-associated antigen) and CA 125 were analyzed.
Results Of the 200 patients who were investigated for PDAC, 60 (30%) were initially considered unresectable (15 patients with locally advanced tumors, 45 patients with distant metastases). Of the 136 (68%) patients who were surgically explored, 19 (9.5%) were detected to have minute metastases on laparotomy. A multivariate analysis revealed that tumor size (≥30 mm) and abnormalities in the levels of DUPAN-2 and CA 125 were independent predictors of unresectability (P = 0.002, 0.014, < 0.001, respectively). The patients with triple positive findings presented with the highest sensitivity (78.8%) for unresectability.
Conclusions Patients with triple positive findings for a tumor size ≥30 mm, abnormalities in the levels of DUPAN-2 and CA 125 should receive precise evaluations for unresectability.

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Keywords Carbohydrate antigen 125 · Distant metastasis · Pancreatic ductal carcinoma · Tumor marker · Unresectability

Introduction

Most cases of pancreatic carcinoma are discovered at an advanced stage due to the lack of any specific signs or symptoms in early stages. Among these cases, the curative resection rate remains less than 23% [1, 2]. There are many reports describing the prognostic/therapeutic value of carbohydrate antigen (CA) 19-9 [3–8]. However, the relationship between the CA 19-9 level and the resectability of pancreatic ductal adenocarcinoma (PDAC) remains unclear. Clinical factors of unresectability include distant metastasis or locally advanced carcinoma. Surgeons sometimes encounter distant metastases intraoperatively, including tiny liver metastases or a small amount of peritoneal metastases, which are difficult to detect preoperatively even using recent modern imaging studies. Few data regarding factors predicting unresectability on the initial medical evaluation in patients with PDAC have been published thus far [8, 9]. Over the past several years, "borderline resectable" tumors have been described in a distinct subset of patients with pancreatic carcinoma. Patients with borderline resectable disease comprise a subset that exhibits an imprecise entity between radiologically and technically resectable and unresectable disease [10–12]. The National Comprehensive Cancer Network (NCCN) previously acknowledged borderline resectable pancreatic carcinoma as a unique substage of pancreatic carcinoma [10], and cancer invading the celiac artery or common hepatic artery precludes radical resection [13, 14]. However, the concrete definition of locally unresectable and borderline resectable pancreatic carcinoma and current surgical strategies are not clear for primary care physicians. Therefore, in order to familiarize physicians

with the general clinical picture in patients with borderline resectable pancreatic carcinoma, simplified information regarding detection is urgently needed. The aim of the present study was to identify indicators that can predict patients with PDAC at high risk for unresectability and to clarify who should receive precise evaluations for distant metastasis and locally advanced unresectability based on an analysis of clinical factors and the initial serum levels of carcinoembryonic antigen (CEA), CA 19-9, DUPAN-2 (pancreatic cancer-associated antigen) and CA 125 among 200 consecutive patients with PDAC.

Patients and methods

Patients

A total of 200 consecutive patients with pancreatic ductal adenocarcinoma (PDAC) who presented to the outpatient clinic of Wakayama Medical University Hospital (WMUH) between June 2009 and October 2012 were analyzed retrospectively. All tumor markers were routinely measured at the outpatient service unit without relation to prior biliary drainage. Consequently, all patients were diagnosed with PDAC or invasive ductal carcinoma derived from intraductal papillary mucinous neoplasm (IPMN) using either one or two specimens obtained with the following examinations: surgical resection, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), percutaneous liver biopsy, peritoneal biopsy on laparoscopy or endoscopic duodenal biopsy. Patients who had undergone any prior therapies against PDAC or other types of pancreatic carcinoma, including noninvasive intraductal papillary mucinous carcinoma, acinar cell carcinoma, anaplastic carcinoma or endocrine carcinoma, were excluded from this study. Unresectable cases that were found to be progression of the disease after NACRT were also excluded from analysis due to the prediction of unresectability.

Definition of locally advanced and borderline resectable disease

The extent of pancreatic cancer was defined as resectable (stage I or II), locally advanced (stage III) according to NCCN criteria. The subset of tumors that blurs distinction between resectable and locally advanced disease were diagnosed as borderline resectable pancreatic carcinoma. Borderline resectable pancreatic carcinoma was defined as resectable at increased risk of disseminated disease and higher likelihood of an incomplete (R1 or R2) resection after surgery without relation to portal vein involvement.

Tumor markers

The levels of four tumor markers (CEA, CA19-9, DUPAN-2 and CA 125) were obtained on the initial medical examination in this study. The normal ranges of each tumor marker in WMUH were as follows: CEA: 0–5 ng/ml, CA19-9: 0–37 U/ml, DUPAN-2: 0–150 U/ml and CA 125: 0–34 U/ml.

Diagnosis of distant metastasis based on the examinations

In this study, the initial diagnostic imaging evaluations of distant metastases were performed based on the findings of plain/dynamic multidetector computerized tomography (MD-CT) and abdominal ultrasonography. The conditions for dynamic MD-CT imaging were as follows: contrast material injection: 99 ml/60 kg, 4 ml/sec (0–25 sec), shooting on 30 sec (early arterial phase), 45 sec (late arterial phase), 65 sec (portal venous phase) and 180 sec (equilibrium phase), 1.25 mm thick from the neck to the pelvis (GE Healthcare, Light Speed VCT). Only the patients who were scheduled to undergo neoadjuvant chemoradiation therapy (NACRT) received closer examinations of MRI and PET-CT for distant metastasis. During the period of this study, no patients underwent sampling or dissection of para-aortic lymph nodes. The metastasis of para-aortic lymph node was diagnosed only by preoperative MD-CT.

Indications for staging laparoscopy

Until January 2010, patients with borderline resectable pancreatic carcinoma underwent surgery first and received subsequent adjuvant chemotherapy. Between January 2010 and October 2011, all patients with pancreatic carcinoma that was initially diagnosed as borderline resectable underwent staging laparoscopy to rule out peritoneal or hepatic metastasis before receiving NACRT as local therapy. Starting in November 2011, patients with borderline resectable carcinoma received neoadjuvant chemotherapy as systemic therapy after histopathological results of PDAC were confirmed without the use of staging laparoscopy.

Cytology via peritoneal lavage

Peritoneal lavage was basically performed for cytology on all patients who underwent staging laparoscopy or laparotomy just after laparotomy. However, the results of cytology did not influence the decision for resection.

Statistical analysis

Statistical comparisons between two groups were made using the χ^2 test, Fisher's exact test or the Mann–Whitney

U-test, where appropriate. The baseline characteristics and clinical variables were compared between the resected and unresected patients and between the patients with normal and abnormal CA 125 levels using the χ^2 test for continuous and categorical variables, respectively. Univariate analyses (χ^2 test) were primarily used to select variables based on a *P*-value of <0.05. The significant variable factors were subjected to a forward logistic regression analysis to determine the net effect for each predictor while controlling the effects of the other factors. A value of $P < 0.05$ was considered to indicate statistical significance. All analyses were performed using the statistical software package SPSS II (version 20.0; SPSS, Chicago, IL, USA).

Results

Patient characteristics and the diagnostic/therapeutic flow of the 200 patients

The patient characteristics of the 200 PDAC patients revealed there were 117 males and 83 females, of whom 157 patients were symptomatic and 43 were asymptomatic. The tumors were located in the pancreatic head in 98 patients and the body/tail in 102 patients. The median age and tumor size (longest diameter) in all patients were 69 (38–86) years and 30 (10–80) mm, respectively. Positive symptoms included abdominal pain, back pain, jaundice, appetite loss, body weight loss, abdominal discomfort and emerging or exacerbation of diabetes mellitus. Negative symptoms included incidentaloma or abnormalities in tumor markers. Figure 1 presents a diagnostic and therapeutic flowchart of the 200 patients. Initially, 60 (30.0%) patients were diagnosed as being positive for distant metastasis (n = 45, 22.5%) or locally advanced unresectable tumors (n = 15, 7.5%), while 140 (70.0%) patients were diagnosed with borderline resectable or resectable pancreatic carcinoma based on the findings of MD-CT and US. Twenty-four patients underwent staging laparoscopy, two of whom were found to have peritoneal metastasis laparoscopically based on histopathological examinations. After receiving NACRT, two patients were found to have new metastases to the liver or disease progression of the primary lesion. Surgery in anticipation of resection was scheduled for 136 (68.0%) patients, 17 (8.5%) of whom were found to have unexpected peritoneal or liver metastases intraoperatively, and two (1.0%) of whom were found intraoperatively unresectable due to local extension of primary disease. Ultimately, 117 (58.5%) patients underwent successful tumor resection and 83 (41.5%) patients did not undergo resection and instead received anticancer agents (Fig. 1). In this series, unresectability was diagnosed due to locally advanced unresectable tumors (n = 18, 9.0%) or distant metastasis

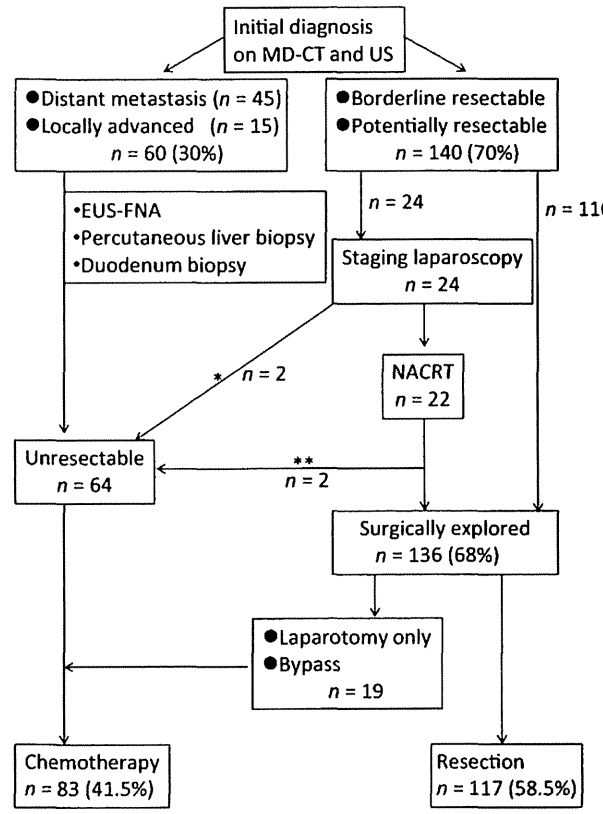

Fig. 1 A diagnostic and therapeutic flowchart of the 200 patients with pancreatic ductal adenocarcinoma. Ultimately, 117 patients underwent successful tumor resection and 83 patients did not undergo tumor resection and instead received anticancer agents. *Two of 24 patients were found to have peritoneal metastasis histopathologically based on staging laparoscopy. **Two patients were found to have new metastases to the liver or disease progression of the primary lesion after receiving neoadjuvant chemoradiation therapy (NACRT), and they were excluded from analysis about the prediction of unresectability. *EUS-FNA* endoscopic ultrasound-guided fine-needle aspiration

(n = 65, 32.5%). The sites of distant metastasis included the peritoneum (n = 16, 8.0%), liver (n = 43, 21.5%), lungs (n = 8, 4.0%), para-aortic lymph nodes (n = 19, 9.5%), adrenal glands (n = 1, 0.5%) and supraclavicular lymph nodes (n = 1, 0.5%). Sixteen patients (8.0%) were diagnosed with distant metastases at more than one site.

Factors predicting unresectability

To determine which factors are independent predictors of unresectability in patients with PDAC, a univariate analysis was used for preliminary screening of variables followed by a stepwise logistic regression analysis of the risk of unresectability using the significant univariate predictors. The univariate analysis (Table 1) identified two clinical factors and three tumor markers (a symptomatic status, tumor size [≥30 mm] and the levels of CEA, DUPAN-2 and

Table 1 Univariate analysis of factors predicting unresectability

Factor		Resection (n = 117)	Unresection (n = 81)	Total (n = 198)	P-value
Age	≥69	63	36	99	0.124
	<69	54	45	99	
Sex	Male	71	45	116	0.283
	Female	46	36	82	
Symptom	Symptomatic	83	72	155	0.002
	Asymptomatic	34	9	43	
Location of the tumor	Head	62	36	98	0.150
	Body/tail	55	45	100	
Tumor size (mm)	≥30	52	63	115	<0.001
	<30	65	18	83	
CEA	Normal	86	44	130	0.004
	Abnormal	31	37	68	
CA 19-9	Normal	24	17	41	0.536
	Abnormal	93	64	157	
DUPAN-2	Normal	60	15	75	<0.001
	Abnormal	54	63	117	
CA 125	Normal	92	37	129	<0.001
	Abnormal	17	38	55	

CA 19-9 carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *n* number of patients

Table 2 Multivariate analysis of factors predicting unresectability

Factor	P-value	Odds ratio	95% confidence interval
Symptomatic	0.144	2.148	0.770–5.995
Tumor size ≥ 30 mm	0.002	3.257	1.516–7.000
CEA > 5 ng/ml	0.387	1.402	0.652–3.015
DUPAN-2 > 150 U/ml	0.014	2.648	1.217–5.763
CA 125 > 34 U/ml	<0.001	3.960	1.843–8.509

CA 19-9 carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen

Table 3 Validity of combined screening using three independent factors predicting unresectability

Positive factors	Sensitivity (%)	Specificity (%)	Accuracy (%)
0 factor	12.8	51.0	43.0
1 factor	18.9	49.6	40.9
2 factors	59.7	67.7	65.1
3 factors	78.8	66.7	68.8

CA 125) to be associated with increased unresectability in patients with PDAC. Table 2 shows the five factors that were retained in the multivariate logistic regression analysis. Tumor size (≥30 mm) and abnormalities in the levels of DUPAN-2 and CA 125 remained significant predictors for unresectability even after controlling for the other variables (P = 0.002, 0.014, < 0.001; odds ratio [OR]: 3.257, 2.648, 3.960; 95% confidence interval [CI]: 1.516–7.000, 1.217–5.763, 1.843–8.509, respectively). In this study, the sensitivity, specificity and accuracy for unresectability were analyzed to compare the findings of combined tests using the three independent predictors. Among the four tumor markers, the serum CA 125 level demonstrated the highest sensitivity (69.6%) and accuracy (70.4%), while the DUPAN-2 level exhibited the highest specificity (80.0%). Tumor size demonstrated a specificity of 78.3% and an accuracy of 65.0% for unresectability. The patients with triple positive findings for the three predictors, including tumor size and the levels of DUPAN-2 and CA 125, presented with the highest sensitivity (78.8%) (Table 3).

Table 4 illustrates the prediction rate for distant metastasis using combined screening with the three independent predicting factors. Triple positive findings for the three factors were identified in six patients (40.0%) with peritoneal metastases, 14 patients (35.0%) with liver metastases, five patients (71.4%) with lung metastases and nine patients (50.0%) with para-aortic lymph node metastases in patients with distant metastasis (n = 45). Seven in 13 (53.8%) triple positive patients with borderline/potentially resectable pancreatic carcinoma (n = 140) revealed to be unresectable finally.

Discussion

The aim of the present study was to identify indicators that can predict unresectability in patients with PDAC. The tumor size and the levels of DUPAN-2 and CA 125 were found to be independent predictors of unresectability.

Table 4 The prediction rate for distant metastasis using combined screening

Positive factors	The sites of distant metastases (n = 45)				Borderline/potentially resectable (n = 140[a])	
	Peritoneum (n = 15)	Liver (n = 39)	Lung (n = 7)	LN (n = 18)	n	Finally unresectable
0 factor	1 (6.7%)	3 (7.7%)	0	0	44	4 (9.1%)
1 factor	1 (6.7%)	5 (12.8%)	0	3 (16.7%)	47	2 (4.3%)
2 factors	7 (46.7%)	17 (43.6%)	2 (28.6%)	6 (33.3%)	27	9 (33.3%)
3 factors	6 (40.0%)	14 (35.9%)	5 (71.4%)	9 (50.0%)	13	7 (53.8%)

LN para-aortic lymph node, *n* number of patients

[a] Three factors were available in 131 patients

Recently, the prognostic and therapeutic value of the CA 19-9 level in patients with pancreatic carcinoma treated with resection, radiotherapy and chemotherapy has been reported and is well established [3–10]. Previous studies reported that the serum concentrations of CA 19-9 and CA 125 exhibit significant increases in cases of disseminated carcinoma [15, 16]. In patients with potentially resectable PDAC, the presurgical and postresection CA 19-9 levels correlate with resectability or overall survival [3, 4]. However, in patients with advanced PDAC, elevated pretreatment levels of CA 19-9 are associated with adverse patient outcomes [17]. Approximately 5% to 10% of the general population is Lewis^{a-b-}; these individuals cannot increase their serum CA 19-9 levels [18, 19]. Those Lewis^{a-b-} patients were termed nonsecretors and were analyzed as a separate group even in the recent literature with one of the largest series of patients [3, 4]. Furthermore, there was the strong association between CA19-9 and biliary obstruction. In the present study, 46 patients (23%) had evidence of jaundice at the time of measurement of tumor markers. Presumably, these features of serum CA 19-9 explain why it was not found to be a predictor for unresectability in this study.

It has been reported that binding of MUC16 and mesothelin expressed by cancer cells mediates heterotypic cell adhesion and may contribute to the metastasis and invasion of ovarian cancer [20]. We previously reported that MUC16, which carries the peptide epitope CA125 [21], clinically represents a prognostic biomarker for PDAC, demonstrating that MUC16 is involved in pancreatic cancer cell invasion and migration [22]. Under the assumption of the presence of a CA 125-presenting disseminated status in PDAC patients, since 2009 we have prospectively investigated the clinical value of the serum CA 125 level by collecting it as an initially obtained tumor marker along with the levels of CA 19-9, CEA and DUPAN-2 and analyzing the data retrospectively with simple clinical factors. The present study demonstrated that tumor size (≥30 mm) and the levels of DUPAN-2 and CA 125 remained significant predictors of unresectability and that the level CA 125 demonstrated the highest accuracy compared to other tumor markers in patients with PDAC. In particular, in regard to the three independent predictors, the patients with triple positive findings presented with the highest sensitivity in all patients, and 7 in 13 (sensitivity 53.8%, specificity 87.3%, accuracy 84.0%) triple positive patients who were diagnosed as borderline/potentially resectable tumor in initial imaging studies revealed to be unresectable finally. Therefore triple positive for these factors is valuable to predict unresectablity in addition to recent modern imaging studies. We suggest using not only the CA 19-9 level to detect the existence of pancreatic carcinoma, but also the DUPAN-2 and CA 125 levels to evaluate the disseminated status as a favorable combination of tumor markers that should be obtained at the initial medical visit in patients with pancreatic tumors.

In conclusion, the CA 125 level is a useful indicator of unresectability in patients with PDAC, and patients with triple positive findings for a tumor size ≥30 mm, a DUPAN-2 level >150 U/ml and a CA 125 level >34 U/ml should receive precise evaluations, including laparoscopy, thin-slice high-resolution MD-CT, magnetic resonance imaging and positron emission tomography/computerized tomography, to assess distant metastasis or locally advanced unresectability.

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Conflict of interest None declared.

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Postoperative prognosis of pancreatic cancer with para-aortic lymph node metastasis: a multicenter study on 822 patients

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Abstract

Background The prognosis of pancreatic cancer patients with metastatic para-aortic lymph node (PALN) has been reported to be extremely poor. In general, PALN metastasis has been considered as a contraindication for pancreatic resection. The aim of this study was to reevaluate the postoperative prognostic value of PALN metastasis in pancreatic cancer and to determine the validity of pancreatic surgery.

Methods Retrospective multicenter analysis of 882 patients who have undergone curative-intent pancreatic resection with pathological evaluation of PALNs for pancreatic ductal adenocarcinoma between 2001 and 2012 was conducted. Clinicopathological data and outcomes were evaluated with univariate and multivariate analysis.

Results In total, 102 (12.4 %) patients had positive metastasis in PALN. Patients with metastatic PALN had significantly poorer survival than those without (17 vs. 23 months; $p < 0.001$). Multivariable analysis of 822 patients identified adjuvant chemotherapy, primary tumor status, regional lymph node metastasis, portal vein invasion, pre- and post-operative serum CA19-9 levels, and tumor grade as independent prognostic factors. In contrast, PALN metastasis did not have a significant prognostic value. Furthermore, the multivariate prognostic analysis in patients with PALN metastasis revealed that adjuvant chemotherapy and the number of metastatic PALN were significantly associated with long-term survival. Lung metastasis as initial recurrence was observed more often in patients with PALN metastasis in comparison with those without.

Conclusions Some pancreatic cancer patients with metastatic PALN may survive for longer than expected after pancreatectomy. Adjuvant chemotherapy and the number of metastatic PALN were critical factors for long-term survival of those patients.

Keywords Pancreatic cancer · Para-aortic lymph node metastasis · Postoperative prognosis

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Introduction

Pancreatic cancer has been increasing in incidence, and it is one of leading causes of cancer-related deaths worldwide [1, 2]. Despite significant progress in the treatment, the overall survival of patients remains extremely poor [3, 4]. Although surgery offers the only chance for cure or long-term survival, the majority of patients were found to be unresectable at diagnosis [5–7]. Common reasons for unresectability include vascular invasion excluding limited portal vein invasion that can be reconstructed, distant lymph node metastases, hepatic metastases, peritoneal metastases, and extra-abdominal metastases including pulmonary metastases. These surgical indications have not been much changed for many years [5, 8].

According to the TNM classification for pancreatic cancer, para-aortic lymph node (PALN) is regarded as distant lymph node and PALN metastasis is classified as distant metastasis [9, 10]. Therefore, if PALN metastasis in pancreatic cancer is suspected by preoperative images or defined by intraoperative pathological examination, pancreatic surgery is generally contraindicated. In fact, several previous studies have emphasized that the patients with metastatic PALN often had early recurrence after surgery and had extremely poor survival [11–16]. Therefore, they concluded that surgical resection did not provide survival benefit in such patients. They also discussed the need for adjuvant treatment or alternative therapeutic strategies for longer survival. However, the number of clinical studies on this issue is limited and the number of patients evaluated in each study is relatively small. Thus, there is limited clinical evidence that PALN metastasis without other distant metastasis is an absolute contraindication to pancreatic resection. In addition, due to treatment advancement including the introduction of new chemotherapeutic agents for pancreatic cancer, we occasionally see unexpected favorable outcome in daily clinical practice [17–20]. Therefore, pancreatic surgery may provide survival benefits to patients with PALN metastasis in some cases.

To address various clinical questions in the surgical treatment for pancreatic cancer including surgical indication, postoperative complications, as well as predictions of recurrence and prognosis, we have recently established a common database of seven high-volume surgical centers in Japan (Multicenter Study Group of Pancreatobiliary Surgery: MSG-PBS). By using this large-scale database, we reevaluate the postoperative prognosis of pancreatic cancer patients with PALN metastasis as a collaborative study. We further investigated risk factors for PALN metastasis and also analyzed the possibility of long-term survival in patients with metastatic PALN.

Patients and methods

Study design and data collection

This study was approved by the institutional review board of each center. We collected and registered consecutive patients who had undergone R0 or R1 pancreatic resection between 2001 and 2012 for pancreatic ductal adenocarcinoma in the database. Patients with R2 resection were not included in the database. Furthermore, patients with distant metastasis such as liver or peritoneal metastasis were also excluded from the database, even if the combined resection of metastatic sites with the primary lesion was performed. From 1,414 patients registered in the database, 592 whose PALNs had not been sampled for pathological examination were excluded. The data of a total of 822 patients with pathological proof of PALN status were collected from the database.

Para-aortic lymph nodes were sampled by harvesting the lymphocellular aortocaval tissue from the upper part of the celiac trunk to the upper part of the origin of the inferior mesenteric artery [11–13]. These lymph nodes were classified as No. 16, according to the Japanese classification [21].

Clinical data included gender, age, body mass index (BMI), neoadjuvant treatment, adjuvant chemotherapy, pre- and post-operative serum CA19-9 level, tumor location, and operation type. For tumors, pathological data included T and N status according to the 7th AJCC/UICC TNM classification, tumor size, histological type, surgical margin status, and portal vein invasion [9, 10]. Some patients received neoadjuvant treatment using chemotherapy or chemoradiotherapy depending on each institution's decision with informed consent. Postoperative adjuvant treatment of gemcitabine- or S-1-based chemotherapy was employed depending on the physicians' choice or the patients' condition.

The primary endpoint of this study was to evaluate the postoperative prognosis of pancreatic cancer patients with PALN metastasis in comparison with those without. Secondary endpoints included the assessment of risk factors for PALN metastasis and the analysis of prognostic factors in patients with PALN metastasis.

Statistical analysis

The clinicopathological parameters were compared between patients with and without PALM metastasis using Student's *t* test, the Chi-square test, or Fisher's exact test as appropriate. Continuous variables were expressed as mean values ± standard deviation. The median survival was estimated using the Kaplan–Meier method, and the difference was tested using the log-rank test. Patients alive at the time of follow-up point were censored. Date of last