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ORIGINAL REPORT

Randomized Phase III Study of Gemcitabine Plus S-1, S-1 Alone, or Gemcitabine Alone in Patients With Locally Advanced and Metastatic Pancreatic Cancer in Japan and Taiwan: GEST Study

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ABSTRACT

Purpose
The present phase III study was designed to investigate the noninferiority of S-1 alone and superiority of gemcitabine plus S-1 compared with gemcitabine alone with respect to overall survival.

Patients and Methods
The participants were chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer. Patients were randomly assigned to receive only gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle), only S-1 (80, 100, or 120 mg/d according to body-surface area on days 1 through 28 of a 42-day cycle), or gemcitabine plus S-1 (gemcitabine 1,000 mg/m^2 on days 1 and 8 plus S-1 60, 80, or 100 mg/d according to body-surface area on days 1 through 14 of a 21-day cycle).

Results
In the total of 834 enrolled patients, median overall survival was 8.8 months in the gemcitabine group, 9.7 months in the S-1 group, and 10.1 months in the gemcitabine plus S-1 group. The noninferiority of S-1 to gemcitabine was demonstrated (hazard ratio, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for noninferiority), whereas the superiority of gemcitabine plus S-1 was not (hazard ratio, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$). All treatments were generally well tolerated, although hematologic and GI toxicities were more severe in the gemcitabine plus S-1 group than in the gemcitabine group.

Conclusion
Monotherapy with S-1 demonstrated noninferiority to gemcitabine in overall survival with good tolerability and presents a convenient oral alternative for locally advanced and metastatic pancreatic cancer.

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Pancreatic cancer (PC) is currently the eighth leading cause of cancer-related mortality worldwide, with an estimated 266,000 deaths in 2008.[1] Gemcitabine became the standard treatment for advanced PC, improving overall survival (OS) compared with fluorouracil.[2] Although various gemcitabine-based combination regimens have been evaluated, only erlotinib added to gemcitabine showed a survival benefit over gemcitabine, and that was marginal.[3]

Fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX), a gemcitabine-free combination regimen, has recently demonstrated a clear survival benefit compared with gemcitabine for patients with metastatic PC who have a performance status of 0 to 1.[4] However, because FOLFIRINOX is associated with significant toxicity, this regimen must be limited to patients with good performance status and requires close monitoring.[5]

In Japan, clinical trials of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) have been conducted since the early 2000s for patients with PC. S-1

is an oral fluoropyrimidine derivative shown to be effective for gastric and various other types of cancers.[6,7] Phase II studies of S-1 as first-line therapy for metastatic PC resulted in good response rates of 21.1% to 37.5%.[8,9] Consequently, S-1 was approved for the indication of PC in Japan in 2006. Development of gemcitabine plus S-1 (GS) studies have also been initiated, mainly in Japan, and two phase II studies reported high response rates of 44.4% to 48.5% and good median OS of 10.1 to 12.5 months.[10,11]

Because S-1 and GS have shown promising activity in PC, the present randomized phase III study (GEST [Gemcitabine and S-1 Trial] study) was designed to evaluate whether S-1 alone is noninferior to gemcitabine and whether GS is superior to gemcitabine alone for locally advanced and metastatic PC with respect to OS.

Study Design

This randomized phase III study, sponsored by Taiho Pharmaceutical in Japan and TTY Biopharm in Taiwan, was conducted as a postmarketing study in Japan and as a registration study in Taiwan and was in compliance with the Declaration of Helsinki. Data were collected by a contract research organization contracted by the sponsors and were analyzed by a bio-statistician (Y.O.). An independent data and safety monitoring committee reviewed efficacy and safety data. The study was approved by the ethics committee or institutional review board of each participating center.

Patients

All patients provided written informed consent. Enrollment criteria were locally advanced or metastatic PC, histologically or cytologically proven diagnosis of adenocarcinoma or adenosquamous carcinoma, no prior chemotherapy or radiotherapy for PC, age of more than 20 years (the protocol was amended to restrict the eligible age to < 80 years after four of the first eight patients who were ≥ 80 years experienced serious adverse events), an Eastern Cooperative Oncology Group performance status score of 0 to 1, and adequate organ functions (see Appendix, online only).

Treatment

Random assignment was performed centrally with stratification by extent of disease (locally advanced disease *v* metastatic disease) and institution using the minimization method. Patients allocated to gemcitabine alone received gemcitabine at a dose of 1,000 mg/m^2 intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Patients allocated to S-1 alone received S-1 orally twice daily at a dose according to the body-surface area (BSA) (< 1.25 m^2, 80 mg/d; ≥ 1.25 to < 1.5 m^2, 100 mg/d; ≥ 1.5 m^2, 120 mg/d) on days 1 through 28 of a 42-day cycle. Patients allocated to GS received gemcitabine at a dose of 1,000 mg/m^2 on days 1 and 8 plus S-1 orally twice daily at a dose according to the BSA (< 1.25 m^2, 60 mg/d; ≥ 1.25 to < 1.5 m^2, 80 mg/d; ≥ 1.5 m^2, 100 mg/d) on days 1 through 14 of a 21-day cycle. The dose levels of S-1 used in the GS group were based on the results of a previous phase II study of GS, in which 1,000 mg/m^2 of gemcitabine was combined with 120 mg/d, 100 mg/d, and 80 mg/d of S-1. In that study, the rate of treatment withdrawal due to adverse events was 41% (22 of 54 patients), the rate of grade 3 or worse neutropenia was 80%, and the dose was reduced in 56% of the patients (30 of 54 patients).[11] Consequently, 20 mg/d lower doses of S-1 than those used in the S-1 monotherapy group were used in the GS group in the present study.

In the event of predefined toxic events, protocol-specified treatment modifications were permitted (see Appendix).

Assessments

Physical examinations, CBCs, and biochemistry tests were usually checked at 2-week intervals in the S-1 group and at each time of administration of gemcitabine both in the gemcitabine group and in the GS group. All adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 3.0. Computed tomography or magnetic resonance imaging was performed every 6 weeks until disease progression, and response was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[12] Quality of life was assessed using the EuroQol 5 Dimension questionnaire[13] at baseline and 6, 12, 24, 48, and 72 weeks after the study treatment had begun.

Statistical Analysis

The primary end point was OS, defined as time from date of random assignment to date of death from any cause. Secondary end points were progression-free survival (PFS), objective response rate, safety, and quality of life. PFS was counted from the date of random assignment to the date of death without progression or of progression as confirmed by the investigator's assessment. The median OS was assumed to be 7.5 months in the gemcitabine group, 8.0 months in the S-1 group, and 10.5 months in the GS group. To maintain a one-sided significance level of .025 for the entire study while testing two hypotheses (ie, noninferiority and superiority), the one-sided significance

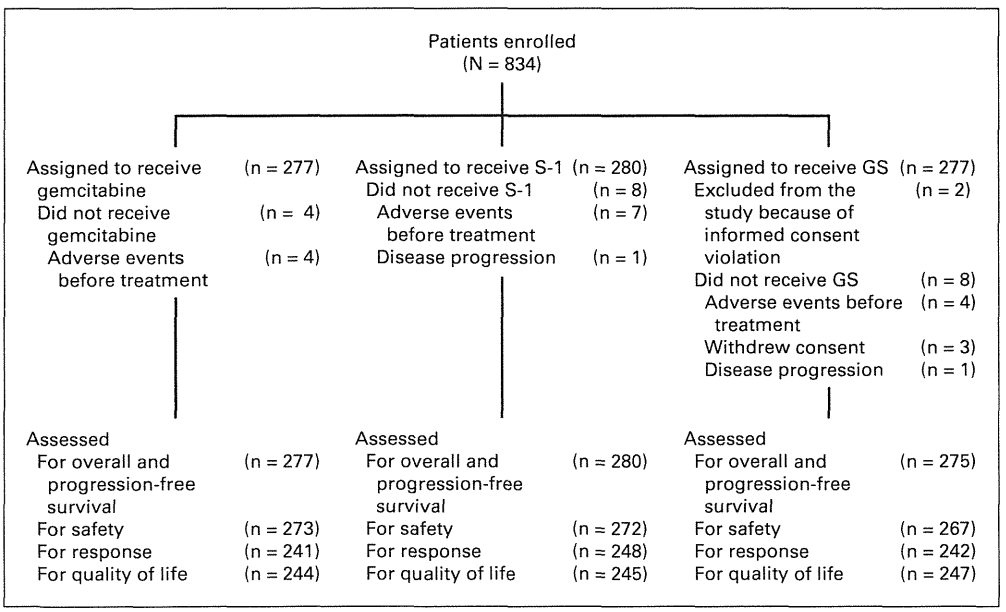

Fig 1. CONSORT diagram. GS, gemcitabine plus S-1.

level for each comparison was set at .0125. The statistical considerations are detailed in the Appendix.

The superiority of GS was evaluated by the stratified log-rank test. To assess the noninferiority of S-1, we used the Cox proportional hazards model to calculate two-sided, 97.5% CIs of the hazard ratio (HR). The noninferiority margin of S-1 was set at 1.33; that is, the null hypothesis was that the median OS with S-1 would be approximately 2 months shorter than with gemcitabine. We decided this setting was justified considering the convenience of S-1 and because there are few effective drugs for the disease. Furthermore, to interpret the obtained data, the Bayesian analysis of the log HR on the basis of the noninformative prior distribution was preplanned. Posterior probability with log HR within a stricter threshold (log 1.15) was also calculated.[14]

In each assigned group, the time-to-event distribution was estimated with the Kaplan-Meier method. The 95% CI of the median survival time was calculated by the method of Brookmeyer and Crowly.[15] In addition, the Greenwood formula[16] was used to calculate the 95% CI for survival rates. In subgroup analyses, interaction tests were performed to assess the homogeneity of the effect of treatment on OS.

The primary end point was analyzed for the full analysis set. All *P* value evaluations were two-tailed. Data analyses were done with SAS, version 9.1.3 (SAS Institute, Cary, NC).

Patients

Between July 2007 and October 2009, a total of 834 patients were enrolled from 75 institutions in Japan and Taiwan (768 in Japan and 66 in Taiwan). Two patients in the GS group were excluded from the study because enrollment was conducted before obtaining written informed consent. The remaining 832 patients were included in the full analysis set and used to calculate OS and PFS (Fig 1). The three treatment groups were well balanced with respect to demographic and baseline characteristics (Table 1).

Study Treatment

The median duration of treatment was 2.6 months in the gemcitabine group, 2.6 months in the S-1 group, and 4.3 months in the GS group. The main reasons for treatment discontinuation were either disease progression (202 patients [72.9%] in the gemcitabine group,

Table 1. Demographics and Baseline Characteristics of Patients (full-analysis set population)

Characteristic	Gemcitabine (n = 277)		S-1 (n = 280)		GS (n = 275)		Total (N = 832)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	170	61.4	170	60.7	158	57.5	498	59.9
Female	107	38.6	110	39.3	117	42.5	334	40.1
Age, years								
< 65	134	48.4	145	51.8	137	49.8	416	50.0
≥ 65	143	51.6	135	48.2	138	50.2	416	50.0
ECOG PS								
0	181	65.3	178	63.6	172	62.5	531	63.8
1	96	34.7	102	36.4	103	37.5	301	36.2
Extent of disease								
Locally advanced	66	23.8	68	24.3	68	24.7	202	24.3
Metastatic	211	76.2	212	75.7	207	75.3	630	75.7
Type of tumor								
Adenocarcinoma	272	98.2	276	98.6	272	98.9	820	98.6
Adenosquamous carcinoma	5	1.8	4	1.4	3	1.1	12	1.4
Pancreas excision								
No	254	91.7	264	94.3	248	90.2	766	92.1
Yes	23	8.3	16	5.7	27	9.8	66	7.9
Tumor location*								
Head	122	44.0	110	39.3	116	42.2	348	41.8
Body	88	31.8	124	44.3	102	37.1	314	37.7
Tail	68	24.5	55	19.6	66	24.0	189	22.7
Biliary drainage								
No	202	72.9	217	77.5	209	76.0	628	75.5
Yes	75	27.1	63	22.5	66	24.0	204	24.5
CEA, ng/mL								
Median	5.7		5.6		5.9		5.7	
IQR	3.0-20.1		2.5-18.4		2.5-20.7		2.6-19.5	
CA19-9, U/mL								
Median	1,044		726		441		712	
IQR	52-5,002		64-5,000		45-5,090		55-5,002	
CRP, mg/dL								
Median	0.40		0.50		0.40		0.43	
IQR	0.11-1.38		0.18-1.57		0.15-1.60		0.15-1.57	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; GS, gemcitabine plus S-1; IQR, interquartile range.
*Including patients with tumors involving multiple sites.

215 [76.8%] in the S-1 group, and 162 [58.9%] in the GS group) or adverse events (40 patients [14.4%] in the gemcitabine group, 38 [13.6%] in the S-1 group, and 76 [27.6%] in the GS group). The median relative dose-intensity was 83.0% in the gemcitabine group, 96.1% in the S-1 group, and 83.3% for gemcitabine and 87.4% for S-1 in the GS group.

Survival

The median duration of follow-up for surviving patients was 18.4 months (range, 0.3 to 36.9 months) as of July 31, 2010. The analysis of OS was based on 710 deaths (85.3%) among the 832 patients. The median OS was 8.8 months (95% CI, 8.0 to 9.7) in the gemcitabine group, 9.7 months (95% CI, 7.6 to 10.8) in the S-1 group, and 10.1 months (95% CI, 9.0 to 11.2) in the GS group (Fig 2A). OS rates at 12 and 24 months were respectively 35.4% and 9.2% in the gemcitabine group, 38.7% and 12.7% in the S-1 group, and 40.7% and 14.5% in the GS group. The noninferiority of S-1 to gemcitabine with respect to OS was demonstrated (HR, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for noninferiority). The Bayesian posterior probability that the HR of S-1 relative to gemcitabine would be less than 1.15 was calculated to be 98% on the basis of the noninformative prior distribution. However, GS failed to improve OS at a statistically significant level as compared with gemcitabine (HR, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$).

The analysis of PFS was based on 793 events (95.3%) among the 832 patients. The median PFS was 4.1 months (95% CI, 3.0 to 4.4) in the gemcitabine group, 3.8 months (95% CI, 2.9 to 4.2) in the S-1 group, and 5.7 months (95% CI, 5.4 to 6.7) in the GS group (Fig 2B). PFS rates at 6 and 12 months were respectively 29.8% and 9.1% in the gemcitabine group, 26.9% and 7.2% in the S-1 group, and 47.9% and 20.3% in the GS group. S-1 was shown to be noninferior to gemcitabine with respect to PFS (HR, 1.09; 97.5% CI, 0.90 to 1.33; $P = .02$ for noninferiority), and GS significantly improved PFS compared with gemcitabine (HR, 0.66; 97.5% CI, 0.54 to 0.81; $P < .001$).

Subgroup analyses of survival according to pretreatment characteristics showed no significant interaction between S-1 and gemcitabine in any subgroup (Fig 3A). However, GS showed a favorable HR compared with gemcitabine in the subsets of patients with locally advanced disease or patients with a performance status of 1 (Fig 3B).

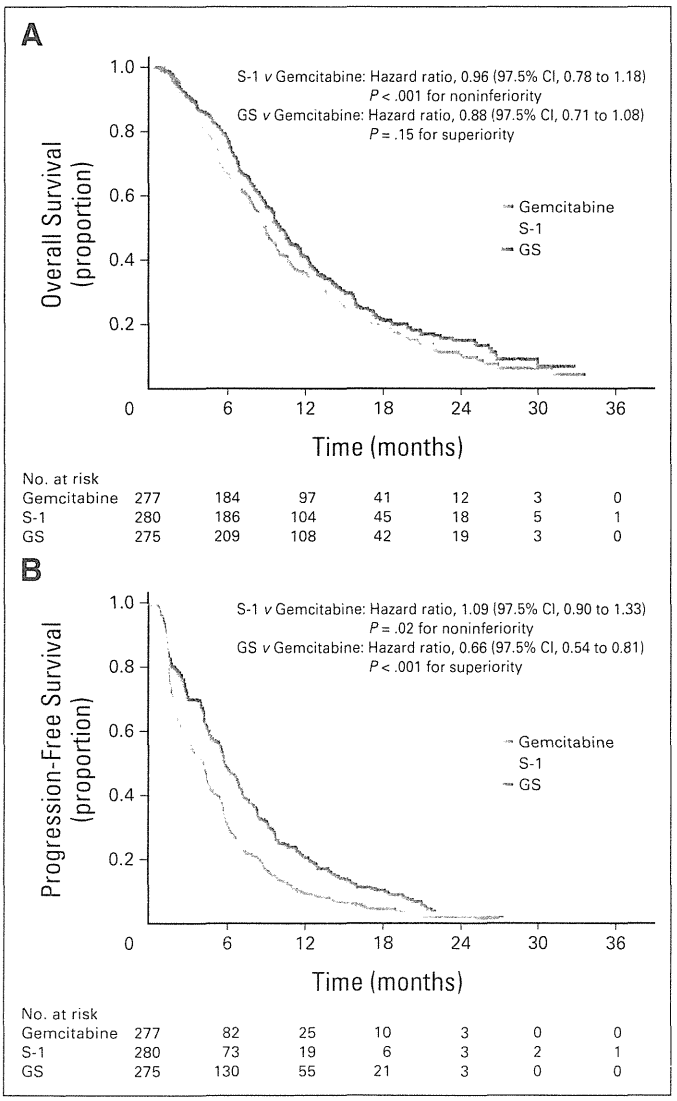

Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival according to treatment group. GS, gemcitabine plus S-1.

Response to Therapy

The objective response rate was 13.3% (95% CI, 9.3 to 18.2) in the gemcitabine group, 21.0% (95% CI, 16.1 to 26.6) in the S-1 group, and 29.3% (95% CI, 23.7 to 35.5) in the GS group (Table 2). The objective response rate was significantly higher in the S-1 group ($P = .02$) and in the GS group ($P < .001$) than in the gemcitabine group.

Second-Line Chemotherapy

Second-line chemotherapy was performed in 184 patients (66.4%) in the gemcitabine group, 185 (66.1%) in the S-1 group, and 172 (62.5%) in the GS group. In the gemcitabine group, 140 patients (50.5%) received S-1 alone or S-1–based regimens, and in the S-1 group 162 (57.9%) received gemcitabine alone or gemcitabine-based regimens as second-line chemotherapy. The most common second-line regimens in the GS group were gemcitabine alone (61 patients), GS (53 patients), S-1 alone (24 patients), irinotecan (six patients), and fluorouracil/leucovorin plus oxaliplatin (four patients). In Japan and Taiwan, the use of treatments such as erlotinib, oxaliplatin, and irinotecan for PC was not approved at the time of this study; hence gemcitabine, S-1, or both were used in most patients as second-line chemotherapy.

Adverse Events and Quality-Adjusted Life-Years

The major grade 3 or worse adverse events are listed in Table 3. Patients in the gemcitabine group had significantly higher incidences of grade 3 or worse leukopenia, neutropenia, thrombocytopenia, elevated AST levels, and elevated ALT levels as compared with patients in the S-1 group. However, the incidence of grade 3 or worse diarrhea was higher in the S-1 group than in the gemcitabine group. Patients in the GS group had significantly higher incidences of grade 3 or worse leukopenia, neutropenia, thrombocytopenia, rash, diarrhea, vomiting, and stomatitis than patients in the gemcitabine group.

There were three deaths considered possibly related to the protocol treatment (interstitial lung disease, sepsis, and acute hepatitis B) in the gemcitabine group, one in the S-1 group (unknown cause), and

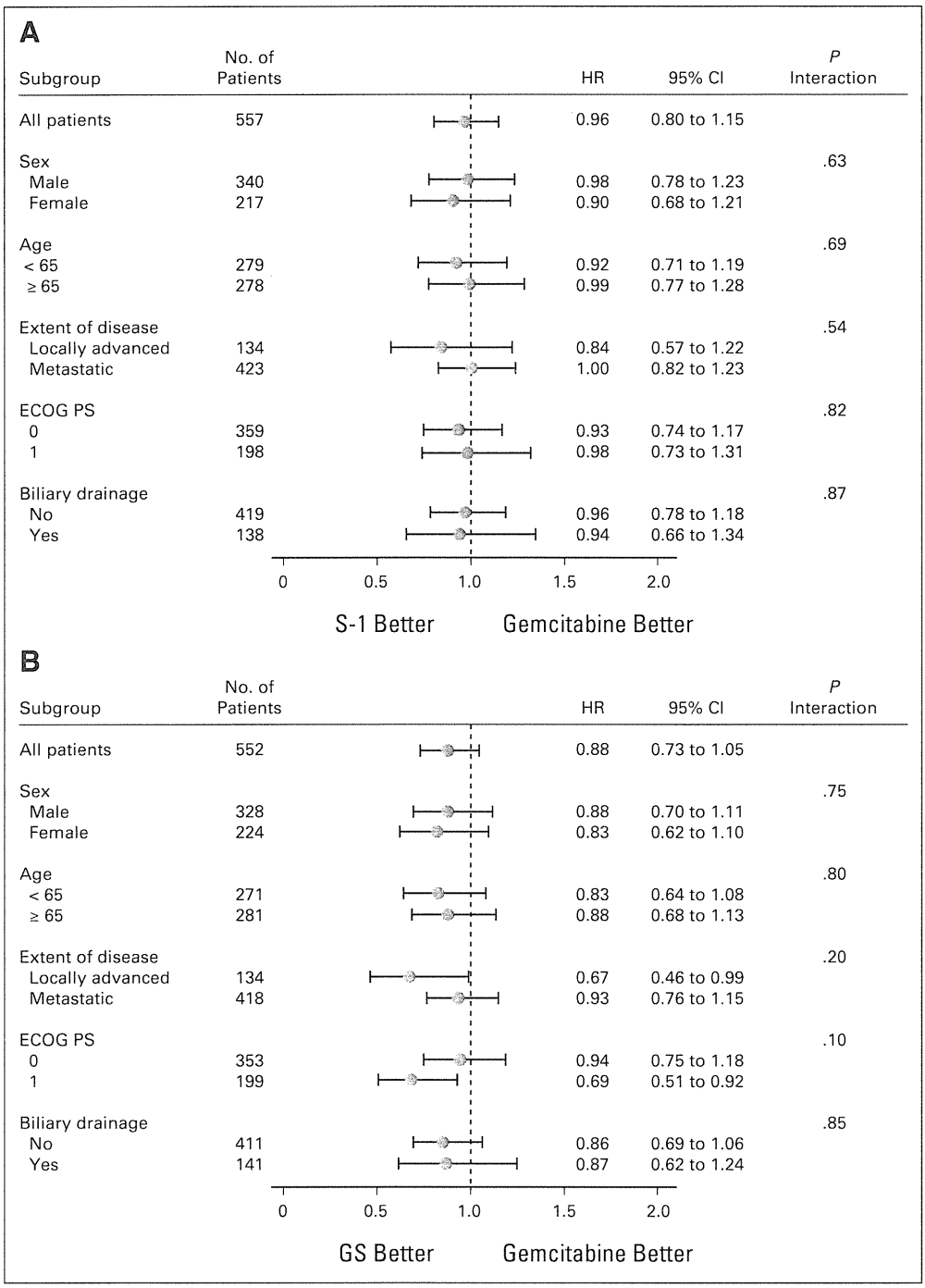

Fig 3. Forest plots of treatment effects on overall survival in subgroup analyses. Forest plots show effects on overall survival of patients in each subgroup. (A) S-1; (B) gemcitabine plus S-1 (GS). Each blue circle shows the treatment response. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

four in the GS group (unknown cause associated with myelosuppression, cerebral infarction, cerebrovascular disorder, and interstitial lung disease). The results of quality-adjusted life-years (QALYs) are in the Appendix and the details of quality-of-life assessments will be reported elsewhere.

The overall and PFS curves in the S-1 group were nearly identical to those in the gemcitabine group, confirming the noninferiority of S-1 to gemcitabine in terms of OS and PFS (Fig 2A, 2B). Toxicity profiles of these two drugs differed slightly: gemcitabine tended to show hematologic toxicity, whereas S-1 tended to show GI toxicity. However, both S-1 and gemcitabine were generally well tolerated. Furthermore, the results of QALY evaluation demonstrated that S-1 and gemcitabine were equivalent. Hence our results suggest that S-1 can be used as first-line therapy as a convenient oral alternative for locally advanced and metastatic PC. To the best of our knowledge, this is the first phase III study to demonstrate the noninferiority of a single anticancer agent to gemcitabine alone for locally advanced and metastatic PC.

Table 2. Objective Response Rates (patients with measurable lesions)

Variable	Gemcitabine (n = 241) No.	Gemcitabine (n = 241) %	S-1 (n = 248) No.	S-1 (n = 248) %	GS (n = 242) No.	GS (n = 242) %	*P* (χ^2 test) Gemcitabine *v* S-1	*P* (χ^2 test) Gemcitabine *v* GS
Response								
Complete response	1	0.4	0	0	2	0.8		
Partial response	31	12.9	52	21.0	69	28.5		
Stable disease	119	49.4	105	42.3	102	42.1		
Progressive disease	75	31.1	69	27.8	37	15.3		
Objective response rate*	32	13.3	52	21.0	71	29.3	.02	< .001
95% CI	9.3 to 18.2		16.1 to 26.6		23.7 to 35.5			
Disease control rate†	151	62.7	157	63.3	173	71.5	.88	.04
95% CI	56.2 to 68.8		57.0 to 69.3		65.4 to 77.1			

Abbreviation: GS, gemcitabine plus S-1.
*The objective response rate was defined as the proportion of patients who had a complete response or partial response.
†The disease control rate was defined as the proportion of patients who had a complete response, partial response, or stable disease.

At the time of planning this study, the participants of nearly all phase III trials included both patients with locally advanced as well as those with metastatic PC. However, because locally advanced and metastatic diseases are two clinical entities, it is recently recommended that patients with locally advanced disease should be studied separately from those with metastatic disease.[17] Although this study included locally advanced disease, subgroup analysis of extent of disease showed no significant interaction between S-1 and gemcitabine (Fig 3A). Moreover, the OS curve in the S-1 group was still similar to those in the gemcitabine group in both locally advanced and metastatic disease (Fig 4A, 4B). Regarding pathologic diagnosis, our study included adenosquamous carcinoma, although its percentage was very low (1.4% of whole population). When the data were reanalyzed after excluding patients with adenosquamous carcinoma, the results for OS for gemcitabine versus S-1 was unchanged (HR, 0.96; 95% CI, 0.81 to 1.15). The selection of one treatment over the other will depend primarily on patient preference, clinical factors, or drug costs, as biomarkers indicating effective use of S-1 or gemcitabine do not exist at this time.

Regarding GS, the OS did not differ significantly from gemcitabine, although the PFS was significantly longer in the GS group. Second-line chemotherapy mainly with S-1 in the gemcitabine group may be one reason for this discrepancy. The median OS in the gemcitabine group was 8.8 months, which is longer than those previously reported for gemcitabine in other phase III studies for locally advanced and metastatic PC.[2,3,18-24] Although the efficacy of second-line

Table 3. Grade 3 or Worse Adverse Events (safety population)

Event	Gemcitabine (n = 273) No.	Gemcitabine (n = 273) %	S-1 (n = 272) No.	S-1 (n = 272) %	GS (n = 267) No.	GS (n = 267) %	*P* (Fisher's exact test) Gemcitabine *v* S-1	*P* (Fisher's exact test) Gemcitabine *v* GS
Hematologic								
Leukocytes	51	18.7	10	3.7	101	37.8	< .001	< .001
Neutrophils	112	41.0	24	8.8	166	62.2	< .001	< .001
Platelets	30	11.0	4	1.5	46	17.2	< .001	.05
Hemoglobin	39	14.3	26	9.6	46	17.2	.11	.41
Nonhematologic								
ALT	41	15.0	16	5.9	29	10.9	< .001	.16
AST	41	15.0	21	7.7	32	12.0	.01	.32
Bilirubin	26	9.5	39	14.3	23	8.6	.09	.77
Fatigue	10	3.7	18	6.6	13	4.9	.13	.53
Rash	2	0.7	2	0.7	11	4.1	1.00	.01
Anorexia	20	7.3	31	11.4	25	9.4	.11	.44
Diarrhea	3	1.1	15	5.5	12	4.5	.004	.02
Mucositis/stomatitis	0	0.0	2	0.7	6	2.2	.25	.01
Nausea	5	1.8	5	1.8	12	4.5	1.00	.09
Vomiting	2	0.7	4	1.5	12	4.5	.45	.006
Febrile neutropenia	1	0.4	1	0.4	5	1.9	1.00	.12
Infection with normal ANC	6	2.2	7	2.6	6	2.2	.79	1.00
Pneumonitis	5	1.8	0	0.0	2	0.7	.06	.45

NOTE. Grades of adverse events were defined according to the Common Terminology Criteria for Adverse Events (version 3.0).
Abbreviations: ANC, absolute neutrophil count; GS, gemcitabine plus S-1.

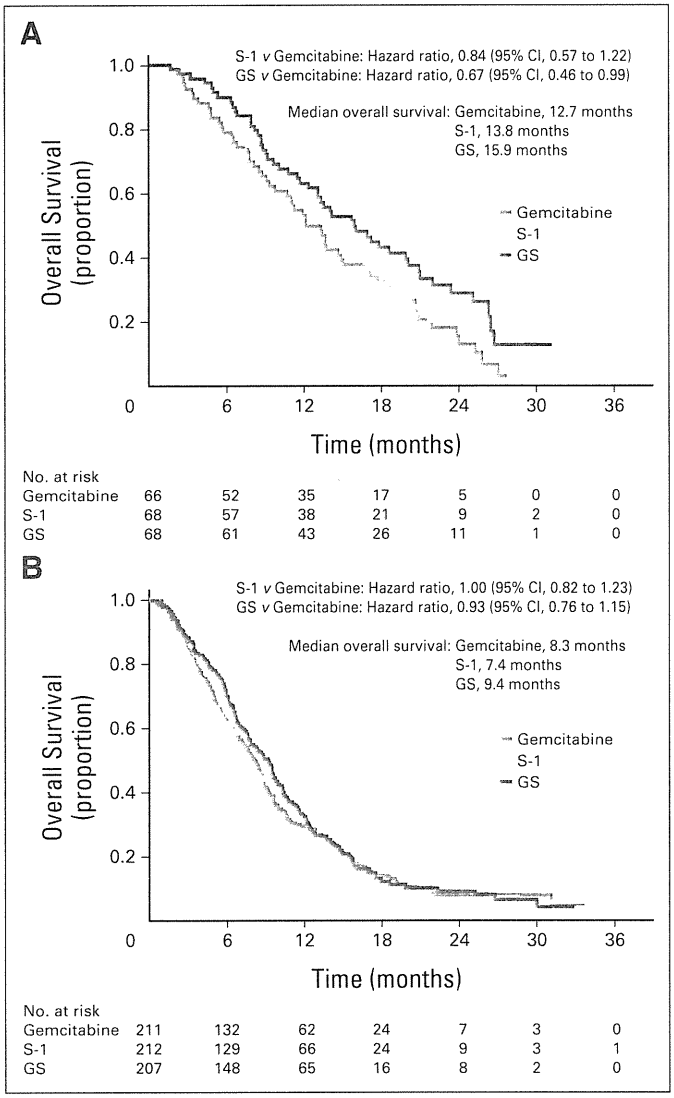

Fig 4. Kaplan-Meier estimates of overall survival in (A) locally advanced disease and (B) metastatic disease. GS, gemcitabine plus S-1.

therapy was not analyzed in this study, a phase II study of second-line S-1 in patients with gemcitabine-refractory PC showed a 15% response rate and 58% disease control rate.[25] Compared with the GS group, which had no promising second-line therapy, the use of S-1 as second-line therapy in the gemcitabine group might have contributed to prolonged survival.

The lack of a significant difference in OS between gemcitabine and GS suggests that gemcitabine and S-1 could be used sequentially rather than concurrently. However, the GS group showed a high response rate and favorable PFS, with a better HR of 0.66 compared with other gemcitabine-based combination regimens in other phase III studies (HR = 0.75 to 1.07).[3,18,20,22,24] Furthermore, the GS group showed a favorable HR for OS in patients with locally advanced disease or patients with a performance status of 1 in the subgroup analyses. Therefore, it is speculated that there may be room to select GS therapy, depending on the profile of the patients and further investigations.

Regarding oral fluoropyrimidines other than S-1, capecitabine has been studied in patients with PC, mainly in the West. In two phase III studies, a combination of gemcitabine plus capecitabine did not significantly prolong survival as compared with gemcitabine alone.[19,20] The results of a meta-analysis of these phase III studies, however, demonstrated that survival was significantly prolonged by combined treatment, with an HR of 0.86,[20] which is similar to the HR for GS in the present study (0.88).

One limitation of our study is that it is uncertain whether our results can be simply extrapolated to Western patients because pharmacokinetics and pharmacodynamics of S-1 between Westerners and East Asians may be different.[26,27] Although S-1 is available for PC only in Japan at the moment, if S-1 is used in Western patients, its effectiveness should be monitored and the dose should be carefully adjusted accordingly. Another potential limitation is that the protocol-specified noninferiority margin of 1.33 may be large. However, the result of point estimate of the HR of S-1 was 0.96 and actual upper limit of the 97.5% CI was 1.18, which was sufficiently lower than the prespecified margin of 1.33. Furthermore, Bayesian posterior probability with log HR within a stricter threshold (log 1.15) was 98%.

Given that most gemcitabine-based combination regimens have not been shown to be significantly superior to gemcitabine alone and that FOLFIRINOX has demonstrated overwhelming superiority to gemcitabine in a phase III study, reporting an HR of 0.57,[4] the development of gemcitabine-free combination regimens for first-line treatment seems to be warranted. However, because FOLFIRINOX requires the placement of a central venous access port for continuous intravenous infusion of fluorouracil, it can be expected that S-1, an oral fluoropyrimidine, will replace the continuous infusion of fluorouracil in the future.

In conclusion, this study has verified the noninferiority of S-1 to gemcitabine, thereby suggesting that S-1 can be used as first-line therapy for locally advanced and metastatic PC. Because S-1 was confirmed to be a key treatment for PC, S-1–based regimens are expected to be developed in the future to improve the management of this formidable disease.

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Appendix

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Details of Adequate Organ Functions in Enrollment Criteria and Main Exclusion Criteria

Adequate organ functions were defined as follows: leukocyte count $\geq$ 3,500/μL, neutrophil count $\geq$ 2,000/μL, platelet count $\geq$ 100,000/μL, hemoglobin level $\geq$ 9.0 g/dL, serum creatinine level $\leq$ 1.2 mg/dL, creatinine clearance $\geq$ 50 mL/min, serum AST and ALT levels $\leq$ 150 U/L, and serum total bilirubin level $\leq$ 2.0 mg/dL or $\leq$ 3.0 mg/dL if biliary drainage was performed.

Main exclusion criteria were as follows: pulmonary fibrosis or interstitial pneumonia; watery diarrhea; active infection; marked pleural effusion or ascites; and serious complications such as heart failure, peptic ulcer bleeding, or poorly controlled diabetes. Pancreatic cancers other than adenocarcinoma or adenosquamous carcinoma (eg, anaplastic carcinoma) were excluded from the study.

Dosage Adjustment Guideline for Toxicities

All treatment cycles were repeated until disease progression, unacceptable toxicity, or patient refusal. If patients had a leukocyte count of less than 2,000/μL, a neutrophil count of less than 1,000/μL, a platelet count of less than $70 \times 10^3/\mu$L, or grade 3 or worse rash, the administration of anticancer agents was postponed. S-1 was temporarily halted both in S-1 and in GS groups if patients had a creatinine level of 1.5 mg/dL or higher or grade 2 or worse diarrhea or stomatitis. Treatment was discontinued if these events did not resolve within 4 weeks after treatment suspension. In patients who experienced febrile neutropenia, grade 4 leukopenia, neutropenia, or thrombocytopenia or grade 3 or worse rash, the dose of gemcitabine was reduced by 200 mg/m^2. In patients with febrile neutropenia; grade 4

leukopenia, neutropenia, or thrombocytopenia; a creatinine level of 1.5 mg/dL or higher; or grade 3 or worse diarrhea, stomatitis, or rash, the dose of S-1 was reduced by 20 mg/d.

Sample Size Determination: Statistical Methods

In the initial plan, the total target number of patients was set at 600, given a statistical power of 80%, an enrollment period of 3 years, and a follow-up period of 2 years. However, because patient enrollment was faster than expected, the target number of patients was revised to 750 to provide the study with a statistical power of 90%. Consequently, the final analysis was performed after the occurrence of 680 events had been confirmed. An interim analysis was not performed. Although the actual median OS in the gemcitabine group was better than initially expected, because an adequate number of patients had been enrolled, a power of $\geq$ 90% was maintained on recalculation of the power on the basis of the actual results.

Quality of Life

To assess the quality of life, the health status of patients on the EQ-5D questionnaire was converted into a single simple utility index ranging from 0 for death to 1 for complete health. Quality-adjusted life-years (QALYs) for individual patients were estimated as the product of the utility index during follow-up and survival time and were compared between the groups, using the generalized Wilcoxon test.

As a result, median QALYs were 0.401 in the gemcitabine group, 0.420 in the S-1 group, and 0.525 in the GS group. The QALY value in the S-1 group was similar to that in the gemcitabine group, and there was no statistically significant difference between the two groups ($P = .56$). The QALY value in the GS group was significantly better than that in the gemcitabine group ($P < .001$). The details of quality-of-life assessments will be reported elsewhere.

RESEARCH ARTICLE

Cigarette Smoking and Pancreatic Cancer Risk: A Revisit with an Assessment of the Nicotine Dependence Phenotype

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Abstract

Background: Cigarette smoking is a well-established risk factor of pancreatic cancer (PC). Although an association between nicotine dependence phenotype, namely time to first cigarette (TTFC) after waking, and the risk of several smoking-related cancers has been reported, an association between TTFC and PC risk has not been reported. We assessed the impact of smoking behavior, particularly TTFC, on PC risk in a Japanese population. Materials and Methods: We conducted a case-control study using 341 PC and 1,705 non-cancer patients who visited Aichi Cancer Center in Nagoya, Japan. Exposure to risk factors, including smoking behavior, was assessed from the results of a self-administered questionnaire. The impact of smoking on PC risk was assessed with multivariate logistic regression analysis adjusted for potential confounders to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Results: Cigarettes per day (CPD) and/or smoking duration were significantly associated with PC risk, consistent with previous studies. For TTFC and PC risk, we found only a suggestive association: compared with a TTFC of more than 60 minutes, ORs were 1.15 (95%CI, 0.65- 2.04) for a TTFC of 30-60 minutes and 1.35 (95%CI, 0.85-2.15) for that of 0-30 minutes (p trend=0.139). After adjustment for CPD or smoking duration, no association was observed between TTFC and PC. Conclusions: In this study, we found no statistically significant association between TTFC and PC risk. Further studies concerning TTFC and PC risk are warranted.

Keywords: Pancreatic cancer - smoking - nicotine - addiction

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Introduction

Cigarette smoking is widely known as a risk factor of pancreatic cancer (PC) (Lin et al., 2001; IARC, 2004; Matsuo et al., 2011; Bosetti et al., 2012). We previously showed that cigarette smoking moderately increased the risk of PC in a Japanese population (Inoue et al., 2003; Matsuo et al., 2011). Although the effect of cigarettes per day (CPD) and/or smoking duration on cancer development can be detected in even a small study, a self-reported smoking behavior like pack-years (PY) is nevertheless only a proxy measure for the smoking uptake.

Recently, several studies reported that a shorter time to first cigarette (TTFC) after waking is associated with an increased risk of head and neck cancer, lung cancer, and esophageal cancer independently of CPD and/or smoking duration (Muscat et al., 2011a; 2011b; Matsuo et al., 2012; Muscat et al., 2012). TTFC is reported to reflect behavioral traits of nicotine addiction, including smoking amount, tolerance, difficulty in smoking cessation, and smoking relapse (Kabat and Wynder, 1987; Heatherton et al., 1989; Kozlowski et al., 1994; Pillitteri et al., 1997; Toll et al., 2007). Unlike conventional smoking parameters, such as CPD, smoking duration, PY, and years since quitting smoking, however, the association between TTFC and PC risk has not been evaluated.

Here, we assessed whether shorter TTFC predicts PC risk independently of CPD and/or smoking duration in a Japanese population. In addition, we revisited the associations between conventional smoking parameters and PC risk in the same study population.

Materials and Methods

Study subjects

Cases and controls were selected from the database of HERPACC-II, which is managed at Aichi Cancer Center Hospital (ACCH). Cases were 341 PC patients with no prior history of cancer, while controls were 1,705 non-cancer outpatients who were randomly selected and matched by sex and age (±3 years) to each case in a 1:5 case-control ratio. The framework of the HERPACC

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studies has been described elsewhere (Tajima et al., 2000; Hamajima et al., 2001). In brief, patients in HERPACC-II were enrolled between January 2001 and November 2005. All first-visit ACCH patients aged 20-79 years were asked to complete a self-administered questionnaire regarding their lifestyle before development of the current symptoms. Questionnaire responses were checked by trained interviewers. More than 95% of eligible patients completed the questionnaire. All data were loaded into the HERPACC database, which is periodically synchronized with the hospital cancer registry system. Approximately 35% of subjects in HERPACC-II were diagnosed with cancer within a year of first visit. In our study, we defined case subjects as patients who were diagnosed with PC within a year of first visit; that is, we considered time lag between first visit and final diagnosis of PC rather than prospectively identifying cases. Our previous study showed that the lifestyle patterns of first-visit outpatients to ACCH correspond with those of individuals randomly selected from Nagoya's general population, confirming the external validity of the study (Inoue et al., 1997b). The present study was approved by the Ethics Committee of Aichi Cancer Center and informed consent was obtained at first visit from all participants.

Assessment of exposure

Exposure to potential risk factors for PC was assessed from responses to the self-administered questionnaire, which were completed before diagnosis during the first visit to ACCH and checked by trained interviewers. All subjects were questioned about their lifestyle before the onset of the symptoms which impelled their visit to ACCH. Daily alcohol consumption in grams was calculated by summing the pure alcohol amount in the average daily consumption of Japanese sake (rice wine), shochu (distilled spirit), beer, wine and whiskey. Height and body weight before the onset of symptoms and weight at age 20 years were self-reported. Body mass index (BMI) was calculated by dividing the weight in kilograms by the height in meters squared, and expressed as kg/m^2. Family history of PC was considered positive when at least one parent or sibling had a history of PC.

Regarding smoking exposure, we categorized smoking status as never, former, and current smoking, and the latter two were further divided by the number of CPD (>0-19, ≥20-29, ≥30-39, ≥40), duration (>0-19, ≥20-29, ≥30-39, ≥40 years), PY of smoking (>0-19, ≥20-39, ≥40), and TTFC (>0-29, ≥30-59, ≥60 minutes). PY is the product of the average number of packs per day and the number of years of smoking. Former smokers were defined as subjects who had quit smoking for at least 1 year, and were further divided by duration since quitting (1-9, ≥10 years).

Statistical analysis

Differences in characteristics between cases and controls were tested using the chi-squared test. To assess the strength of the associations between smoking and PC risk, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression models adjusted for potential confounders although analyses about TTFC and PC risk in ever-smokers were conducted using unconditional logistic model to increase statistical power. Potential confounders considered in multivariate analysis were age, sex, current BMI (<18.5, ≥18.5-22, ≥22.5-24.5, ≥25-27, or ≥27.5 kg/m^2), BMI at age 20 (<18.5, ≥18.5-22, ≥22.5-24.5, ≥25-27, or ≥27.5 kg/m^2), drinking habit (non-drinker, <23, ≥23-45, or ≥46 g/day), history of diabetes mellitus (yes or no), and family history of PC (yes or no). All analyses were carried out using Stata version 10 (Stata Corp., College Station, TX, US), and P-values less than 0.05 were considered statistically significant.

Results

Background characteristics of all subjects are shown in Table 1. Age and sex were exactly matched between the cases and controls. Compared to the control group, the case group had a lower current BMI (p=0.073), higher BMI at age 20 (p<0.001), and higher prevalence of a history of diabetes mellitus (p<0.001). The distribution of other characteristics was similar, including drinking status and family history of PC.

Table 2 shows adjusted ORs and their 95% CIs of PC according to smoking behavior. Compared with never smokers, the OR for current smokers was 2.16 (95%CI, 1.54-3.03) and that for former smokers was 1.59 (95%CI, 1.10-2.32). In former smokers, those who had a long duration (≥10 years) since quitting smoking showed a tendency toward the null (OR=1.29, 95%CI: 0.78-2.14).

Table 1. Distribution Comparison of Pancreatic Cancer Patients and Controls with Respect to Selected Characteristics

		Case (%) n=341	Control (%) n=1705	p values**
Age	<40	15 (4.4)	72 (4.2)	0.999
	≥40-49	33 (9.7)	162 (9.5)	
	≥50-59	114 (33.4)	562 (33.0)	
	≥60-69	117 (34.3)	591 (34.7)	
	≥70	62 (18.2)	318 (18.7)	
Sex	Male	234 (68.6)	1,170 (68.6)	1.000
	Female	107 (31.4)	535 (31.4)	
Current BMI* (kg/m^2)	<18.5	28 (8.2)	104 (6.1)	0.073
	≥18.5-22	152 (44.6)	649 (38.1)	
	≥22.5-24.5	94 (27.6)	556 (32.6)	
	≥25-27	41 (12.0)	258 (15.1)	
	≥27.5	22 (6.5)	125 (7.3)	
	Unknown	4 (1.2)	13 (0.8)	
BMI* at age 20 (kg/m^2)	<18.5	22 (7.6)	208 (12.2)	<0.001
	≥18.5-22	206 (60.5)	1,090 (63.9)	
	≥22.5-24.5	70 (19.5)	295 (17.3)	
	≥25-27	15 (6.0)	51 (3.0)	
	≥27.5	9 (3.2)	23 (1.4)	
	Unknown	19 (3.2)	38 (2.2)	
Drinking (g ethanol/day)	Non	111 (32.6)	649 (38.1)	0.399
	<23	92 (27.0)	444 (26.0)	
	≥23-45	78 (22.9)	348 (20.4)	
	≥46	56 (16.4)	246 (14.4)	
	Unknown	4 (1.2)	18 (1.1)	
History of diabetes mellitus	Yes	56 (16.4)	139 (8.2)	<0.001
	No	285 (83.6)	1,566 (91.9)	
Family history of PC	Yes	14 (4.1)	62 (3.6)	0.676
	No	327 (95.9)	1,643 (96.4)	

*BMI: body mass index. **p values were calculated by Chi-squared test

Table 2. Adjusted Odds Ratios (ORs)* and 95% Confidence Intervals (CI) for Pancreatic Cancer and Smoking Habit

	Case (n)	Control (n)	ORs (95% CI)
Smoking status			
Never	115	757	1 (Reference)
Ever	226	945	1.91 (1.39-2.63)
Former (years)	84	443	1.59 (1.10-2.32)
quit for ≥1-9	37	124	2.59 (1.47-4.58)
quit for ≥10	47	319	1.29 (0.78-2.14)
Current	142	502	2.16 (1.54-3.03)
Unknown	0	3	
Pack-years of smoking (p trend<0.001)			
>0-19	53	268	1.58 (1.07-2.35)
≥20-39	62	311	1.66 (1.10-2.48)
≥40	109	355	2.72 (1.86-3.99)
Unknown	2	14	
Smoking duration (years) (p trend<0.001)			
>0-19	39	222	1.37 (0.87-2.14)
≥20-29	41	183	1.91 (1.22-2.98)
≥30-39	74	290	2.20 (1.45-3.33)
≥40	70	241	2.40 (1.56-3.71)
Unknown	2	12	
Smoking frequency (cigarettes/day) (p trend<0.001)			
>0-19	54	279	1.44 (0.97-2.14)
≥20-29	86	353	2.13 (1.46-3.11)
≥30-39	35	128	2.45 (1.51-4.00)
≥40	50	177	2.55 (1.62-4.01)
Unknown	1	11	
Time to first cigarette (min) (p trend<0.001)			
>0-29	162	612	2.08 (1.48-2.91)
≥30-59	35	165	1.77 (1.11-2.82)
≥60	26	142	1.54 (0.93-2.55)
Unknown	3	29	

*Conditional logistic regression model adjusted for current BMI, BMI at age 20, drinking habit, diabetes mellitus, and family history of PC

Table 3. Odds Ratios (ORs) and 95% Confidence Intervals (CI) for Pancreatic Cancer and Time to First Cigarette in Ever-Smokers

	Age, sex-adjusted ORs (95% CI)	Multivariable-adjusted ORs* (95% CI)
Time to first cigarette (min)		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.19 (0.68-2.08)	1.15 (0.65-2.04)
>0-29	1.48 (0.94-2.34)	1.35 (0.85-2.15)
p trend	0.065	0.139
Adjusted for pack-years‡		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.12 (0.63-1.99)	1.08 (0.60-1.94)
>0-29	1.21 (0.73-2.00)	1.09 (0.65-1.83)
p trend	0.326	0.490
Adjusted for total years§		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.11 (0.63-1.95)	1.07 (0.60-1.90)
>0-29	1.25 (0.78-2.01)	1.17 (0.72-1.89)
p trend	0.280	0.355
Adjusted for cigarettes per day†		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.11 (0.63-1.96)	1.05 (0.58-1.87)
>0-29	1.29 (0.79-2.10)	1.12 (0.68-1.85)
p trend	0.170	0.324
Adjusted for smoking status¶		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.16 (0.66-2.03)	1.12 (0.64-1.99)
>0-29	1.34 (0.84-2.13)	1.24 (0.77-1.99)
p trend	0.213	0.315
Adjusted for years since quitting††		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.10 (0.63-1.94)	1.08 (0.61-1.91)
>0-29	1.26 (0.79-2.01)	1.18 (0.73-1.91)
p trend	0.325	0.437

*Unconditional logistic regression model adjusted for age, sex, current BMI, BMI at age 20, drinking habit, diabetes mellitus, and family history of PC. ‡Pack-years (PY): 0-19, 20-39, ≥40. §Total years: <20 years, 20-29 years, 30-39 years, ≥40 years. †Cigarettes per day: 0-19, 20-29, 30-39, ≥40 cigarettes. ¶Smoking status: ever or current. ††Years since quitting: ≥10 years, 1-9 years, current

Regarding other conventional smoking parameters, an elevated risk of PC was observed with increasing PY (p trend<0.001), smoking duration (years, p trend<0.001), and CPD (p trend<0.001). A significant association was also seen between shorter TTFC and increased risk of PC compared with never smokers (p trend<0.001).

Compared with a TTFC of more than 60 minutes, unadjusted ORs in ever smokers were 1.19 (95% CI, 0.68-2.08) for a TTFC of 30-60 minutes and 1.48 (95%CI, 0.94-2.34) for that of 0-30 minutes (p trend=0.065) (Table 3). ORs adjusted by potential confounders without smoking were 1.15 (95%CI, 0.65-2.04) for TTFC of 30-60 minutes and 1.35 (95%CI, 0.85-2.15) for that of 0-30 minutes (p trend=0.139). After adjustment for conventional smoking parameters, such as PY, smoking duration, CPD and years since quitting smoking, no association was seen between TTFC and PC risk.

Discussion

Our case-control study confirmed our previous findings that cigarette smoking is significantly associated with an increased risk of PC in Japanese. We also evaluated the association between TTFC and PC risk, but found only a suggestive association between them. To our knowledge, this is the first study to evaluate the association of TTFC with PC risk.

Although cigarette smoking is probably a weak PC carcinogen, smoking behavior has been consistently reported to be associated with an increased risk of PC (Lin et al., 2001; IARC, 2004; Matsuo et al., 2011; Bosetti et al., 2012). Compared to never or non-smokers, odds ratios for current smokers in previous case-control studies has ranged from 1.4 to 5.7 (Lin et al., 2001). A meta-analysis of Japanese studies calculated a summary estimate for ever smoking relative to never smoking of 1.68 (95%CI, 1.38-2.05) (Matsuo et al., 2011). We therefore consider our findings to be consistent with previous studies. In addition, our study showed that after quitting smoking for more than ten years, the PC risk for ever smokers was almost identical to that for never smokers. Several other studies have also reported a risk reduction of PC after smoking cessation (Silverman et al., 1994; Fuchs et al., 1996; Muscat et al., 1997; Partanen et al., 1997; Nilsen and Vatten, 2000), and together suggest a modest but rigid causal relationship between smoking and PC, as well as the importance of smoking cessation for people at high risk of PC.

TTFC is one determinant of the nicotine dependence phenotype. The "low" dependent phenotype are smokers who smoke >30 minutes after waking and ≤20 cigarettes per day, and the "high" dependent phenotype are smokers who smoke ≤30 minutes after waking (Muscat et al., 2009). In addition, TTFC is thought to reflect the intensity of smoking, such as the depth and frequency of

puffing, which has not been satisfactorily measured by conventional smoking parameters (Matsuo et al., 2012; Muscat et al., 2012). Recently, an association was reported between TTFC and smoking-related cancers, namely lung cancer and upper aero-digestive tract (UADT) cancer (Muscat et al., 2011a; 2011b; 2012; Matsuo et al., 2012). Although PC is also a smoking-related cancer, we were unable to detect a statistically significant association between TTFC and PC risk. Since the association of smoking with PC is not as strong as that with lung or UADT cancer (Lin et al., 2001; 2002; Inoue et al., 2003; Polesel et al., 2008; Lee et al., 2012), TTFC may be less strongly associated with the risk of PC. Confirmation of our findings awaits further investigation in a larger study.

This case-control study has several methodological issues and limitations which warrant mention. First, control subjects were selected from non-cancer patients at ACCH. We consider that this was the same population from which the case subjects arose, which would warrant the internal validity of this study. Second, regarding external validity, we previously confirmed that randomly selected subjects from our control population were similar to the general population of Nagoya City in terms of the exposure of interest (Inoue et al., 1997a). Nonetheless, the medical background of the controls would remain the potential souse of bias. In this regard, our previous study in women demonstrated that this matter had only limited impact: more than 66% of non-cancer outpatients at ACCH have no specific medical condition, while the remaining 34% have specific diseases such as benign tumors, non-neoplastic polyps or both (13.1%), mastitis (7.5%), gastrointestinal disease (4.1%), or benign gynecologic disease (4.1%) (Kanda et al., 2009; Kawase et al., 2009). The situation for men is thought to be comparable. Third, case-control studies have an intrinsic information bias. However, the HERPACC system is less prone to this bias than typical hospital-based case-control studies as the data for all participants are collected before diagnosis. In addition, responses to self-administered questionnaires may be inaccurate and provide considerable variation. Any such misclassification would be non-differential, however, and would likely underestimate the causal association (Suzuki et al., 2008). Fourth, residual confounding by known and unknown risk factors might have been present; and given the modest number of cases, our findings require replication in larger studies. Last, this study was limited to a Japanese population, and the results cannot necessarily be extrapolated to other populations.

In conclusion, our study reconfirmed the association between conventional smoking parameters and the risk of PC. We did not detect a statistically significant association between TTFC and PC risk. A comprehensive understanding of the association between TTFC and PC risk awaits further studies in a variety of ethnic groups.

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ORIGINAL ARTICLE

Influence of preoperative anti-cancer therapy on resectability and perioperative outcomes in patients with pancreatic cancer: Project study by the Japanese Society of Hepato-Biliary-Pancreatic Surgery

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Abstract
Background Little is known about the effects of neoadjuvant therapy on outcomes in patients with pancreatic cancer. This study evaluated the effects of neoadjuvant therapy on resectability and perioperative outcomes.
Methods A total of 992 patients were enrolled, with 971 deemed eligible. Of these, 582 had resectable tumors and 389 had borderline resectable tumors, and 388 patients received neoadjuvant therapy. Demographic characteristics and peri- and postoperative parameters were assessed by a questionnaire survey.
Results The R0 rate was significantly higher in patients with resectable tumors who received neoadjuvant therapy than in those who underwent surgery first, but no significant difference was noted in patients with borderline resectable tumors. Operation time was significantly longer and blood loss was significantly greater in patients who received neoadjuvant therapy than in those who underwent surgery first, but there were no significant differences in specific complications and mortality rates. The node positivity rate was significantly lower in the neoadjuvant than in the surgery-first group, indicating that the former had significantly lower stage tumors.
Conclusions Neoadjuvant therapy may not increase the mortality and morbidity rate and may be able to increase the chance for curative resection against resectable tumor.

Keywords Neoadjuvant · Pancreatic cancer · Perioperative outcome · Resectability · Surgery

Introduction

Patients with pancreatic cancer have a dismal prognosis, even when tumors are resectable. Both local and systemic recurrences are common after curative (R0) resection, and long-term survival rates are low. The standard treatment for patients with resectable pancreatic cancer is surgery followed by adjuvant chemotherapy [1–5], but the 2-year postoperative survival rate remains below 50% [3–5].

Neoadjuvant therapy has been used as an alternative approach in other types of cancer, including breast and esophageal cancers. In breast cancer patients, neoadjuvant chemotherapy has been shown to effectively reduce tumor burden in the breast and axilla without compromising survival [6]. In esophageal cancer patients, preoperative chemotherapy was found to result in longer overall survival than postoperative chemotherapy, and therefore, neoadjuvant chemotherapy became the standard treatment strategy for patients with resectable esophageal cancer [7]. Although reports from single institutions and prospective phase II trials found that neoadjuvant treatment had survival benefits in patients with pancreatic cancer [8–11], no large randomized trials have been performed yet to confirm these results.

The neoadjuvant strategy is subject to two major hypothetical risks: (1) possible increases in operative morbidity and mortality; and (2) the possibility that the disease may metastasize or become unresectable during the course of neoadjuvant chemotherapy [12]. The resectability and perioperative outcomes in patients with resectable and borderline resectable pancreatic cancer could not be assessed in prospective trials of adjuvant chemotherapy [3–5] because these trials did not include patients with metastases detected intraoperatively or soon after surgery, patients who died due to surgical complications, and those who experienced severe morbidity and delayed surgical recovery. A survey is required to evaluate the effects of neoadjuvant treatment in patients intended for pancreatic resection.

Therefore, to clarify this situation, the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHPBS) surveyed high-volume centers throughout Japan that had experience with neoadjuvant therapy to evaluate the influence of neoadjuvant therapy on resectability and perioperative outcomes.

Patients and methods

A questionnaire was sent to all patients with pancreatic cancer who were scheduled to undergo resection with curative intent between January 2007 and December 2009 at the 17 high-volume centers participating in the JSHPBS study. This study was approved by the institutional review board of Tohoku University.

The eligibility of this study was invasive ductal adenocarcinoma of the pancreas, which was resectable or borderline resectable intending to surgery. Other types of histology were ineligible, such as acinar cell carcinoma, neuroendocrine tumor, cystic neoplasms. The demographic and clinical characteristics evaluated included patient age, gender, body mass index (BMI), comorbid illness, preoperative tumor staging and resectability [13], and pre- and post-treatment levels of tumor markers. Preoperative treatment data included chemotherapeutic agents; whether or not radiation was administered; the planned and administered doses of both; and adverse events (AEs), both hematological and non-hematological, during preoperative treatment, as assessed by Common Terminology Criteria for Adverse Events ver3.0 [14]. Operative findings included macroscopic tumor stage and intraoperative parameters, such as blood loss, duration of operation, and blood transfusion requirements. Pathological findings included pathological staging, residual tumor status, the effect of preoperative treatment, and intraoperative mortality. Postoperative data included postoperative complications such as pancreatic

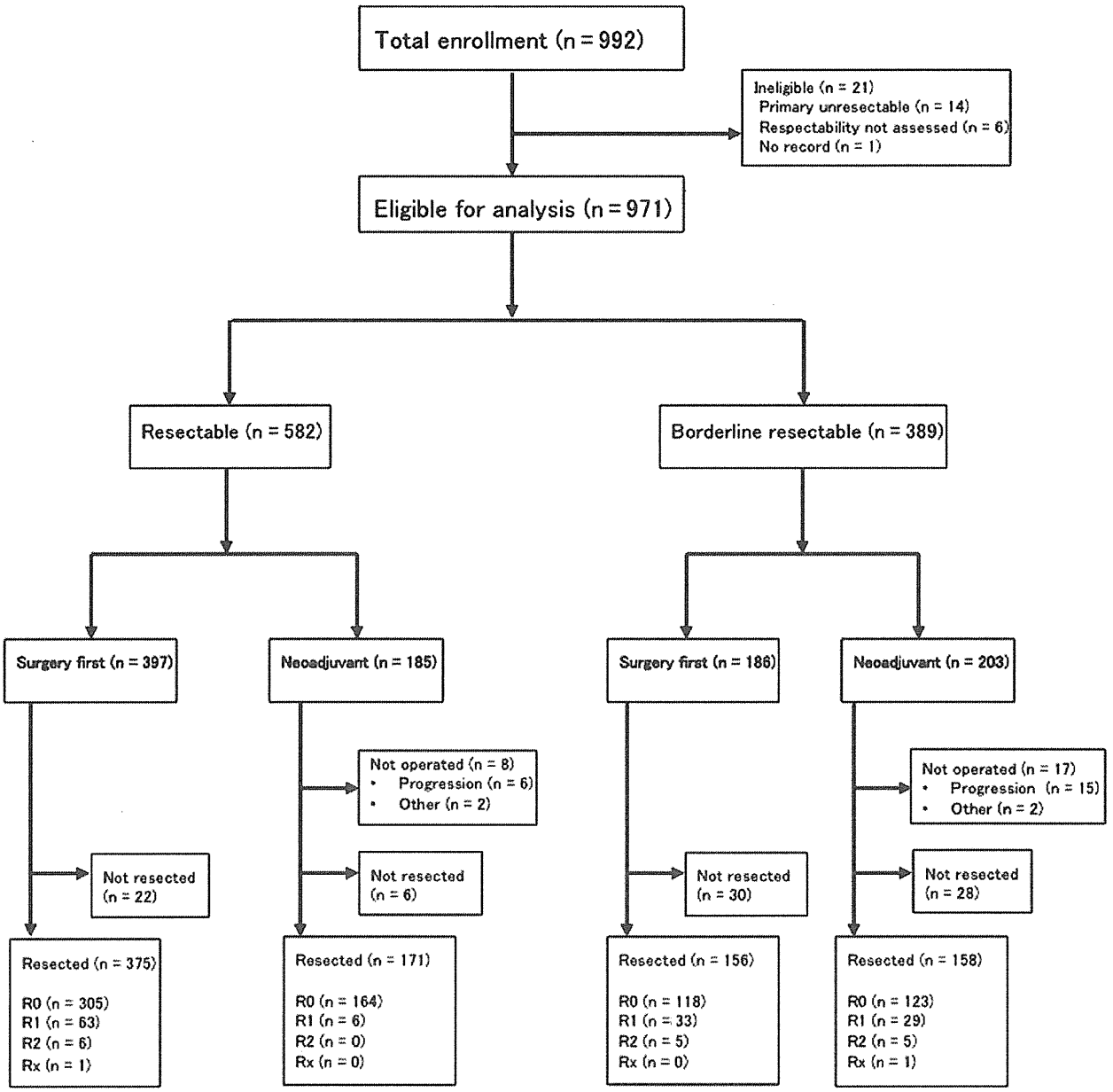

Fig. 1 Flow diagram

fistula, defined according to ISGPF (postoperative pancreatic fistula: an international study group) criteria [15]; delayed gastric emptying, as defined by the ISGPS [16]; other non-abdominal complications; postoperative hospital stay; and types of adjuvant treatment.

Of the 992 patients enrolled, 21 were excluded: 14 with primary unresectable tumors, six who were not assessed for resectablity, and one with no clinical records. Thus, 971 patients were included. Primary outcomes included resectability and perioperative morbidity and mortality. To minimize biases associated with tumor stage, all eligible patients were stratified according to the presence of resectable or borderline resectable tumors, as defined by the National Comprehensive Cancer Network (Fig. 1). The tumor without any abutment of major vessel including portal vein/superior mesenteric vein (PV/SMV), superior mesenteric artery, hepatic artery, celiac artery was categorized in resectable. The tumor with impingement of PV/SMV but reconstructable and/or major arterial abutment within 180 degrees, which was considered to be separable at surgery was categorized as borderline. The indication of resection depended on each institution surveyed.

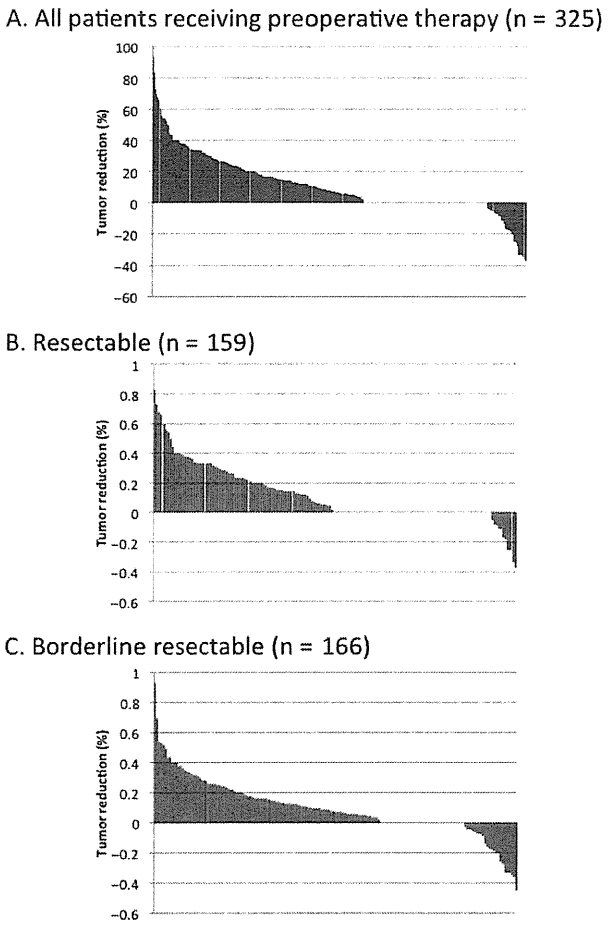

Fig. 2 Radiological tumor response

Assessment of resectability was answered by questionnaire survey. Resectability and R0-resectability were calculated on an intention-to-treat basis, and therefore, patients who did not undergo surgery for any reason were included. Perioperative morbidity and mortality of patients receiving neoadjuvant therapy (neoadjuvant patients) and those undergoing surgery without neoadjuvant therapy (surgery-first patients) were compared separately in subgroups of patients with resectable and borderline resectable tumors, because of differences in operative procedures, such as major vessel resection (Tables 4,5). The efficacy of neoadjuvant therapy could be assessed radiologically in 325 of the 389 patients (83.5%). Best percentage change from baseline in the size of the primary tumor was shown by waterfall plot analysis (Fig. 2).

Statistics

Continuous variables were expressed as median and range. Between group differences in patient characteristics and perioperative and postoperative factors were compared using χ^2 tests, Fisher's exact test, and Mann–Whitney's U-test, as appropriate. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

Of the 971 included patients, 582 had resectable and 389 had borderline resectable tumors. The clinical characteristics of these patients are shown in Table 1. Patients with borderline resectable tumors were significantly younger ($P < 0.001$) and had jaundice followed by biliary drainage more frequently ($P < 0.001$) than those with resectable disease. Pre-treatment serum concentrations of tumor markers were significantly higher in patients with borderline resectable tumors than in those with resectable tumors. Medical history did not differ significantly, except that previous malignancies were significantly more frequent in the resectable group ($P = 0.012$). In each subgroup, of patients with resectable and borderline resectable tumors, there were no statistically significant differences in age, sex, presence of jaundice, and serum tumor markers between patients who received neoadjuvant treatment and those who underwent surgery first (data not shown).

Neoadjuvant therapy

A total of 388 patients (40%) received neoadjuvant treatment, including 254 who received radiotherapy or chemoradiotherapy and 115 who received systemic chemotherapy. Types of therapy and agents are summarized in Table 2. Neoadjuvant treatment was significantly more common in patients with borderline resectable than in those with resectable cancers (52% vs. 32%, $P < 0.0001$). Gemcitabine or a gemcitabine-based regimen was the most frequently provided for chemoradiotherapy and systemic chemotherapy. In regard to neoadjuvant radiotherapy, the duration of preoperative therapy in the resectable group was significantly longer than that in the borderline group (99.5 days vs. 82 days). Whereas in regard to neoadjuvant chemotherapy, the duration in the resectable group was significantly shorter than that in the borderline group (28 days vs. 81.5 days).

Feasibility and efficacy of neoadjuvant therapy

Hematological and non-hematological AEs during neoadjuvant therapy are shown in Table 3. There were no neoadjuvant therapy-related deaths. Neutropenia and