Table 2
Compliance of protocol according to treatment arm.

Arm	A (n = 46)	B (n = 45)
RT stopped at 30 Gy	2	1
Full compliance (60 Gy + CT × 4)	25 (54%)	16 (36%)
Partial compliance (60 Gy + CT × 2)	16 (35%)	16 (36%)
Reasons for partial compliance		
Non-CR, PD	13	8
Renal toxicity G1/2	1	3
Comorbidity, toxicities	2	3
Refusal of further CT	0	2
Non-compliance	5 (11%)	13 (29%)
Reasons for non-compliance		
Leukopenia	1	8
Renal toxicity G1/2	2	1
NC, PD, fistula	1	2
Other toxicities	1	2

CR, complete response; NC, no response; PD, progressive disease.

arm A recovered quickly from leukopenia, the compliance rate was better in arm A than in arm B.

Table 3 shows the acute toxic effects associated with CRT. Although grade-3 leukopenia and esophagitis were noted frequently in both arms, there was no significant difference in the incidence of acute toxicities. In arm A grade-4 leukopenia was noted in four patients, but there was no grade-4 leukopenia in arm B. However, grade-2 or -3 leukopenia was prolonged in arm B. As rare grade-4 toxicities, consciousness loss due to hyperammoniemia in arm A and esophageal bleeding due to Mallory–Weiss syndrome in arm B were noted in one patient each. Both patients recovered quickly with appropriate treatment.

Late toxicities associated with CRT were scored for 87 patients excluding four patients who died within 4 months (Table 3). The follow-up period ranged from 4.5 months to 73 months (median; 19.5 months). There were no significant differences in late toxicities between the two arms. In total, 22 patients (25%) showed grade-2 or higher late toxicities, and 12 patients (14%) had toxicities of grade-3 or higher. Grade-4 heart toxicities were noted in three patients.

Table 3
Acute and late toxicities according to treatment arm (NCI-CTC version 2.0, RTOG/EORTC late radiation morbidity scoring scheme).

Arm	A (n = 46)	B (n = 45)
Acute toxicities		
WBC G3/4	16/4	25/0
Hb G3/4	2/0	0/3
Plt G3/4	2/0	2/0
PS G3/4	5/3	5/0
Vomit G3/4	3/0	1/0
Esophagitis G3/4	11/0	7/1
Infection G3/4	5/0	4/0
Consciousness G3/4	0/1	0/0
Cardiac ischemia G3/4	0/0	1/0
Kidney: CRN G1/2/3	4/1/0	5/1/0
Liver G1/2/3	0/1/1	0/1/1
Arm	A (n = 42)	B (n = 45)
Late toxicities		
Esophagus G2/3/4	1/1/0	2/1/0
Heart G2/3/4	2/2/1	2/1/2
Lung G2/3/4	2/0/0	0/1/0
Pleura[a] G2/3/4	0/2/0	4/2/0
Hypothyroid[a] G2/3/4	3/0/0	3/1/0
Kidney[a] G2/3/4	0/0/0	0/1/0
Patient max G2/3/4	4/4/1	6/5/2
Patient max ⩾G2	9 (21%)	13 (29%)

Note: Four patients who died within 4 months were excluded from the analysis of late toxicities.

[a] Late toxicities graded according to the NCI-CTC version 2.0.

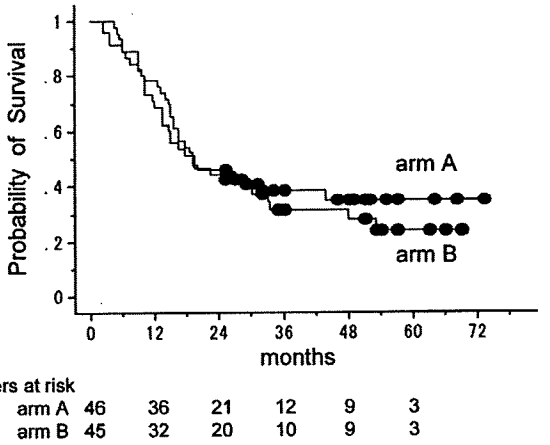

Fig. 3. Intent-to-treat analysis of overall survival curves for arm A and arm B.

All 91 patients were evaluated in terms of survival based on the intent-to-treat principle. As of August 2008, all 91 patients could be followed-up, and 30 patients (arm A, 17 patients; arm B, 13 patients) are alive with a median follow-up period of 48 months, ranging from 25 months to 73 months. Fig. 3 shows the overall survival curves for both arms. The 2-year and 5-year survival rates for arm A were 46% (95% confidence interval (CI); 31–60%) and 35% (95% CI; 20–49%), respectively. Those for arm B were 44% (95% CI; 30–59%) and 24% (95% CI; 10–38%), respectively. There was no significant difference in both the 2-year survival rates as the primary endpoint, and in the overall survival curves (P = 0.536).

Fig. 4 shows the PFS curves for both arms. The 2- and 5-year PFS rates for arm A were 30% (95% CI; 17–44%) and 30% (95% CI; 17–44%), while those for arm B were 29% (95% CI; 16–42%) and 12% (95% CI; 2–22%), respectively. Although there was also no significant difference between the two curves (P = 0.430), late recurrences after 2 years were noted only in arm B. In arm A, 13 patients (28%) were progression-free at 24 months, whereas 10 patients (22%) were progression-free at 24 months in arm B. Six patients in arm B showed recurrences after 2 years, and all of the recurrences were loco-regional. As per protocol rate was significantly higher in arm A than in arm B, PFS was analyzed only for patients with per protocol (Fig. 5). Although there was also no significant difference between the two curves (P = 0.476), a similar trend of late recurrences was noted only in arm B.

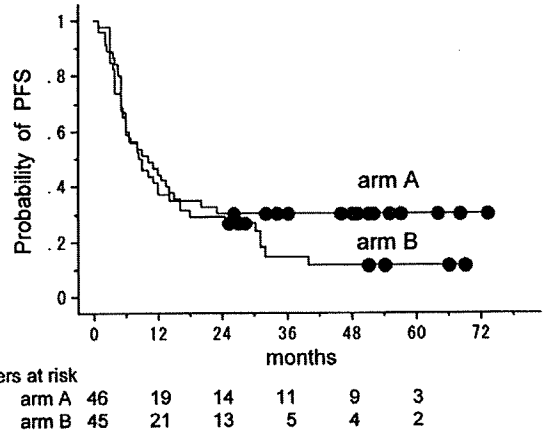

Fig. 4. Intent-to-treat analysis of progression-free survival (PFS) for arm A and arm B.

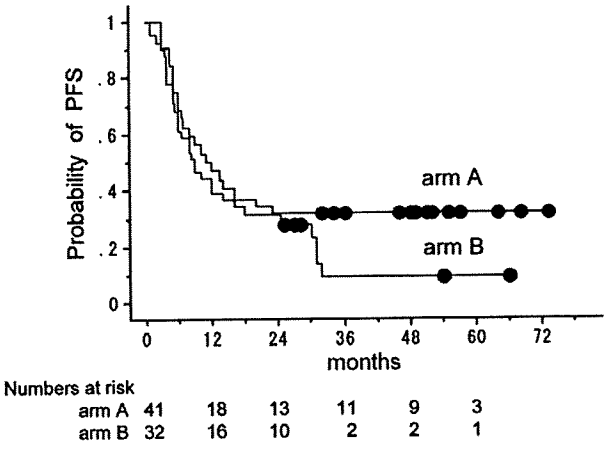

Fig. 5. Per-protocol set analysis of progression-free survival (PFS) for arm A and arm B.

When residual or recurrent tumors were detected after 60 Gy of CRT, appropriate treatment was chosen by the attending physicians, and salvage surgery was performed for 15 patients. For 11 patients (six patients in arm A and five in arm B), potentially curative resection was achieved, while non-curative resection was achieved in four patients (two patients in arm A and two in arm B).

Discussion

This study is the first randomized clinical trial comparing the type of infusion CT in definitive CRT for esophageal cancer. In the present study, both arms used the same total RT dose of 60 Gy and the same total dose of cisplatin and 5-FU to evaluate the effect of type of infusion CT. The 2-year survival rate as the primary endpoint was not different between full-dose short-term infusion CT (arm A) and low-dose protracted infusion CT (arm B). There was also no significant difference in acute and late toxicities between the two arms (Table 3). However, the compliance rate of the protocol as a secondary endpoint was significantly higher in arm A than in arm B, and the late recurrences after 2 years occurred only in arm B. Thus, our hypothesis that daily administration of low-dose protracted CT is better than full-dose short-term CT in reducing acute toxicities and in enhancing radio-sensitization effects was not proved.

In Japan, low-dose protracted infusion CT combined with full-dose RT of 60–66 Gy is a popular regimen for locally advanced esophageal squamous cell carcinomas [5–9]. A main reason for the preference of protracted infusion CT is weak acute toxicities. As expected, low-dose protracted infusion CT was associated with slightly lower incidences of high grade nausea and vomiting and grade-4 leukopenia in the present study. However, there was no significant difference in the rate of acute and late toxicities between the arms (Table 3). Sai et al. [9] reported that modification or reduction of CT dose was frequently necessary for low-dose protracted infusion CT due to leukopenia or decreased renal function. In fact, compliance with the protocol was significantly worse in arm B, mostly due to prolonged leukopenia (Table 2).

Cisplatin is known not only as a cytotoxic agent but also as a radiosensitizer [13]. For unresectable non-small cell lung cancer, a randomized clinical trial comparing RT alone of 55 Gy/20 fractions, same RT dose with daily administration of cisplatin of 6 mg/m^2, and same RT dose with weekly administration of cisplatin of 30 mg/m^2 combined with RT has been reported [14]. In that study, overall survival was significantly improved in the daily-cisplatin group as compared with the RT alone group. The daily-cisplatin group showed a slightly longer median PFS time than the weekly-cisplatin group without significance. Thus, it was postulated that daily protracted infusion CT has the advantage of maximum radiosensitizing effect compared with weekly or intermittent CT. Unfortunately, this rationale was not proved for esophageal cancer. In the per protocol analysis, there were still many late loco-regional recurrences in arm B (Fig. 5). It is suggested that the poor long-term control in arm B is not related to the low compliance with protocol in arm B, but that low-dose protracted CT has a lower sensitizing effect than full-dose short-term CT.

Another potential advantage of the protracted infusion CT is to avoid a rapid depopulation of massive T4 tumors by full-dose CT [13]. Ahmed et al. [15] reported that malignant fistulae disappeared completely in four of five patients treated with 5-FU (400–600 mg/m^2) by protracted continuous infusion and RT of 60 Gy. Koike et al. [6] reported that malignant esophageal fistulae were closed in seven (44%) of 16 tumors with fistulae by low-dose protracted CT of similar regimen in arm B. As T4 tumors with fistulae were excluded in the present analysis, protracted infusion CT may still have some advantage for T4 tumors with fistula.

In arm A, the 2-year and 5-year overall survival rates were as good as 46% and 35%, respectively, even though 46% of the tumors had T4 disease. In the RTOG-8501 trial, the 2-year survival rate of patients treated with 50 Gy CRT was 36% [1,2]. In this trial, T4 tumors were not included. In the INT-0123, T4 tumors comprised 9%, and the 2-year survival rates for the 50.4 Gy arm and 64.8 Gy arm were 40% and 31%, respectively [4]. In our protocol, the total dose of RT was 60 Gy with 1-week split. This split may be attributable to the high compliance rate of 89% in arm A. In terms of late toxicities, grade 3 and grade 4 late toxicities were noted in 14% of the patients. This rate is much lower than 37% in the 50.4 Gy arm of the INT-0123 or 29% in the CRT arm of RTOG-8501 [2,4]. Thus, our arm-A protocol is promising in overall survival rate and in the incidence of late toxicities.

In conclusion, our results suggest that low-dose protracted infusion CT with RT is not superior to full-dose short-term infusion CT with RT for esophageal cancer.

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Serum CA19–9 Alterations During Preoperative Gemcitabine-Based Chemoradiation Therapy for Resectable Invasive Ductal Carcinoma of the Pancreas as an Indicator for Therapeutic Selection and Survival

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Objective: To evaluate serum CA19–9 alterations during preoperative gemcitabine-based chemoradiation therapy (CRT) for resectable pancreatic cancer (PC) in the earlier identification of patients who are likely to benefit from subsequent resection.

Summary Background Data: One of the advantages of the preoperative CRT strategy for patients with advanced PC is that undetectable systemic disease may be revealed during preoperative CRT, thus avoiding unnecessary surgery. Serum CA19–9 has been evaluated as a predictive indicator of the treatment efficacy and outcome in various clinical settings.

Methods: We retrospectively reviewed 64 consecutive patients with resectable PC (at diagnosis) who received preoperative CRT at our hospital between 2002 and 2008. Patients were divided into 2 groups (efficacy grouping) to evaluate the efficacy of preoperative CRT according to the clinical course. Group A included patients who were unable to receive the subsequent resection due to the development of unresectable factors during preoperative CRT and those who received the subsequent resection but developed recurrent disease within 6 months after surgery; group B included patients who received the subsequent resection and survived without recurrences for more than 6 months after surgery. We developed a new classification utilizing pretreatment CA19–9 and proportional alteration of CA19–9 2 months after the initiation of treatment. The categories were defined as: I (increased), MD (modestly decreased), and SD (substantially decreased). Clinicopathological variables and CA19–9 alteration status were correlated with the efficacy grouping and overall survival.

Results: All of the category I patients were included in group A, 93.5% of the category SD patients in group B, and approximately half of the category MD patients in group A. CA19–9 alteration status was a single independent variable associated with efficacy grouping and overall patient survival, with the 1-year survival rate of category I patients, and the 4-year survival rate of category MD and SD patients being 22.2%, 34.1%, and 58.9%, respectively.

Conclusions: CA19–9 alteration status is useful in identifying those who will benefit from the preoperative CRT and subsequent resection and those who will not; it was a significant predictor for patient prognosis in the setting of the preoperative CRT strategy for resectable PC.

Key Words: pancreas, cancer, preoperative chemoradiation therapy, CA19-9

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Despite recent advances in diagnostics and therapies, pancreatic cancer remains quite difficult to cure. Complete resection is still the only treatment option that can offer the hope of a cure if patients do not reveal any distant diseases. However, the 5-year survival rate of patients with resectable pancreatic cancer is as low as 15% to 25% due to a high risk of distant and/or local failure even after curative resection, indicating a high probability of undetectable tumor cell spreading even in seemingly localized disease.[1,2]

The number of reports describing positive outcomes in the preoperative treatment of pancreatic cancer are gradually increasing despite the fact that the majority of patients with respectable pancreatic cancer receive up-front surgery.[3–9] In reviewing previous reports on preoperative treatment for pancreatic cancer, several authors have suggested its advantage in accurately identifying those who are unlikely to benefit from surgery.[3,4,6–9] In our recent report on the feasibility and efficacy of full-dosage preoperative gemcitabine-based chemoradiation therapy (CRT) for patients with pancreatic cancer, 13.2% of the patients who were diagnosed with localized diseases upon initiation of preoperative gemcitabine-based CRT developed detectable distant disease at the time of restaging after preoperative treatment or at laparotomy, and thus avoided subsequent resections.[5] Evans et al reported a preoperative CRT strategy in which 19.8% of patients avoided resection due to the occurrence of distant disease at restaging after preoperative treatment.[3] Partly because of these selection effects, preoperative treatment strategies have improved the surgical outcome of pancreatic cancer, exhibiting a 5-year survival rate ranging from 36% to 53%.[3,5] However, a significant number of patients still develop recurrent disease immediately after the preoperative treatment and subsequent surgical resection. A more effective selection strategy for identifying those patients who are most likely to benefit from resection is needed.

Carbohydrate antigen (CA) 19–9 is a sialylated Lewis-blood-group antigen that was first described by Koprowski et al in 1981.[10] The concentration of serum CA 19–9 is increased in more than 80% of patients with advanced pancreatic cancer, and its measurement is routinely used for various purposes.[11–13] A monoclonal antibody against CA19–9, 1116 NS 19–9, reacts with the sialylated Lewis[ab]

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blood group moiety.[10] Five to ten percent of the general population is, by inheritance, negative for the Lewis-blood-group antigen (Lewis^{a-b-}); such individuals thus posses no detectable serum CA19–9, even if they develop advanced pancreatic cancer.[14,15] However, the prognostic and therapeutic significance of CA19–9 has been intensely investigated in patients with resectable, locally advanced, and metastatic pancreatic cancer, although whether alterations in CA19–9 during treatment can serve as an indicator that reflects therapeutic significance remains controversial. Some authors have demonstrated the clinical significances of CA19–9 as an indicator of therapeutic responses during chemotherapy,[16–20] but others have not come to the same conclusion.[14] There have been no previous reports describing the significance of CA19–9 in the setting of preoperative CRT for pancreatic cancer as a predictive indicator for identifying patients who will benefit from subsequent resection or as a prognostic factor.

In the present era of preoperative CRT followed by surgery, it is critically important to identify patients who will benefit from surgical resection after preoperative CRT to avoid the complications of unnecessary surgery. Furthermore, early identification of patients who will not benefit from the preoperative CRT strategy could prevent delays in starting alternative treatments. The aims of this study were as follows: (1) to evaluate the applicability of serum CA19–9 alterations during preoperative chemoradiation as an early predictive indicator to differentiate patients who are likely to benefit from the preoperative CRT and subsequent surgery from those who will not, and (2) to evaluate the potential role of serum CA19–9 alteration as a prognostic factor in the setting of preoperative gemcitabine-based CRT for patients with pancreatic cancer.

METHODS

Patients

Sixty-four consecutive treatment-naive patients with potentially resectable pancreatic cancer, proven based on either histologic or cytologic examination, who received preoperative gemcitabine-based CRT between 2002 and 2008 at Osaka Medical Center, were included in the study. Patients with the following characteristics were excluded: (1) postoperative follow-up term were less than 6 months, (2) serum CA19–9 before initiation of treatment within normal limits (ie, less than 37 U/mL), or (3) unstable biliary drainage (ie, serum total bilirubin concentration more than 2.0mg/dL), and/or clinically evident cholangitis or pancreatitis during preoperative treatment based on a weekly assessment of serum total bilirubin, amylase, and lipase concentration (because insufficient control of the biliary system or pancreatitis could raise serum CA19–9 concentrations). In patients with obstructive jaundice due to a pancreatic head tumor, biliary drainage was achieved by endoscopic retrograde biliary drainage, endoscopic nasobiliary drainage, or percutaneous transhepatic cholangiodrainage before and during the preoperative treatment.

Preoperative Chemoradiation Therapy

The details of preoperative gemcitabine-based CRT have been described previously.[5] In brief, 3-dimensional radiation was targeted to the following fields and administered at a total radiation dose of 50 Gy with a daily fraction of 2 Gy 5 times/wk: the primary pancreatic tumor, celiac and superior mesenteric arteries, retroperitoneal soft tissue, and para-aortic region. Intravenous administration of gemcitabine (1000 mg/m^2) was initiated concurrently on days 1, 8, and 15 during each 4-week cycle; this was performed repeatedly for 3 cycles, such that the preoperative CRT was completed in 3 months after initiation.

Determination of Resectability and the Surgical Procedure

Resectability of pancreatic cancer was evaluated before initiation of preoperative CRT, at the completion of preoperative CRT, ie, 3 months after initiation of preoperative CRT, and at laparotomy. The evaluation was performed by a radiographic imaging study, including thin-sliced abdominal computerized tomography, magnetic resonance imaging, or celiac/superior mesenteric arteriography, and it was performed intraoperatively in cases of laparotomy (not by serum CA19–9). Our exclusion criteria for resection of pancreatic cancer were as follows: presence of metastatic lesions in the liver, lung, para-aortic lymph nodes, perineum or other distant organs (M1), and cancer invasion into the celiac truncus, superior mesenteric artery, or confluent point of the right colic vein to the superior mesenteric vein. When a patient was determined to be unresectable upon completion of preoperative chemoradiation therapy, further surgical treatment was avoided: these patients were treated with clinically relevant chemotherapy. In patients whose pancreatic cancer was intraoperatively determined to be unresectable, gastrointestinal and/or choledocointestinal bypass was performed if clinically necessary; these patients were treated with clinically relevant chemotherapy after surgery. Our surgical approach after completion of preoperative gemcitabine-based CRT included pancreatectomy accompanied by extensive lymphatic and connective tissue clearance, and postoperative liver perfusion chemotherapy. A detailed description of our surgical procedure and postoperative liver perfusion chemotherapy has been published previously.[21] When recurrence of pancreatic cancer was determined, further treatment was not specified, and various chemotherapies and/or radiation therapies were applied based on the clinical indications. This treatment strategy for pancreatic cancer has been conducted in our institute since 2002, and clinicopathological data have been collected prospectively in our clinicopathological database.

Measurement of Serum CA19–9

The serum CA19–9 concentration was measured using a commercial chemiluminescent enzyme immunoassay with a normal upper limit of 36 U/mL. Serum CA19–9 was routinely measured just before initiation of preoperative CRT (Pre-CA19–9) and every 4 weeks thereafter. Because the aim of this study was to investigate whether CA19–9 alterations during preoperative CRT can identify, prior to completion of preoperative CRT, those who will benefit from the preoperative CRT and subsequent surgery, we focused on and analyzed Pre-CA19–9, serum CA19–9 2 months after initiation of the preoperative CRT (Post-CA19–9), and the proportional alteration between Pre-CA19–9 and Post-CA19–9 (%Post: Post-CA19–9/Pre-CA19–9 [%]).

Clinical Factors Analyzed in This Study

Figure 1 shows disease-free survival after resection (n = 50) during the early postoperative period, indicating that a majority of early recurrences occurred within approximately 6 months after resection. Patients with early recurrences might represent those who would not benefit from resection after preoperative CRT. Therefore, patients were divided into 2 groups to determine the efficacy of preoperative CRT and subsequent surgery (efficacy grouping), group A included patients who did not receive resection due to the occurrence of unresectable factors before surgery or at laparotomy and those with recurrences within 6 months after resection (patients who would not benefit from subsequent surgery after preoperative CRT); group B included patients without any recurrences for more than 6 months after resection (patients who would benefit from subsequent surgery after preoperative CRT). Figure 2 shows an algorithm of the clinical processes based on the efficacy grouping.

Of the 64 patients, 14 (21.8%) patients did not receive resection due to the occurrence of unresectable factors before laparotomy (8 patients) and at laparotomy (6 patients). Of the 50 patients who underwent resection of pancreatic cancer, tumor recurrence was detected within 6 months after surgery in 7 patients (10.9%). The 21 patients who did not receive resection of pancreatic cancer or had recurrences within 6 months after surgery were classified as group A. The remaining 43 patients who had been free from tumor recurrences for more than 6 months after resection were classified as group B. Among 50 patients who received resection, the following major postoperative morbidities developed: intra-abdominal bleeding, 8% (4/50); intra-abdominal infection, 4% (2/50); liver abscess, 2% (1/50); and bile leakage, 2% (1/50). The overall in-hospital mortality rate was 2% (1/50). Figure 3 indicates the log distribution of Pre-CA19–9, Post-CA19–9, and %Post in groups A and B. Even though Post-CA19–9 and %Post were significantly higher in group A (*t* test), such a broad overlap of the values obtained for Post-CA19–9 and %Post was observed between groups A and group B

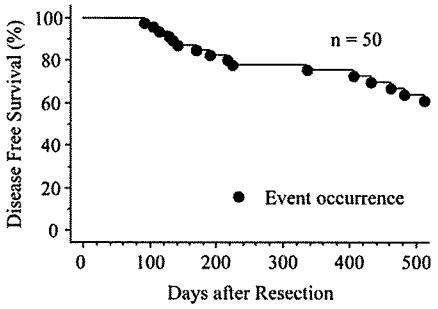

FIGURE 1. Disease-free survival curve after preoperative CRT and subsequent resection during the early postoperative period (n = 50). A majority of early recurrences were observed within approximately 6 months after resection. Patients with early recurrence after resection might represent those patients who would not benefit from resection after preoperative CRT.

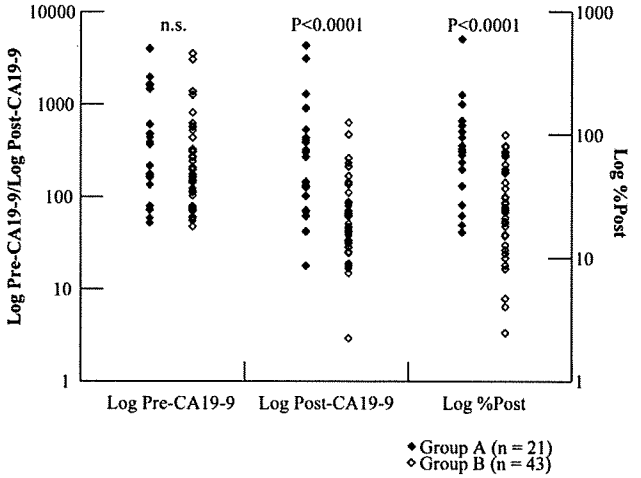

FIGURE 3. Distribution of Pre-CA19–9, Post-CA19–9, and %Post (Post-CA19–9/Pre-CA19–9 [%]) according to the efficacy grouping. Pre-CA19–9, Post-CA19–9, and %Post were defined as serum CA19–9 just before initiation of preoperative CRT, those 2 months after initiation of the preoperative CRT, and the proportional alteration between Pre-CA19–9 and Post-CA19–9 (Post-CA19–9/Pre-CA19–9 [%]), respectively. Although statistically significant differences in Post-CA19–9 and %Post were observed (*t* test), a wide range of overlapping value was obtained for Post-CA19–9 and %Post between groups A and B.

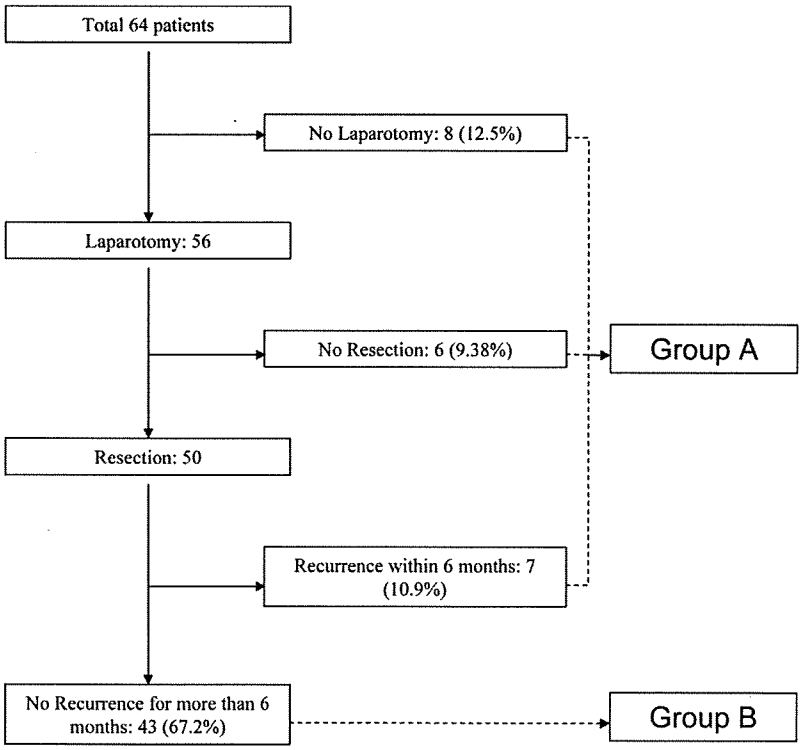

FIGURE 2. Algorithm of the clinical processes according to the efficacy grouping (n = 64). Among the 64 patients, 14 (21.8%) did not receive resection due to the occurrence of unresectable factors before laparotomy (8 patients) and at laparotomy (6 patients). Among 50 patients who underwent resection of pancreatic cancer, tumor recurrence was detected within 6 months after surgery in 7 patients (10.9%). Those 21 patients who did not undergo resection of pancreatic cancer or had a recurrences within 6 months after surgery were classified as group A. The remaining 43 patients who had been free from tumor recurrences for more than 6 months after resection were classified as group B.

that it was difficult to discriminate between them based solely on these values. Considering that %Post is dependent on both of Pre-CA19–9 and Post-CA19–9, we developed a new classification system (CA19–9 alteration status) to assess the alterations in serum CA19–9 and divided patients into 3 classes based on the distribution of Pre-CA19–9 and %Post (described below in "Results"). The following pretreatment variables were correlated with the efficacy grouping and overall survival: gender (male vs. female), age (under 65 years vs. equal to or over 65 years), tumor location (pancreas head vs. body and tail), local extension of tumor (without portal and/or splenic vessel invasion vs. with portal and/or splenic vessel invasion), Pre-CA19–9 (below the median value vs. equal to or above the median value), Post-CA19–9 (below the median value vs. equal to or above the median value), %Post (below the median value vs. equal to or above the median value), and CA19–9 alteration status.

Statistical Analyses

Cross tabulations using Pearson (uncorrected) χ^2 tests and Mann-Whitney U test were performed. Comparisons of continuous variables by efficacy grouping status were performed using t-tests. Multivariable logistic stepwise regression analysis was also performed to determine independently significant factors associated with the efficacy grouping. Univariable and multivariable analyses of overall patient survival were performed using Cox stepwise regression. In each of these analyses P-values were calculated by the score test and only variables with a univariable $P \leq 0.1$ were considered for entry into the multivariable Cox model to avoid the possibility of obtaining spurious results. The log value of each Pre-CA19–9, Post-CA19–9, and %Post was used in the visual display of their distributions due to the skew of those values. Kaplan-Meier curves were created for visual display of the effect of CA19–9 alteration status on overall survival. P-values below 0.05 were considered as significant. All analyses were performed using the SPSS statistical software package (version 11.0, SPSS, Inc., Chicago, IL).

RESULTS

Patient demographics are summarized in Table 1. Among 64 patients, there were 45 males and 19 females. Twenty-five patients were 65 or older, and 39 were younger than 65. Forty-five patients who had pancreatic cancer primarily located in the pancreatic head were considered for pancreaticoduodenectomy at the time of surgery, and 19 patients with cancer primarily in the pancreatic body and tail were considered for distal pancreatectomy at surgery. Based on the pretreatment evaluation, all patients had pancreatic cancer extending beyond the pancreatic confines, ie, T3 tumor according to the 6th edition UICC classification. In 45 patients, tumor invasion to portal, superior mesenteric or splenic vessels was suspected by preoperative radiographic examination. Median values for Pre-CA19–9, Post-CA19–9, and %Post were 178.5 (49 to 4144), 69.0 (3 to 4315), and 34.2% (2.5 to 594.6), respectively. Figure 4 shows the distributions of the value of Pre-CA19–9 and %Post. Based on this distribution, we developed a new classification system (CA19–9

TABLE 1. Patient Demographics (n = 64)

		Efficacy Grouping			
	Total (64)	Group A (21)	Group B (43)	Univariable	Multivariable
Gender					
Male	45	16	29	0.5678	NA
Female	19	5	14		
Age					
65≤	25	8	17	>0.9999	NA
65>	39	13	26		
Tumor Location					
Head	45	15	30	>0.9999	NA
Body/tail	19	6	13		
Local extension of tumor					
Negative for vascular invasion*	19	4	15	0.2507	NA
Positive for vascular invasion*	45	17	28		
Pre-CA19–9 (median: 178.5)					
178.5≤	32	12	20	0.5950	NA
178.5>	32	9	23		
Post-CA19–9 (median: 69.0)					
69.0≤	32	18	14	0.0001	NS
69.0>	32	3	29		
%Post (median: 34.2)					
34.2≤	32	17	15	0.0011	NS
34.2>	32	4	28		
CA19–9 alteration					
Substantially decreased (SD)	31	2	29	<0.0001	<0.007
Modestly decreased (MD)	27	13	14		
Increased (I)	6	6	0		

*Vascular invasion indicates tumor spread to any of portal vein, superior mesenteric vein, and splenic vein.
NA indicates not applicable; NS, not significant.

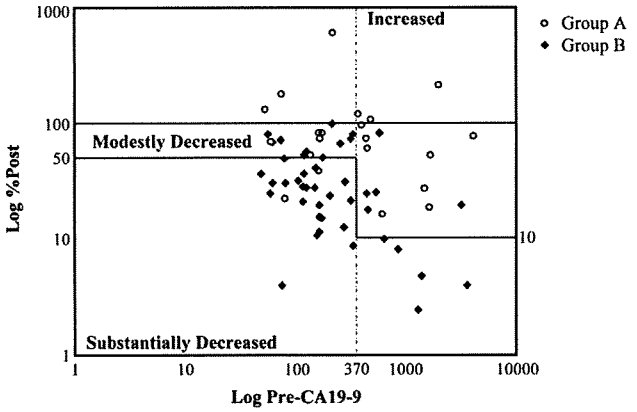

FIGURE 4. Distribution of Pre-CA19–9 and %Post (Post-CA19–9/Pre-CA19–9 [%]) and the definition of CA19–9 alteration status. Patients with a %Post >100 were defined as "Increased" (category I, n = 6); patients having Pre-CA19–9 > 370 U/mL with 100 ≥ %Post > 10 or Pre-CA19–9 ≤ 370 U/mL with 100 ≥ %Post > 50 were "Modestly Decreased" (category MD, n = 27); patients having Pre-CA19–9 > 370 U/mL with %Post ≤ 10 or Pre-CA19–9 ≤ 370 U/mL with %Post ≤ 50 were "Substantially Decreased" (category SD, n = 31).

alteration status), and patients were divided into the following 3 categories: Increased (category I, n = 6), including patients with %Post >100; Modestly Decreased (category MD, n = 27), including patients with Pre-CA19–9 > 370 U/mL and 100 ≥ %Post > 10 as well as those with Pre-CA19–9 ≤ 370 U/mL and 100 ≥ %Post > 50; Substantially Decreased (category SD, n = 31), including patients with Pre-CA19–9 > 370 U/mL and %Post ≤ 10 as well as those with Pre-CA19–9 ≤ 370 U/mL and %Post ≤ 50.

Patients demographics stratified according to groups A and B are also shown in Table 1. All category I patients were found to be in group A. Of the 27 category MD patients, 13 (48.1%) were in group A. Only 2 of 31 category SD patients (6.5%) were in group A. Statistically significant variables associated efficacy grouping in the univariable analysis were Post-CA19–9 ($P = 0.0001$), %Post ($P = 0.0011$), and CA19–9 alteration status ($P < 0.0001$) (Table 1). Multivariable logistic stepwise regression analysis indicated CA19–9 alteration status as the single independently significant variable associated with efficacy grouping (Table 1, $P = 0.007$). Unresectable factors and sites of recurrence among 21 group A patients are summarized in Table 2. Seventeen patients (80.9%) were classified as group A due to the presence of diseases distant from the target field of preoperative radiation therapy, including liver metastasis (n = 12), peritoneal dissemination (n = 4), and lung metastasis (n = 1).

Univariable and multivariable analysis of overall survival are summarized in Table 3, and Figure 5 shows the Kaplan-Meier curve for overall survival stratified by CA19–9 alteration status, with 4-year survival rates of patients in category SD, MD, and I being 58.9%, 34.1%, and 0%, respectively. No patients in category I survived for more than 1.5 years. Two factors, exhibiting a Post-CA19–9 below its median value of 69.0 U/mL and a CA19–9 alteration status of category MD or category I, were associated with significantly unfavorable survival based on univariable analysis (Table 3). In a multivariable Cox regression model, having a CA19–9 alteration status of category MD or category I was the single independent factor associated with significantly unfavorable survival (Fig. 5, Table 3 and 4).

DISCUSSION

The advantages of preoperative treatment strategies for pancreatic cancer have been reported previously.[3–9,22,23] Evans et al and our research group reported the high efficacy and tolerability of preoperative gemcitabine-based CRT for patients with advanced pancreatic cancer, with 5-year overall survival rates being 27% and 41%, respectively.[3,5] There are several presumable effects of preoperative CRT. First, the macroscopic and microscopic downstaging before surgery could render a lower rate of R1 or R2 resection and fewer positive regional lymph nodes, resulting in a lower incidence of local recurrence after resection compared with patients without preoperative CRT.[3,5,8,24] Second, the administration of systemic chemotherapy and radiation therapy before surgery provides early treatment of micrometastatic diseases that are most likely present in the majority of patients with pancreatic cancer at diagnosis. Initiation of chemoradiation therapy during a time at which low systemic tumor burden is present might maximize the antitumor effect of CRT.[3] Lastly and most importantly, the preoperative CRT strategy discriminates between patients who are likely to benefit from subsequent surgery and those who are not.[3,5]

Seemingly resectable pancreatic cancer based on radiographic imaging examinations comprises an inhomogeneous patient population: (1) "truly" localized and resectable (ie, without any distant diseases) cases; (2) "seemingly" localized and resectable cases with microscopic distant diseases that can be controlled by systemic chemotherapy; and (3) "seemingly" localized and resectable cases with microscopic distant diseases that are difficult to control with systemic chemotherapy. The first 2 cases would potentially benefit from surgical resection, but third case would not. To avoid unnecessary postoperative complications and delayed initiation of alternative therapy, it is quite important to differentiate between those who should avoid such an invasive operation as pancreatectomy and those with a higher likelihood of being cured by surgical resection. In the present study, 21 group A patients (32.8%) of the total 64 patients were considered as those who were most likely better off avoiding surgery. Because of the selection effect of the preoperative CRT strategy, 8 of the 21 group A patients could avoid laparotomy, but 6 patients could not avoid laparotomy, and 7 could not avoid

TABLE 2. Details of Group A Cases (n = 21)

			Distant Disease			
Group A	Total	Local Disease	Liver Metastasis	Peritoneal Dissemination	Lung Metastasis	Total
No laparotomy	8	1	7	0	0	7
No resection	6	3	1	2	0	3
Recurrence within 6 mo	7	0	4	2	1	7
Total	21	4	12	4	1	17

TABLE 3. Univariable and Multivariable Analysis of Overall Survival (n = 64)

	Univariable	Multivariable
Gender		
Male vs. female	0.121	NA
Age		
<65 vs. ≥65	0.925	NA
Tumor location		
Head vs. body/tail	0.864	NA
Local extension of tumor		
Vascular invasion positive vs. negative	0.889	NA
Pre-CA19–9 (median: 178.5)		
178.5≤ vs. 178.5>	0.076	NS
Post-CA19–9 (median: 69.0)		
69.0≤ vs. 69.0>	0.008	NS
%Post (median: 34.2)		
34.2≤ vs. 34.2>	0.160	NA
CA19–9 alteration		
SD* vs. MD† vs. I‡	<0.0001	<0.0001

*SD: Substantially Decreased.
†MD: Modestly Decreased.
‡I: Increased.
NA indicates not applicable; NS, not significant.

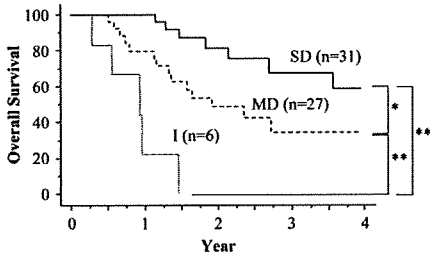

FIGURE 5. Kaplan-Meier curve for overall survival stratified according to CA19–9 alteration status. The 4-year survival rates of category SD, MD, and I patients were 58.9%, 34.1%, and 0%, respectively; no patients in category I survived for more than 1.5 years. Statistically significant differences between each of these categories were obtained. I: category I, MD: category MD, SD: category SD, *$P = 0.002$, **$P < 0.0001$.

TABLE 4. Hazard Ratio for Overall Survival (n = 64)

CA19–9 Alteration	Hazard Ratio	95% CI
Substantially decreased (n = 31)	Reference	
Modestly decreased (n = 27)	2.85	2.49–3.18
Increased (n = 6)	16.9	4.81–58.8

even resection and had recurrent diseases within 6 months after surgery. If we could have identified these patients earlier (ie, before resection, before laparotomy, or even at an earlier stage of preoperative treatment), they could have benefited by receiving alternative treatment which might have been more suitable for their particular pathophysiological conditions, instead of wasting time receiving ineffective treatment. In this regard, our newly developed classification of CA19–9 alteration status during preoperative CRT was shown to be a useful indicator in identifying patients who will benefit from subsequent surgery, as well as those who will not. In the present study, all category I patients were determined to be group A, defined as those not likely to benefit from the preoperative CRT and subsequent surgery, and a majority of category SD patients (93.5%) were determined to be group B, defined as those likely to benefit from the preoperative CRT and subsequent surgery. Category I and category SD consisted of very homogeneous patient populations in terms of the efficacy of preoperative CRT, such that at 2 months after treatment initiation we were able to determine whether or not those patients would benefit from continued preoperative CRT. In contrast, because category MD patients represented an inhomogeneous patient population, approximately half of them were group A and the other half group B, thus, determination of whether or not the category MD patients would be likely to benefit from the preoperative CRT and subsequent surgery could not be made based on their CA19–9 alteration status 2 months after treatment initiation.

Serum CA19–9 could be used for 3 different purposes in terms of the management of pancreatic cancer: (1) serum CA19–9 might play a significant role in the evaluation of whether patient is eligible for resection; (2) preoperative serum CA19–9 could serve as a significant prognostic factor; (3) alterations in serum CA19–9 could represent a response to treatment.[11] The prognostic significance of early alterations in serum CA19–9 during chemotherapy for unresectable pancreatic cancer, typically 2 months after initiation of treatment, is still controversial. Some reports successfully showed a prognostic significance, although others failed to do so.[13,14,16,18–20,25] In this context, we attempted to establish a selection algorithm (CA19–9 alteration status) employing measurements of early alterations in serum CA19–9 combined with pretreatment CA19–9 to establish a therapeutic selection in the setting of preoperative CRT and the subsequent surgical resection strategy. The principle of CA19–9 alteration status is based on the assumption that an increase or an insufficient decrease in CA19–9 during preoperative CRT represents the presence of undetectable distant tumor involvement away from the locoregional area covered by radiation therapy. Furthermore, these distant tumors would not be controlled by systemic administration of gemcitabine. This assumption is supported by results from previous reports of preoperative CRT, in which the excellent locoregional effects of preoperative CRT and the significance of the recurrence with distant diseases were described.[3,5,8,9] In this study, increases and insufficient decreases in CA19–9 (category I and MD) were significantly associated with a higher probability of being a Group A patient, and approximately 80% of Group A patients were classified as such due to the presence of distant diseases. CA19–9 alteration status is useful in evaluating the potential risk of the early occurrence of distant disease in seemingly localized and resectable cases. Krishnan et al reported a treatment strategy for locally advanced pancreatic cancer in which initial treatment with induction chemotherapy precedes subsequent chemoradiation therapy.[26] In their strategy, induction chemotherapy is expected to serve as a therapeutic screening test to identify the micrometastatic lesion, which cannot be controlled by systemic chemotherapy in the seemingly locally advanced pancreatic cancer, as well as to increase the systemic potency of chemotherapy at an early stage of systemic disease. Patients exhibiting systemic tumor progression during the preceding induction chemotherapy are considered to have already had uncontrollable micrometastatic disease and are not eligible for locoregional treatment, such as chemoradiation therapy. In addition to the therapeutic screening effect of systemic administration of gemcitabine, our gemcitabine-based preoperative CRT strategy utilized the advantage of gemcitabine as a

potent radiosensitizer.[27–30] More effective eradication of local tumor burden with radiation therapy sensitized by gemcitabine accentuates the presence of distant diseases, magnifying the difference in early alterations in CA19–9 between those with only localized disease and those with distant as well as localized disease. In fact, CA19–9 alteration status is the single independent factors significantly associated with Group A.

In the present study, we evaluated CA19–9 alteration status, Pre-CA19–9, Post-CA19–9, %Post (Post-CA19–9/Pre-CA19–9 [%]), and other preoperative factors as prognostic predictors in the setting of preoperative CRT strategy. Many previous studies have indicated the prognostic significance of the level of pretreatment CA19–9, post-treatment (eg, postresection) CA19–9, and the proportional decrease in CA19–9 during treatment using a variety of cut-off values, such as the median value of those factors within each study population.[13–16,18,31–34] However, in the present study, multivariable analysis indicated that CA19–9 alteration status was the only independent variable significantly associated with overall patient survival. The statistical significance of CA19–9 alteration status suggests that not only the initial tumor burden (Pre-CA19–9) but also the response to preoperative CRT (%Post) are compositely associated with the efficiency of the preoperative CRT strategy and the clinical outcome. In other words, (1) even if the pretreatment serum CA19–9 is highly increased (ie, Pre-CA19–9 $>$ 370 U/mL), a rapid (ie, 2 months after the initiation of preoperative CRT) and substantial decrease in serum CA19–9 (ie, %Post $\leq$ 10) during preoperative CRT indicates a better response to the gemcitabine-based preoperative CRT and the possibility of a favorable clinical outcome; (2) even if the pretreatment serum CA19–9 is lower (ie, Pre-CA19–9 $\leq$ 370 U/mL), an increase or insufficient decrease in serum CA19–9 (ie, %Post $>$ 50) indicates a poorer response to the treatment and the possibility of an unfavorable clinical outcome. Although in determining the cut-off values for CA19–9 alteration status only clustering each of group A and group B patients, not overall patient survival, was taken into consideration with the goal of developing an earlier and more accurate identification of those who are unlikely to benefit from preoperative CRT and the subsequent resection strategy, CA19–9 alteration status was the single independent variable found to be significantly associated with overall patient survival. Therapeutic characteristics of the preoperative CRT strategy, such as patient selection and early treatment for the potential micro spread of tumor cells, other than those of conventional surgery or surgery along with adjuvant chemotherapy and/or chemoradiation therapy might alter prognostic factors, which should be taken into consideration in the management of pancreatic cancer in the setting of preoperative CRT. Although further validation is needed, CA19–9 alteration status can potentially be employed as one of the prognostic predictors in a prospective study to assess the effectiveness of preoperative CRT strategies for pancreatic cancer.

There are several issues that should be addressed regarding CA19–9 alteration status. First, as described above, although categories I and SD based on CA19–9 alteration status are relatively enriched patient populations, category MD still comprises an inhomogeneous population in terms of evaluation of the efficacy of preoperative CRT and subsequent surgery. Further modification of category MD patients is required for the better therapeutic selection. Second, the management of patients who are diagnosed as having a high likelihood of not benefiting from preoperative CRT and subsequent resection strategy based on their CA19–9 alteration status (ie, category I and MD patients) is quite important. Although CA19–9 alteration status is significantly associated with the efficacy of preoperative CRT and the subsequent resection strategy, CA19–9 alteration status does not confirm the diagnosis of resectability. To avoid denying preoperative CRT and subsequent resection to a patient who would benefit from this treatment strategy, the final decision as to whether to continue preoperative CRT and subsequent resection should be made by concrete evidence demonstrating the presence or absence of eligibility for resection confirmed by radiographic imaging studies or other diagnostic modalities, not solely by CA19–9. CA19–9 alteration status enables the efficient selection of patients having a higher probability of unresectable factors, which remained undetectable by routine evaluations before completion of preoperative CRT. Those patients might be better off receiving additional diagnostic evaluations of their eligibility for continuation of preoperative CRT and a subsequent resection strategy, which may reveal hidden unresectable factors before laparotomy or even at an earlier stage of preoperative treatment. Positron emission tomography/computed tomography and laparoscopic staging with cytologic examination of the peritoneal lavage may be appropriate modalities for additional diagnostic evaluations considering that 80% of the group A patients in the current study were classified as Group A due to the presence of distant diseases, including liver metastasis, peritoneal dissemination, and lung metastasis.[35–39] A prolonged preoperative chemotherapy (ie, more than 3 cycles of gemcitabine administration) and delayed restaging of the eligibility for subsequent surgery may be another option for the selected patients (category I or MD), improving the therapeutic selection by revealing any hidden metastatic diseases prior to laparotomy. Those modifications of the protocol for preoperative CRT and the subsequent resection strategy in the selected patients based on CA19–9 alteration status may effectively enhance the selection effect of this strategy, and more patients who would not benefit from preoperative CRT and the subsequent resection strategy may avoid unnecessary invasive procedures, including pancreatectomy or even laparotomy, as well as time wasted on ineffective treatments. In this regard, patients who developed recurrences within 6 months after resection as well as those who received laparotomy but did not undergo resection due the occurrence of unresectable factors at laparotomy may benefit from selection based on CA19–9 alteration status and subsequent additional evaluations of their eligibility for continuation of preoperative CRT and a subsequent resection strategy, and this subset of patients corresponds to approximately 20% of the total patient population evaluated in the current study. Further investigation of a larger cohort is required to evaluate the management of each patient population selected according to CA19–9 alteration status and improve the selection effect of the preoperative CRT and subsequent resection strategy. Third, although CA19–9 is the most common and reliable tumor marker of pancreatic cancer, not all patients had elevated serum CA19–9 upon initiation of preoperative CRT. Such patients cannot be assessed based on CA19–9 alteration status. In addition, carcinoembryonic antigen (CEA) is another recognized tumor marker for pancreatic cancer that is commonly measured. However, the sensitivity of CEA for pancreatic cancer is relatively low, reported to be approximately 40%, and even lower than that in patients with resectable pancreatic cancer.[40] Indeed, only 25.0% of the patients included in this study showed serum CEA values above normal limits of 5.0 ng/mL before initiation of preoperative CRT (data not shown). Utilization of another tumor marker which has relatively high diagnostic sensitivity for pancreatic cancer, such as DUPAN-II, instead of or in addition to CA19–9 will expand the population of patients eligible for CA19–9 alteration status determination and may improve therapeutic selection. Fourth, in this study, approximately 10% of patients were excluded from the analysis because of potentially inaccurate serum CA19–9 due to biliary problems. Careful management of the biliary system is mandatory for use of CA19–9 as an indicator, although such practices are sometimes difficult.

In conclusion, CA19–9 alteration status based on pretreatment serum CA19–9 and the proportional alteration in CA19–9 2 months after initiation of preoperative CRT for potentially resectable pancreatic cancer effectively identifies those who will benefit from the preoperative CRT and subsequent resection (category SD patients) and those who will not (category I patients); the efficacy of preoperative CRT could not be determined for category MD patients. Early evaluation of the efficacy of the preoperative CRT and subsequent resection might alter the treatment strategy for patients who seem resectable but are likely unresectable due to undetectable tumor spread beyond the locoregional area, with the aim of avoiding unnecessary surgical complications and delayed initiation of alternative treatment. Further investigations of a larger cohort are required to evaluate how best to manage those patients demonstrating a higher probability of not benefiting from preoperative CRT and subsequent resection strategy based on the assessment of CA19–9 alteration status to improve therapeutic selection. In the analysis of preoperative CRT for potentially resectable pancreatic cancer, CA19–9 alteration status merits evaluation not only as a therapeutic selection factor, but also as a prognostic factor, along with other conventional prognostic factors.

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Retrospective Analysis of Concurrent *vs.* Sequential Administration of Radiotherapy and Hormone Therapy Using Aromatase Inhibitor for Hormone Receptor-positive Postmenopausal Breast Cancer

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Abstract. *Background: The optimal sequence of adjuvant aromatase inhibitors and postoperative radiotherapy for postoperative patients with hormone receptor-positive breast cancer treated with breast-conserving surgery is unknown. Patients and Methods: Retrospective analyses of the association of the treatment sequence (concurrent or sequential) of postoperative radiotherapy and adjuvant hormone therapy using aromatase inhibitors with breast cancer outcomes such as ipsilateral breast tumor recurrence, relapse-free and overall survival, and treatment-related complications were performed. Patients were grouped as concurrent (aromatase inhibitors given during radiotherapy followed by continued aromatase inhibitors; 113 patients) and sequential (radiotherapy followed by aromatase inhibitors; 151 patients). Results: At a median follow-up of 2.9 years, there were no differences in the breast cancer outcomes and treatment-related complications between the two treatment groups. In addition, the frequencies of grade 3-5 treatment-related complications were very rare for both treatment groups. Conclusion: Both concurrent and sequential use of postoperative radiotherapy and adjuvant hormone therapy using aromatase inhibitors may be allowed in terms of the breast cancer outcomes and treatment-related complications.*

For breast cancer patients with positive hormone receptor status treated with breast-conserving surgery, adjuvant hormone therapy and postoperative radiotherapy are often used together. However, the optimal sequence of hormone therapy and radiotherapy is unknown. Due to improved disease-free survival, aromatase inhibitors have become standard adjuvant therapy for postmenopausal women with hormone receptor-positive early breast cancer (1, 2). Preclinical results from concurrent treatment with aromatase inhibitors and radiation indicate that this combination therapy could enhance cytotoxicity and improve tumor response (3). However, few clinical data are available on the rationale for the concomitant use of aromatase inhibitors in adjuvant radiotherapy settings.

The aim of this study was to assess the effect of sequencing of aromatase inhibitor therapy and radiotherapy on outcomes in breast cancer and treatment-related complications.

Patients and Methods

Between October 2001 and August 2008, 1,205 patients with stage I or II unilateral breast cancer underwent breast-conserving surgery at Osaka Medical Center for Cancer and Cardiovascular Disease. Of these patients, 264 postmenopausal patients who underwent breast irradiation and received adjuvant aromatase inhibitor were selected for this retrospective study.

Patients were excluded if the data for the sequencing of their aromatase inhibitor and radiation therapy were unavailable. Only patients with a minimum of 6 months' post-radiotherapy follow-up were included. Patients who also received chemotherapy were included. Any patients with a prior or synchronous contralateral breast cancer or other prior malignancy were also excluded. Patients with noninvasive breast cancer or more advanced disease were not included in this analysis.

Radiotherapy was administered to the breast (not including regional lymph nodes) to a total median dose of 50 Gy in 2-Gy fractions. If the surgical margin resulted in microscopically involved tissue, radiotherapy was followed by an electron beam boost to the primary tumor bed to a total median dose of 63.2 Gy.

Aromatase inhibitors (anastrozole 1 mg or letrozole 2.5 mg) were administered daily for 5 years postoperatively.

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Patients were grouped as concurrent (aromatase inhibitors given during radiotherapy followed by continued aromatase inhibitors) and sequential (radiotherapy followed by aromatase inhibitors).

Outcomes for the two groups were compared for any local recurrence, relapse-free survival, and overall survival. Complications were also assessed during treatment and at each follow-up appointment. Grade 3, 4 or 5 pneumonitis, rib fracture, and axillary vein thrombosis were evaluated according to the Radiation Therapy Oncology Group Late Toxicity Criteria (4). Grade 3, 4 or 5 arm edema was assessed according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (5).

Statistical comparisons of clinical, pathological, and treatment-related factors and complications were assessed using the chi square test or Fisher's exact test. Three-year overall survival, relapse-free survival and local failure curves were calculated using the Kaplan-Meier estimates, with time beginning at the surgery. Comparisons for survival curves are based on the log-rank test. All of the statistical tests and p-values were two-tailed and p-values of <0.05 were considered significant.

Results

Of the 264 patients who were treated with aromatase inhibitors and radiotherapy, 113 were identified as having started aromatase inhibitors before radiotherapy or concurrently with radiotherapy (the concurrent group), whereas 151 received aromatase inhibitors after radiotherapy was completed (the sequential group). Most (97%) of patients were administered anastrozole and 3% of them were administered letrozole. Patients were generally treated with aromatase inhibitors for a total of 5 years, except 8 patients (3%) who were switched to tamoxifen because of adverse events.

Patient characteristics for both the concurrent and sequential study groups of patients are shown in Table I. The concurrent group had a significantly shorter follow-up than the sequential group (2.0 years concurrent *vs.* 3.4 years sequential; $p<0.0001$). Moreover, the concurrent group also had significantly more progesterone receptor-positive tumors (74% concurrent *vs.* 60% sequential; $p<0.04$). Between the two treatment groups, there were no different frequencies of chemotherapy use (17% both), but types of chemotherapy regimens were different. A taxane-based regimen was used more frequently in the concurrent group (37% concurrent *vs.* 0% sequential). Other clinicopathological factors were similar in the two groups (all $p>0.1$).

At a median follow-up of 2.9 years, out of the 113 patients in the concurrent group, there was no death; while in the 151 patients in the sequential group, there was 1 death. Relapse in the ipsilateral breast was observed in 1 patient of the concurrent group, whereas no patient in the sequential group experienced local relapse. One patient in the concurrent group developed regional relapse, whereas 2 patients in the sequential group developed regional relapse. Distant metastasis was observed in 1 patient in the concurrent group compared with 3 patients in the sequential group. The sequence of therapy did not influence the 3-year ipsilateral breast tumor recurrence rate (both 0%; p-value could not be calculated), overall survival (both 100%; p-value could not be calculated), or relapse-free survival (concurrent, 100%; sequential, 98%; $p=0.68$).

Toxicities were reviewed by the sequence of aromatase inhibitor and radiotherapy. No significant differences were observed in grade 3 to 5 toxicity between the two cohorts,

Table I. *Patient and tumor characteristics of patients receiving aromatase inhibitors and radiotherapy.*

	Concurrent n (%)	Sequential n (%)	p-Value
No. of patients	113	151	
Age, years			
Median	60	60.5	0.87
Range	48-81	49-80	
Median follow-up, years	2.0	3.4	<0.0001
T-stage			
T1	67 (59)	82 (54)	0.68
T2	43 (38)	62 (41)	
T3	2 (2)	3 (2)	
Unknown	1 (1)	4 (3)	
Positive node status			
0	83 (73)	113 (75)	0.91
1-3	18 (16)	26 (17)	
4+	6 (5)	5 (3)	
Unknown	6 (5)	7 (5)	
Pathology			
Infiltrative ductal	108 (96)	142 (94)	0.84
Other	2 (2)	4 (3)	
Unknown	3 (3)	5 (3)	
Surgical margins			
Negative	106 (94)	135 (89)	0.37
Positive	7 (6)	15 (10)	
Unknown	0 (0)	1 (1)	
Estrogen receptor status			
Negative	2 (2)	8 (5)	0.31
Positive	110 (97)	141 (93)	
Unknown	1 (1)	2 (1)	
Progesterone receptor status			
Negative	28 (25)	59 (39)	0.04
Positive	84 (74)	90 (60)	
Unknown	1 (1)	2 (1)	
Total radiation dose (Gy)			
50	107 (95)	141 (93)	0.66
63.2	6 (5)	10 (7)	
Adjuvant chemotherapy			
No	94 (83)	125 (83)	0.93
Yes	19 (17)	26 (17)	
Type of chemotherapy			
CMF	0 (0)	1(4)	0.008
Taxane-based	7 (37)	0 (0)	
Anthracycline-based	10 (53)	21 (81)	
Combination of anthracycline and taxane	2 (11)	4 (15)	

CMF: Cyclophosphamide, methotrexate, 5-fluorouracil.

with 2 out of 113 (2%) in the concurrent group compared with 1 out of 153 (1%) in the sequential group (p=0.40). Grade 3 to 5 rib fracture, and axillary vein thrombosis did not occur in either group. Grade 3 pneumonitis occurred in 1 patient (1%) of the concurrent group and none of the sequential group. Grade 3 arm edema occurred in 1 patient of each group.

Discussion

Hormone therapy and radiotherapy are both quite important for breast cancer patients treated with breast-conserving surgery and whose tumors are hormone receptor positive. However, to date, the optimal sequence of hormone therapy and radiotherapy is unknown.

Over three decades, tamoxifen has been used for the treatment of early breast tumors that are positive for hormone receptor in premenopausal and postmenopausal women, and the effect of tamoxifen on overall survival has been established in the adjuvant therapy of breast cancer (6).

However, there are little data regarding the effect of timing of tamoxifen and radiotherapy. Although some basic studies have demonstrated reduced radiosensitivity of human tumor cells pretreated with tamoxifen, others have suggested enhanced radiosensitivity (7-9). To date, no randomized trials have investigated the clinical effect of the sequencing of tamoxifen and radiotherapy. Retrospective studies suggest that in practical application, concurrent administration of tamoxifen with radiotherapy does not compromise breast cancer outcomes (10-12) but might increase subclinical toxicity (13, 14).

This question of sequencing of hormonal therapy and radiation is still a clinical concern because of the increasing use of aromatase inhibitors. Several recent randomized controlled trials showed that aromatase inhibitors were superior to tamoxifen in terms of improved disease-free survival for postmenopausal patients with hormone receptor-positive tumors (1, 2). To date, there are few clinical data regarding the effect of the sequencing of aromatase inhibitors and radiotherapy (15). To our knowledge, this is the first such report. No significant differences were observed in ipsilateral breast tumor recurrence rates, overall survival and relapse-free survival between the two cohorts. In addition, the incidence of clinically relevant complications from the use of aromatase inhibitors and radiotherapy was very low in both the treatment groups. Results of this retrospective analysis are similar with findings from the reports of tamoxifen and radiotherapy (10-12).

This study has several limitations. The major limitations are a small sample size and short follow-up period. In addition, the important limitation of this study is the difference of the length of follow-up between the two cohorts. Patients treated with radiation therapy and aromatase inhibitors sequentially were observed for a significantly longer period of time (3.4 *vs.* 2.0 years; p<0.0001). Due to this difference, chemotherapy regimens were different. In the concurrent group, more patients were administered newer chemotherapy regimens (taxane-based), and fewer patients were treated with anthracycline-based regimens (16). If taxane-based regimens were superior to anthracycline-based regimen in terms of breast cancer outcomes, the concurrent group could have a better outcome. Due to a gradual shift in practice pattern over time, the frequency of the concurrent use of aromatase inhibitors and radiotherapy was increasing after several reports regarding the sequencing of tamoxifen and radiotherapy have been published (10-12).

Despite several limitations, this retrospective analysis may suggest that between the two treatment modes (concurrent or sequential use), there were no differences in the breast cancer outcomes and treatment-related complications.

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Feasibility and Efficacy of Combination Therapy With Preoperative Full-Dose Gemcitabine, Concurrent Three-Dimensional Conformal Radiation, Surgery, and Postoperative Liver Perfusion Chemotherapy for T3-Pancreatic Cancer

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Objective: To evaluate both the feasibility and efficacy of our combined therapy, which consisted of preoperative chemoradiation, surgery, and postoperative liver perfusion chemotherapy (LPC) for patients with T3 (extended beyond the pancreatic confines) cancer of the pancreas.

Summary Background Data: Because of the high incidence of local recurrence and liver metastasis, long-term outcomes for patients after resection of T3-pancreatic cancer are extremely poor.

Methods: During the period from 2002 to 2007, 38 patients with T3-pancreatic cancers consented to receive a combination of preoperative chemoradiation, surgery, and postoperative LPC. With the aid of 3D radiation planning, irradiation fields were constructed that included both the primary pancreatic tumor and retropancreatic tissues while taking care to exclude any section of the gastrointestinal tract. The total dose of radiation was 50 Gy (2 Gy × 25 fractions/5 weeks) and was administered in combination with gemcitabine treatments (1000 mg/m^2/week × 9/3 months). Preoperative restaging via computerized tomography and intraoperative inspection were used to determine if pancreatectomy was indicated. For respected cases, one catheter was placed into the gastroduodenal artery and another one into the superior mesenteric vein. Postoperatively, 5-FU (125 mg/day × 28 days) was infused via each of these 2 routes.

Results: Preoperative chemoradiation was completed for all 38 patients, including 3 patients who required gemcitabine-dose reduction. Seven patients (18%) did not undergo surgical resection because either distant metastases or progressive local tumors had been detected after chemoradiation. The remaining 31 patients (82%) underwent pancreatectomy plus postoperative LPC, without postoperative or in-hospital mortality. The 5-year survival rate after pancreatectomy was 53%, with low incidences of both local recurrence (9%) and liver metastasis (7%). Postoperative histopathologic study revealed a marked degenerative change in cancer tissue, showing negative surgical margins (R0) for 30 patients (96%) and negative nodal involvement for 28 patients (90%).

Conclusion: Results of this trial suggest that a combination of preoperative full-dose gemcitabine, concurrent 3D-conformal radiation, surgery, and postoperative LPC is feasible for the treatment of T3-pancreatic cancer. Using the method described in this article, we were able to effectively reduce the incidence of both local and liver recurrence. Therefore, this type of combination therapy seems promising for improving long-term outcomes for patients with T3-cancers of the pancreas. This study is registered with University hospital Medical information Network clinical trials Registry number, UMIN000001804.

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In the treatment of invasive ductal adenocarcinoma of the pancreas, surgical resection still offers the only hope for a complete cure. However, long-term outcomes after pancreatic cancer resection remain extremely poor: the overall 5-year survival rate has been reported to be a mere 10% to 30%.[1–3] In the course of our work, we commonly encounter patients whose primary pancreatic tumors have extended beyond the pancreatic confines (T3 according to the International Union against Cancer [UICC]-classification, sixth edition[4]), occasionally involving the regional lymph nodes, nerve plexus, portal vein, and some other major vessels. This is true even for those cases where no distant metastases have been detected at the time of laparotomy. Furthermore, due to the high incidences of both locoregional recurrence (mainly in the pancreatic bed)[5,6] and liver metastasis,[3,7] the 5-year survival rate is 20% or less for curative surgical removal of such advanced tumors. Based on this observation, we have come to the conclusion that it is necessary to employ adjuvant therapies in conjunction with surgical removal of the tumor to deal effectively with these 2 types of cancer recurrence.

To date, the clinical benefit of preoperative chemoradiation as a local disease control after pancreatic cancer resection has been supported by an increasing number of authors.[8–11] Moreover, some of them[12] were able to show a marked decrease in viable cancer cells and this was particularly evident at the advancing margin of the pancreatic tumor on microscopic examination of resected specimens. Thus, this type of preoperative treatment seems to be effective for downstaging locally advanced cancers, allowing for a more curable surgery by reducing the chance of residual cancer cells at the surgical margin or in the pancreatic bed. At present, gemcitabine is well established not only as a systemic agent for pancreatic cancer but also as a potent radiosensitizer.[13] McGinn et al[14] showed that significant gastrointestinal toxicity developed when a full dose (1000 mg/m^2) of gemcitabine was administered together with a wide field of irradiation but that this risk could be significantly decreased in cases where a limited field of irradiation was used. This observation seems to have been confirmed by Talamonti et al[11] who recently reported that a preoperative full dose of gemcitabine combined with 3D-radiation was well tolerated by patients. In addition,

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this course of treatment had the dual advantages of both a high completion rate and a low rate of postoperative mortality. Another problem to be considered is how to reduce the incidence of liver metastasis after pancreatic cancer resection. In a previous study conducted at our institute,[15] we achieved a significantly decreased incidence of liver metastasis through the use of postoperative liver perfusion chemotherapy (LPC) consisting of a continuous infusion of 5-FU via both the hepatic artery and the portal vein.

Therefore, the present study is designed to evaluate the feasibility and efficacy of a combination of therapies consisting of a full dose of gemcitabine, concurrent 3D-radiation, surgery, and postoperative LPC; all used concurrently in an attempt to more effectively deal with T3-pancreatic cancer.

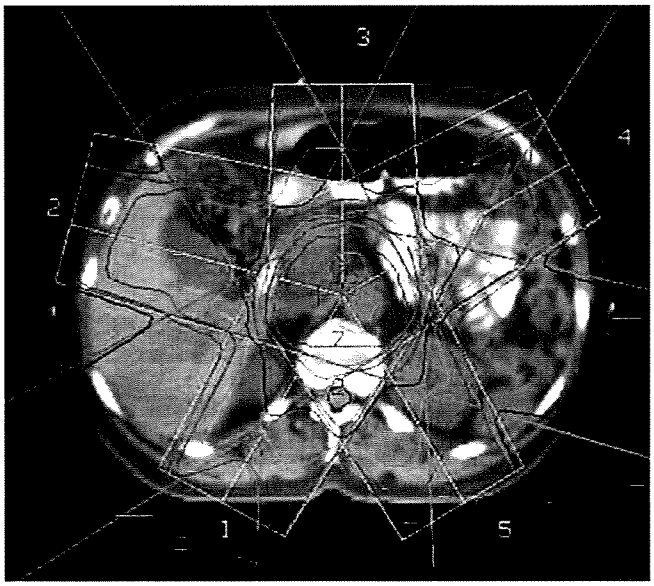

FIGURE 1. The field of 3D radiation in the present study. The radiation field included not only the primary pancreatic tumor but also the retropancreatic areas including the aorta, celiac, and superior mesenteric arteries as the target volume. The gastrointestinal tract was carefully excluded from the field.

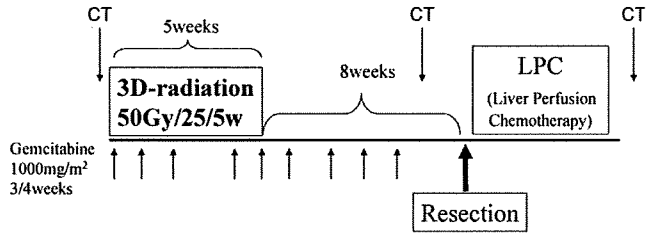

FIGURE 2. The treatment schedule: preoperative chemoradiation, surgery, and postoperative LPC. A 50 Gy (2 Gy/day × 25 fractions/5 weeks) of preoperative radiation was administered along with a concurrent intravenous infusion of gemcitabine (1000 mg/m^2; 3/4 weeks for 3 cycles). When neither new lesion nor progressive disease developed, surgical exploration was performed within 3 weeks after the final IV infusion of gemcitabine. When pancreatectomy was indicated, lymphatic and connective tissue clearance was done. Immediately after surgery, LPC was done.

PATIENTS AND METHODS

Eligibility Criteria

During a period of 5 years between May 2002 and June 2007, 38 patients with T3 (UICC-classification, sixth edition[4]) cancer of the pancreas, consented to enroll in our trial, which consisted of preoperative chemoradiation, pancreatectomy, and postoperative 5-FU-based LPC (Figs. 1, 2). Before registration, patients underwent radiologic imaging, including thin-slice abdominal computerized tomography (CT), magnetic resonance imaging, or celiac/superior mesenteric arteriography. Based on these examinations, the present study included the patients whose primary pancreatic tumors had obviously extended beyond the posterior confines of the pancreas (T3), involving the retropancreatic soft tissues and occasionally the portal/superior mesenteric vein (PV/SMV) (Table 1). They also included the patient whose surrounding organ (stomach, colon, or adrenal gland) or hepatic artery was involved in part by cancer. However, the patients were excluded when they showed metastatic lesions in the liver, lung, or lymph nodes in the para-aortic region (M1), and when they showed cancer invasion to the following vessels: celiac truncus; superior mesenteric artery; branching point of the SMV to the right colic vein; or a proximal part (1.5 cm in length) of the gastroduodenal artery from the branching point of the common hepatic artery (because this part should be used for catheter placement). In all 38 patients, the diagnosis of pancreatic adenocarcinoma was confirmed either by cytology of the pancreatic juice collected during endoscopic retrograde pancreatography or by the cytology or histology of the biopsy specimens obtained by endoscopic ultrasonography- or US-guided fine-needle aspiration. An endoscopic ultrasonography was also used as the subsidiary modality for diagnosing tumor invasion of the stomach or duodenum. Patients were excluded from the present study under the following conditions: (i) when their performance status (ECOG criteria[16]) was below grade 2; (ii) when the patient's common hepatic artery

TABLE 1. Clinical Characteristics of Thirty-Eight Patients Who Received Preoperative Chemoradiation

Characteristics	
No. patients	38
Age, yr (range)	66 ± 9 (41–81)
Gender (male/female)	25/13
Location of pancreatic tumor*	
Head	29 (76%)
Body/tail	9 (24%)
Size of tumor before chemoradiation (cm)*	
Mean ± SD	3.4 ± 1.2
Range	2.0–7.0
Tumor extension beyond pancreas (T3 in UICC classification, 6th edition)*	38 (100%)
Lymph node enlargement*†	12 (38%)
Cancer involvement of large vessels*	29 (76%)
PV/SMV	24 (63%)
Splenic vessels	7 (18%)
Hepatic A	4 (11%)
IVC	1 (3%)
Other organs involved by cancer* (stomach, colon, or adrenal gland)	3 (8%)

*Assessment with radiologic imaging before chemoradiation.
†This study did not include the patients who had enlarged lymph node in the para-aortic area but included those in any other regions.
IVC indicate inferior vena cava.

showed such unusual type of running, for instance being branched from the superior mesenteric artery, that made it difficult to place a catheter into the gastroduodenal artery; (iii) when they had a past history of other malignant disease, chronic hepatitis, renal dysfunction, or severe coronary diseases; (iv) when they showed an inadequate bone marrow reserves as measured by a total white blood cell count of 3.0×10^9/L or less and a platelet count of 100×10^9/L or less; or (v) when their laboratory tests indicated abnormal data such as: activated partial thromboplastin time >50 seconds (normal <45 seconds); asparagic aminotransferase >100U/L (normal <40 U/L); alanine aminotransferase >100 U/L (normal <40U/L); or creatinine ≥1.5 mg/dL (normal <1.4 mg/dL).

Treatment Schedule

Preoperative Chemoradiation

Three-dimensional radiation was planned for the following areas: the primary pancreatic tumor, retropancreatic soft tissues, the para-aortic region, and the celiac and superior mesenteric arteries. However, the gastroduodenal tracts were carefully excluded from the field of irradiation. The posterior margin of the target volume was placed 1.0 to 1.5 cm behind the anterior margin of vertebral bodies. The anterior, right, or left margins were limited with duodenum or stomach; therefore, the fields resulted in the shape of a pentagon (Fig. 1). For the purpose to achieve irradiation toward this field, patients first drank a positive contrast medium along with dilute barium sulfate before thin-section CT scanning of the upper abdomen. The radiation fields were delineated in each of multiple CT cut-sections and planning target volumes were thereby constructed. The total radiation dose was 50 Gy delivered in daily fractions of 2 Gy 5 times per week (Fig. 2), usually from 5 portals (Fig. 1). Patients were administered a 30-minute IV infusion of gemcitabine (1000 mg/m^2) on days 1, 8, and 15 of each 28-day cycle and this was repeated for 3 cycles (total dose of gemcitabine: 9000 mg/m^2). These preoperative treatments were administered at our outpatient clinic.

All patients received routine physical check-ups on a weekly basis to monitor performance status; body weight; and the presence or absence of jaundice, fever, appetite loss, dyspnea, or rash. Laboratory examinations included a complete blood cell count (weekly), serum levels of CEA, CA 19–9, albumin, alanine aminotransferase, asparagic aminotransferase, alkaline phosphatase, amylase, and bilirubin (biweekly). The grades of treatment toxicity were determined according to the National Cancer Institute Common Toxicity Criteria Version 2. When they experienced hematologic toxicity of grade 3, gemcitabine infusion was skipped for one week, and dose-reduction was considered if the toxicity was not thereby reduced. When grade 3 gastrointestinal toxicity developed, we made the decision to interrupt radiation therapy. Both types of treatments were interrupted when any grade 4 adverse effects developed.

Re-Evaluation of Resectability and Surgical Procedures

At the completion of gemcitabine infusions, a restaging CT was done to determine if laparotomy was indicated. If neither distant metastasis nor cancer progression were detected, a surgical exploration was scheduled for 3 weeks after the final IV infusion of gemcitabine. When neither liver metastasis nor peritoneal implantation were observed by a careful inspection, a pancreatectomy together with lymphatic and connective tissues clearance[5] was performed. In cases where the pancreatic tumor was fixed with the PV/SMV, it was resected together with the pancreas (en bloc resection). Even when the PV/SMV looked intact and were easily isolated from the pancreas or tumor, we were careful to perform an intraoperative cytodiagnosis for the touch smear of the disclosed vein wall.[17] When positive result was shown by cytodiagnosis, the PV/SMV was additionally resected, and reconstruction was undertaken using an end-to-end anastomosis. When cytology proved negative, no further resection was made for the PV/SMV. With regard to GI-tract reconstruction procedures: hepatic duct-jejunostomy, gastrojejunostomy, and jejuno-jejunostomy were all done after total pancreatectomy; pancreatogastrostomy was added to the above 3 procedures after pancreaticoduodenectomy; and none of the anastomotic procedure were done after caudal pancreatectomy.

Intraoperative Catheterization for Postoperative Liver Perfusion Chemotherapy

After all reconstruction procedures were finished, catheterization was performed via 2 routes using techniques described in our previous reports.[18,19] Briefly, a catheter with a portal reservoir at the opposite end (MRI implant Port, Medicon, Osaka, Japan) was inserted into the gastroduodenal artery in a retrograde manner. The tip of this catheter was introduced into the branching point from the common hepatic artery. The reservoir was then placed in the subcutaneous layer of the abdominal wall and was punctured percutaneously with a thin needle when the infusion was initiated. When this artery looked fragile due to atherosclerosis and/or inflammatory changes, intraoperative catheterization was foregone (9 patients). Alternatively, immediately after surgery, a catheter was placed into the common hepatic artery by using the Seldinger's method. Another catheter (Medicut LCV-UK kit, Nippon Sherwood, Shizuoka, Japan) was placed into one of the branching veins of the ileocecal vein; the other end of which was drawn out through the abdomen wall. Beginning immediately after surgery, 125 mg/day of 5-fluorouracil was infused continuously into both the hepatic artery and portal vein simultaneously. The infusion was initiated immediately after surgery and continued for 28 postoperative days with the aid of an infusion-pump (Terufusioni, TERUMO, Tokyo, Japan). After the LPC, no further chemo- or radiation therapies were added.

Pathologic Assessment and Postoperative Follow-Up

The resected specimens were fixed in a 10% formalin solution, sliced into 5-mm sections, and embedded in a paraffin block. A 4-μm section was obtained from each block, stained with hematoxylin-eosin, and microscopically observed by 2 expert pathologists. The population of degenerated cancer cells was determined for each case. The degenerated cancer cells were defined as those having absent, pyknotic, or irregular-shaped nuclei with acidophilic, swollen, or vacuolated cytoplasm. In the present study, a "pathologic responder" was defined according to Evans's criteria[20]; a case in which the population of degenerated cancer cells exceeded 50%.

Postoperative follow-up consisted of a routine physical examination and laboratory tests including the serum levels of CEA (normal <5 ng/mL) and CA19 to 9 (normal <37 U/mL). Both chest x-ray and CT/ultrasonography of the abdomen were done every 3 to 6 months, and the presence or absence of cancer recurrence was carefully monitored. If subsequent tumors developed, the site of recurrence was classified into one of the following groups: local (the pancreatic bed including the peripancreatic lymph nodes), liver, lung, bone, or peritoneal cavity. Peritoneal recurrence was defined as confirmation by aspiration cytology of the presence of cancer cells in newly developed ascites.

Statistical Analysis

Survival was calculated as the interval from registration until death using the Kaplan-Meier method,[21] and the difference in survival between the subgroups was compared using the log-rank test. Liver metastasis-free (or local recurrence-free) survival was calculated as the interval from registration to the postoperative diagnosis of liver metastasis (or local recurrence). The cumulative

rate of liver metastasis was calculated by the following formula: 1-liver metastasis-free survival rate. Likewise, cumulative rate of local recurrence was calculated by the following formula: 1-local recurrence-free survival rate.

RESULTS

Thirty-eight patients were enrolled in the present study consisting of a combination of neoadjuvant chemoradiotherapy, surgery, and postoperative LPC. These patients consisted of 25 men and 13 women with a median age of 66 ± 9 years (Table 1). Twenty-nine patients (76%) had cancer of the pancreatic head, and 9 (24%) had cancer of the pancreatic body. Before chemoradiation, CT scan measurements indicated the median size of the primary pancreatic tumors to be 3.4 ± 1.2 cm (range: 2.0–7.0) and all of them extended beyond the pancreatic confines (T3 in the UICC classification, sixth edition). Among the 38 patients, 29 (76%) were definitively judged as having positive cancer invasion at one of the following major vessels: the portal vein, the superior mesenteric vein, the splenic vessels, the hepatic artery, or the inferior vena cava. Three patients (8%) were found to have cancer invasion involving the surrounding organs (stomach, colon, or adrenal gland). Lymph node enlargement was pointed out in 12 of 38 patients (32%) by the diagnostic thin slice CT before preoperative treatments.

During preoperative chemoradiation, no patient experienced grade 4 hematologenic or grade 4 gastrointestinal toxicity (Table 2). One patient experienced grade 3 gastrointestinal toxicity, which developed immediately after the final fraction of irradiation; therefore, all of 38 patients completed full dose of radiation without interruption. Grade 3 hematologenic toxicity was experienced in 21 patients (leucocytopenia in 20 patients and thrombocytopenia in 1 patient). Among 38 patients, 19 patients (50%) completed full course (9 times) of gemcitabine infusion without skip or dose reduction; 12 patients needed one time of skip; and 7 patients needed two times of skip. Three patients needed reduced dose of Gemcitabine to 600 mg/m^2 after skipping. The performance status of patients was maintained at grade 0 or grade 1 in 37 patients (97%), and no patient required hospitalization. According to the Response Evaluation Criteria in Solid Tumor[22] scale, 6 patients (16%) showed a partial response and 28 patients (74%) showed stable disease. Of 4 patients (10%) who showed progressive disease, one patient revealed an increase in the size of the primary pancreatic tumor and 3 were found to have newly developed distant metastases (liver metastases = 2 and lung metastases = 1). As shown in Figure 3, laparotomy was abandoned for these 4 patients. In 34 informative cases, the serum level of CA 19 to 9 was decreased from 511 ± 956 U/mL (range: 5–4141 U/mL) to 138 ± 520 U/mL (range: 3–2951 U/mL), and 24 patients (70%) showed a >50% reduction in CA19 to 9 levels. After preoperative treatments, the serum level of CA19 to 9 was 675 ± 1167 U/mL in the 6 (informative) patients who did not undergo surgical resection due to distant metastasis or local progression, and 23.5 ± 16 U/mL in 28 (informative) patients who underwent the surgical resection (P = 0.0001).

Among 34 patients who received laparotomy, 3 patients were excluded from pancreatectomy for the following reasons: one patient was found to have an unsuspected liver metastasis, one had peritoneal seeding, and one had severe cancer invasion to the common hepatic artery and celiac axis (Fig. 3). These 3 patients received palliative by-pass procedures (gastrojejunostomy and choledocojejunostomy). Therefore, a total of 31 patients underwent curative resection of the pancreatic cancer: 21 receiving pancreaticoduodenectomies; 6 receiving caudal pancreatectomies; and 4 receiving total pancreatectomies (Table 3). Among 24 patients who had been once diagnosed as having involved PV/SMV by the CT-scan before the chemoradiation, 19 patients were performed pancreatectomy. PV/SMV was isolated from pancreatic tumor and

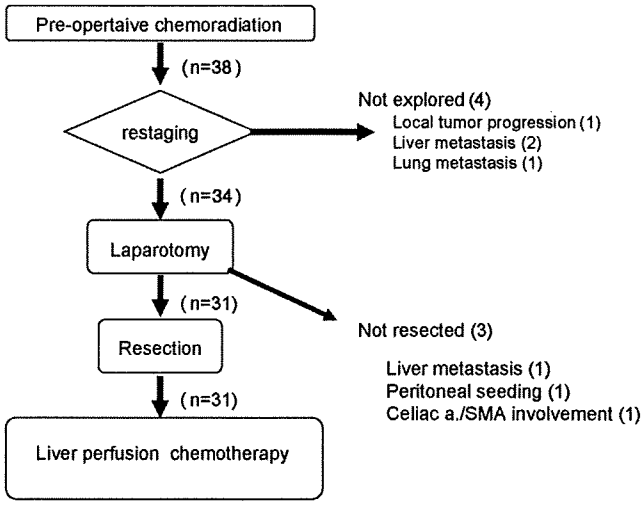

FIGURE 3. Flow chart in 38 patients who received preoperative chemoradiation. Of the 38 enrolled patients, 4 patients did not undergo laparotomy due to local tumor progression or distant metastasis detected by preoperative restaging. During laparotomy, 3 patients were judged as unsuitable candidates for surgical resection because unsuspected liver metastases, peritoneal seeding, or celiac artery involvement was discovered. As a result, pancreatectomy was performed for 31 patients and all of them received postoperative LPC.

TABLE 2. Toxicity and Clinical Response to Preoperative Chemoradiation (Thirty-Eight Cases)

Toxicity	
Gastrointestinal	
Grade 0–2	37 (97%)
Grade 3	1 (3%)
Grade 4	0 (0%)
Hematologenic	
Grade 0–2	17 (45%)
Grade 3	21 (55%)
Grade 4	0 (0%)
Interruption of radiation	0 (0%)
Events for GM-toxicity	
No skip or no dose-reduction	19 (50%)
Skip: 1 time	12 (33%)
Skip: 2 times	7 (18%)
Dose reduction (600 mg/m^2) after skipping	3 (8%)
Needs for hospitalization due to severe toxic effects	0 (0%)
Response (judged by CT/MRI)*	
Partial response	6 (16%)
Stable disease	28 (74%)
Progressive disease	4 (10%)
CA 19–9 levels, median (range) in informative 34 cases	
Before preoperative treatment	511 ± 956 U (5–4141 U)
After preoperative treatment	138 ± 520 U (3–2951 U)

*Response was judged according to "Response Evaluation Criteria in Solid Tumor" GM indicate gemcitabine.