Oncological Benefits of Neoadjuvant Chemoradiation With Gemcitabine Versus Upfront Surgery in Patients With Borderline Resectable Pancreatic Cancer

A Prospective, Randomized, Open-label, Multicenter Phase 2/3 Trial

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Objective: This study was performed to determine whether neoadjuvant treatment increases survival in patients with BRPC.

Summary Background Data: Despite many promising retrospective data on the effect of neoadjuvant treatment for borderline resectable pancreatic cancer (BRPC), no high-level evidence exists to support the role of such treatment.

Methods: This phase 2/3 multicenter randomized controlled trial was designed to enroll 110 patients with BRPC who were randomly assigned to gemcitabine-based neoadjuvant chemoradiation treatment (54 Gray external beam radiation) followed by surgery or upfront surgery followed by chemoradiation treatment from four large-volume centers in Korea. The primary endpoint was the 2-year survival rate (2-YSR). Interim analysis was planned at the time of 50% case enrollment.

Results: After excluding the patients who withdrew consent (n = 8) from the 58 enrolled patients, 27 patients were allocated to neoadjuvant treatment and 23 to upfront surgery groups. The overall 2-YSR was 34.0% with a median survival of 16 months. In the intention-to-treat analysis, the 2-YSR and median survival were significantly better in the neoadjuvant chemoradiation than the upfront surgery group [40.7%, 21 months vs 26.1%, 12 months, hazard ratio 1.495 (95% confidence interval 0.66–3.36), $P = 0.028$]. R0 resection rate was also significantly higher in the neoadjuvant chemoradiation group than upfront surgery (n = 14, 51.8% vs n = 6, 26.1%, $P = 0.004$). The safety monitoring committee decided on early termination of the study on the basis of the statistical significance of neoadjuvant treatment efficacy.

Conclusion: This is the first prospective randomized controlled trial on the oncological benefits of neoadjuvant treatment in BRPC. Compared to upfront surgery, neoadjuvant chemoradiation provides oncological benefits in patients with BRPC.

Keywords: borderline resectable pancreatic cancer, gemcitabine, neoadjuvant chemoradiation, upfront surgery

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Pancreatic cancer is an aggressive and lethal malignancy. Despite many recent improvements in diagnostic techniques and multimodality treatments, pancreatic cancer remains a devastating disease. Early diagnosis of pancreatic cancer remains challenging. Only 20 to 30% of patients diagnosed with pancreatic cancer undergo curative resection that results in improved survival.[1–3] At initial diagnosis, 50% to 60% of patients presenting with metastasis are candidates for palliative chemotherapy or conservative treatment. For patients with borderline resectable pancreatic cancer (BRPC) and locally advanced pancreatic cancer, some surgeons have performed aggressive surgical treatment including major vessel resection. However, the role of aggressive surgical treatment is questionable because of the high morbidity, low R0 resection, and high early systemic recurrence.[2,4]

A neoadjuvant approach for the treatment of BRPC or unresectable pancreatic cancer has many theoretical advantages, including early systemic treatment for undetected micrometastases, increased R0 resection rate, and reduced pancreatic leakage.[5,6] However, there are some disadvantages to this approach in BRPC. Delayed resection can reduce the chance of cure and result in an exaggerated effect because of selection bias. Furthermore, significant downstaging after neoadjuvant treatment is limited and varies among previous reports owing to the lack of highly effective treatment regimens.[7,8]

The National Comprehensive Cancer Network (NCCN) guidelines recommend neoadjuvant treatment rather than upfront surgery for BRPC, despite lacking high-level evidence. Owing to a lack of consensus and evidence, many surgeons still prefer upfront surgery as a treatment for BRPC. Therefore, in this study, we compared the outcomes of neoadjuvant treatment followed by surgical resection with upfront surgery followed by adjuvant treatment in BRPC.

METHODS

Study Design

This randomized controlled parallel-group trial compared neoadjuvant treatment followed by surgery to upfront surgery followed by adjuvant treatment for BRPC (specifically, pancreatic ductal adenocarcinoma). Patients were enrolled in 4 tertiary referral hospitals. The protocol was approved by the Korean Food and Drug Administration (KFDA 201005150) and the institutional review board of each participating center including the Seoul National University Hospital, Samsung Medical Center, National Cancer Center, and Gangnam Severance Hospital (SNUH 1109–109–379, SMC 2011–01–078, NCCCTS-12–617, and KNSH 3–2011–0226). The full trial protocol can be accessed at https://cris.snuh.org/ncris/. This study is registered with ClinicalTrials.gov (NCT01458717).

Patients

Patients were included if they met the following inclusion criteria: willing and able to comply with the protocol, between 18 and 75 years of age and providing written informed consent, radiologic evidence of BRPC according to the 2012 NCCN guidelines,[9] histologically or cytologically proven pancreatic cancer, no history of previous chemoradiation therapy, and adequate bone marrow, hepatic, and renal function according to laboratory test results.

Patients were excluded if they had undergone concomitant unplanned antitumor therapy (eg, chemotherapy, radiotherapy, immunotherapy), had a concomitant or previous malignancy (except cancer that had been in complete remission for >5 years), or had uncontrolled systemic disease (eg, infectious disease and cardiovascular disease).

Randomization, Masking, and Data Management

To determine each patient's radiologic eligibility for BRPC, specialized radiologists from each hospital checked the Multi Detector Computed Tomography to measure tumor size, configuration, length, and degree of contact with adjacent vessels, as listed in the NCCN guidelines, and filed a standardized case report form.[9]

After confirming each patient's eligibility, study information was delivered to the patients. Randomization was performed via a web-based system, after obtaining written informed consent from the participants. To eliminate confounding and uncontrollable factors caused by a surgeon's preference during perioperative management, the allocation sequence was randomly computer-generated and stratified by each surgeon. Patients were randomly allocated on a one-to-one basis to receive either treatment with neoadjuvant chemoradiation or upfront surgery. Blinding was not performed in this study and information regarding allocation and treatment was open to all participating patients, multidisciplinary medical care providers, research assistants, and analysts. Data management and analysis were performed by analysts unrelated to this study. An independent data and safety monitoring board blinded to the treatment groups periodically reviewed all event information, and compared safety outcomes between the 2 groups.

After randomization, all clinicopathologic information was uploaded and stored in a central database. All serious adverse events were submitted to the Clinical Trials Unit, Seoul National University Hospital, Seoul, Korea.

Treatment Protocol

Neoadjuvant Treatment

In the neoadjuvant group, a 3-dimensional treatment plan was established using radiotherapy-planning computed tomography (CT) before starting chemoradiation. Chemoradiotherapy consisted of 45 gray (Gy) in 25 fractions and 9 Gy in 5 fractions (5 times a week for a total of 6 weeks), plus intravenous gemcitabine (gemcitabine hydrochloride, Dong-A ST Co., Ltd. Korea) at 400 mg/m^2 with 150 mLK of normal saline administered an hour before radiation therapy at the start of each week. After chemoradiation, patients underwent a 4- to 6-week rest period. CT, positron emission tomography, and magnetic resonance imaging were performed to reassess the extent of disease before determination of surgery according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).[10] Surgery with curative intent was performed if no distant metastasis or progression was observed. Baseline tumor burden was assessed before randomization. The assessment method used to evaluate each patient throughout the treatment period was kept consistent. The assessment was carried out at 3-month intervals, along with an evaluation of tumor markers, including carbohydrate antigen 19–9.

Upfront Surgery

In the upfront surgery group, surgery was performed according to the participating surgeons' guidelines regarding dissection of the nerve plexus of major vessels and D2 lymph node dissection (including station 16 nodes). The surgical extent was identical to the neoadjuvant group. According to the depth and length of adjacent vessel invasions, the surgeons used their discretion to decide on the optimal methods of resection and anastomosis of vessels to achieve R0 resection. After surgery, chemoradiation was performed within 8 weeks using the same protocol as the neoadjuvant group, provided the patients' condition was acceptable.

Maintenance Chemotherapy

Maintenance chemotherapy was performed within 4 to 6 weeks after completion of surgery and chemoradiation regardless

order of treatment in both groups. Gemcitabine at 1000 mg/m^2 was administered as an intravenous infusion over 30 to 40 minutes on days 1, 8, and 15, followed by 1 week of rest, every 4 weeks for 4 cycles.

Endpoints and Sample Size Calculation

The primary outcome of this study was the 2-year survival rate (2-YSR). The secondary outcomes were the 1-YSR and R0 resection rate. Our trial was powered for the superiority of survival data at 2 years according to the treatment, assuming that the 2-YSR associated with neoadjuvant treatment would be 27% higher than that associated with upfront surgery. Enrollment of 110 patients provides 80% power to detect superiority of the procedure, with 1-sided $\alpha = 0.05$ and $\beta = 0.2$, by Freedman formula.

Statistical Analysis

Statistical analysis was performed using SPSS version 18.0 (IBM, Armonk, NY). Results are presented as mean and standard deviations. Nominal and continuous variables were compared using the Chi square test and Student *t* test, respectively. Survival rates were calculated using the Kaplan–Meier method, and the log-rank test was used to analyze the differences. The survival time was calculated from the start of chemoradiation in the neoadjuvant group, or surgery in the upfront surgery group. Variables that were statistically significant in univariate analysis were included in multivariate analysis using the Cox proportional hazards regression. Two-sided *P* values of <0.05 were considered significant.

Per-protocol (PP) analysis was performed on patients who underwent the allocated treatment. PP1 analysis included patients who underwent both chemoradiation and surgery, and PP2 analysis included patients who underwent both treatments as well as maintenance chemotherapy. An interim analysis was planned at the time of 50% case enrollment. The analysis was performed in conjunction with the data safety monitoring committee, located at Seoul National University Hospital, after the first enrollment of the trial. The committee decided on early termination or the continuation of this study on the basis of the statistical significance of the efficacy and safety issues.

RESULTS

Patient Characteristics

In total, 58 patients were enrolled from March 1, 2012 to October 31, 2014. Eight patients (3 in the neoadjuvant group and 5 in the upfront surgery group) were deemed ineligible because they withdrew consent. These patients were excluded from the intention-to-treat analysis. Of the 50 patients enrolled, 27 were randomly assigned to Arm 1 (neoadjuvant treatment) and 23 to Arm 2 (upfront surgery) (Fig. 1). Both arms were well balanced regarding baseline characteristics such as age, sex, general status, tumor size, and clinical cancer stage (Table 1).

Completion of Treatment

In Arm 1, 26 of 27 patients completed chemoradiotherapy, whereas 1 patient did not complete therapy because of disease progression. According to the RECIST criteria, the radiologic response was categorized as a partial response ($n = 7$), stable disease ($n = 11$), or progressive disease ($n = 9$). Of the 26 patients who completed neoadjuvant treatment, one patient refused operation and the other had progressive disease (liver metastasis was detected in preoperative imaging work-up) (Fig. 1). Of the 24 patients who underwent surgery after completion of chemoradiotherapy, Seventeen underwent tumor resection and the remaining patients underwent exploratory laparotomy. Fourteen patients in Arm 1 achieved R0 resection ($n = 14$, 51.8%). Fourteen of the 17 patients who underwent tumor resection received maintenance chemotherapy, and 8 of them completed treatment. Three patients did not received maintenance chemotherapy because of poor general condition. Six of the 14 patients who underwent tumor resection and maintenance chemotherapy did not complete the protocol because of disease progression. Only 8 patients completed maintenance chemotherapy in Arm 1.

In Arm 2, 23 patients underwent surgery. Eighteen patients underwent tumor resection and 5 patients underwent exploratory laparotomy. Six patients achieved R0 resection (26.1%), and 9 ($n = 9$, 50.0%) and 3 ($n = 3$, 16.7%) achieved R1 and R2 resection, respectively. Adjuvant chemoradiation was performed in 13 patients, and 5 of the 18 patients who underwent tumor resection did not receive adjuvant chemoradiation because of their general condition ($n = 3$) or withdrawal from the study ($n = 2$). Only 6 patients completed maintenance chemotherapy; 7 could not continue treatment because of disease progression. Major adverse events related to chemoradiation and surgical complications are shown in Table 2.

Pathology and Survival Outcomes

Pathologically, an R1-positive margin is defined as $\geq$1 cancer cells within 1 mm of any surface or margin (R1 $<$1 mm). A clear (R0) resection margin is then defined as tumor cells 1 mm away from any margin or surface (R0 $>$1 mm). Pathologic findings and tumor responses of patients undergoing surgical resection are shown in Table 3. Tumor size was significantly smaller in the neoadjuvant chemoradiation group than in the upfront surgery group (2.9 ± 1.4 vs 3.9 ± 0.9 cm, $P = 0.014$). In addition, the number of positive lymph nodes was significantly lower in the neoadjuvant chemoradiation group compared to the upfront surgery group ($n = 0.5 \pm 0.9$ vs $n = 1.9 \pm 1.6$, $P = 0.003$). Furthermore, R0 resection rate was higher in the neoadjuvant group at 82.4% compared to 33.3% in the upfront surgery group ($P = 0.010$).

The overall 2-YSR was 34.0% with a median survival of 16 months (Fig. 2). In the intention-to-treat analysis, the 1-YSR, 2-YSR, and median survival duration in Arm 1 (74.1%, 40.7%, and 21 months) were significantly higher than those in Arm 2 (47.8%, 26.1%, and 12 months). The 2-YSR showed a hazard ratio (HR) of 1.97 [95% confidence interval (CI), 1.07–3.62] and a *P* value of 0.028.

In the PP1 analysis, there was no difference in the 2-YSR between Arm 1 and Arm 2 [41.2% vs 41.7%, HR 1.50 (95% CI, 0.66–3.36), $P = 0.337$]. The median survival duration of Arm 1 and Arm 2 was 22.0 and 19.5 months, respectively. In the PP2 analysis, there was no difference in the 2-YSR between Arm 1 and Arm 2 [75.0% vs 66.7%, HR 1.88 (95% CI, 0.53–6.60), $P = 0.326$].

There was no difference in the recurrence pattern between the 2 arms ($P = 1.000$). The recurrence rate was 88.2% in Arm 1 and 88.9% in Arm 2. Most recurrences were systemic with the liver being the most frequent site of recurrence in both groups (41.2% in Arm 1 vs 66.7% in Arm 2) (Table 4).

The safety monitoring committee decided on early termination of this study on the basis of the statistical significance of neoadjuvant treatment efficacy, in consideration of patient safety.

DISCUSSION

This is the first prospective randomized study to show the superiority of neoadjuvant therapy in BRPC. In the intention-to-treat analysis, the 1-YSR and 2-YSR in the neoadjuvant treatment group (74% and 41%) were nearly twice as high as in the upfront surgery group (48% and 26%). There are several potential reasons for improved survival in the neoadjuvant treatment group, including

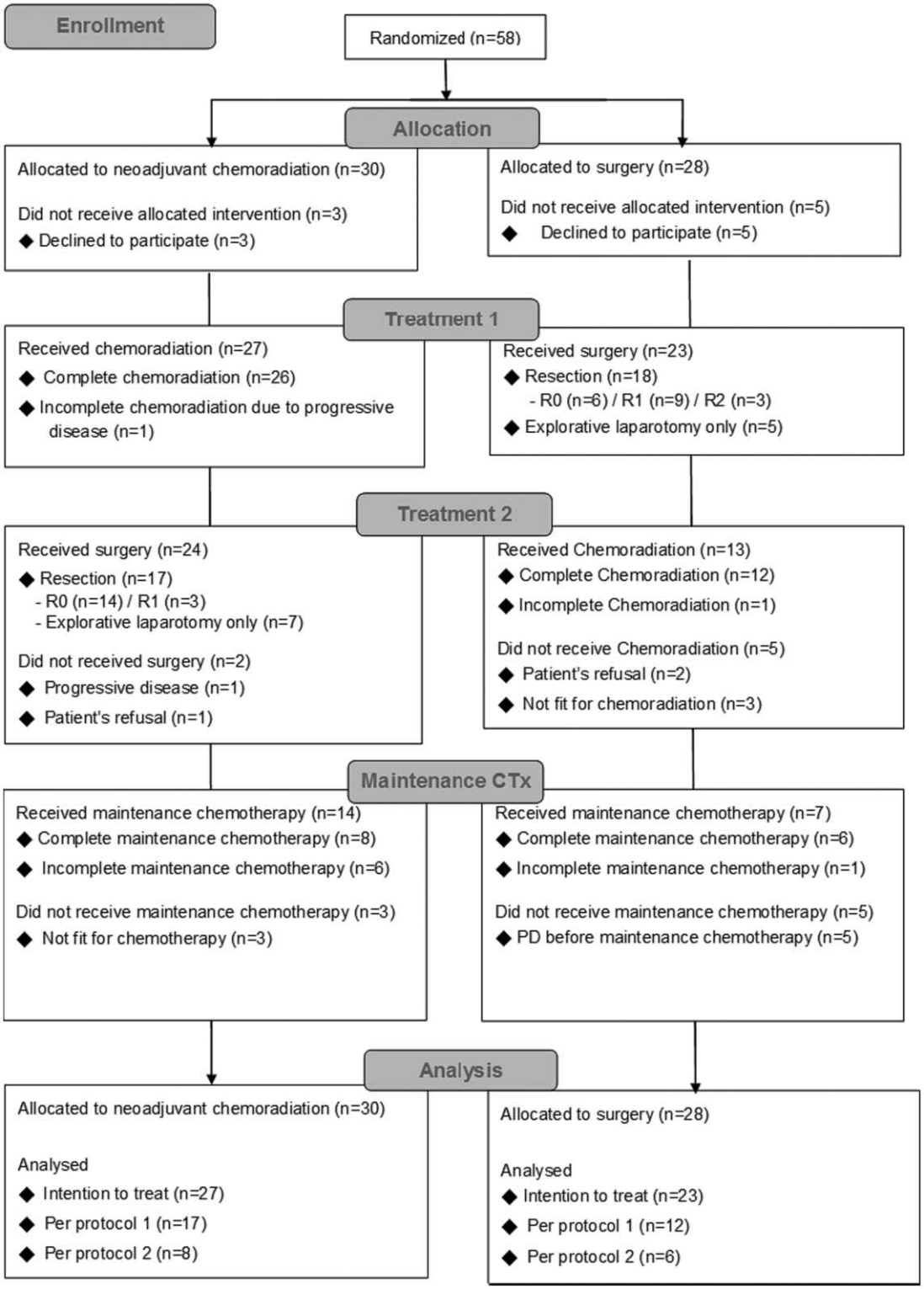

FIGURE 1. CONSORT diagram.

TABLE 1. Patient Demographics and Clinical Characteristics

	Arm 1 (n = 27)	Arm 2 (n = 23)
Age, (mean ± SD) y	59.4 ± 8.4	58.9 ± 11.3
Sex, n (%)		
Male	17 (63.0)	15 (65.2)
Female	10 (37.0)	8 (34.8)
BMI, (mean ± SD), kg/m^2	21.7 ± 4.7	22.2 ± 2.6
Serum albumin, (mean ± SD) g/dL	4.1 ± 0.5	4.1 ± 0.5
ECOG, n (%)		
0	18 (66.7)	17 (73.9)
1	9 (33.3)	4 (17.4)
2	0 (0)	2 (8.7)
Jaundice, n (%)	7 (25.9)	8 (34.8)
CA 19–9, (mean ± SD), U/mL	1042.3 ± 2465.0	1257.8 ± 2539.6
Tumor size, (mean ± SD), cm	3.4 ± 0.8	3.5 ± 0.9
Clinical T stage, n (%)		
3	21 (77.8)	14 (60.9)
4	6 (22.2)	9 (39.1)
Clinical N stage, n (%)		
0	17 (63.0)	8 (34.8)
1	10 (37.0)	15 (65.2)
Vessel invasion, n (%)		
SMV/PV	24 (88.9)	19 (82.6)
IVC	2 (7.4)	2 (8.7)
HA	4 (14.8)	6 (26.1)
SMA	6 (22.2)	4 (17.4)
Celiac axis	2 (7.4)	4 (17.4)
Type of vessel invasion, n (%)		
Artery	10 (37.0)	11 (47.8)
Vein	17 (63.0)	12 (52.2)
Tumor location, n (%)		
Head	23 (85.2)	17 (73.9)
Body/tail	4 (14.8)	6 (26.1)
Resection rate, n (%)	17 (63.0)	18 (78.3)

BMI, body mass index; CA 19–9, carbohydrate antigen 19–9; ECOG, Eastern Cooperative Oncology Group; HA, hepatic artery; IVC, inferior vena cava; PV, portal vein; SD, standard deviation; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

early systemic treatment for undetected micrometastasis, R0 resection rate increment, and optimal selection of patients for surgery. In this study, the initial clinicopathologic findings were similar in both groups. Although a similar resection rate in both groups was achieved (63.0% vs 78.3%), the neoadjuvant group showed a higher R0 resection rate (51.8% vs 26.1%). In this study, pathologic R1 positive margins are defined as $\geq$1 cancer cells within 1 mm of any surface or margin, which is a widely accepted criterion that is included in the AJCC 8th Staging. Considering anatomical characteristics of BRPC (exposure to pancreas surface or adhered to vessels), the high R1 resections observed during upfront surgery could be anticipated, even after extended dissection of nerve plexus or lymph nodes and vessel resections. Our data demonstrate the potential effect of adopting neoadjuvant treatments on increasing R0 resection rates.

Responsiveness to neoadjuvant treatment varied greatly; however, tumor size decreased after neoadjuvant treatment. In addition, the pathologic lymph node involvement of the tumor was markedly lower ($n = 29.4$ vs $n = 83.3$) and the number of retrieved lymph nodes in the neoadjuvant group was lower ($n = 19.1$ vs $n = 30.7$). Considering that the extent of lymph node dissection was standardized in both groups, neoadjuvant treatment reduces the tumor burden of the primary tumor on the adjacent lymph node. After 50% enrollment, an intermediate analysis was performed because of high cancer-related death in patients receiving upfront surgery. Therefore, this study was terminated early because of the definite difference in survival outcomes between the neoadjuvant treatment group and the upfront surgery group.

Surgical resection has been considered the only curative treatment for pancreatic cancer. Owing to nonspecific symptoms and anatomic peculiarity of the pancreas, many pancreatic cancer patients are diagnosed with locally advanced cancer or metastasis. Aggressive resection in advanced pancreatic cancer has been performed, including resection of adjacent organs to increase resectability with R0 margins.[11,12] Although some promising results have been reported, a gain in overall survival has not been proven with aggressive surgical resection. This is because of high margin positive rates and early systemic control failure for locally advanced pancreatic cancer.[13] Some surgeons advocate a different treatment approach for one population of locally advanced pancreatic cancers, namely BRPC, that has a relatively lower invasive status and a higher chance of curative resection. However, BRPC is fundamentally different from resectable pancreatic cancer in that it has a higher risk of positive resection margins, involves a more complex surgical resection procedure, and is associated with the presence of occult distant metastasis.[4] A collection of radiographic criteria, characterizing a subset of nonmetastatic pancreatic ductal adenocarcinoma with intermediate anatomic features between resectable and unresectable, has been described.[14] With the introduction of the potential benefits of neoadjuvant therapy to achieve R0 resection, the NCCN adopted and established the concept of BRPC in 2006.[14,15] However, there are no universally accepted criteria for BRPC. The indications for curative resection and the resectability of the tumor vary according to the surgeon's judgment and experience along with the pathologic criteria. There are 3 commonly cited definitions of BRPC that are used in the clinical setting.[9,16,17] A total of 40.3% of patients diagnosed with BRPC using the definition of the AHPBA/SSO/SSAT can be reclassified as resectable.[18] The reported outcomes of BRPC treated with neoadjuvant therapy are thus variable and in need of standardization.[15,19] Studies based on the definition recently adopted by the NCCN and Intergroup Trial are yet to be reported.

Some surgeons still favor initial aggressive surgical resection in BRPC, especially in those with portal vein/superior mesenteric vein invasion, concerning the unresponsiveness to neoadjuvant treatment and the potential loss of chance for curative resection.[20] However, because of the theoretical advantages and promising outcomes of neoadjuvant treatment,[18,21–24] many clinicians prefer preoperative treatment rather than upfront surgery. Therefore, unlike the previous guidelines, the updated NCCN guidelines recommend neoadjuvant treatment for BRPC.[25] No randomized trial that demonstrates the superiority of preoperative chemotherapy with or without radiation over adjuvant treatment in BRPC has been performed. Events such as drug toxicity or disease progression can hinder the completion of the initial treatment in pancreatic cancer. A recent prospective randomized clinical trial showed that only 57% of patients underwent surgery after neoadjuvant therapy and only 21% finished the entire treatment protocol, even in patients with initially resectable pancreatic cancer.[26] In this study, 62.9% of BRPC patients underwent resection after neoadjuvant treatment and 52.2% underwent chemoradiation after surgical resection ($P = 0.59$), whereas 28% completed maintenance chemotherapy. These results illustrate the difficulties faced by clinical trials in pancreatic cancer and the possibility of selection bias when interpreting outcomes of neoadjuvant treatment, especially in the retrospective study setting. In most retrospective studies, patients who underwent neoadjuvant treatment followed by resection showed better survival because of tolerable response to preoperative treatment, and performance status. Thus, randomized prospective studies are mandatory to adjust selection bias based on intention-to-treat analysis.

TABLE 2. Major Adverse Event of Chemoradiation and Surgical Complications

	All grade, n	%	Grade ≥3, n	%	All grade, n	%	Grade ≥3, n	%	
Chemoradiation	**Arm 1 (n = 27)**				**Arm 2 (n = 23)**				***P***
Neutropenia	14	51.9	0	0	6	46.2	0	0	0.739
Thrombocytopenia	10	37.0	0	0	3	23.1	0	0	0.383
Abdominal pain	12	44.4	0	0	2	15.4	0	0	0.133
Anorexia	12	44.4	0	0	8	61.5	0	0	0.317
Cholangitis	5	18.5	3	11.1	1	7.7	1	7.7	0.643
Diarrhea	1	3.7	0	0	3	23.1	0	0	0.092
Dizziness	1	3.7	0	0	2	15.4	0	0	0.242
Constipation	7	25.9	0	0	1	7.7	0	0	0.182
Epigastric pain	4	14.8	0	0	1	7.7	0	0	0.529
Fatigue	6	22.2	0	0	3	23.1	0	0	0.952
Insomnia	4	14.8	0	0	0	0	0	0	0.284
Nausea	16	59.3	0	0	7	53.8	0	0	0.749
Vomiting	7	25.9	0	0	2	15.4	0	0	0.690
Surgical complications	**Arm 1 (n = 17)**				**Arm 2 (n = 18)**				***P***
Delayed gastric emptying	0	0	0	0	3	16.7	1	5.6	0.248
Fluid collection	1	5.9	1	5.9	3	16.7	0	0	0.638
Wound infection	1	5.9	1	5.9	2	11.1	1	5.6	1.000
Hepaticojejunostomy stricture	1	5.9	1	5.9	0	0	0	0	0.977
Portal vein thrombosis	0	0	0	0	2	11.1	1	5.6	0.492
Superior mesenteric vein occlusion	1	5.9	1	5.9	0	0	0	0	0.977
Pneumonia	0	0	0	0	1	5.6	0	0	1.000
Postoperative pancreatic fistula	0	0	0	0	1	5.6	0	0	1.000

TABLE 3. Pathological Findings and Tumor Responses of Patients Undergoing Surgery

	Arm 1 (n = 17)	Arm 2 (n = 18)	*P*
Tumor size, (mean ± SD), cm	2.9 ± 1.4	3.9 ± 0.9	0.014
Vessel resection, n (%)	6 (35.3)	5 (27.8)	1.000
Pathologic T stage, n (%)			0.064
0	2 (11.8)	0 (0)	
1	1 (5.9)	0 (0)	
2	0 (0)	1 (5.6)	
3	13 (76.5)	10 (55.6)	
4	1 (5.9)	7 (38.9)	
Pathologic N stage, n (%)			0.002
0	12 (70.6)	3 (16.7)	
1	5 (29.4)	15 (83.3)	
Totally retrieved LN, (mean ± SD)	19.1 ± 9.8	30.7 ± 11.9	0.004
Number of positive LN, (mean ± SD)	0.5 ± 0.9	1.9 ± 1.6	0.003
Margin status, n (%)			0.010
R0	14 (82.4)	6 (33.3)	
R1	3 (17.6)	9 (50.0)	
R2	0 (0)	3 (16.7)	
Perineural invasion, n (%)	15 (88.2)	16 (88.9)	1.000
Angiolymphatic invasion, n (%)	6 (35.3)	11 (61.1)	0.181
Microvenous invasion, n (%)	6 (35.3)	12 (66.7)	0.094
RECIST criteria, n (%)			
Partial response	6 (35.3)		
Stable disease	10 (58.8)		
Progressive disease	1 (5.9)		
Tumor regression, n (%)			
Complete response	2 (11.8)		
Moderate response	3 (17.6)		
Minimal response	12 (70.6)		

LN, lymph node; RECIST: Response Evaluation Criteria in Solid Tumors; SD, standard deviation.

Although we found neoadjuvant treatment to be more effective than upfront surgery for BRPC, with improved survival followed by increased R0 resection, there was no difference in recurrence patterns. The recurrence rate was 88.2% in the neoadjuvant treatment group and 88.9% in the upfront surgery group. Most recurrences were systemic with the liver as the most common site. More effective systemic therapy, to reduce metastasis and recurrence even after neoadjuvant treatment followed by resection, must be investigated to improve long-term survival.

As shown in other reports, the survival outcome can differ markedly according to the extent of tumor involvement and types of vessels involved. Therefore, BRPC should not be regarded as a single entity but rather as a spectrum of disease that needs further clarification and a standardized definition. Yamada et al[19] reported that the median disease-free survival durations in patients with pancreatic cancer and portal vein, hepatic artery, and superior mesenteric artery invasion were 12.0, 7.4, and 6.7 months, respectively ($P < 0.05$). Patients with portal vein invasion had different survival outcomes according to the degree of invasion.[20] Another study showed similar survival outcomes according to vessel involvement.[24] To overcome the heterogeneity of BRPC, several radiologic organizations have attempted to introduce a standardized reporting system. Standardization can help facilitate research by using consistent staging with respect to resectability status and allowing for comparison among different institutions. Recently, a multicenter prospective study based on standardization of the radiologic criteria was performed.[15,27] In this study, a standardized radiologic reporting system for tumor invasion, including the extent and degree, was used. With the accumulation of cases and utilization of a standardized evaluation system of the extent of vessel involvement, a more specific definition of BRPC can be established and the optimal treatment candidate can be selected.

Another issue in BRPC is the optimal treatment regimen. Although the use of neoadjuvant therapy results in a higher R0 resection rate than surgery and provides treatment for subclinical

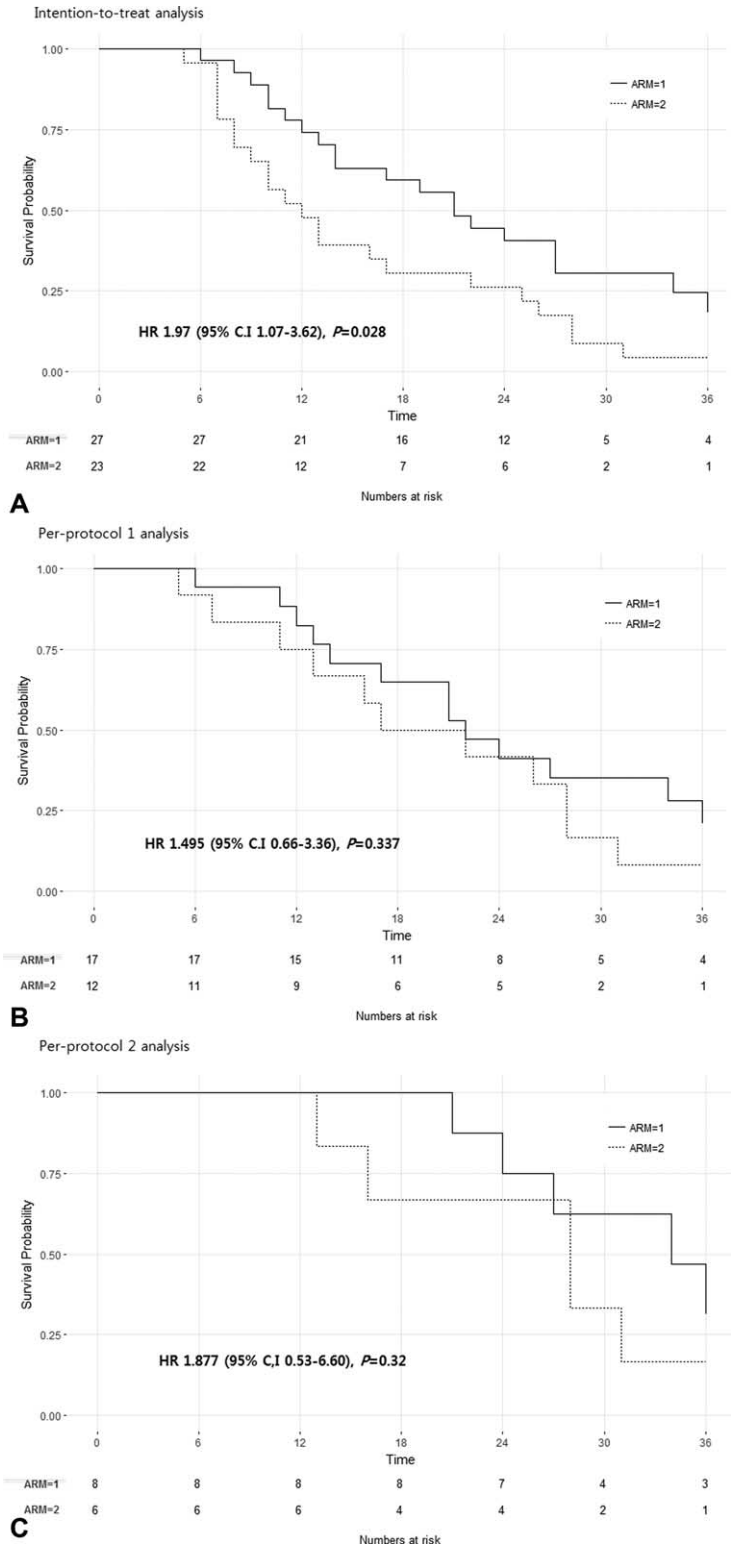

FIGURE 2. Survival outcome in (A) intention-to-treat analysis, (B) per-protocol 1 analysis (patients who underwent both chemoradiation and surgery), and (C) per-protocol 2 analysis (patients who underwent both chemoradiation/surgery and maintenance chemotherapy).

TABLE 4. Recurrence Pattern

	Arm 1 (n = 17)	Arm 2 (n = 18)	*P*
Overall recurrence, n (%)	15 (88.2)	16 (88.9)	1.000
Locoregional recurrence, n (%)	6 (35.3)	5 (27.8)	
Systemic recurrence, n (%)	12 (70.6)	16 (88.9)	
Liver	7 (41.2)	12 (66.7)	
Lung	1 (5.9)	1 (5.6)	
Bone	2 (11.8)	0 (0)	
Peritoneal seeding	4 (23.5)	4 (22.2)	
Para-aortic lymph node	0 (0)	2 (11.1)	

metastases, no standardized regimen is available at this time. In this trial, we applied chemoradiation; neoadjuvant chemoradiation is expected to provide good local control and increase R0 resection rates in BRPC. Currently, the chemotherapy such as FOLFIRINOX and gemcitabine combined with protein-bound paclitaxel (nab-paclitaxel, Abraxane) regimens are widely used due to the relatively high response rate.[28,29] More high-level evidence is needed in selecting the appropriate treatment regimen. Several clinical trials have actively evaluated the use of various combinations of cytotoxic agents or targeted therapies with/without concurrent radiotherapy in BRPC.[20,22,30,31]

In conclusion, this is the first randomized clinical trial to investigate the oncological benefits of neoadjuvant treatment in BRPC. Neoadjuvant treatment, rather than upfront surgery, should be considered for patients with BRPC. Future studies are needed to identify more effective systemic treatments that control local disease and reduce systemic metastasis after treatment.

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