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【 ORIGINAL ARTICLE 】

A Prospective Study of Neoadjuvant Gemcitabine Plus Nab-paclitaxel in Patients with Borderline-resectable Pancreatic Cancer

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Abstract:

Objectives Neoadjuvant therapy followed by radical resection improves the borderline-resectable pancreatic cancer (BRPC) prognosis; however, the optimal therapeutic regimen remains unclear. Gemcitabine plus nab-paclitaxel (GnP) showed a high anti-tumor effect in primary lesions in a prospective study for metastatic disease. However, evidence concerning its feasibility is still lacking in patients with BRPC. We therefore evaluated the tolerability of neoadjuvant GnP (NAC-GnP) for BRPC.

Methods This single-center prospective study evaluated 10 patients with BRPC who were treated with two cycles of NAC-GnP. The primary endpoint was feasibility for NAC-GnP. Treatment feasibility was defined as a successful outcome in at least eight patients.

Results Ten patients who had BRPC in contact with the celiac artery (n=5), superior mesenteric artery (n=3), or hepatic artery (n=2) were enrolled. The median age was 75 (range, 40-82) years old. Grade 3 anorexia and grade 2 pneumonia occurred in one patient each, so treatment was feasible in eight patients. The median primary tumor reduction and response rates were 33% (range, 0-68%) and 60%, respectively. Six of eight patients who had abnormal CA19-9 levels at the time of enrolment showed a decrease in CA19-9 levels, with a median decrease of 72%. Five patients underwent radical resection, including R0 resection in four. Postoperative grade IIIa Clavien-Dindo complications occurred in one patient (upper gastrointestinal bleeding and pancreatic fistula).

Conclusion Two-cycle NAC-GnP is a feasible treatment for patients with BRPC. Further studies on NAC-GnP in patients with BRPC are warranted.

Key words: borderline resectable, chemotherapy, pancreatic ductal adenocarcinoma, surgery

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Introduction

Pancreatic cancer (PC) has an extremely poor prognosis, with a 5-year overall survival (OS) rate of only 10% (1). Based on local and/or distant tumor extension, PC can be categorized into resectable, borderline resectable (BR), unresectable locally advanced (UR-LA), and metastatic (2). Approximately 19-36% of all PCs are resectable and can be managed with radical resection (3). Specifically, the primary

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treatment modality for resectable PC involves curative resection followed by adjuvant chemotherapy (4-6). In Japan, adjuvant chemotherapy using S-1, an oral fluoropyrimidine, has become a standard therapy based on the results of the JASPAC-01 trial (7).

However, the optimal multimodal treatment strategy for patients with BR or UR-LA PC remains controversial. Upfront surgery for BRPC is associated with a high possibility of incomplete resection, such as R1 or R2 resection, leading to early recurrence (8, 9). In contrast, several studies have shown that neoadjuvant therapy followed by radical resection improved the prognosis of patients with BRPC (10-13). However, the optimal therapeutic regimen for BRPC remains unclear.

Gemcitabine plus nab-paclitaxel (GnP) and 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) are the standard chemotherapy regimens in patients with metastatic PC based on the results of the MPACT and PRODIGE 4/ACCORD 11 trials, respectively (14, 15). GnP showed a high anti-tumor effect, with a response rate (RR) of 58.8% and a median primary tumor reduction rate of 43.4% in a Japanese validation study (16). Although both of these chemotherapeutics can be candidate neoadjuvant chemotherapy (NAC) regimens for BRPC, GnP is the more promising one because of its lower risk of adverse events (AEs), such as gastrointestinal toxicity and febrile neutropenia (16-18).

In the present study, we evaluated the feasibility of NAC-GnP in patients with BRPC. We selected 2 cycles for NAC-GnP because the median time to response was 43.0 days in patients with metastatic PC treated with GnP (16).

Materials and Methods

Study design and ethical considerations

This open-label, single-arm, single-center study was approved by the Institutional Review Board of Kyorin University (approval number: 670) and conducted in accordance with the Declaration of Helsinki. All patients who participated in this study provided their written informed consent. The trial was registered as UMIN000023591. Long-term follow-up for the survival analysis was approved by the Institutional Review Board of Kyorin University (approval number: 1862).

Patients

Patients with pancreatic cancer diagnosed by imaging and histologically or cytologically confirmed adenocarcinoma were recruited between June 2016 and September 2018. The inclusion criteria were as follows: 1) no distant metastasis, 2) a BRPC diagnosis based on National Comprehensive Cancer Network guidelines version 2.2015 (19), 3) no ascites and/or pleural effusion, 4) age ≥20 years old, 5) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, 6) peripheral sensory or motor neuropathy of grade 0-1 based on the Common Terminology Criteria for Adverse Events 4.0, 7) no prior chemotherapy or radiotherapy for malignancy, and 8) a preserved organ function (white blood cell count ≤10,000/mm^3, neutrophil count ≥2,000/mm^3, hemoglobin level ≥9.0 g/dL without blood transfusion within 7 days, platelet count ≥100,000/mm^3, serum creatinine level ≤1.2 mg/dL, serum total bilirubin level ≤1.2 mg/dL, serum aspartate transaminase and alanine transaminase levels ≤100 IU/L, serum albumin level ≥3.0 g/dL).

The exclusion criteria were as follows: 1) pulmonary fibrosis or interstitial pneumonia; 2) active double cancer; 3) serious complications, such as heart failure, bowel obstruction, and uncontrollable diabetes mellitus; 4) active infections requiring systemic therapy; 5) psychosis or severe mental disorder; 6) regular systemic steroid therapy; 7) severe drug allergy; 8) pregnant or lactating women or women of childbearing potential; and 9) men hoping to get a partner pregnant.

Study endpoints and definitions

The primary endpoint was the feasibility of 2 cycles of NAC-GnP. Feasibility was defined as the absence of the following: 1) grade 4 neutropenia persisting for more than 7 days; 2) febrile neutropenia affecting the continuation of GnP; 3) grade 4 thrombocytopenia persisting for more than 7 days; 4) grade ≥3 severe non-hematological toxicity (nausea, vomiting, diarrhea, or fatigue) not controlled by appropriate supportive care; 5) grade ≥3 severe non-hematological toxicity, excluding nausea, vomiting, diarrhea, or fatigue, affecting the continuation of GnP; and 6) treatment-related AEs deemed intolerable to radical resection after 2 cycles of GnP. If the patient's condition conflicted with these criteria, feasibility was determined after a multidisciplinary conference. Two cycles of NAC-GnP were considered feasible if at least 8 out of 10 patients met the definition of feasibility. The secondary endpoints were AEs, serious AEs, treatment-related death, response rate, R0 resection rate, and histological effects. AEs were evaluated according to the Common Terminology Criteria for Adverse Events 4.0.

Preoperative chemotherapy

Eligible patients were administered GnP. Nab-paclitaxel was administered intravenously at a dose of 125 mg/m^2 for 30 minutes, followed by intravenous administration of gemcitabine at a dose of 1,000 mg/m^2 for 30 minutes on days 1, 8, and 15 of a 28-day cycle for a total of 2 cycles. Two dose-level modifications of toxicity were allowed. The reduced doses were set at 100 mg/m^2 and 75 mg/m^2 for nab-paclitaxel, and 800 mg/m^2 and 600 mg/m^2 for gemcitabine. Nab-paclitaxel or gemcitabine monotherapy was allowed based on the physician's decision. The treatment was continued until completion of the two cycles, disease progression, the emergence of intolerable AEs, or patient refusal to continue treatment.

Surgery and adjuvant chemotherapy

Treatment efficacy within 28 days after the completion of

Table 1. Patient Characteristics.

Characteristic	n=10
Age, years	75 (40-82)
Sex, male/female	6/4
ECOG PS, n	
0	10
Primary tumour site, n	
Head	3
Body	7
Tumour size, mm	28 (11-67)
Resectability, n	
BR-A	10
Contact with CA	5
Contact with SMA	3
Contact with CHA	2
Clinical N stage, n	
0	10
Biliary drainage, n	
Yes/no	3/7
Alb, g/dL	4.0 (3.2-4.5)
CRP, mg/dL	0.42 (0.03-1.89)
CEA, mg/dL	3.8 (1.1-76.0)
CA19-9, U/mL	540 (<2-4,740)

Continuous variables are shown as medians and ranges.

ECOG PS: Eastern Cooperative Oncology Group performance status, BR: borderline resectable, A: artery, CA: celiac artery, SMA: superior mesenteric artery, CHA: common hepatic artery, Alb: serum albumin, CRP: serum C-reactive protein, CEA: serum carcinoembryonic antigen, CA19-9: serum carbohydrate antigen 19-9

NAC-GnP was evaluated using computed tomography (CT). The resection criteria after treatment were as follows: 1) no distant metastasis; 2) R0 or R1 resection was possible by pancreatectomy; 3) tolerable pancreatectomy; and 4) no distant metastasis at laparotomy or staging laparoscopy. Staging laparoscopy was not mandatory. Pancreatectomy was performed via laparotomy. Radical resection was performed 7-42 days after the last GnP dose. When R0 or R1 resection was achieved, 6-month S-1 was started within 10 weeks after radical resection if the patient's condition allowed.

Evaluations

The diagnosis of BRPC was confirmed by CT within four weeks before enrolment. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were also measured within four weeks before enrolment. As mentioned above, CT was performed after the completion of GnP. Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1. RR was defined as the proportion of patients who experienced a complete response (CR) or partial response (PR). Furthermore, CEA and CA19-9 levels were measured after completion of GnP and before surgery.

Surgical complications were evaluated using the Clavien-Dindo classification (20). The postoperative pathological response to GnP was evaluated using the Evans classification (21). Before the initiation of S-1 as adjuvant chemotherapy, the absence of recurrence was confirmed by CT within four weeks. In addition, CEA and CA19-9 levels were measured within four weeks before initiating S-1. If S-1 was initiated, CT and CEA and CA19-9 measurements were performed every three months.

Statistical analyses

The planned sample size for this study was 10 patients. Although this sample size was not significant, we considered it to be sufficient to evaluate the feasibility of NAC-GnP, as GnP is widely used in patients with unresectable PC. If NAC regimen was already widely used in unresectable settings, the feasibility can be evaluated in about 10 patients (22). This was the reason why sample size of this study was set 10 patients. The progression-free survival (PFS) was measured from the date of study enrolment to the date of disease progression, recurrence, or any-cause death. The OS was measured from the date of enrolment to the date of death any-cause death. If progressive disease, disease recurrence, or death was not confirmed, patients were censored for the PFS and OS at the last date of confirmation of no events. The PFS and OS were calculated using the Kaplan-Meier method.

All statistical analyses were performed using the statistical software package SPSS version 22.0 for Windows (IBM, Armonk, USA).

Results

Patient characteristics

Ten patients (six men and four women) with an ECOG PS of 0 were enrolled. The patient characteristics are shown in Table 1. The median patient age was 75 (range, 40-82) years old. The primary tumor site was the body of the pancreas (70%). Arterial contact was observed in all primary tumors. The median tumor size was 28 (range, 11-67) mm. The median CA19-9 value was 544.8 (range, <2.0-4742.2) U/mL.

Feasibility

The feasibility outcomes are presented in Table 2. Two-cycle NAC-GnP was not feasible in two patients. Although patient 3 (a 76-year-old woman) was indicated for radical surgery because of a 58% reduction in the primary tumor volume after 2 cycles of NAC-GnP, she developed grade 3 anorexia on day 35 of cycle 2. She developed duodenal stenosis due to tumor progression during hospitalization. Patient 10 (a 78-year-old man) developed grade 2 pneumonitis on day 15 of cycle 2. Although his pneumonitis recovered without treatment, he developed bone metastasis on day 56 of cycle 2. Overall, NAC-GnP was considered feasible because 8 of 10 patients met the definition of feasibility.

Table 2. Summary of Feasibility Outcomes.

Patient no.	Age, years	Primary tumour site	Tumour size at enrolment, mm	Primary tumour reduction, %	Response	CA19-9 at enrolment, U/mL	CA19-9 after NAC, U/mL	CA19-9 change from enrolment, %	Tolerability	Re-staging/ surgery
1	60	Head	41	68	PR	197.5	30.6	-85	Yes	R1 resection
2	40	Body	45	20	SD	2.9	<2.0	-	Yes	Presence of liver metastasis at laparotomy
3	76	Head	26	58	PR	4,742.2	680.4	-86	No	
4	77	Body	20	30	PR	<2.0	<2.0	-	Yes	Technically unresectable
5	76	Head	28	46	PR	551.4	63.5	-88	Yes	R0 resection
6	74	Body	28	4	SD	1,426.3	302.0	-79	Yes	R0 resection
7	82	Body	28	10	PD	436.0	537.1	+23	Yes	Progressive disease at re-staging after NAC
8	70	Body	67	0	SD	653.8	234.4	-64	Yes	R0 resection
9	73	Body	26	42	PR	692.3	322.2	-53	Yes	R0 resection
10	78	Body	11	36	PR	538.2	654.9	+22	No	

CA19-9: serum carbohydrate antigen 19-9, NAC: neoadjuvant chemotherapy, PR: partial response, SD: stable disease, PD: progressive disease

Table 3. Treatment-related Adverse Events (n=10).

	Any grade, %	Grade 3/4, %
Hematological toxicities		
Neutrophil count decreased	90	80
White blood cell decreased	90	60
Anaemia	80	0
Decreased platelet count	50	10
Febrile neutropenia	-	20
Non-hematological toxicities		
Alopecia	100	-
Anorexia	60	20
Rash	50	0
Malaise	40	-
Fever	40	0
Nausea	30	10
Diarrhea	30	0
Mucositis	20	0
Constipation	20	0
Dysgeusia	20	-
Peripheral sensory neuropathy	20	0
Arthralgia	10	0
Pneumonitis	10	0
Enterocolitis infections	0	10

AEs and efficacy

Treatment-related AEs (TRAEs) are summarized in Table 3. The most common TRAEs were decreased white blood cell and neutrophil counts, anemia, alopecia, and anorexia. Febrile neutropenia occurred in two patients. Serious TRAEs occurred in one patient (grade 3 anorexia). No treatment-related deaths occurred during the study period.

Waterfall plots for the response to NAC-GnP are shown in Figure. The RR and disease control rate (DCR) were 60% and 90%, respectively. The median primary tumor reduction rate was 33% (range, 0-68%). Eight patients had abnormal CA19-9 levels at the time of enrolment. Among them, the median CA19-9 change was -72% (range, -88% to 23%). Overall, six of the eight patients showed a decrease in CA 19-9 levels (Table 2).

Surgery and the survival

A summary of the patients who underwent resection is shown in Table 4. Overall, 5 of the 10 patients underwent resection, with 4 and 1 patient achieving R0 and R1, respectively. The Evans classification was 1 for grade IIa and 4 for grade I. Postoperative grade IIIa Clavien-Dindo complications occurred in one patient; this patient developed upper gastrointestinal bleeding and pancreatic fistula.

At the data cut-off (October 2021), all patients who underwent resection (n=5) had relapse, and 7 out of 10 patients died. The median follow-up period was 14.7 (range, 5.6-46.0) months. The median OS was 9.0 [95% confidence interval (CI), 0.0-29.0] months in all enrolled patients in this study. The median PFS was 8.2 (95% CI, 6.6-9.9) months, and the median OS was 30.4 (95% CI, 14.9-45.8) months in patients who underwent resection.

Discussion

Neoadjuvant GnP therapy is promising as an optimal multidisciplinary strategy for BRPC owing to its high anti-tumor effect, but evidence concerning its feasibility is still lacking. In this study, although 2 of the 10 patients developed grade 3 anorexia and grade 2 pneumonitis, the definition of prespecified feasibility was met, indicating the feasibility of 2-

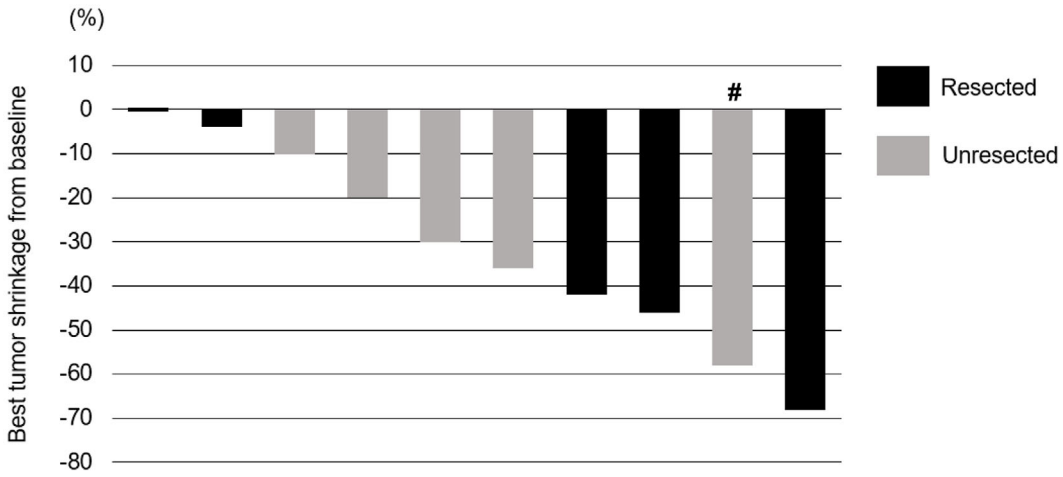

Figure. **Waterfall plot of radiological tumor response to neoadjuvant gemcitabine plus nab-paclitaxel. The response and disease control rates are 60% and 90%, respectively. The median primary tumor reduction rate is 33% (range, 0-68%). # Although radical surgery was indicated in this patient because of a 58% reduction in the primary tumor volume after 2 cycles of neoadjuvant gemcitabine plus nab-paclitaxel (NAC-GnP), she did not undergo laparotomy due to grade 3 anorexia, which was attributed to intolerance to 2 cycles of NAC-GnP.**

Table 4. **Clinicopathological Findings and Survival Outcomes (n=5).**

Patient no.	R status	T stage	N stage	Vessel resection	Evans classification	Postoperative complications (≥Grade IIIa C-D classification)	Adjuvant chemotherapy	PFS, months	OS, months	Outcome
1	R1	T4	N1	Common hepatic artery	Grade I	None	S-1	13.9	30.4	Dead
5	R0	T4	N0	Portal vein	Grade I	Upper gastrointestinal bleeding Pancreatic fistula	None	31.1	46.0	Alive
6	R0	T3	N1	None	Grade I	None	S-1	8.2	21.9	Alive, lost to follow-up
8	R0	T3	N1	None	Grade I	None	S-1	7.5	20.5	Dead
9	R0	T3	N0	None	Grade IIa	None	S-1	7.0	7.5	Dead

C-D: Clavien-Dindo, PFS: progression-free survival, OS: overall survival

cycle NAC-GnP for patients with BRPC. Two cycles of NAC-GnP achieved tumor reduction in most patients (n=9, including 6 patients with ≥30% primary tumor shrinkage). The RR and DCR were 60% and 90%, respectively. Furthermore, among the 8 patients with high CA19-9 levels at enrollment, 6 showed a decrease after treatment, with the CA 19-9 decrease ranging from 53% to 88%. Collectively, these results indicate the promising efficacy of NAC-GnP in patients with BRPC. To our knowledge, this is the first study on NAC-GnP for BRPC in which the feasibility of NAC-GnP was defined in the protocol.

A previous prospective study evaluated the safety and feasibility of NAC-GnP, but the sample size was small, and the definition of feasibility was lacking (23). In the MPACT trial and Japanese phase I/II trials, the most common TRAE of GnP in metastatic PC was neutropenia, with grade 3 and 4 neutropenia occurring in 38% and 70.6%, respectively (14, 16). The proportion of grade 3-4 neutropenia in our study was similar to that in a Japanese phase I/II trial, and no new AEs occurred. Furthermore, two cycles of NAC-GnP did not have a negative effect on the postoperative course.

Two retrospective studies (24, 25) that compared NAC-GnP and upfront surgery for BRPC also showed no negative impact on the postoperative course. The incidence of Clavien-Dindo ≥grade IIIa complications ranged from 11% to 14% in the NAC-GnP group and 15% to 18% in the upfront surgery group (24, 25). In a phase I trial of NAC-GnP in patients with BRPC, 2 of 8 (25%) patients had Clavien-Dindo ≥grade IIIa morbidity (23). Similarly, 1 of 5 (20%) patients in the current study developed Clavien-Dindo ≥grade IIIa morbidity. One of these morbidities was gastrojejunal anastomotic ulcer that led to upper gastrointestinal bleeding on day 40 after subtotal stomach-preserving pan-

creatoduodenectomy (SSPPD). Gastrojejunal anastomotic ulcer is widely recognized as a cause of morbidity after SSPPD (26). Furthermore, this occurred after about two months after the last GnP dose. Therefore, we consider upper gastrointestinal bleeding not to be a GnP-related AE.

This study provides important information regarding the safety of NAC-GnP in patients with BRPC. In total, a high proportion of patients (8 of 10) were ≥70 years old. The incidence of PC increases with aging. In Japan, an aging country, approximately 60% of all patients who died of PC in 2019 were ≥75 years old (27). Therefore, physicians need an optimal strategy for the treatment and management of chemotherapy in elderly patients with PC. Although the MPACT trial also included patients >75 years old who received GnP for metastatic PC included, they only accounted for 10% of the trial population (14).

Furthermore, patients >75 years old were not included in the Japanese phase I/II trial (16). This means that the efficacy and safety of GnP in patients >75 years old remains unclear. Therefore, physicians should carefully consider patient selection and management of AEs associated with GnP in patients >75 years old in this setting. In the present study, 2 patients who did not meet the definition of feasibility were elderly patients >75 years old. However, grade 2 pneumonitis was not associated with age. Furthermore, 3 patients, including a patient >80 years old, were eligible for 2 cycles of NAC-GnP. The efficacy and safety of neoadjuvant treatment in elderly patients with PC should be investigated in larger populations.

Nab-paclitaxel treatment depletes the desmoplastic stroma (28) and softens the primary lesions of PC (29), thus allowing easier resection. Therefore, we considered GnP as a promising regimen for patients with BRPC. Indeed, two retrospective studies that compared NAC-GnP and upfront surgery in patients with BRPC reported promising results of NAC-GnP (24, 25). Although our study demonstrated efficacy, with a median primary tumor reduction rate of 33% (range, 0-68%), the resection rate of 50% is lower than in other prospective studies that reported resection rates of 56-80% after neoadjuvant treatment in patients with BRPC (10, 23, 30-33).

All patients in this study had BR-A; in contrast, the proportion of BR-A patients in previous studies was 37% in a Korean trial, 80% in a phase I trial of NAC-GnP for BRPC, and 85% in the JASPAC05 trial, which was a single-arm, phase II study that evaluated S-1 plus radiation followed by surgery. The resection rate of BR-A is lower than that of BR-PV (34). Therefore, a comparison between these studies is difficult. In addition, the histological effects may have been insufficient. We speculate that the treatment duration may affect the pathological response. Although we selected two cycles because the median time to response was 43.0 days in the Japanese phase I/II trial in patients with metastatic PC (16), the optimal duration of NAC-GnP in patients with BRPC remains controversial.

To improve the prognosis of this challenging disease, the optimal neoadjuvant treatment (NAT) regimen and duration should be explored. Delayed resection can decrease the chance of remission. Short-duration NAT, such as the two-cycle approach adopted in the current study, may help avoid missing the chance to achieve remission. Conversely, some patients may experience benefits, such as an increased R0 resection rate, thereby improving the pathological effects of long-duration NAT. Other patients may be able to avoid early recurrence caused by micrometastasis. This may prevent patients from undergoing unnecessary pancreatectomy. An evaluation of circulating tumor DNA may help resolve the dilemma of NAT duration. Circulating tumor DNA as assessed with a liquid biopsy may aid in the diagnosis of occult metastasis and the monitoring of the response to NAT (35). As a result, optimal patient selection for pancreatectomy will be possible in patients with BRPC.

At present, the optimal NAT regimen has not yet been established. The differences in the efficacy between FOLFIRINOX and GnP need to be evaluated in a randomized controlled trial in patients with BRPC. Furthermore, the role of concurrent or subsequent radiotherapy merits further investigation in patients with BRPC. A phase I trial of GnP and subsequent GnP with concurrent radiation for BRPC has shown promising efficacy, with a resection rate of 74%, R0 resection rate of 96%, and a destruction rate of ≥90% of tumor cells of 38% (36).

Several limitations associated with the present study warrant mention. First, this was a single-center study with a small sample size. Second, the diagnosis of borderline-resectable tumors was not evaluated in the central review. The JASPAC05 trial demonstrated the importance of a central review, as the diagnosis in 11 of 52 (21%) patients was converted to locally advanced PC by a central review (33). Although we discussed resectability in multidisciplinary teams, including radiologists, non-resected patients and those with metastatic PC in this study had an extremely poor prognosis. Finally, although the protocol of this study set radical resection to be performed at 7-42 days after the last GnP dose, patients actually underwent radical resection after at least 14 days had passed since the final GnP dose. Therefore, the safety of radical resection within two weeks cannot be established.

In conclusion, a two-cycle NAC-GnP modality is feasible in patients with BRPC. Further studies on NAC-GnP in patients with BRPC, including the elderly, are warranted.

Author's disclosure of potential Conflicts of Interest (COI).

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