Benefits of neoadjuvant chemotherapy with gemcitabine plus S-1 for resectable pancreatic ductal adenocarcinoma

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Abstract. Currently, neoadjuvant chemotherapy (NAC) is usually performed even for resectable pancreatic ductal adenocarcinoma (rPDAC). The present study investigated the benefits of NAC with gemcitabine plus S-1 for rPDAC. The medical records of 170 patients diagnosed as having rPDAC based on preoperative imaging were reviewed retrospectively. Clinicopathological factors in the NAC group were compared with those in the upfront surgery (UpS) group. NAC was administered to 30 of the 170 patients. The period from first visit to treatment in the NAC group was shorter than that in the UpS group (P<0.001). Staging laparoscopy detected occult distant metastases in 12 of the 170 patients (7%), of whom all 12 were in the UpS group. All patients in the NAC group underwent surgical resection (P=0.028). Among the 158 patients who underwent pancreatectomy, the NAC group showed rapid induction of the treatment, non-inferior operative outcomes and a higher R0 rate compared with the UpS group. Rates of early recurrence (within 6 months) after surgery were 10% (3/30) in the NAC group and 29% (37/128) in the UpS group (P=0.021). NAC for rPDAC is beneficial in terms of rapid induction of the treatment, fewer occult metastases, and lower rate of early recurrence.

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Abbreviations: NAC, neoadjuvant chemotherapy; PDAC, pancreatic ductal adenocarcinoma; UpS, upfront surgery; SL, Staging laparoscopy; Gemcitabine plus S-1; CT, computed tomography; OR, odds ratio; CI, confidence interval; PR, partial response; SD, stable disease; GnP, gemcitabine plus nab-paclitaxel

Key words: pancreatic ductal adenocarcinoma, neoadjuvant chemotherapy, pancreatectomy, staging laparoscopy, distant metastasis

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis with an overall 5-year survival rate of 8% (1). Radical resection is currently the only treatment that can increase the 5-year rate of survival to 10-25% (2-5). However, only around 20% of patients suffering from PDAC are suitable candidates for radical resection at the time of diagnosis due to the lack of early symptoms or to its aggressive nature (4,6).

Because of the poor prognosis even in the patients with resectable PDAC (rPDAC), adjuvant chemotherapy has commonly been performed. Its introduction has improved prognosis and is one of the factors mainly associated with long-term survival. Despite the use of the most effective regimens, such as modified FOLFIRINOX, the recurrence rate of the disease still remains high, with a disease-free survival rate at 5 years of only 26.1% (7). This poor outcome can be caused by early recurrence and the significantly higher rate of an incomplete resection compared to resection for other gastrointestinal cancers. Therefore, effective neoadjuvant chemotherapy (NAC) is being sought for patients with rPDAC. The results of various randomized controlled trials of NAC for rPDAC such as NEONAX (8), SWOG S1505 (9), and the NORPACT-1 study (10) have been reported. In Japan, the Prep-02/JSAP05 trial was the first to show a survival benefit of NAC with gemcitabine plus S-1 (GS) in patients with resectable PDAC, and NAC-GS is now the standard regimen for rPDAC in Japan (11,12). Nevertheless, as it remains controversial whether NAC is actually required for rPDAC (13), the importance of NAC and whether NAC-GS is appropriate therapy for rPDAC require examination.

Staging laparoscopy (SL) has been shown to identify small peritoneal or liver metastases not observed in preoperative imaging (14,15). For patients with distant occult metastases, SL is more beneficial than exploratory laparotomy due not only to its lower invasiveness but also rapid patient recovery, which consequently leads to early induction of chemotherapy (15,16). Therefore, it is meaningful to identify the patients at possible risk of distant metastasis from PDAC.

Therefore, the aim of this study was to investigate the benefits of NAC for patients with rPDAC.

Patients and methods

Study population. In total, 170 patients who were diagnosed as having rPDAC preoperatively at the Oita University Faculty of Medicine from May 2005 to August 2023 were enrolled in this study. Patient characteristics were retrospectively collected from the patients' charts. This study was approved by the Ethics Committee of Oita University Faculty of Medicine (approval number: 1502). The need for written informed consent was waived owing to the retrospective nature of the study.

Preoperative evaluation of PDAC with computed tomography (CT). According to general rules for the study of pancreatic cancer edited by the Japan Pancreas Society (17), rPDAC was defined on CT imaging as no contact with the major arteries (celiac axis, superior mesenteric artery, or common hepatic artery), and no contact with the superior mesenteric vein or portal vein or ≤ 180˚ contact without vein contour irregularity. When a spicula-like protrusion was observed toward the surrounding fat tissue of the pancreas beyond the anterior or posterior pancreatic capsule, it was classified as either invasion of the serosal side of the anterior pancreatic tissue or invasion of retroperitoneal tissue. Extrapancreatic invasion of the nerve plexus was diagnosed when a continuous lesion surrounding the celiac artery or superior mesenteric artery was observed. These invasions, except for the major vascular invasion mentioned above, are diagnosed as rPDAC according to these general rules.

Neoadjuvant chemotherapy. Until 2019, all patients who were diagnosed as having rPDAC preoperatively underwent upfront surgery (UpS). NAC was started from 2020 for all patients diagnosed as having rPDAC preoperatively, and all patients were treated with GS (intravenous gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8 plus S-1 orally at a dose based on body surface area (BSA) (<1.25 m^2, 40 mg; BSA 1.25-1.5 m^2, 50 mg; BSA >1.50 m^2, 60 mg) twice daily on days 1-14 of a 21-day cycle). The patients were divided into two groups: the UpS group and the NAC group, and their selection was determined by the period in which the treatment was performed. Tumor response was assessed preoperatively according to RECIST version 1.1. by CT. For pathological assessment, grading of the extent of residual carcinoma in specimens was performed according to the grading scheme reported by Evans *et al* (18), which is based on the percentage of residual tumor cells present.

Staging laparoscopy. SL was performed for all patients at the beginning of the surgery intended for resection. When occult distant metastases were detected, the metastatic lesions were examined for a diagnosis by a pathologist (19). Fig. 1 shows the treatment strategy and examinations of this study.

Statistical analyses. All variables are expressed as the mean±standard deviation for continuous data. Prior to analysis, continuous data were divided into two groups using averages or abnormal values. Univariate analyses were performed with the Student *t*-test for continuous variables and the chi-squared test for categorical variables. Statistical significance was defined as P<0.05. All statistical analyses were performed using JMP 17 (SAS Institute Inc., Cary, NC, USA). There were no missing data for the factors examined in the 170 patients in this study, and all were eligible for inclusion.

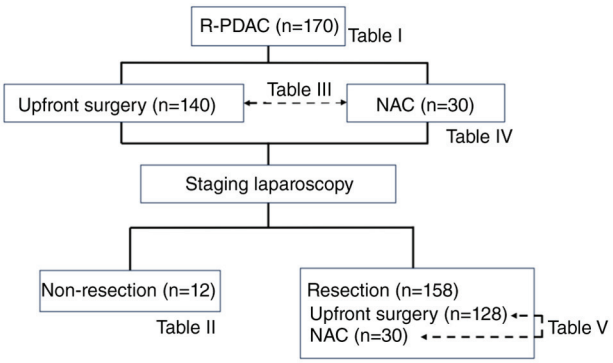

Figure 1. Treatment strategy and examinations of the present study. R-PDAC, resectable pancreatic ductal adenocarcinoma; NAC, neoadjuvant chemotherapy.

Results

Patient characteristics. The mean age of the 66 women and 104 men was 70.7±8.6 years (Table I). Tumors were located at the pancreatic head in 89 patients (52%) and in the pancreatic body and tail in 81 (48%), and the mean tumor size was 24.6±10.4 mm. Among the 170 patients receiving SL, occult distant metastases were found in 12 patients (7%), with peritoneal dissemination recognized in 7 patients, liver metastases in 4, and both in 1 (Table II). The remaining 158 patients (93%) were diagnosed as having rPDAC, and these patients were assigned to undergo resection.

Comparison of pre-treatment clinical and imaging factors between the UpS and NAC groups for all patients. Preoperative and imaging factors of the UpS group and NAC group are shown in Table III. There were no significant differences in patient characteristics and blood test data between the two groups. The period from the first visit to treatment in the NAC group was shorter than that in the UpS group (P<0.001). There were no significant differences between the imaging factors. All patients with occult distant metastases diagnosed by SL were in the UpS group, and all patients in the NAC group underwent resection (P=0.028).

Comparison of tumor-related factors before and after NAC. All patients received GS therapy, and one patient received gemcitabine plus nab-paclitaxel (GnP) after GS (Table IV). Tumor size and CA19-9 level decreased after NAC, but the differences were not significant. In the preoperative imaging evaluation, 4 patients had a partial response (PR) and 26 had stable disease (SD). All patients underwent surgery, and the numbers of patients with pathological responses of 1a, 1b, 2, and 3 were 7, 18, 3, and 2, respectively.

Comparison of perioperative factors between the UpS and NAC groups in the 158 patients undergoing resection. There were no significant differences in patient characteristics and blood test data between the two groups (Table V). The period from the first visit to treatment in the NAC group was shorter than that in the

Table I. Patient characteristics (n=170).

Characteristics	Value
Preoperative factors	
Age, years	70.7±8.6
Sex (female/male)	66 (39%)/104 (61%)
Body mass index, kg/m^2	22.6±4.0
Serum albumin, g/dl	4.0±0.5
HbA1C, %	6.8±1.4
CEA, ng/ml	4.7±5.8
CA19-9, U/ml	691±1811
Period from first visit to treatment, days	22.9±12.5
Radiological findings	
Tumor location (Ph/Pbt)	89 (52%)/81 (48%)
Tumor size, mm	24.6±10.4
Serosal side of the anterior pancreatic tissue invasion, (-/+)	42 (25%)/128 (75%)
Retroperitoneal tissue invasion, (-/+)	58 (34%)/112 (66%)
Extrapancreatic nerve plexus invasion, (-/+)	132 (78%)/38 (22%)
Contact with portal vein, (-/+)	157 (92%)/13 (8%)
Lymph node metastasis, (-/+)	130 (76%)/40 (24%)
Treatment	
Neoadjuvant chemotherapy, (-/+)	140 (82%)/30 (18%)
Operation (resection/non-resection)	158 (93%)/12 (7%)

HbA1c, hemoglobin A1c; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; Ph, pancreatic head; Pbt, pancreatic body and tail.

Table II. Characteristics of patients with unresectable PDAC diagnosed by staging laparoscopy (n=12).

Characteristics	Value
Metastatic site	
Peritoneal dissemination	7
Liver metastasis	4
Peritoneal dissemination and liver metastasis	1
Operation	
SL	8
SL and gastrojejunostomy	1
SL and colostomy	2
Operation time, min	96±35
Blood loss, ml	0
Postoperative complications	
Gastritis	1
Pancreatitis	1
Postoperative hospital stay, days	12.9±6.8
Duration between SL and induction of chemotherapy, days	11.8±4.4

PDAC, pancreatic ductal adenocarcinoma; SL, staging laparoscopy.

UpS group (P<0.001). Operative outcomes in the NAC group were not inferior to those in the UpS group. Pathological examination showed the pancreatic cut end margin and dissected peripancreatic tissue margin to be negative in all NAC cases, indicating that all cases were R0 resections in the NAC group. The rates of early recurrence within 6 months after surgery were 10% (3/30) in the NAC group and 29% (37/128) in the UpS group (P=0.021).

Discussion

The survival benefits of UpS and adjuvant therapy for rPDAC remain limited, but NAC may result in an improved outcome. NAC offers the following advantages over UpS: elimination of micro-metastases before surgery and a high tolerance rate among patients. These advantages can contribute to improvement in the rate of negative margin resection, reduced nodal involvement, and better survival. However, there are two concerns regarding this approach: risk of tumor progression and toxicities during NAC. Furthermore, NAC-related adverse events could worsen the patient's condition, thereby delaying surgery and potentially depriving them of a chance for a cure.

In this patient series, NAC-GS was started from 2020 for all patients diagnosed as having rPDAC preoperatively, and all patients were treated with GS. We compared UpS and NAC and found that the NAC group showed early delivery of the therapy and no unresectable conditions after NAC. All 12 patients in whom SL revealed occult distant metastases were treated with UpS. Furthermore, NAC did not appear to reduce the complexity of the surgery and showed a high rate of R0 resection. Compared with UpS, NAC was not inferior in terms of perioperative factors, and importantly, the rate of recurrence-free survival at 6

Table III. Clinical and imaging factors before treatment with UpS and NAC in all cases.

Factor	UpS (n=140)	NAC (n=30)	P-value
Preoperative factors			
Age, years	70.8±9.0	70.5±6.5	0.895
Sex (female/male)	55/85	11/19	0.789
Body mass index, kg/m^2	22.5±4.1	22.8±3.7	0.775
Serum albumin, g/dl	4.0±0.5	4.0±0.5	0.345
HbA1C, %	6.8±6.7	6.7±1.1	0.686
CEA, ng/ml	4.9±6.2	4.2±2.9	0.565
CA19-9, U/ml	684±1888	696±1390	0.976
Period from first visit to treatment, days	25.2±11.6	12.7±11.0	<0.001
Imaging findings			
Tumor location (Ph/Pbt)	78/62	11/19	0.057
Tumor size, mm	24.2±10.7	26.4±8.7	0.325
Serosal side of the anterior pancreatic tissue invasion, (-/+)	37/103	5/25	0.244
Retroperitoneal tissue invasion, (-/+)	52/88	6/24	0.062
Extrapancreatic nerve plexus invasion, (-/+)	105/35	27/3	0.055
Contact with portal vein, (-/+)	132/8	25/5	0.063
Lymph node metastasis, (-/+)	105/35	25/5	0.314
Treatment			
Operation (resection/non-resection)	128/12	30/0	0.028

HbA1c, hemoglobin A1c; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; Ph, pancreatic head; Pbt, pancreatic body and tail; UpS, upfront surgery; NAC, neoadjuvant chemotherapy.

Table IV. Tumor-related factors before and after NAC.

Factor	Number	Before NAC	After NAC	P-value
Regimen (GS/GS→GnP)	29/1			
Tumor size, mm		27.7±9.6	25.7±9.1	0.406
Serum albumin, g/dl		4.0±0.5	3.8±0.5	0.138
CEA, ng/ml		4.2±2.9	4.3±3.2	0.855
CA19-9, U/ml		696±1389	288±787	0.167
Imaging evaluation (CR/PR/SD/PD)	0/4/26/0			
Pathological evaluation (1a/1b/2/3)	7/18/3/2			

GS, gemcitabine plus S1; GnP, gemcitabine plus nab-paclitaxel; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NAC, neoadjuvant chemotherapy.

months was significantly lower with NAC. These results suggest that NAC-GS may be a suitable regimen for rPDAC, although the response rate of NAC-GS was relatively low.

Some randomized controlled trials for NAC have been reported. The NEONAX study (8) showed an R0 resection rate of 88% and median OS of 25.5 months in the patients who were treated with GnP, whereas NAC could not be shown to prolong RFS, which was the primary endpoint. SWOG S1505 (9) reported the short-term outcome of patients who were treated with modified FOLFIRINOX or GnP. This report showed a high tolerance to these systemic therapies by the patients, successful surgical resection without prohibitive perioperative complications, and a major pathologic response rate of 33%. Immunotherapy using pembrolizumab in NAC has also been reported, and no additive effects were shown (20). Randomized ongoing trials are eagerly awaited with more active combined regimens including modified FOLFIRINOX (21).

Our study showed that occult distant metastases were still found in 7% of the patients with PDAC when performing SL. It is difficult to predict unresectable cases preoperatively, and we reconfirmed the benefit of SL for the patients potentially having rPDAC. SL has a precise effect in identifying patients with unsuspected unresectable lesions and, therefore, in decreasing the number of unnecessary laparotomies. Stefanidis *et al* reported that SL could identify unsuspected metastases in a significant proportion of patients (15-51%) (22). Karabicak *et al* also

Table V. UpS vs. NAC in the resected cases.

Parameter	UpS (n=128)	NAC (n=30)	P-value
Patient characteristics			
Age, years	70.9±8.9	70.5±6.5	0.822
Sex (female/male)	76/52	19/11	0.689
Body mass index, kg/m^2	22.5±4.2	22.8±3.7	0.771
Serum albumin, g/dl	4.0±0.5	3.7±0.5	0.011
HbA1C, %	6.8±1.5	6.7±1.1	0.679
CEA, ng/ml	4.9±6.4	4.2±2.9	0.538
CA19-9, U/ml	695±1936	696±1390	0.999
Period from first visit to treatment, days	26±12	13±11	<0.001
Operation			
Open/laparoscopy	113/15	17/13	0.000
PD/DP/TP	75/50/3	11/18/1	0.145
Operation time, min	444±124	395±126	0.056
Blood loss, ml	830±707	440±399	0.004
Postoperative course			
POPF (≥grade B)	16 (13%)	2 (7%)	0.338
Postoperative hospital stay, days	29±18	20±20	0.031
Pathological findings			
Tumor size, mm	30.3±12.9	26.1±9.7	0.094
UICC T stage (1/2/3)	27/78/23	8/20/2	0.241
LN metastasis (-/+)	58/70	16/14	0.429
PCM (-/+)	122/6	30/0	0.108
DPM (-/+)	113/15	30/0	0.010
Early recurrence (≤6 months) after surgery	37 (29%)	3 (10%)	0.021

HbA1c, hemoglobin A1c; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; POPF, postoperative pancreatic fistula; LN, lymph node; PCM, pancreatic cut end margin; DPM, dissected peripancreatic tissue margin; NAC, neoadjuvant chemotherapy; UpS, Upfront surgery.

reported that occult distant metastases could be detected by SL in 20% of patients with PDAC although the diagnostic accuracy of CT has improved (23). Therefore, SL is a valuable option for PDAC staging. Nevertheless, some reports noted that SL was not recommended in all cases for two reasons: the number of occult cancers detected by SL has decreased due to the increased sensitivity of CT, and the cost-effectiveness of SL (24,25). However, some papers supported the cost-effectiveness of SL (26,27). In their recent guidelines, the Japan Pancreas Society also recommended performing SL when distant metastasis cannot be ruled out in patients with resectable or locally advanced pancreatic cancer (28). De Rosa *et al* reviewed 24 studies to try to identify indications for SL (29) and concluded that patients with rPDAC identified by CT and who have a CA19-9 level ≥150 U/ml or tumor size >3 cm should be considered for SL.

The limitations of this study include its retrospective study design and small number of patients. Thus, it will be necessary to examine long-term outcomes to further clarify the significance of NAC-GS administration.

In conclusion, surgery after NAC can be performed safely, and NAC for rPDAC is useful in terms of rapid induction of the treatment, fewer occult distant metastases, and lower rate of early recurrence.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TH, KT, YN, HO, MK, AF, HT, YK, TM, YE and MI substantially contributed to the conception and design of the study and performed the acquisition of data for the study. TH and KT performed analysis and interpretation of the data and drafted the manuscript. MI contributed to the review and/or critical revision of the article. Each author has participated sufficiently in the work to be considered an author and agrees to be accountable for all aspects of the work by ensuring that questions related to the

accuracy or integrity of any part of the work are appropriately investigated and resolved. TH and KT confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Oita University Faculty of Medicine (approval no. 1502).

Patient consent for publication

The need for written informed consent was waived owing to the retrospective nature of the study.

Competing interests

The authors declare that they have no competing interests.

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