exclude disease progression and to assess resectability. Relative dose intensity (RDI) for each individual drug was calculated and defined as the dose intensity achieved relative to the standard schedule of each drug.

Resectability and surgery

After NAC, patients who demonstrated potentially or borderline resectability without newly detected distant metastases were referred for R0-directed pancreatectomy. After the exploration and confirmation of resectability, subtotal-stomach-preserving pancreatoduodenectomy (SSPPD) for neoplasm in the head lesion or distal pancreatectomy (DP) for neoplasm in the body or tail was performed. A subtotal-stomach-preserving total pancreatectomy (SSPTP) was performed for the neoplasm extending from the head to body. When the tumor was not separable from the superior mesenteric artery or aorta, the case was considered to be unresectable. For neoplasm infiltrating the portal vein (PV), en bloc vascular resection was performed. For neoplasm in the body or tail involving the common hepatic artery, en bloc celiac axis resection (DP-CAR) was performed (24).

Assessment of treatment responses and surgical outcomes

Radiographic responses were determined by a comparison of pretreatment MD-CT and preoperative scans. Response Evaluation Criteria in Solid Tumors (RECIST) were used to assess the type of response (25, 26). Serum tumor marker response was determined by a comparison of pretreatment and preoperative levels of carbohydrate antigen 19–9 (CA19-9) values. In the case of biliary obstruction, pretreatment bilirubin level was recorded as the total-bilirubin level < 3.0 mg/dL after biliary drainage. Post-resection level of tumor marker was also measured within 2 months after operation to evaluate for post-resectional normalization.

Information regarding surgery after the completion of the protocol included the type of operation, the duration of the operation, estimated blood loss, complications, and the 30-day

mortality rate. Designated pathologists at each institution examined resected specimens, and their review included the size of the primary tumor, resection margins, and lymph node status. Tumor grade and stage were reported according to the American Joint Committee on Cancer (AJCC) staging manual (27). Pathological response by the chemotherapy was evaluated by central review according to the classification reported by Evans et al. (28).

Survival

Patient follow-up was performed by MD-CT every 2 months and serum tumor marker level every month after resection. Patients not undergoing operation or resection were followed at the treating institutions or by their primary physicians.

Statistics

In this single-arm, phase II trial, the primary endpoint was 2-year survival rate. The study was designed to detect an increase in the 2-year survival rate from 25% expected NAC to 45%, with a one-sided alpha of 5% and a power of 80%. Secondary endpoints were the resectability, histological and tumor marker response, and disease-free survival. Both the 2-year survival rate and the disease-free survival were estimated according to the Kaplan-Meier method. Variables were compared with the Student t-test using JMP software ver. 10.0.

RESULTS

Patient characteristics

Of the 36 patients enrolled, 35 were eligible for participation in this clinical trial. One ineligible case had distant metastases that were discovered after study enrollment (Figure 1). Feasibility of NAC was assessed in 35 patients, and patient demographics are shown in Table 1A. The treating surgeon determined the initial assessment of resectability, with subsequent confirmation by the central reviewer (F. M.). Among all eligible cases, 19 patients (54%) were considered to have resectable disease and 16 patients (46%) were considered to have borderline disease, according to our criteria, which were similar to those of the National Comprehensive Cancer Network guidelines (29).

Dose intensity and toxicity

Of 35 eligible patients, 30 (86%) received two planned cycles of NAC. Five patients required termination of NAC, including two patients who were limited to 0.5 cycles due to grade 3 skin rash and three patients who were limited to 1.5 cycles due to gastritis or cholangitis. Dose reduction was required in three patients because of grade 4 neutropenia. Mean RDI of gemcitabine and S-1 was 92.2% and 96.5%, respectively.

All eligible patients were assessable for adverse events. NAC-related toxicities are listed in Table 1B. Four patients developed grade 3 skin rash, and NAC was early terminated in two of these patients. Other grade 3 non-hematological toxicities included cholangitis and gastritis, which required treatment interruption. The most common non-hematological toxicities were elevations in aminotransferases. In terms of hematological toxicity, neutropenia (63%) and leukopenia (49%) were commonly noted. Three patients who experienced grade 4 neutropenia required dose reduction of gemcitabine. One patient developed grade 3 thrombocytopenia. All patients recovered, and there was no treatment-related death in the preoperative period.

Radiologic tumor response

Of the 35 patients, 33 had data pairs for baseline and post-NAC follow-up MD-CT available for centralized review. In one patient, tumor size was not measureable due to an inability to radiologically identify the border of the tumor. Of the remaining 32 patients with evaluable CTs, the estimated median pre-treatment size of the tumor was 25 mm, ranging from 12 to 70 mm. Partial response was documented in six patients (19%) as determined by RECIST of the pre- and post-NAC. The other 26 patients had stable disease. There was no progressive disease (PD) documented radiologically. A waterfall plot of the response to characterize antitumor activity showed that 22 patients (69%) had some degree of tumor shrinkage (Figure 2A).

Tumor marker response

Of 35 patients, 33 had data pairs for baseline and post-NAC serum tumor marker levels. Of 33 patients, 27 patients had levels of CA19-9 above the cut-off (37 U/ml). The median value of CA19-9 for the 27 assessable patients decreased from 274.9 U/ml at baseline to 83 U/ml after NAC ($p<0.0001$ by Wilcoxon T test). A waterfall plot of the response showed that 24 of 27 patients (89%) had some degree of CA19-9 decrease and that 15 (56%) of 27 patients had a more than 50% decrease in the CA19-9 value (Figure 2B).

Resectability and surgical outcomes

According to operative findings, five patients were judged to have unresectable disease due to distant metastases and aggressive local extension (Figure 1). Thirty (86%) cases underwent resection with curative intent. Of the operative procedures performed for resection, 19 SSPPD, seven DP, and four SSPTP were performed. Half of operations were standard pancreatectomies with combined resection of adjacent major vessels. Overall perioperative morbidity was 40% for patients who underwent pancreatectomy. The details of the postoperative

complications are listed in Table 2A. There was one postoperative death. In this case, there were no abdominal complications, but the patient experienced sudden death due to suspected lethal arrhythmia at 2 weeks after surgery. Postoperative gemcitabine was administered in 24 cases (80%).

Pathological findings, including grade, stage, and response to neoadjuvant treatment

Histological assessment of resected specimens in 30 cases treated with NAC-GS is summarized in Table 2B. The majority of the patients had neoplasm with T3. Nodal involvement was observed in 15 cases (50%). Three cases had M1 stage IV disease due to the nodal metastases within resected para-aortic lesions. There was no case of macroscopic residual tumor (R2) in resected cases. R0 resection was performed in 26 cases (87% in resected cases). Histological response evaluation according to Evans' classification revealed six cases that were Grade IIB. More than half of the cases were documented as Grade IIA.

Survival and recurrence

The median follow-up time was 19.7 months (95% confidence interval (CI); 17.2 – 24.6) for all cohorts. The median overall survival was 19.7 months (13.7 – not reached (NR)) based on an intent-to-treat analysis. Actuarial 2-year survival rate was 45.7% (Figure 3A). Patients who underwent resection without distant metastases (n=27) after NAC-GS had an increased median overall survival (34.7 months) when compared with 10.0 months for those without resection or resection with distant metastases (n=8, Figure 3B). The actuarial 2-year survival rate of the patients with resection was 55.6%, which was significantly better that the value (12.5%) in those without resection or with resection including metastases. Median recurrence-free survival for resection without metastases was 20 months. The survival probability at 2-year for initially resectable tumor (n=19) was 57.9%, which was marginally higher than that for borderline tumors (n=16, 31.5%) (p=0.071, Figure 3C).

Discussion

This study investigated outcomes after NAC-GS for resectable and borderline PDAC. The adverse effects of NAC-GS were similar to those of the same regimen when used for unresectable disease (30). These adverse effects were manageable, and loss of operative chance due to toxicity was not noted, although there were three cases of early termination of NAC. When compared with other gemcitabine-based regimens (14-16), NAC-GS was acceptably safe.

One of the potential advantages of NAC is to deliver high dose intensity without the potential delays caused by surgical complications and delayed recovery. The RDI of NAC-GS was >90% for both agents. Two thirds of the cases had documented radiological tumor shrinkage, and the vast majority showed a reduction in tumor markers during NAC. These results indicated that NAC-GS had a modest effect in most cases. A potential drawback of NAC is that delaying surgery may allow disease in some patients to progress to an unresectable stage. In this series, approximately 10% of the cases showed radiological tumor progression, although none of the progressive changes reached the PD criteria defined by RECIST. All patients, including the patients in whom the tumor progressed but remained resectable or borderline at the time of surgery, had a favorably high resection rate (86%) and R0-resection rate (74%, intent-to-treat based) when compared with previous series (31-33).

The survival impact of neoadjuvant therapy is difficult to estimate or compare with that from other reports. This is primarily due to the heterogeneity of the patient population among previous studies (34). The optimal strategy for resectable and borderline PDAC remains controversial. Surgery followed by post-resectional systemic chemotherapy with gemcitabine provided a 2-year survival rate of 45-50%, which was significantly better than that provided by surgery alone (8-10). Although adjuvant chemotherapy is the optimal therapy for patients with PDAC that is resected without macroscopic residual tumor, all patients who underwent planned

resection did not gain a survival benefit. This is because metastatic and/or severe local extension was found after laparotomy in some patients or because these patients experienced delayed recovery from surgical morbidity (35). Taking these factors into consideration, the 2-year survival obtained with surgery and adjuvant chemotherapy for eligible patients in this study would be estimated as approximately 30 to 40%, based on an estimated resectability of 70 to 80% (when compared with 45.7% of all cohorts in this study). Since no controlled randomized trials have ever compared adjuvant to neoadjuvant therapy, comparison between subgroups could only be performed in a descriptive manner.

A phase III study was recently initiated to determine the efficacy of neoadjuvant gemcitabine and platinum for patients with resectable PDAC (36). GS may also be a good candidate for control studies comparing adjuvant and neoadjuvant therapy. In conclusion, NAC-GS was well tolerated and safe when used in a multi-institutional setting. The R0 resection rate and 2-year survival rate are encouraging for patients with resectable and borderline PDAC.

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Figure Legends

Figure 1. Flow chart showing the number of patients proceeding through each stage of the study with reasons for exclusion.

Figure 2. Waterfall plot of reduction rate for radiological tumor size and serum CA19-9.

a. Radiological tumor reduction rate (n=33). The data represent the rate of tumor size reduction (Baseline – Post-treatment) / Baseline. There were five cases with 0% reduction.

b. Serum CA19-9 reduction rate (n=32). The data represent the rate of CA19-9 reduction (Baseline – Post-treatment) / Baseline.

Figure 3. Kaplan-Meier plots of survival.

a. Overall survival for the entire cohort (n=35).

b. Survival comparison between with and without resection.

Solid line indicates resection without distant metastases (n=27). Dashed line indicates patients without resection or resection with distant metastases (n=8).

c. Survival comparison between initially resectable and borderline tumors.

Solid line indicates the initially resectable tumors (n=19). Dashed line indicates the initially borderline tumors (n=16).

Table 1 A. Patient's demographics

Total cohort eligible	35
Gender (Male: Female)	20 : 15
Age: median (range)	65 (47 - 77)
Location (Head: Body-Tail: Whole)	25 : 9 : 1
Tumor size: median (range, cm)	2.5 (1.2 – 7.0)
Pre-treatment Resectability (Resectable: Borderline)	19 : 16
Pre-treatment CA19-9 value: median (range, U/ml)	157.5 (<2.0 – 5,000)

Table 1 B. Treatment-related adverse events (n=35)

	Grade					
	1	**2**	**3**	**4**	**1-4 (%)**	**3/4 (%)**
Hematological						
Anemia	7	1	0	0	8 (23)	0
Leukopenia	3	10	4	0	17 (49)	4 (11)
Neutropenia	2	8	9	3	22 (63)	12 (34)
Thrombocytopenia	7	1	1	0	9 (26)	1 (2.9)
Non-Hematological						
Fatigue	4	0	0	0	4 (11)	0
Diarrhea	2	0	0	0	2 (5.7)	0
AST elevation	6	4	0	0	10 (29)	0
ALT elevation	5	3	0	0	8 (23)	0
Anorexia	3	0	0	0	3 (8.6)	0
Nausea	3	0	0	0	3 (8.6)	0
Vomiting	1	0	0	0	1 (2.9)	0
Mucositis	4	1	0	0	5 (14)	0
Hyperpigmentation	4	0	0	0	4 (11)	0
Constipation	4	2	0	0	6 (17)	0
Dermatitis	0	1	0	0	1 (2.9)	0
Cholangitis	0	1	2	0	3 (8.6)	2 (5.7)
Rash	3	0	4	0	7 (20)	4 (11)
Gastritis	0	0	2	0	2 (5.7)	2 (5.7)

***Worst grade reported during the preoperative period**

Table 2A. Post-operative complications (n=30, resection).

Complications n (%)	Grading by Clavien-Dindo Classification*1	
	Any Grade	Grade 3b or more
Pancreatic fistula*2	3 (10)	0 (0)
Delayed gastric emptying*2	1 (3.3)	0 (0)
Bile leak	0 (0)	0 (0)
Surgical site infection	2 (6.7)	1 (3.3)
Catheter-related infection	1 (3.3)	0 (0)
Lymph leak	2 (6.7)	0 (0)
Antibiotic-related enterocolitis	1 (3.3)	0 (0)
Cardiovascular complications	1 (3.3)	1 (3.3)
Pulmonary complications	0 (0)	0 (0)
Urinary complications	0 (0)	0 (0)
Total	12 (40)	2 (6.7)

***1: Post-operative complications were listed by grading according to the classification reported by Dindo et al. (37).**
***2: Pancreatic fistula and delayed gastric emptying were defined according to the international definition reported by Bassi et al. (38) and Wente et al. (39).**

Table 2B. Pathological findings (N=30, resected tumors).

Factors	Category	Number (%)
T	T1	1 (3)
	T2	1 (3)
	T3	28 (93)
N	N0	15 (50)
	N1	15 (50)
M	M0	27 (90)
	M1	3 (10)
Stage	IA	1 (3)
	IB	0 (0)
	IIA	13 (43)
	IIB	13(43)
	III	0 (0)
	IV	3 (10)
Residual tumor	R0	26 (87)
	R1	4 (13)
Treatment effect*	I	7 (23)
	IIA	17 (57)
	IIB	6 (20)
	III-IV	0 (0)

*** Pathological response by the chemotherapy was evaluated by central review according to the classification reported by Evans et al. (28).**

Figure 1.

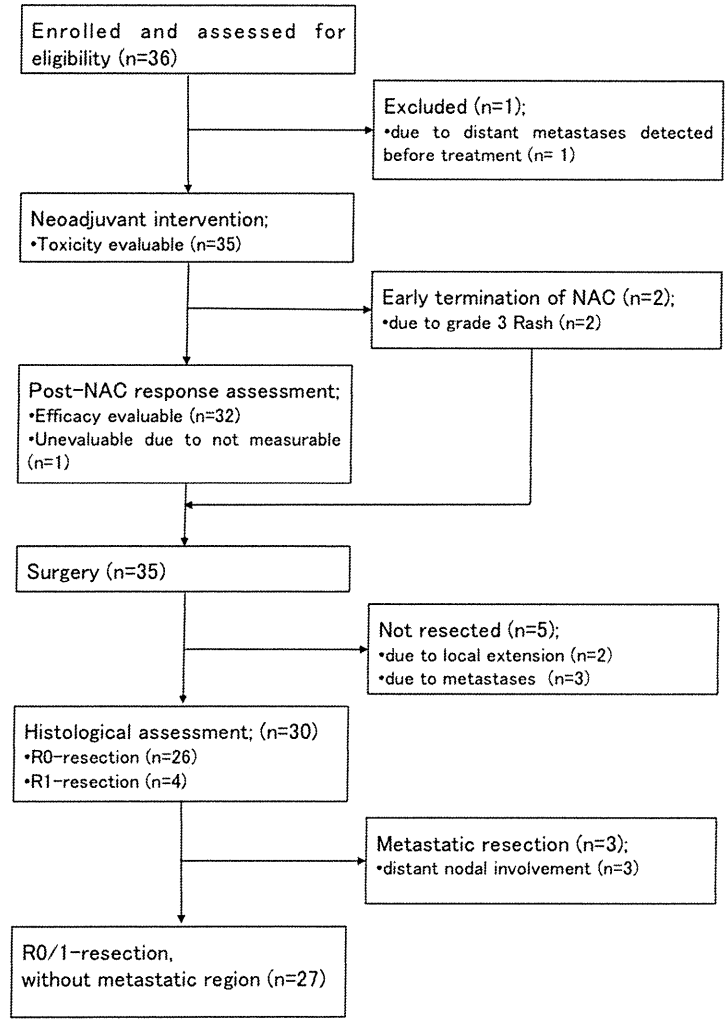

Figure 1
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Figure 2.

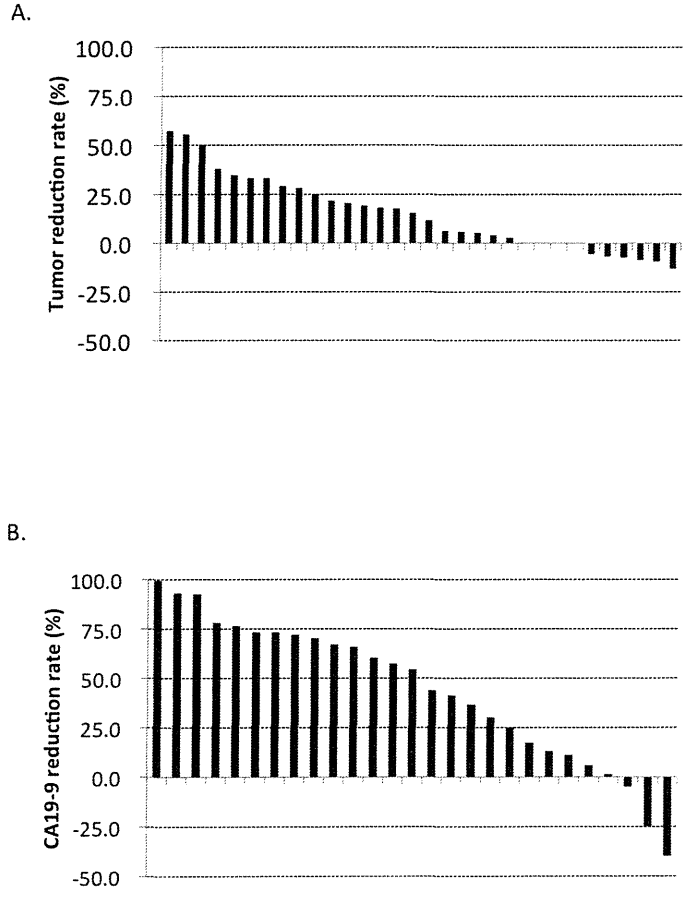

Figure 2A and 2B
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Figure 3

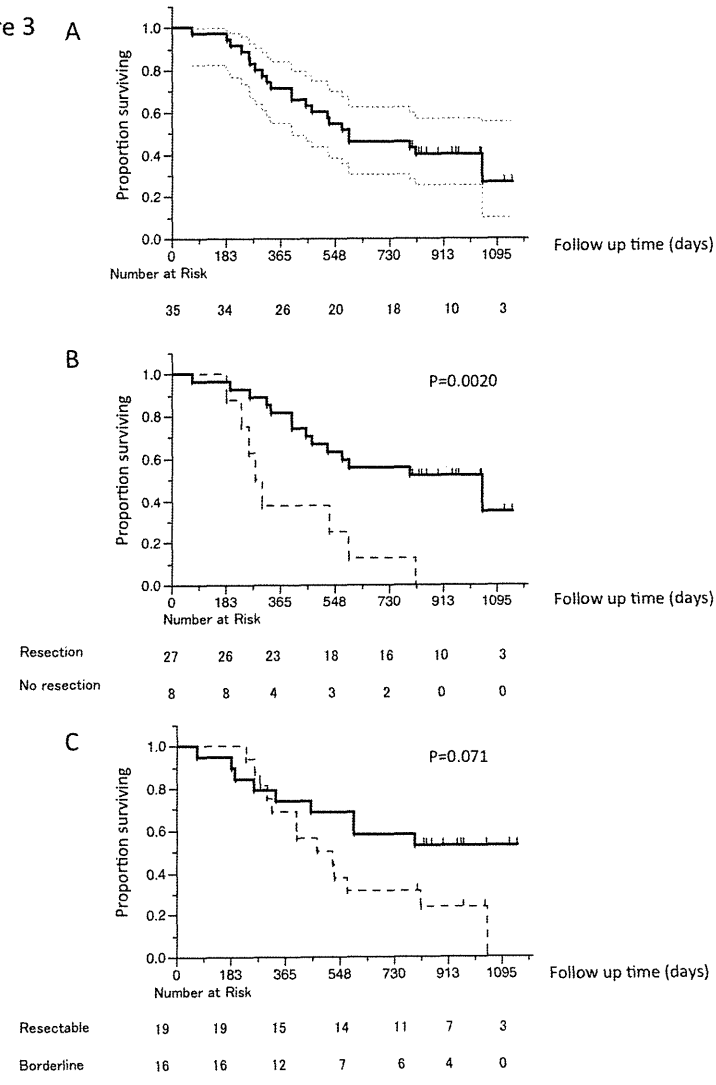

Figure 3A 3B 3C
549x732mm (72 x 72 DPI)

切除可能膵癌に有効な補助療法とは

①術前補助化学療法の立場から

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治療戦略上のメリット

術前補助化学療法のメリットには，診断時に存在した微小な転移巣への治療が速やかに開始できること，術前治療によるダウンステージングで，切除率，治癒切除術が増加，また隣接臓器などの温存を図ることができること，術後補助療法の効果・副作用予測となること等が挙げられる。また，リンパ節郭清や血行改変が行われた術後とは異なり，局所への血流が阻害されておらず，全身状態のよい術前に治療することでintensity，complianceの高い治療が可能となる。さらに，術前の観察期間を設けられることで，不適切な症例を除外することができる。

治療戦略上のデメリット

術前治療が奏効しなかった症例では手術治療を行う機会を喪失することにつながるのが最大のデメリットと考えられる。術前治療中の有害事象を考慮する必要もあり，術前治療による術中および周術期合併症の増加が起こることも注意が必要となる。さらには治癒切除へのこだわりがなくなることも危惧される。

はじめに

膵癌は5年生存率は約5%と報告されているように，現代においても最難治性癌の一つである[1]。また日本においては，癌死の第5位となる年間22,000人もの死亡者があることから，膵癌の治療成績改善は急務である。膵癌根治への唯一の道は外科切除であるが，切除率は低く，また切除しても5年生存率は10%から20%程度と，治療成績は甚だ不良である[2]。そのため，治療成績向上に向けた創意工夫がなされているが，治療成績向上に結びついたものは少ない。

本ディベートでは，膵癌の術前治療について紹介する。膵癌の術前化学(放射線)治療は近年注目されてきており，2011年の日本肝胆膵外科学会では，多くの施設が術前治療に取り組んでいることが明らかとなった。まさに，大きな潮流となりつつある術前治療であるが，いまだ標準治療として確立されたものではないことに留意されたい。

I. 膵癌術前治療が注目される理由

近年，膵癌治療に関するいくつかの無作為化試験の結果が明らかになり，膵癌治療の方向性が変化してきている。術前治療が注目されてきたのは，治療戦略の変化と密接に関わっているので，この点にまず触れることとする。

進行膵癌の手術適応に関して，手術とその他のmodalityとの無作為化試験が日本において行われた。その結果，局所進行膵癌であるステージ4a(膵癌取扱い規約第4版のS2またはRP2またはPV2，かつN0またはN1のstageⅣa)までの膵癌は根治を目指した手術切除療法を行うことが勧められる，との結果が示された[3]。また膵癌に対する拡大リンパ節・神経叢郭清の意義に関して，本邦からの無作為化試験が報告され，拡大手術の有効性が否定された[4]。さらに，術後補助化学療法としてのゲムシタビンの有効性が示され[5-7]，治癒切除術後にはゲムシタビンによる6ヵ月または3ヵ月の術後補助化学療法を行う