Abstract. Background: Local antitumor efficacy and the outcome of neoadjuvant chemoradiotherapy (NACRT) with low-dose gemcitabine and wide irradiation area for borderline resectable and unresectable pancreatic cancer were evaluated. Patients and Methods: Thirty-four cases of borderline resectable and unresectable pancreatic cancer were recruited. Three-dimensional conformal radiotherapy to the pancreatic bed and the region scheduled for lymph node dissection was performed to a total dose of 50.4 Gy28 fractions with gemcitabine at a dose of 150 mg/m² weekly. Clinical and pathological results were examined. Results: Twenty-seven patients (79.4%) completed the protocol. Grade 3/4 leucopenia (n=10), and grade 3 anorexia (n=1) occurred. Seven cases were excluded (two refused treatment; five had progressive disease), 20 underwent laparotomy, and 16 resected (47.1%) cases achieved R0 resection. Median survival time, and 3-year and 5-year survival rates were 39.0 months, and 56.3% and 28.1% in resected cases, respectively. Conclusion: NACRT with low-dose gemcitabine and wide irradiation area achieved 100% R0 resection and acceptable prognosis.

Pancreatic ductal adenocarcinoma (PDAC) has recently increased in incidence and is the fourth to sixth leading cause of cancer-related death in Western countries and Japan (1). This disease has a poor prognosis, with a 5-year survival rate of around 5% for patients overall (2, 3). Adjuvant chemotherapy with gemcitabine or S-1 after 81-88% of R0 surgical resections improved patient outcome, resulting in a 5-year survival rate of 20-24% with gemcitabine (4-6) and 44% with S-1 (7). Although R0 surgical resection is a prognosis factor for long-term survival, 15-85% of surgical resections were margin-positive, which are associated with worse overall survival (8-10).

A standard therapeutic strategy for PDAC was proposed by the National Comprehensive Cancer Network (NCCN) guideline according to disease progression (11). Regarding the local progression of tumors, several criteria define resectability into three categories: potentially resectable, borderline resectable (BR), and unresectable (UR) (12-14). These categories are defined by the degree of tumor invasion in the vascular structure such as superior mesenteric vein (SMV) and portal vein (PV), and in arteries such as superior mesenteric artery (SMA), common hepatic artery (CHA) and celiac artery (CA). For BR PDAC, neoadjuvant therapy prior to surgery is recommended by the NCCN guideline (11).

As neoadjuvant therapy for BR to UR PDAC, we introduced gemcitabine-based neoadjuvant chemoradiotherapy (NACRT) which is intended to achieve R0 resection. Our focus is on controlling micrometastasis to surrounding tissues, thus our regimen has the characteristic feature of being applied to a wide irradiation area, which includes not only the tumor and surrounding area, but also the area of lymph node dissection, CA-CHA, and SMA nerve plexus. Here, we report the results of our gemcitabine-based neoadjuvant chemoradiotherapy based on this concept.

Patients and Methods

Patient examination and definition of BR and UR PDAC. Between January 2006 and 2013, 34 patients with histologically proven BR and UR PDAC were enrolled for our gemcitabine-based NACRT protocol. Multidetector computed tomography (MDCT), contrast-enhanced ultrasonography (CEUS), gadoxetic acid-enhanced
magnetic resonance imaging, and 18F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) were performed to examine local progression and distant metastasis. The definition of BR and UR PDAC followed the guidelines of a National Cancer Institute-designated National Comprehensive Cancer Network (NCCN) (14).

Neoadjuvant treatment plan and assessment. This study was performed with the approval of the Internal Review Board on ethical issues at Hokkaido University Hospital, Sapporo, Japan (approval number 008-0040). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

All patients were treated with three-dimensional conformal radiotherapy using the 3- or 4-field technique from directions that avoided exposure of the kidney, an organ at risk. Based on the CT images, the gross tumor volume (GTV), which included the main tumor and lymph nodes of more than 1 cm in diameter, was defined. Clinical target volume 1 (CTV1) was defined as the GTV plus a 5-mm margin in all directions, and CTV2 was defined as the field that contained the regional lymph nodes prescribed by sixth edition of the Union for International Cancer Control TNM classification (15) and extrapancreatic nerve plexus along with SMA and CA-CHA. The planning target volume (PTV) was basically defined as CTV1 and CTV2 plus a uniform 15-mm margin, which comprised the internal and the set-up margins (Figure 1). The total radiation dose delivered was 50.4 Gy in 28 fractions (five fractions/week). The dose was prescribed at the center of the PTV. The dose constraints for organs at risk were as follows: spinal cord: maximum dose <45 Gy; liver: volume of the liver receiving a dose of at least 35 Gy (V35)<33%; kidney: V20 of both kidneys<50% and V20 of each individual kidney<67%.

Patients were administered an infusion of gemcitabine at a dosage of 150 mg/m² weekly. Within 4-6 weeks after the completion of NACRT, the patients were reassessed by CT, MRI and FDG-PET. If we determined that resection with curative-intent was possible, surgery was performed. Safety assessment was performed before each cycle with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0) (16). Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) (17).

Surgical procedure and postoperative complications. Pancreatoduodenectomy and distal pancreatectomy were performed according to conventional methods (18, 19). Requirement of resection and reconstruction of PV and SMV were judged when it was not possible to detach the vessels from the tumor and were performed at an arbitrary time. Dissection of the pancreatic nerve plexus was basically performed as follows: dissection of the nerve plexus of hepatoduodenum ligament, CHA, right side of CA, and right side of SMA was undertaken for pancreatectoduodenectomy, and dissection of nerve plexus of CHA, left side of CA, and left side of SMA was performed for distal pancreatectomy. Additional nerve plexus dissection was performed according to the tumor extension to nerve plexus evaluated by MDCT before NACRT.

Postoperative complications were graded according to the Clavien-Dindo classification (20). Postoperative pancreatic fistula was graded according to the International Study Group on Pancreatic Fistula classification (21).

Postoperative follow-up. After discharge, administration of gemcitabine or S-1 for at least 6 months was planned. All patients were evaluated every 3 months by physical examination and laboratory tests including serum levels of carcinoembryonic antigen (CEA) and cancer antigen (CA)19-9, plus MDCT.

Evaluation of histological response. Formalin-fixed and paraffin-embedded specimens were retrieved from the surgical pathology files of the Pathology Department of Hokkaido University Hospital. Sections were cut and stained with hematoxylin-eosin (H&E) for routine histopathological examination. Histological response to neoadjuvant chemoradiotherapy was evaluated according to Evans et al.’s histological criteria (22).

Statistical analysis. Comparison of categorical variables was performed using Fisher’s exact test, and continuous variables were analyzed by Mann–Whitney rank-sum test. Statistical significance was defined as a p-value of less than 0.05. Kaplan–Meier curves were used to determine survival, with the date of neoadjuvant initiation as time 0. All statistical analyses were performed using statistical analysis software (JMP Pro 13.1.0 for Windows; SAS Institute Inc. Cary, NC, USA).

Results

Preoperative characteristics of enrolled patients. According to the definitions of BR and UR PDAC described above, of the 34 enrolled patients, disease in 28 was classified as BR and in six as UR. PV-SMV involvement was confirmed in 18 (52.9%) patients, and arterial involvement was confirmed in 26 (76.5%) patients (Table I). Reasons for disease being defined as UR was the finding of tumor abutment of the SMA exceeding greater than 180 degrees of the circumference in five patients, and PV-SMV occlusion in one patient. Twenty-seven patients (79.4%) completed NACRT, and 16 patients (47.1%) underwent resection with curative intent. Grade 3 or higher adverse effects in white blood cell/neutrophil counts defined by CTCAE ver 4.0 occurred in 10 patients (37%) and the relative dose intensity of gemcitabine was 85.2%. During the study, nine patients (26.3%) were excluded from resection criteria because of distant metastasis, and two patients (5.9%) with local progression were excluded. The flow of all 34 patients through the treatment schema is depicted in Figure 2.

Tumor response to NACRT and surgical results. The tumor responses of the 27 patients who completed the NACRT protocol were analyzed (Table II). Local tumor response assessed by RECIST criteria were as follows: partial response was observed in eight (29.6%) patients, stable disease in 14 (51.9%) patients, and progression disease in four (14.8%) patients. Median reduction ratio of the value of CA19-9 before and after NACRT was 54.6% and that of

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FDG-PET SUV value was 53.7%. These parameters did not statistically significantly differ between the resected and unresected groups. Finally, 16 out of 34 patients underwent surgical resection with curative intent. Total pancreatectomy was performed in one case. PV/SMV resection was performed in 12 (75.0%) patients and hepatic arterial resection was performed in one (6.25%) patient. Clavien-Dindo classification IIIa was observed in four (25.0%) and

Figure 1. Irradiation area of three-dimensional conformal radiotherapy using the 4-field technique. Images indicate typical isodose lines encompassing a region including not only the tumor but also a lymph node dissection area.
there were no patients over Clavian-Dindo IIIb. According to an international study group of postoperative pancreas fistula definition (21), pancreatic fistula grade B occurred in three patients (18.8%), including both cases treated by distal pancreatectomy.

Pathological results. Pathological stage T3 was observed in 15 patients (93.7%) and only one patient achieved down-staging to T2 (Table II). Four patients (25%) had lymph node metastasis, but only five (1.0%) lymph nodes were metastatic amongst 495 dissected lymph nodes from 16 patients who underwent resection.

According to Evans et al.’s histological criteria, nine out of 16 patients (56.3%) were classified over grade IIb, which meant more than 50% tumor cells were destroyed by NACRT. As a result, 100% R0 resection was achieved in these 16 patients.

Patient outcome. The survival period was calculated based on the time from when NACRT was started. Intention-to-treat analysis of all 34 patients showed that the median overall survival time (MST) was 19.9 months (Figure 3A). The MST, and 3-and 5-year overall survival rates of resected patients (with 39.0 months of median follow-up duration) were 39.0 months, and 56.2% and 28.1%, respectively, and those of unresected patients were 14.9 months, and 0.0% and 0.0%, respectively (p<0.001) (Figure 3B). MST of unresected patients with completion of NACRT and without completion of NACRT were 14.9 months, and 8.3 months, respectively (p=0.0326). Among the 16 patients who completed NACRT and underwent surgical resection, 13 (81.3%) developed recurrence; the median time to recurrence was 14.9 months (range=1.3-33.5 months) (Figure 3C). The first sites of recurrence were as follows: 10 patients (62.5%) had distant organ metastasis (five liver, five lung), one patient (6.25%) had peritoneal dissemination, and two patients (12.5%) had local recurrence.
Table II. Outcome of patients who completed neoadjuvant chemoradiotherapy (NACRT) (n=26*).

| Variable                                      | Resected (n=16) | Not resected (n=10) | p-Value |
|-----------------------------------------------|----------------|---------------------|---------|
| Local response                                |                |                     |         |
| CR                                            | 0              | 0                   | 0.612   |
| PR                                            | 6              | 2                   |         |
| SD                                            | 0              | 6                   |         |
| PD                                            | 2              | 2                   |         |
| Median CA19-9 (range), U/ml                   | 47.45 (11.4-605.9) | 124.35 (24.1-3122.8) | 0.1354  |
| Perioperative Reduction rate (%)              | 53.3           | 64.8                | 0.5923  |
| Median FDG-PET SUV (range)                    | 6.0 (3.09-13.964) | 8.461 (2.7-13.1)    | 0.6977  |
| Operative procedure n (%)                     |                |                     |         |
| Pancreaticoduodenectomy                        | 13 (81.3)      |                     |         |
| Distal pancreatectomy                         | 2 (12.5)       |                     |         |
| Total pancreatectomy                          | 1 (6.25)       |                     |         |
| PV/SMV resection/reconstruction               | 12 (75.0)      |                     |         |
| Arterial resection/reconstruction              | 1 (6.25)       |                     |         |
| Blood loss, ml                                |                |                     |         |
| Median (range)                                | 642 (180-2620) |                     |         |
| Operative time, min                           |                |                     |         |
| Median (range)                                | 600 (458-834)  |                     |         |
| Clavien-Dindo classification n (%)            |                |                     |         |
| I                                             | 8 (50.0)       |                     |         |
| II                                            | 4 (25.0)       |                     |         |
| IIIa                                          | 4 (25.0)       |                     |         |
| ISGPF classification, n (%)                   |                |                     |         |
| A                                             | 0 (0.0)        |                     |         |
| B                                             | 3 (18.8)       |                     |         |
| C                                             | 0 (0.0)        |                     |         |
| Evans grade, n                                |                |                     |         |
| I                                             | 1              |                     |         |
| IIa/IIb                                       | 6/7            |                     |         |
| III/IIIM                                      | 1/1            |                     |         |
| IV                                            | 0              |                     |         |
| al/db, n (%)                                  | 9 (56.3)       |                     |         |
| Pathological stage, n (%)                     |                |                     |         |
| T1                                            | 0 (0.0)        |                     |         |
| T2                                            | 1 (6.3)        |                     |         |
| T3                                            | 15 (93.7)      |                     |         |
| N0                                            | 12 (75.0)      |                     |         |
| N1                                            | 4 (25.0)       |                     |         |
| LN, n (%)                                     | 5/498 (1.0)    |                     |         |
| R0 operation, n (%)                           | 16 (100)       |                     |         |

NACRT: Neoadjuvant chemoradiotherapy; SMV: superior mesenteric vein; PV: portal vein; SMA: superior mesenteric artery; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; FDG-PET: 18F-fluorodeoxyglucose positron-emission tomography; SUV: standardized uptake value; LN: lymph node. *One patient was excluded due to refusal of reassessment and surgery.

Discussion

R0 surgical resection is considered to be one of the essential prognostic factors for predicting long-term survival of patients with PDAC (8-10). For locally advanced PDAC, neoadjuvant therapies are recommended in the NCCN guidelines. There are many points to consider when selecting neoadjuvant therapy, such as chemotherapy or...
chemoradiotherapy, antitumor agent, and method of radiation. NACRT is considered to achieve a high R0 surgical resection rate, with rates of 94% (23) and 98% (24) previously reported. To achieve R0 resection, we intended to control micrometastases that had spread to surrounding tissue, lymph nodes, and nerve plexus by applying a wide irradiation area. Of the various antitumor agents tested for NACRT (23, 25-28), we selected gemcitabine as a radiosensitive agent (29). Various doses of gemcitabine, from full dose at 1,000 mg/m² (24) to 50 mg/m² (30) were administered for gemcitabine-based NACRT (31, 32); we administered low-dose gemcitabine in our protocol, according to past experience of chemoradiotherapy against recurrent lesions. However, despite this low-dose, R0 resection was achieved in all 16 patients treated using our protocol.

We then examined the acceptable locoregional effects of our NACRT protocol on tumor. The histological criteria of Evans et al. showed that more than half of the resected cases (56.3%) were judged to be over grade IIb. This result was similar to past reports (23, 26, 28), but Takahashi et al. reported that NACRT with full-dose gemcitabine resulted in Evans histological criteria over grade III (more than 90% tumor cells injured) in 16% of resected cases (24). This suggests the possibility of enhancing the local antitumor effect by using more potent anticancer drugs. The grade of pathological response after NACRT influenced patient prognosis in rectal cancer (33, 34) and gastro-esophageal cancer (35). The relationship between anticancer drug, pathological response, and prognosis in neoadjuvant therapy for PDAC should be considered in the future.

NACRT for PDAC is thought to reduce local recurrence and lymphatic nodal metastasis. Groot et al. reported that the local recurrence rate in 1103 patients with PDAC was at least 43% (36). However, the local recurrence rate after NACRT was reported as 9-14% (23, 24), and our data showed a local recurrence rate of 12.5%. Regarding lymph node metastasis, 12 out of 16 patients (75%) were negative for lymph node metastasis, and the proportion of positive lymph node metastasis was only 1.0% in all dissected lymph nodes. These results were comparable to other reports demonstrating negative lymph node metastasis rates of 61-81% (23, 24, 26). Regarding the local effect, NACRT with low-dose gemcitabine was also effective. We speculate that irradiation would be more important for the locoregional effects on the tumor than the selection of antitumor agents.

It is necessary to discuss the systemic effects resulting from the use of low-dose gemcitabine in NACRT. The resection rate after NACRT for BR PDAC differs in literature, ranging from 40-88.8% (23, 24, 26, 28, 30, 32, 37). The resection rate in our protocol was 47.1%, and nine patients (26.3%) were excluded from the resection criteria after exhibiting distant metastasis during the neoadjuvant therapy. Takahashi et al. (24) reported the results of NACRT with full-dose gemcitabine.
for 80 BR PDAC patients; the resection rate was 47.1%, and 11 patients (13.8%) were excluded because of distant metastasis (28). Kobayashi et al. reported the results of NACRT with gemcitabine administered at 800 mg/m² weekly for 44 patients with BR PDAC; the resection rate was 81.8%, and six patients (13.6%) were excluded because of distant metastasis (32). This suggests that the dose of gemcitabine during NACRT would influence the occurrence of distant metastasis.

However, high resection rates are not necessarily related to patient prognosis. Kim et al. reported a resection rate of 61.5% and MST of 25.4 months for patients treated with NACRT with full-dose gemcitabine and oxaliplatin (28). As previously mentioned, Kobayashi et al. reported an 81.8% resection rate and MST of 24.3 months (32). The MST of our protocol was 39.0 months, while Katz et al. reported MST of 40 months, with a 41.3% resection rate and 20.6% distant metastasis (23). If there is a role of ‘patient selection’ in NACRT with gemcitabine, low-dose gemcitabine might select for patients more strictly as good prognosis, there is a need to enhance systemic effects using other more effective antitumor drugs.

**Conclusion**

In conclusion, NACRT with low-dose gemcitabine and wide irradiation area for locally advanced PDAC provided acceptable locoregional effects and resulted in a high rate of R0 resection. In addition, a good prognosis was obtained in resected cases. To increase the resection rate and achieve better prognosis, there is a need to enhance systemic effects using other more effective antitumor drugs.

**Conflicts of Internet**

The Authors have no financial relationships to disclose.

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